February 1999 Issue | Michael R. Lyon, M.D.

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Welcome to *Functional Medicine Update*™ for February 1999. This month we will discuss the brain, focusing on functional neurology from a pediatric perspective. We are confronted with increasing numbers of diagnoses related to brain and behavior, such as attention deficit disorder (ADD) or autism, which we discussed in the January, 1999 issue of *FMU*. We might ask if a common theme weaves these disorders together, something clinicians can use to assist parents and children to achieve higher levels of function. Individuals with autism or ADD suffer through years of low self-esteem, problems in school, and dysfunction in the home. Their adulthood may be negatively affected, since the bad experiences of childhood make the person feel like a loser, with loss of locus of control. Poor self-esteem and self-value can translate into both behavior disorders and physiological problems.

This theme will be amplified and discussed at the Sixth International Symposium on Functional Medicine, to be held May 24–26 in Tucson, Arizona. The focus will be on intercellular messengers and functional medicine intervention, and problems related to dysfunctional communication among organs, tissues, and cells in individuals. We might subtitle this symposium "Functional Medicine's Interface with Body/Mind Medicine."

Some exciting speakers will present from this perspective. Dr. Candice Pert and Dr. Michael Ruff will talk about their extraordinary discoveries of neurotransmitter receptor sites on white blood cells, and how the whole body is communicating external messages into immunological and neurological function. We will look at melatonin as a cell-signaling molecule with polyorgan effects, with Dr. David Blask, MD, PhD, whose specialty is neuroendocrine signal-regulating effects. We will have discussions of cancer gene intercellular communication and modification of expression with Vincent Castronovo, who is now working as the head of the Chemical Carcinogenesis and Oncogenesis Laboratory at the University of Liege Medical School in Belgium (previously from the National Cancer Institute). Dr. Johanna Lampe will talk about soy isoflavones, and Dr. George Zabrecky will speak on zinc finger modulation and oncogene expression.

Robert Sapolsky, PhD, a Stanford University neurophysiologist at the medical school, will talk about stress mediators and messengers and their relationship to sex steroid hormones and discuss his new book, *The Trouble with Testosterone and Other Essays on the Biology of the Human Predicament.* Some of those essays relate to modulation of behavior by small molecules, fascinating work that came out of his previous book, *Why Zebras Don't Get Ulcers.*Dr. Robert Lerman from Boston University Medical School will discuss fatty acids, eicosanoids, heart disease, and cell signaling interrelationships. Kilmer McCully will be back to discuss what has happened in the area of homocysteine over the course of this last year. It will be an interesting series of discussions about the functional medicine interface with body/mind

medicine. Afternoon workshops will delve into the clinical application of these topics. Symposium dates are May 24–26 in Tucson, Arizona.

Dr. Scott Anderson, a physician in Fairfax, California, is a long-standing functional medicine supporter and a clinician for whom I have great respect. He wrote to me suggesting that I cover some of the material described in the 7th Edition of *Metabolic and Molecular Bases of Inherited Disease*,[1] which is considered the text of record that helps us understand inherited disease. According to Dr. Anderson, the 7th Edition contains materials presented as fact that greatly resemble the foundations of functional medicine and the molecular medicine concept of Dr. Linus Pauling. He feels *FMU* listeners should know we have evolved from a period of speculation and conjecture to a period of acceptance and understanding.

In a letter, Dr. Anderson wrote: "The 7th Edition of *Metabolic and Molecular Bases of Inherited Disease* must be read. Although you have been stressing that nutritional modification is one of the main strategies we have to 'modify gene expression,' these authors go the step further to suggest that genetics is rapidly becoming the very basis of medicine. Thus, the ideas that you have been teaching us 'from the margin' have here become certified Grade A mainstream!

"Furthermore, Childs, in his '*A Logic of Disease*' chapter, gives a most elegant presentation of how clinical practice can be built on these ideas. I've spoken to Childs about making his chapter into a book."

Dr. Anderson thinks this may be a way of teaching doctors about the underpinnings of future medicine. In its preface, the 7th Edition of the *Metabolic and Molecular Bases of Inherited Disease* says something prescient and timely. We in functional medicine can take some credit for being on target. We have been traveling in the direction that mainstream medical thinking is taking us. According to the preface:

"A reviewer of the sixth edition reminds us of the original plan for the book: to present 'the pertinent clinical, biochemical and genetic information concerning those metabolic anomalies grouped under Garrod's engaging term, inborn errors of metabolism.'"

The term *molecular* was added belatedly as a consequence of understanding more of what Dr. Linus Pauling discussed in his landmark 1949 article, titled "Sickle Cell Anemia, A Molecular Disease."

"The inborn errors of metabolism are simply our most obvious illustrations of the genetic variation that affects health and the molecular underpinnings of that variation. A corresponding analysis of multifactorial diseases is the obvious next step in the understanding of disease."

In the preface, the authors list a number of new topics that have been added to *Metabolic and Molecular Bases of Inherited Disease,* including pharmacogenetics, a topic we have discussed extensively in *FMU*. It is the study of the relationship of genetic uniqueness in detoxification of various substances, and the potential adverse effects of exposure to those substances, based upon that uniqueness in detoxification. The pharmaceutical industry is concerned about pharmacogenetics because of the increasing recognition that certain genotypes of detoxification status are unable to metabolize certain families of drugs, and those genetic imperfections or mutations significantly increase their risk of adverse drug reactions.

Genomics - Mapping the Genes

The preface also states that the mapping of genes, the field of genomics, has become a major part of molecular and inherited diseases, with the increased awareness that mutant gene expression may involve more than conventional Mendelian inheritance. We know, for example, about imprinting and mosaicism, which are indications that it is not simply Mendelian transference factors that give rise to the pleiotropic and polymorphic expression of genes.

Finally, how do cellular organelles, such as the mitochondrion, protein targeting, and post-translational modification like phosphorylation or glycation or glucuronidation, and the HLA complex, affect expression of genetic disease? Each may be influenced by environmental factors that change the expression of the genotype to phenotype. Although the genotype itself has obviously not changed, the relative way the genotype is expressed into its phenotype has changed as a consequence of these environmental exposures that alter both gene expression and the post-translational effect on genes, creating secondary effects on health and disease.

This interesting start to this month's *FMU* brings us to recognize that genetics, biochemistry, and the molecular basis of variant human phenotypes represent the emerging view of age-related, chronic, degenerative disease. We are just beginning to develop the tools, the perspective, and the intervention applications to these understandings to prevent unnecessary disease in an individual whose genetic uniqueness plunges him or her into a harmful environment that creates a disease risk.

Dr. Archibald Garrod was the first to discover and describe inborn errors giving rise to disease. It wasn't until Beadle and Tatum developed the one gene/one enzyme concept later in the 20th century, however, that it began to have validity. Practitioners had seen phenylketonuria and alkaptonuria clinically, for example, but they had not understood the connection of these diseases to genes and metabolism. Biochemistry originated only at the start of the 20th Century, so it was still an infant science. It took a while for this concept to catch on as part of medicine and the etiology of disease. Beadle and Tatum, with their one-gene/one enzyme concept that connected metabolic function to genetic inheritance factors, furthered the understanding of this concept.

In 1949, Pauling's classic work on sickle cell anemia gave birth to the concept of molecular disease. Other investigators who moved into this field enhanced and amplified that concept. Watson and Crick's landmark discovery of the double-stranded helix configuration of the DNA molecule gave rise to molecular biology. We went from there to the molecular basis of gene expression. We began to understand the molecular flow of information along the gene. DNA could, through the triplet code, turn on or off specific characteristics. Certain agents and influences would either suppress or upregulate gene expression.

We then moved to the understanding that at the genetic level there is much more significant diversity in biochemical genetics from individual to individual than we might expect by looking at their number of toes, fingers, eyes, or noses. Humans look pretty similar to one another, and we appear to be fairly similar within a narrow range of function. Not so at the biochemical level, according to research that gave rise to the recognition of what Dr. Roger Williams described as biochemical individuality. He described genetotrophic disease, which comes about as the result of the unavailability of the levels of specific nutrients necessary for improved expression of genes. The lack of sufficient amounts of these nutrients resulted in imperfect expression, or the phenotype of disease.

The genetic linkage to disease has become an important part of medical research and clinical thinking. We have moved beyond the frank genetic metabolic diseases of infancy, such as Tay Sachs disease, Gaucher's disease, Wilson's disease, or Fabry's disease. We now recognize functional abnormalities that are not so early in their penetration, which produce increasing risk of midlife disorders that previously have been attributed to complex etiology without a single cause. Such "wear and tear" conditions as coronary heart disease, certain forms of cancer, autoimmune disease, and certain types of digestive disorders arise in midlife as a consequence of the imperfect match between genotype and the environment.

In the nearly 100-year evolution of medicine, we have moved from a theoretic base to an esoteric base, with just a few cases of frank genetic metabolic diseases of infancy per 100,000 births to a basis that may lead to new therapies for virtually all chronic degenerative diseases of midlife.

Barton Childs, in his chapter titled "A Logic of Disease," in *Metabolic and Molecular Bases of Inherited Disease,* says the following:

"It might be claimed that what used to be spoken of as a diathesis is nothing else but chemical individuality. But to our chemical individualities are due our chemical merits as well as our chemical shortcomings; and it is more nearly true to say that the factors that confer upon us our predispositions to and immunities from the various mishaps which are spoken of as diseases, are inherent in our very chemical structure: and even in the molecular groupings which confer upon us our individualities, and which went to the making of the chromosomes from which we sprang."

Although this quote sounds prescient and has a contemporary ring, it was taken from Archibald Garrod's *The Inborn Factors in Disease,* published by Oxford University Press in 1909. We learn old things in new ways. It wasn't until Beadle and Tatum developed the one-gene/one enzyme concept that the prescience of Archibald Garrod was understood in medicine. It has taken another 60 years to understand this concept in terms of the variations in the ways genes are expressed. We now appreciate its significance in the management and production of either health or chronic disease in midlife.

The "A Logic of Disease" chapter by Dr. Barton Childs discusses the inborn error as a central theme in medicine. We might contrast Archibald Garrod to William Osler who was, at the same time in history, considered a premier physician of his age. There is a prophetic symbolism in the succession. Osler dominated medicine in his time as few have done since then. To a large degree, that ideal persists to this day. Osler's concept is that disease is simply a matter of fact, and it is part of the doctor's responsibility to deal with it, because nothing can be done about it. It is a very deterministic view, built on a Mendelian view of the gene as unmodifiable, producing risk of disease, and the physician can deal only with the outcome.

Osler's book, *The Principles and Practice of Medicine,* begins on the first page with diagnosis and treatment of typhoid fever. There is no preliminary discussion of the nature of the disease, who is likely to be sick, who escapes the disease, or why anyone would ever be sick at all. Indeed, it would have been thought eccentric to start the book in any such way. That book provided the basis of medical education, the understanding that disease is something that afflicts a person, that the principal responsibility of the doctor is to treat the disease, and that its etiology is of little clinical importance in the physician's treatment of it.

Obviously, that view is changing now. It is changing dramatically, in what Dr. Childs calls the "Garrod resurgence." Garrodism, or the molecular basis of disease, is re-emerging to explain why people in midlife get ill. It is not a single vector that produces a single disease, such as pneumonia, smallpox, diphtheria, typhoid. Instead, a complex, interwoven web of interaction takes place among the person's genes, exposure to agents that could be considered triggers, and the response of those genes to those triggers give rise to mediators, signs, and symptoms.

I thank Dr. Barton Childs for contributing to our education in the evolution of the explanation of disease. Functional medicine looks at the genetic underpinnings and the agents and influences from the environment that modify expression. It can help us understand that ultimate pathology in individuals in midlife, results from a series of changes in function that have occurred over many years, ultimately arriving at pathology.

The theme of this month's *FMU* is cognitive dysfunction in children. The belief persists in many sectors that genes determine cognitive function, and cognitive function is just the luck of the genetic draw. According to the authors of a recent article, titled "The Genetics of Cognitive Abilities and Disabilities," which appeared in the May 1998 issue of *Scientific American,*[2] it would be reasonable to think that the environment is the sole source of differences in cognitive skills, that we are what we learn. They ask how genes and environment intermix to give rise to specific cognitive abilities, such as vocabulary or mathematical skills.

The Hawaii Family Study of Cognition, a collaborative project between researchers at the University of Colorado at Boulder and the University of Hawaii, involved more than 1,000 families and sibling pairs. It showed that family members are, in fact, more alike than unrelated individuals on measures of specific cognitive skills. This suggests a strong genetic underpinning, but it doesn't lead us to the conclusion that cognitive ability follows Mendelian determinism. Correlations for identical twins greatly exceed those for fraternal twins on tests of both verbal and spatial abilities in children, adolescents, and adults. In fact, even in animal studies, there is strong correlation between the genes of the animal and its ability to complete maze and other spatial tests successfully, suggesting genetic influence on cognitive function

Genetic influence on school achievement has also been found in twin studies of elementary school-age children, as well as in work with the Colorado Adoption Project. Results are surprising, as educators have long believed that achievement is more a product of effort in the educational system than the ability of the child from his or her genetic determinants.

We get into an old debate when we start talking about genes and environment—are they deterministic or self-regulatory? We arrive at the same answer we have reached in the last 50 years of ongoing discussion in medicine, politics, and sociology: it is a mixture of genes and environment. Children with the reading disability known as dyslexia have difficulty comprehending and reading out loud. Studies by investigators like DeFries have shown that reading disability runs in families, and genetic factors do contribute to the similarity among family members. The identical twin of a person diagnosed with reading disability, for example, has a 68 percent risk of being similarly diagnosed, while a fraternal twin has only a 38 percent chance. Once again, this fact leads some people to conclude cognitive ability is genetically determined. Identifying Quantitative Trait Loci

"Research in mice and fruit flies has succeeded in identifying single genes related to learning and spatial

perception, and investigations of naturally occurring variations in human populations have found mutations in single genes that result in general mental retardation." Generally, these are considered the frank genetic metabolic diseases, like phenylketonuria and fragile X syndrome.

The most important part of the story, however, is that normal cognitive function is almost certainly orchestrated by many subtly acting genes working together, rather than by single genes operating in isolation. These collaborative genes are thought to affect cognition in a probable rather than deterministic manner. To the geneticist, they are known as quantitative trait loci (QTLs). The name, which applies to genes involved in a complex dimension like cognition, emphasizes the quantitative nature of certain physical and behavioral traits. QTLs have already been identified for such diseases as diabetes, obesity, and hypertension and for behavioral problems involving drug sensitivity and dependence.

The authors of the *Scientific American* article give the important takeaway message for us in terms of functional medicine, which focuses on improving physiological, cognitive, emotional, and physical functioning. "The discovery of genes for disorders and disabilities will also help clinicians design more effective therapies and to identify people at risk long before the appearance of symptoms."

The apo E4 gene characteristic may encode for increased risk of dementia and cognitive decline in the elderly. If you know you carry that genotype, you can start practicing the right things earlier in life to prevent the expression of that characteristic, which is associated with premature decline in central nervous system function. The authors close by saying, "We cannot emphasize too much that genetic effects do not imply genetic determinism, nor do they constrain environmental interventions."

This story provides a good example of what we are trying to relate in this month's *FMU.* Yes, we are all given our genetic blueprint or roadmap, but within that roadmap are many different routes of travel. The routes of travel we select to take will, in part, depend upon the decisions we make, how we live, act, feel, and believe, and how we reinforce the life experience. Do we select the right foods, think the right thoughts, live in an unpolluted environment, stay away from toxic substances, and get regular activity? These are the things that James Fries talked about in his classic paper, which I have described in *FMU*, about compression of morbidity and prolongation of health span associated with practicing characteristics that lead to good gene expression.

Obviously, some individuals happen, by chance, to be born with genetic characteristics more likely to be maladapted to their environment than others. This is certainly the case in children with genetic metabolism disorders. Molecular disorders sometimes appear in young children, expressing themselves as central nervous system defects. Even cases in which a mutation or array of mutations gives rise to suboptimal brain function may be modifiable in their phenotype if we learn to practice the right things. That practice may include providing the right biochemical environment, as Drs. Pauling and Hoffer years ago described providing the right orthomolecular environment for the mind. Or it may require the right patterning so the individual can use the plasticity of neuronal function to move beyond the blocking characteristic of their genes to improve their phenotype.

Let me give you an example. A 10-year-old boy had seizure disorders and serious cognitive difficulty.[3] He was unable to speak, had spasticity of the muscles. and had not grown normally. He was short and developmentally retarded. His parents had spent time, energy, and great anguish trying to assist their son. Recently, his blood plasma and urine organic acids, amino acids, and other metabolites were

analyzed. This particular multi-analyte profile was an attempt to see if a pattern of dysfunctional metabolism could be associated with the central nervous system problems he was expressing.

One might assume, on the basis of the severe difficulties this child was experiencing, that he had a frank, unmodifiable disorder of genetic metabolism. i.e., genes that were broken. Or one might assume that although his genes were producing a suboptimal outcome in his phenotype, there might be other routes of escape if the roadblocks could be removed. His multi-analyte profile revealed elevated lactic acid levels in his urine. His pyruvate levels were marginally elevated, suggesting that his body was trying to produce enough energy to maintain function through extra mitochondrial anaerobic glycolysis. This might indicate a mitochondrial disorder.

A muscle biopsy, however, did not show any frank mitochondrial mutations. It could be a conditional mitochondrial disorder caused by other events that could poison mitochondria or uncouple mitochondrial function. The places where mitochondrial function is most important are those involved with very active glycolysis and oxygen utilization, such as the brain, heart, liver, white blood cells, and gastrointestinal mucosa. He was demonstrating lactic acidosis of a marginal, chronic state.

He also had some other interesting aberrations in his profile. There was elevation in Krebs cycle intermediates of *cis*-aconitate and citrate, strongly suggesting blocks in the Krebs cycle, which again is a marker for mitochondrial function. Upregulation of nitric oxide production, due to immune dysfunction or immune upregulation, can then uncouple neuronal Krebs cycle activity in the mitochondria. In so doing, it causes an elevation of citrate and *cis*-aconitate, because that nitric oxide uncoupling occurs at the enzyme step *cis*-aconitase. Therefore, he was showing the lactic acidosis of mitochondrial interruption. He was showing the uncoupling of Krebs cycle activity, and the blockage appeared to occur at the point related to *cis*-aconitase activity, which suggests excessive nitric oxide output from the glia or the microglia.

Nitric oxide comes as a consequence of the stimulation of the immune cells and, in the brain, that is the microglia, to be in an immune-activated state. The proinflammatory cytokines can initiate upregulation of the expression of the inducible form of nitric oxide synthase. It converts arginine to nitric oxide in the cells. Subsequently, by diffusion-controlled reaction, it travels rapidly across the mitochondrial membrane of an adjacent cell and can uncouple its mitochondria and, in so doing, produces mitochondrial suicide, or oxidative stress.

Some evidence suggested that this child was experiencing mitochondrial toxicity or mitochondrial uncoupling. It did not appear to be a consequence of an inherited mitochondrial mutation. Something else seemed to be contributing to this.

Examination of the other analytes in his multi-analyte profile revealed evidence for bacterial byproducts that might be elevated, metabolites from various types of organisms that could, in fact, influence glia cell activity and nitric oxide output. Various types of fatty acid metabolites were also elevated, indicating that oxidative damage to long-chain, unsaturated fatty acids might also contribute to these problems.

From this profile, there is evidence of a possible induced mitochondrial dysfunction energy deficiency in the central nervous system, increased oxidative stress, a feed-forward mechanism of being locked into a loop of damage. Therefore, how do you break that loop? First of all, you want to try to quell or quench

the excessive oxidative production within mitochondria that are uncoupled. One thinks about coenzyme Q10, vitamin E, lipoic acid, N-acetyl-carnitine, and N-acetyl-cysteine. Generally, the doses given in these cases because of the increased level of oxidant stress are beyond that which you would give for normal maintenance; they're more therapeutic.

In fact, Drs. Wallace and Shoffner at the Center for Molecular Diseases at Emory Medical School have treated children with melas (melasma?) and other mitochondrial dysfunction with very high doses of some of these electron transport regulators. They have used 200 mg of coenzyme Q10 and several thousand mg of sodium succinate in an attempt to encourage metabolism around these metabolic blocks. One might consider coenzyme Q10, N-acetyl-cysteine, lipoic acid, and N-acetyl-carnitine, and vitamin E administration to try to promote better mitochondrial oxidative phosphorylation and Krebs cycle function.

In addition, one also wants to lower the load of substances that might upregulate the immune-inducible form of nitric oxide and increase nitric oxide output and the poisoning of neurons. You do that by looking at the offenders. Could it be a food antigenic substance? Could it be an environmental antigenic substance? Could dysbiosis be producing a secondary byproduct that has effects across the blood/brain barrier on microglia activity? Could a parasitic organism be having an effect on the systemic immune production of things like proinflammatory cytokines, which have influence across the blood/brain barrier? We are looking at web-like interconnections in the gut, liver, and brain, and ultimately their effects on neuronal function.

Using this logic, the practitioner put the boy on an oligoantigenic diet, recultured his gut with appropriate bacteria (using the 4R program—remove, replace, reinoculate, repair), and used higher doses of Krebs cycle-modulating nutrients that help reduce oxidative stress in mitochondria. His function started to improve very rapidly. In fact, he started to communicate for the first time, at age 10. His muscle spasticity was significantly reduced, and his overall function and quality of life (if I can use that term advisedly) was markedly improved. He didn't become a normal, active, fully functioning 10-year-old, but he did achieve considerable improvement over what we might have thought his genes had locked him into. She is an example, at one extreme of the continuum, of a situation in which genetic susceptibility combines with environmental dysregulation to produce a phenotype of neuronal injury.

By the way, the initial damage to this child's nervous system occurred in infancy when he had viral encephalitis. He had sustained a viral inflammation of his brain, which locked in this feed-forward mechanism of immune upregulation and neuronal damage due to mitochondrial uncoupling. Breaking that loop by reducing immune activation and by increasing the buttressing effects of antioxidants, Krebs cycle-supportive nutrients, and mitochondrial protection, the balance between function and dysfunction can be moved back toward the functional state. This is one application of the model of the Archibald Garrod/Linus Pauling concept of molecular medicine.

One of the most common defects we see in children who have brain chemical disturbances in infancy or youth is amino-acid-related dysfunction. They cannot properly metabolize, through transamination and Krebs cycle oxidation, the various carbon skeletons related to the amino acid families. A paper in *Clinical Chemistry* discussed age-specific distribution patterns of plasma amino acid concentrations in pediatric populations.[4] In the past, we have not had good enough data to know what deviation from a healthy population of various-age infants and children can relate to amino acidurias that can produce chronic symptoms and dysfunction. This particular study looked at children from 0 to 18 years of age.

They evaluated 23 plasma free amino acids in 148 presumably healthy children and looked at the age distribution of these amino acid profiles. The nine amino acids they studied included alanine, arginine, asparagine, methionine, ornithine, phenylalanine, proline, threonine, and tyrosine. Essential amino acids on the list included phenylalanine, tyrosine, and methionine. There was a decrease in their concentrations during the first year of life, which may indicate they are being used for the construction of new body tissue and part of the pool of active essential amino acids from which new proteins will be synthesized. Five amino acids—aspartic acid, citrulline, glutaminc acid, serine, and taurine—did not follow these two common profiles. Nor did cysteine, glutamate, glycine, histidine, isoleucine, leucine, lysine, tryptophan, and valine, which actually increased steadily from infancy into later childhood.

We certainly can see the utility of amino acid profiling, as well as fatty acid and organic acid profiling when we are trying to understand some of the metabolic defects that are producing neurologic or immunologic dysfunction in children. In utilizing amino acid patterns, we certainly want to make sure we look at age-adjusted patterns, because the plasma levels of these amino acids change as a child goes from infancy into adolescence. By using the right reference range, we are better able to see where pattern dysfunction might result. Then we can design specific nutritional intervention or therapeutic pharmacological nutrition programs to try to balance these amino acid dysfunctions.

Amino acids reflect broader issues pertaining to energy economy, mitochondrial function, and basic metabolism. The amino acidurias are often a consequence of the downstream effects from the poor metabolism of specific amino acids (which produce a buildup of the carbon skeletons) or the organic acids from these amino acids, like alphaketoglutaric acid or valeric acid (which can produce symptoms of dysfunction). We might look at amino acids, fatty acids, and organic acids, therefore, as three sets of data that help us understand defects in metabolism. These may not be just the frank inborn errors of genetic metabolism diseases, but functional errors in metabolism that can produce dysfunction in behavior, brain chemistry, or immune function.

We have talked about biochemistry and its impact on function. Going one step further, what about the environment? What about enriching a child’s intelligence and neuronal patterning as a consequence of the things that happen to the child in his or her environment? This is a very important part of the balance and integration of functional medicine. Dr. Marian Cleeves Diamond, a professor of integrative biology at the University of California at Berkeley, was a presenter at our Third International Symposium on Functional Medicine in Vancouver, British Columbia. Her talk, "Beyond Heredity: Maximizing Nervous System Function," was derived from her nearly 30 years of research in animals. That research showed that by enriching the animals’ environment by intellectual stimulation and challenge, you can actually observe dendritic branching, increased synaptic function, and thickening of the cortex. A deprived environment does the opposite and results in a deprivation of neuronal function and reserve. This is a classic example of improving organ reserve by enriching the environment.

Dr. Diamond’s book, *Enriching Heredity: The Impact of the Environment on the Anatomy of the Brain*, published in 1988, describes the results of her work and the research of many collaborators showing actual improved physiology and anatomy of the brain as a consequence of stimulation.[5]

We are talking not just about biochemistry alone and the molecular environment, but also the functional environment. This is the basis of what the Institutes for the Achievement of Human Potential has done for nearly 50 years, with Glenn Doman as its founder. Mr. Doman received the first International Linus

Pauling Award in Functional Medicine for the extraordinary work he and his colleagues have done at the Institutes over many decades in helping to develop patterning programs and enrichment programs for children for various types of brain biochemical, behavioral, physiological, and physical dysfunction. Many of these children might have been considered beyond help, but with the Institutes program they have achieved tremendously improved function as they move into adulthood. They practiced the right things, using patterning and neuronal plasticity to benefit the children and enrich their intelligence.

In a recent review article in the *Annual Review of Neuroscience*,[6] investigators from the Department of Neuroscience and Cell Biology at the Robert Wood Johnson Medical School and the Department of Physical Therapy at the College of Allied Health, Temple University, discuss patterning, its effects on the cerebral cortex, and the development of cerebral cortical function. This paper ties together mechanistic neurobiology and neurophysiology with observed clinical outcome in people's function as well as any I have seen. It is a detailed review of neuroanatomy and neurophysiology.

Practicing the right things, being involved with an enriched molecular environment, and not seeing these disturbances as rigid and deterministic is a threshold for the new medicine.

This takes us to Side II of this month's *FMU* and our Clinician of the Month, who will speak from his experience as a researcher and clinician. He will explain how these seemingly esoteric concepts relate to improved function in children who have experienced difficulties in school or been labeled as ADD. An approach toward their improved function might be the integration of cortical stimulation, i.e., the enriched environment and molecular milieu that produces the opportunity for full expression of their genes. This is functional medicine at the clinical applied level.

INTERVIEW TRANSCRIPT

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Functional Medicine Update™ subscribers indicate the section of *FMU* they most look forward to each month is the Clinician of the Month interview. This month's Clinician will share information related to the way functional medicine plays out in both research and clinical application. Dr. Michael Lyon is a physician who practices on Vancouver Island in British Columbia, Canada. He received degrees in biology and medicine at the University of Calgary. He has a rich resume of extraordinary experiences, including, but not limited to, work as team physician of the Canadian Olympic Bobsleigh Team, and the pursuit of drug-free sports, enhancing sports performance with appropriate nutrition and health promotion concepts. He has also been actively involved in the development and application of the functional medicine model at the research institute he directs—the Oceanside Functional Medicine Research Institute in Nanaimo, British Columbia. In this capacity, Dr. Lyon has overseen and developed research that examines the application of functional medicine. He interfaces with the clinicians and staff at the center

who see patients who are on various functional medicine programs. His experience combines research and clinical application.

JB: Dr. Lyon, welcome to *Functional Medicine Update*™. I am pleased that you have chosen the name Functional Medicine Research Institute for the facility where you focus your studies. One of the things you are looking at is attention deficit disorder, or ADD, in children. It might seem to be a stretch to be studying ADD with a functional medicine model. Can you describe how they fit together and what led you into this kind of research?

ML: The conventional world and the majority of the medical realm consider ADD to be virtually genetic. It places a stamp on the child and there is really nothing one can do, other than to markedly and rapidly alter their brain metabolism through some sort of powerful drug. I think most of us, at the gut level, and those of us who have been pursuing nutritional and functional medicine, realize there is always something deeper. There are always antecedent factors that lead to the changes we see manifested as definable diseases. Our interest in ADD was to look at children from a functional medicine point of view and try to define the antecedents and triggers that eventually lead to a highly disruptive child, or a child who has a terribly poor prognosis. Many people in this field, in fact, suggest these children often have elements of brilliance. They can often be tapped as being prodigies, or kids with tremendous creative capabilities. Why should these kids be burdened with some sort of label that is also accompanied by a terrible prognosis? This was our motivation. We weren't the first to look at this, but we may have had a look at the children's underlying physiology in a more thorough way than has been done before.

JB: Could you tell us a little bit about your study? I know it' is an extensive study that involves patient selection, evaluation, and the web-like functional perspective, rather than just a single contributor to the condition.

ML: We selected children from the community who had the classical ADD "sentence" and would be clearly diagnosed as such. Many of these kids were on drugs or have been on drugs in the past. These were kids whose parents were potentially interested in looking deeper into the problem, rather than just having their kids on drugs. We had a pretty normal selection of kids with ADD, then divided the group into three randomly. One third of the kids went into a control group, and two thirds of the kids went into a study group. We had the parents come to weekly classes and had them alter their nutrition in various ways. Before we actually had any intervention with these kids, we had them supply us with blood, urine, and stool samples, and we tested them in numerous ways to try to look at underlying physiological factors that might be part of their condition. For instance, we looked at their essential fatty acid blood profiles and tried to determine whether this was a factor in their condition. We did the comprehensive digestive stool analysis (CDSA) with parasites to see if these kids had dysbiosis. If so, that would suggest some immune impairment or problem with poor digestion. We also did the intestinal permeability test to see if these kids had a leaky gut or problems with absorption. The goal of these tests was to see if something was functionally impairing these kids that would be antecedent to the actual neurological problem leading to their behavior or attention problems.

The parents of the children in the study groups attended weekly classes. We gave them intensive help to get their kids off junk food and to identify and remove potential or likely food allergens in their diets. We taught the parents principles of good nutrition and tried to get them motivated through the use of weekly potluck dinners, where they would bring selected recipes. Half of the children in the two groups that were

going to the classes were randomly selected to receive a medical food product, UltraCare for Kids™ It contains low allergy potential substances that are targeted for children with atopic disorders or ADD. We wanted to compare dietary intervention alone, using a modified elimination diet, with the elimination diet combined with this medical food product. As we know from our experience with the UltraClear®products, in some cases these medical food products can make an enormous difference, so we wanted to have a close look at what this did in these kids.

JB: When you looked at essential fatty acid profiles in the children, did you find any alterations in the omega-3, 6, or 9 families relative to what had been observed in some of the previous published studies?

ML: Yes. In fact, the samples that we received back were a little bit surprising. In the past, there have been suggestions that these kids have some impairment of their delta-6 desaturase enzyme activity. Thus, they would have a uniform lack of their long-chain omega-3 and omega-6 essential fatty acids (the GLA, DGLA, omega-6 region) and perhaps arachidonic acid, and in the omega-3 fatty acids (the DHA and EPA). In fact, what we found was that very few of these kids had any deficiencies in the omega-6 fatty acids. They actually had very high levels of the basic starting point, the linoleic acid in most cases. And they had, almost uniformly across the board, low levels of DHA, particularly. It looks as though these kids may be selectively impairing their delta-6 desaturase, and maybe because they're receiving so much omega-6 in their diet, it's essentially shunting it toward that direction, rather than having enough precursor to make the omega-3. It supports the notion that DHA is probably the one that you want to give these kids, if you're going to give them fatty acid supplements.

JB: How about the gut biosis indicator and the gut permeability studies? Did you find anything of significance from those results?

ML: Yes. About 75 percent of the kids very clearly had a leaky gut or increased gut permeability. Their lactulose-to-mannitol ratio was quite elevated. You've got to dig deeper to find out the cause, of course, but I think based on what we found with the response to the diet that the majority of these kids have a leaky gut because they have food allergies and sensitivities, combined with real marked dysbiosis. We found in the CDSA that these kids have marked dysbiosis. About 65 percent had intestinal protozoan parasites, sometimes as many as four different parasites in one child. Also, about a third of them had very heavy growths of candida yeast. There were heavy growths of various potentially parasitic bacteria like klebsiella, proteus, and so on. Very few of these kids had high amounts of desirable flora, the acidophilus or bifidus bacteria.

Across the board, it looked as though these kids had significant dysbiosis and could benefit from an intensive 4Rä program. What we did in terms of the 4R program was to remove one of the major things, which was food allergens. The diet we selected removed potential food allergens from these kids' diets. Then we added fructooligosaccharides (FOS), which would be the *replace* part of the 4R program, with something considered to be prebiotic. FOS is a carbohydrate that helps nourish the desirable gut flora. Now we've gathered the final samples and are anxiously awaiting the results to see what we have accomplished with our intervention.

JB: You talked a lot about the prevalence of dysbiosis and gut permeability changes in the ADD children. How about in the control group? Was there a difference between the two groups in the prevalence of those conditions?

ML: We saw the same kinds of problems in all kids across the board. We randomly selected who went to which group, and it appears that our randomization worked. We had quite a nice, even distribution of test results among the three groups.

B: That's very interesting. Have you noted any parental qualitative comments concerning subjective improvements in the children in one group versus another, or is it too premature to say if there's any difference?

ML: It is not at all too premature. Two thirds to three quarters of the parents in the intervention groups that had dietary change have been absolutely *astounded*. I don't use that word lightly. We have seen parents who have been beside themselves, not knowing what to do, desperate to help these kids. They are now reporting that their kids are remarkably improved, that the changes have been astounding.

One child is giving a presentation to his school this morning. He is extremely bright, but he just could not stop being disruptive in class. He spent most of his days in the school principal's office. Today he's giving a presentation to his class to explain why he's such a different boy. He's such a bright boy that he's able to stand up and articulate like a little politician. He's only about 10 years old. The school principal and the teachers are amazed at the results he's obtained by dietary change and being on this medical food product.

We have had a number of reports like that, where the results have been so significant that the parents want to start support groups in the city to continue this momentum. They wanted to contact the media to discuss what's going on. It's really been quite exciting. A lot more has come out of the study than we expected already, without even getting the lab results back.

Behavior during blood testing is another example of the changes we have seen. It was interesting at the beginning to see how disruptive and difficult these kids were. It was pretty tough to draw blood on these kids when they first came in, since they were ADD kids and some of them had a defiant disorder on top of that. We found uniformly that not one single child in the intervention groups gave us any trouble at all drawing the blood in follow-up. In contrast, we had to have as many as four people holding down kids in the control group, with screaming, hollering, and the whole business. Only in the control group did we have these problems when we were re-testing them in follow-up. That was one observation that all the staff made. We found it quite interesting that uniformly the kids in the intervention group were fine as far as getting their blood redrawn. Maybe that's an interesting test we can add to the list of tests for ADD disorder.

JB: It sounds like an incredible neurological stress test.

ML: It's a stress test—that's for sure.

JB: Let me summarize and make sure that I got it right as to what you've just presented. You recruited a group of ADD children with parental consent. You separated them into three groups. One was a control group that did not receive any specific intervention therapy. The other two groups received diet classes and an elimination diet, and one of those two groups also received a medical food product. With all three groups you tracked gut biosis indicators, permeability, and essential fatty acids, before and after a period of intervention. You have not yet received the laboratory results of the intervention data, but the

qualitative signs indicate a pretty marked performance improvement in the children who had the diet, and the diet plus medical food, as contrasted to the control group. Is that an accurate summary of what you've just told us?

ML: Yes. That's a good summary. I should have mentioned that in addition to parental observation, we have gathered some qualitative data based on the Connor Screening Questionnaires. There's a form that parents or teachers can fill out that contains about 80 questions. These forms rate the child's ADD symptoms, so it's a good way of going beyond the anecdote to getting some actual quantitative data about the child's behavior. We have the parents and teachers fill out these forms before starting the study and again afterward. We don't have our statistical data on this yet, but I should mention that I have looked at a number of the before and after Connor tests that have come back in. It's quite clear that some of the children in the intervention group have had remarkable improvement on their Connor scores.

JB: That is very encouraging. It seems to follow nicely from the model you have been pursuing for some years at the Oceanside Functional Medicine Research Institute regarding toxicity and detoxification. We were privileged to have you present information on this topic at the on-site Applying Functional Medicine in Clinical Practice teaching sessions for clinicians here in Gig Harbor, Washington, a few months ago. Would you give us an overview regarding detoxification toxicity? This seems to be one application of it in a wider range of potential implications.

ML: Yes. In fact, one of the reasons we are interested in ADD is that we believe there's a very strong common link between ADD and the kinds of functional disorders that individuals can experience later in life. One clue that led us to this belief occurred when we were doing a study last summer on adults with ADD. We found they had a very high incidence of fibromyalgia and chronic fatigue syndrome. When we started testing these adults, we found they had many of the same features we believed would be present in these ADD kids. We have now confirmed that belief with the functional tests we've done on these kids. It may be that we're seeing a manifestation of the same toxicological problem, simply at a different age.

Children can even have a prenatal exposure to environmental toxicants during uterine development—mercury from the mother's amalgams, various organochlorines, lead from the mother's environment, cigarette smoking, etc. In some cases the child may be born into a toxic environment with some sort of genetic predisposition, but the toxicology is likely where all this originates. It's probably a real primary antecedent that is common between chronic fatigue and ADD. We have found, in terms of chronic fatigue and fibromyalgia, a tremendous amount of data indicating that these disorders are indeed arising from a toxicology problem.

In one of the next phases in our ADD research we intend to look more thoroughly at the toxicology of ADD. Some researchers have done this. Some have looked at it in a cursory way, doing blood lead levels and so on, but it would be nice to get some sort of a broad range of assessment of the toxicological stress on these kids, compared to nonaffected kids.

JB: Not too many years ago in *FMU* we had an extensive discussion about the first signs of chronic toxicity being seen as neurotoxicology and immunotoxicological impacts. It seems that is what you might be seeing, both in children and adult patients you've studied, showing chronic neurological and immunological alterations.

ML: The nervous system and the immune system have two features in common. One is that they are highly sensitive. They are sensitive to oxidative stress and xenobiotic influence. Second, they both have very powerful memory, which plays out in many different ways. When individuals have xenobiotic exposure, their immune system never forgets. They become potentially increasingly sensitized to these things as their immune system builds antigenic memory—antigenic memory, or some other more mysterious memory—against these things. We don't quite understand it.

In classical studies, rats were given some sort of poison and a whiff of camphor at the same time. Later on, just a sniff of camphor causes some sort of serum sickness or autoimmune crisis, because their immune system associates the camphor with the poison, and their immune system never forgets. We are at the threshold of discovering that our immune and nervous systems are far more sensitive than we ever figured. We have been playing with our immune and nervous systems with the environment we live in, with very little regard for the things we expose ourselves to all the time. The time is coming when these disorders, like ADD, chronic fatigue syndrome, and fibromyalgia, are going to put such a stress on our society that we'll have to look at them from a toxicological point of view, or our whole society is greatly threatened.

JB: In 1979, Dr. Herbert Needleman published a paper in the *New England Journal of Medicine*, describing the relationship between the level of lead in the dentine of deciduous teeth of school kids in the Boston metropolitan area and their IQ. He pointed out that children who had high lead dentin levels in their deciduous teeth had lower attention span, as measured by a test they used. The kids with high lead had a short ability to stay at task, and those with low lead levels stayed much longer at-task time. This finding led him to conclude that children in the school system with chronic lead exposure and body burden may have impaired cognitive function. That impaired function is acted out in school as attention or behavior disorder. It ends up in the wrong place, in the school counselor's office, instead of being considered as a toxic burden to their nervous system. He followed that up with extensive studies of the effect of lead on IQ. He was vilified, as I recall, for about 15 years for this position, but now he is considered a leader in our understanding of the role of toxic metals, including lead, cadmium, and mercury, on the nervous system. Have you looked at toxic metal contributions, as well?

ML: Yes, I have followed closely the work of Dr. Needleman and many others now in this field. I was pleased when I saw that lead levels considered toxic in the blood of children were lowered to 10 mcg per deciliter from, I think, originally 50.

We have come a long way toward recognizing the impact of very low levels of some of these toxicants on our children. But we still don't recognize two things. We don't realize that we share the same neurons as our children and are also susceptible to very low levels of some of these toxicants. Also, perhaps even more significantly, there is a tremendous synergy among the thousands of chemicals that we're exposed to. It isn't just the 10 mcg per deciliter of lead. It's also mercury, cadmium, arsenic, PCBs and other organochlorines, the solvent residues, the other petrochemical residues, the organophosphate pesticide residues. All these things work together in a kind of evil synergy within us.

It's really quite a leap to go from saying 10 mcg per deciliter of lead in blood as the magic factor, to saying that one day we'll analyze 10,000 or 15,000 different chemicals and be able to determine who's really neurotoxicologically affected. But that's the area we have to strive toward as a way to measure who's really neurotoxicologically impaired, or whose immune system is impaired by the synergy among

all these chemicals, not only the levels of these things, but the injuries they've left behind. It's very complex, but I think we're going to get our biggest bang for the buck, so to speak, in terms of treating chronic illness, by looking at it from a toxicology point of view.

JB: Last month's Clinician on *FMU* was Dr. Jeffrey Kopelson, who has been using secretin in the management of autism in children. He talked about the work of Dr. William Shaw, Dr. Sidney Baker, and Dr. Bernard Rimland, who have been considering autism as potentially a result of autointoxication from the development of certain kinds of neurotoxic chemicals that deliver specific brain biochemical-modulating effects. He postulated that the reason secretin might be working is that it might result in improved integrity of the GI mucosa, thus helping the child to defend against autointoxication from some gut-derived substances that influence brain chemistry. From your experience, do you think the work you're doing with ADD is part of a general sequelae of neurological problems associated with toxicity that are seen with different genetic susceptibilities in individuals of various ages?

ML: Yes, I have little doubt of that. I'm glad you mentioned the work of Bernie Rimland and Dr. Shaw and Dr. Baker. Although we don't have any of results from our study back yet, we did send the urine to Dr. Shaw for analysis for organic substances, gut-derived organic acids. On top of the toxicology that we talked about before from the environment, as you mentioned, the secretin work that has been done on the kids with autism suggests that when you give these kids secretin, the levels of gut-derived toxins can go down quite remarkably. They have been following organic acids in these kids and finding that some of the very toxic gut-derived organic acids from microbial metabolism can go way down in these kids following even one or two injections of secretin. That suggests significant gastrointestinal impairment in these kids. It is primarily in their immune system, and their gut is remarkably impaired. This allows the overgrowth of organisms that are potentially highly toxic. It suggests some sort of potential for something like secretin to reset some sort of rhythm of the immune system that allows the gut mucosa to heal and allows the immune system, the secretory IgA, to come back on line. It's almost like rebooting a computer. I think all of these things are pieces of a puzzle.

If we step back now to look even at the data we have now, say you improve a child's overall nutrition, and you remove potential food allergens from their diet; you help to remove environmental toxins from their bodies by improving their nutrition. If you add essential fatty acids in a targeted way, if you work with these kids behaviorally and educationally, if you do all these things as pieces of a puzzle, I think even now, the majority of these kids can be remarkably helped. It just takes education of the parents. It takes clinicians who are very aware of the whole picture and where we are right now. I think we can see really stunning results in the majority of these kids.

JB: That's an optimistic and uplifting close to a fascinating description of the research you are overseeing at the Oceanside Functional Research Institute with ADD children. We'd like to check with you after your results are finalized and hear about the conclusion. It reminds me of an interview we had a number of years ago with Dr. Nsouli at Georgetown University Medical School. He described his research work with children who had recurrent serous otitis media. By removing foods to which the children were sensitive, he was able to reduce the recurrence of middle ear infections by as much as 80 percent. That is certainly a different approach from the way pediatricians had previously thought of this condition, as a bacterial infection requiring amoxicillin or other antibiotic therapies. It seems we are developing a more functional view of some complex pediatric health problems, showing that functional medicine cuts across a wide variety of ages. Thank you so much for your hard work and for sharing it

with us.

ML: You're very welcome. It's been a pleasure.

JB: For those of you who want to follow-up on Dr. Lyon's comments and learn more about the clinical study he is involved with at the Oceanside Functional Medicine Research Institute on ADD children, the address there is 203-1808 Bowen Rd., Nanaimo, British Columbia, Canada V9S5W4. The phone number there is 250.753.3030, fax: 250.753.3006.

Many people continue to wonder why anyone would support nutritional supplementation in cases where the person does not present with the classic beri beri, scurvy, pellagra, or rickets. They still feel supplementation in healthy people is not justified. Few topics in medicine have generated energy and controversy than that of micronutrient supplementation. Recognizing that debate, I was interested in the paper by Drs. James Goodwin and Michael Tangum, which appeared in the *Archives of Internal Medicine*.[7] I want to thank Mr. Kirk Hamilton for bringing this article to my attention. He passed it on to me saying this is what we have all been talking about for the past 20 years. The article is titled "Battling Quackery—Attitudes about Micronutrient Supplements in American Academic Medicine."

Dr. Goodwin was also the author of a classic article titled "The Tomato Effect—Rejection of Highly Efficacious Therapies," which appeared in the *Journal of the American Medical Association.* In that article he explained why for a long period of time people refused to eat tomatoes. They considered tomatoes toxic because they had the "doctrine of signatures," which meant their leaves looked like devil's pitchforks. People concluded tomatoes (and potatoes, too) were the work of Satan and would not eat them. Our intuition is sometimes not rational, Dr. Goodwin points out, and we reject things that really do work.

Explaining Medicine's Resistance to Nutrition

In the article on battling quackery, Goodwin and Tangum point out that throughout the 20th century, American academic medicine has resisted the concept that supplements of micronutrients might have health benefits beyond the treatment of the frank nutritional deficiency diseases. This resistance was apparent in the uncritical acceptance of news of toxicity, such as the belief that vitamin C supplements cause kidney stones. Leading medical textbooks have employed an angry, scornful tone in discussions of micronutrient supplementation, and they ignored evidence for possible efficacy of micronutrient supplements, as in the case of vitamin E for intermittent claudication.

Part of the resistance, according to the authors, seems to stem from the fact that the potential benefits of micronutrients were advanced by outsiders who took their message directly to the public. It did not come from the academic medical community, and it did not go through the traditional process of sieving, evaluation, and peer review. Similarly, in the book, The Crime of Galileo, Galileo was vilified, not so much because he talked about the heliocentric view of the universe (Kepler had talked about it many years earlier), but because he wrote in Italian. Copernicus, 70 years before Galileo, had written about it extensively. The difference was that Copernicus wrote his work in Latin, which was not accessible to the common person, and Galileo had the affront to take his message directly through the language of the people (Italian) so everyone could understand it. Therefore, he was vilified as a usurper and a popularizer. Copernicus, who remained an esoteric academician, was not.

Resistance to evidence suggesting the efficacy of nutritional supplementation has been demonstrated in several ways. Bad news about micronutrient supplements has been readily accepted. Medical textbooks have discussed micronutrient supplements in a scornful or dismissive tone. And claims for efficacy of micronutrients relative to other therapies have, for the most part, simply been ignored. Those who brought this evidence directly to the public, rather than through the potential academic review system, were perceived as subverting the traditional medical establishment and control of information.

In this electronic age and era of the web, there is no such thing as control of information. Information is much more freely displayed. Some of it is good and some is bad, but at least it is all out there for evaluation.

In their article, Goodwin and Tangum describe the scornful, dismissive tone of medical textbooks. The language used to describe nutritional supplementation, they point out, appears nowhere else in medical criticism. Harrison's *The Practice of Routine Use of Multivitamins* was condemned in the 1950s, 1960s, and 1970s in terms these authors believe are unique. There appears to be a stronger emotional reaction to vitamin supplements than anything else published in the medical world.

You may wonder why this resistance persists. Resistance in the medical community to the concept that scurvy, beriberi, and rickets were caused by vitamin deficiencies was initially very strong, and it took a long time to overcome. There has been an historic adversarial relationship to nutrition and disease. It probably goes back to the concept developed by Osler, whom we discussed earlier, that disease is something that happens, often from a single vector. Doctors have the role to treat the disease the best they can. Other molecular mechanisms are esoteric concerns for the laboratory and the research scientists. They have little benefit or value in clinical practice.

Pathologists who dominated academic medicine in the late 19th and early 20th centuries lacked the vocabulary to integrate the public health observations of vitamin deficiency into a pathophysiological model of the time, which was dominated by germ theory. This inability to embrace a new concept is similar to the concept of incommensurability, which Thomas Kuhn described in his book, *The Structure of Scientific Revolutions.* Goodwin and Tangum, the authors of the *Archives of Internal Medicine* article, have written before on this topic. As they have explained, treatments that do not make sense can be rejected in favor of less effective or more toxic therapies that better fit in with the current understanding of the pathophysiology, i.e., staying within the catechism.

In the current paper, Goodwin and Tangum conclude there are only three important questions to ask when one is evaluating a potential treatment: 1. Does it work? 2. What are its adverse effects? 3. How much does it cost? Ideally, discussions of the theory underlying the treatment or the guild to which the proponents of the treatment belong should be irrelevant to the fundamental questions of efficacy, toxicity, and cost. They close by saying, "The history of the response of academic medicine to micronutrient supplementation suggests that we have not attained that ideal." This is a powerful article. It is good to know the world of publications is still willing to accept critical reviews and publish them in the spirit of free intellectual enterprise.

How did we get locked into the model that insists, "Don't fix it until it's broken"? Part of the explanation is the success of the pharmaceutical industry in developing antibiotics and, later, corticosteroid drugs. Even more recently, these concepts have been incorporated into medical teaching to treat dreaded

antibiotic-sensitive infectious diseases and various inflammatory conditions that could respond to corticosteroid drugs. Education in the use of prescription medicine has been an increasing part of standard algorithms for clinical management of disease. Most medications that have come out after corticosteroid drugs and antibiotics have been medications that blocked, inhibited, or stopped function to arrest an immediate problem. Problems arose when we began to extend the application of these drugs into chronic conditions, and adverse drug reactions became more prevalent. The darker side of the coin was revealed with the suppression of favorable effects of the functions that had been blocked.

A recent issue of the *Journal of the American Medical Association* contained an article titled "Prescription Drug Use and Self-Prescription Among Resident Physicians."[8] The authors found that most physicians start to self-prescribe medication and treat themselves in their years of medical school and residency. Most of these prescriptions are for antibiotics, but many self-prescriptions are for allergy, gastrointestinal, analgesic, psychotropic, and cardiovascular drugs.

A nice, tight system is being built, in which everything is internally consistent. Symptoms are treated with a medication that reduces them. This alters the laboratory finding, which results in the ability of the person to continue to move ahead without paying attention to molecular underpinnings that explain why the symptoms arose in the first place. They do not evaluate the complex interaction of their genes and their environment, and they become candidates for recurrence or reevaluation in a different quarter with a new disease, whichever perpetuates the cost and effectiveness of the disease-care delivery system.

Following is a quote from a recent editorial in the *New England Journal of Medicine,* titled "Making Medicines Safer—The Need for an Independent Drug Safety Board."[9] "Adverse reactions to drugs are a major cause of morbidity and mortality; it has been estimated recently that approximately 100,000 Americans die every year as a result of such adverse reactions. Independent agencies exist to investigate airline accidents, railroad mishaps, and radiation spills, and to make recommendations to prevent them. However, no independent entity exists with the responsibility to monitor and investigate adverse events due to drugs and to make recommendations to prevent them. Currently, after a drug is approved for marketing we rely on a voluntary reporting system based on the assumption that a drug is safe unless case reports of adverse effects call that assumption into question. It is remarkable that at a time when the technology for collecting and analyzing large amounts of data is readily available, an independent, comprehensive, and systematic program of post-marketing drug surveillance does not exist."

The authors of this editorial call for a post-marketing drug-safety program that is independent of the agency responsible for drug approval. In the United States that approving agency is the Food and Drug Administration. They continue:

"So, although the United States is often the first country to approve new drugs as a consequence of an accelerated drug approval process, neither the FDA nor the medical community has the infrastructure to detect, investigate, and prevent their unwanted consequences. The resources of the FDA’s Division of Pharmacovigilance and Epidemiology are inadequate to provide ongoing review, either of the increasing number of newly approved drugs or of the almost 5000 approved older drugs. In addition to dexfenfluramine, other unexpected, major adverse side effects have included encainide (Enkaid), zomepirac (Zomax), ticrynafen (Selacryn), benoxaprofen (Oraflex), terfenadine (Seldane), and troglitazone (Rezulin)."

All of these drugs have been found to give rise to serious adverse side effects in some individuals. Questions have been raised regarding their routine use or even their safety. The authors state: "In conclusion, we must expect that predicted and unpredicted adverse events from drugs will continue to occur. If we accept that the true safety profile of a new drug is dependent on the 'experiment' that necessarily follows the drug's release into the marketplace, then we must fund and implement mechanisms to ensure that the experiment is properly monitored, the data appropriately analyzed, and the conclusions disseminated rapidly."

In this issue of *FMU* we have described a new medical paradigm, which considers these inborn errors, alterations, or differences in metabolism, how we modify them to improve genotype conversion to phenotype. If we fail as a society to embrace this new paradigm, we may be locked into this cycle of treatment of symptoms, increased risk of adverse effects, and subsequent increased need for greater medical services.

We can use certain markers to evaluate dysfunctional metabolism, and those markers may provide insight into where gene expression is increasing the risk or likelihood of various diseases, including heart disease, arthritis, and cancer. One analyte that is receiving more attention is C-reactive protein.[10] C-reactive protein, serum amyloid A, fibrinogen, neopterin, and ferritin are all analytes that have been used to evaluate immunological markers. "C-reactive protein is a noteworthy member of this group because of the speed and degree to which its concentration increases after a variety of inflammatory states or injuries to tissues—including myocardial injury or infarction."

CRP can be assessed through a simple and effective screening test for occult bacterial infection or tissue injury. CRP, therefore, might be considered as a marker for individuals with inflammatory response that could contribute to altered gene expression associated with risk for many degenerative diseases. The authors go on to say that an isolated CRP concentration cannot be used to assess risk for an individual, because many factors other than atherosclerosis can alter CRP concentrations. Checking CRP level over time and looking at its trend or vector of change can be a very useful tool for assessing risk and altered cellular gene expression associated with the transition from an inflammatory state to a normal state.

This is an interesting use of one simple test that may provide information, not just about a single disease, but about a variety of disorders associated with chronic inflammation.

One family of drugs that is receiving considerable attention recently is the nonsteroidal anti-inflammatory drugs (NSAIDs). A series of papers have appeared in the *Archives of Internal Medicine*, describing some of the adverse side effects of NSAIDs and how they produce gastropathies. One of these papers, titled "Gastrointestinal Tract Complications of Nonsteroidal Anti-inflammatory Drug Treatment in Rheumatoid Arthritis," was written by a number of authors, including Dr. James Fries from the Stanford University School of Medicine.[11] It describes an observational prospective cohort study looking at the appearance of gastrointestinal dysfunction, increased intestinal small bowel permeability, and gastric bleeding from the continued use of NSAIDs at the recommended dose.

The authors point out that if you wait for symptoms to develop before worrying about adverse side effects, it is too late. The majority of the patients experience no acute symptoms of pain or other chronic dysfunction until there is a serious problem with perforation and bleeding. Therefore, the authors state, virtually all individuals who are taking NSAIDs at the recommended dose for an extended period of time

are at risk for gastrointestinal inflammatory dysfunction. Approximately 15 percent of patients in this study—1921 patients—reported an NSAID-induced GI side effect during the two-and-a-half- year observation period. I emphasize that if you wait for symptoms before you do something, pathology may already exist.

"Conservative calculations estimate that approximately 107,000 patients are hospitalized annually for NSAID-related gastrointestinal complications. At least 16,500 NSAID-related deaths occur each year with arthritis patients alone."[12]

This is a very serious problem, and there are no reliable warning signals. More than 80 percent of patients with serious GI complications have no prior GI symptoms. Independent risk factors for serious GI events were age, prednisone use, NSAID use, disability level, and previous NSAID-induced GI symptoms. Antacids and H2 antagonists do not prevent NSAID-induced gastric ulcers. Therefore, patients on long-term management of arthritis pain need to be concerned about this possibility.

One might ask how to deal with this issue. New selective COX2 blocking agents are going to be released and approved by the FDA, but they are not totally selective. They still have some COX1 cyclooxygenase-1 inhibition activity, so they do have some adverse risk. In lowering the load on the inflammatory cascade and increasing the protection against inflammation that begins in the gut, as is the case with these inflammatory mediators, you need to also consider gut restoration programs or systemic antiinflammation programs. This may at least lower the load of inflammatory mediators and reduce dependence on NSAIDs or other antiinflammatory medications. Again, this strategy differs from simply assuming that if you have a symptom, you take a drug and hope for the best. We are looking at a clinical strategy that combines a treatment program that protects health in the long term as it improves it in the immediacy.

We have provided you with an introduction to the concept of molecular medicine as it is evolving, applying it to childhood behavior disorders and other adverse drug-related dysfunction in individuals for whom total treatment programs need to be developed. We will move to the next level in our March, 1999, issue of *FMU*, in which we will start looking at applications to a variety of chronic, degenerative diseases.

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