February 2000 Issue | Dr. Stejskal's paper M.D.

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Welcome to *Functional Medicine Update* for February 2000. We are creating a paradigm shift at the beginning of this new millennium. It is something closer to home than the extraterrestrial imaginings my peers and I came up with when I was a boy. We are creating the age of the individual more than the age of outer space. I believe the genome revolution will change the way health care is practiced as the age of the individual unfolds in the next decade.

Having said that, I would like to talk about folate, a nutrient we discussed in a previous issue of *FMU*. I paid tribute to Dr. Charles Butterworth, Jr. for his contributions to our understanding of folate's role in maintaining epithelial tissue integrity and the connection of folate insufficiency to cervical dysplasia. Those contributions, made through empirical observation, have now gained a foothold in medical science. We understand of the mechanism by which folate participates, as part of the tetrahydrofolate cycle, in regulating the architecture of rapidly growing cells of the epithelium.

In praising Dr. Butterworth, however, I overlooked the contribution made by another important investigator, Dr. R.W. Smithells. In the early 1970s, Dr. Smithells wrote a paper on folate insufficiency and neural tube defects, which appeared in the editorial section of the *Lancet*.[1] Through some very good medical detective work, Dr. Smithells had been able to extract information about these birth defects from epidemiological data. He suggested that women who gave birth to more than one child with the neural tube defect spina bifida cystica were folate-insufficient. They were not frankly folate-deficient, with megaloblastic anemia. They merely had insufficiencies in folate.

This proposition, which was remarkable in the early 1970s, did not meet with a consensus of approval in the fields of nutrition, medicine, developmental biology, or teratology. Medical professionals generally believed it was impossible for something as simple as folate to have such a dramatic effect on the developing nervous system as to produce neural tube defects, spina bifida, or anencephaly. Dr. Smithells persevered, however, and continued to look at epidemiological evidence suggesting that folate insufficiency was associated with this dysfunction. Eventually, more investigators began to look seriously at the Smithells hypothesis.

According to Dr. Smithells, although the RDA of 400 mcg/day of folate might be adequate to "meet the needs of practically all healthy people," it would not be enough in certain cases. A woman might have a genetic need for higher levels of folate to promote fetal development. Folate, B12, and B6 status prior to conception, would be determinants in the first trimester of fetal development. If a woman's folate status was compromised relative to her need, significant suboptimal development might occur in the fetal nervous system during the first trimester of pregnancy. These effects could occur before the woman even

knew she was pregnant. Therefore, it was very important for a woman to be properly nourished with folate at doses appropriate for her own biochemistry, regardless of the RDA.

The paths of Dr. Butterworth, Dr. Smithells, and Dr. McCully began to converge. The work of these men all pointed to something remarkable about folate metabolism and methylation, and the role of folate, B12, B6, and methyl donors like betaine in this process. Insufficiency of these nutrients could have wide-ranging effects. They included birth defects during fetal development (particularly in the first trimester) and conditions related to epithelial tissue integrity, including cervical dysplasia, atherosclerosis, and stroke, as Dr. McCully observed. These dysfunctions resulted from the insufficiency—not crisis deficiency—of a single family of nutrients, as dictated by the biochemical uniqueness encoded within an individual's genome.

This example of molecular medicine echoes the theme Dr. Linus Pauling originated in 1949. Together with Dr. Charles Itano, he wrote a landmark article on sickle cell anemia that was published in *Science* magazine that year.[2] They described sickle cell anemia as a molecular disease and defined, for the first time, how a single point gene mutation on the genome could create a substitution of one amino acid for another on the heavy chain of the globin of hemoglobin. That substitution produced a change in the shape

Nearly 50 years after Dr. Pauling had published his original paper, the *New England Journal of Medicine* in 1993 published an article validating the sickle cell theory.[3] Investigators reported they could upregulate the gene expression of fetal hemoglobin in individuals who carry the genetic characteristic of the sickled hemoglobin by administering an infused level of sodium butyrate, the sodium salt of the simple 4-carbon fatty acid butyric acid. When its expression was upregulated in the adult, the fetal hemoglobin could dilute the sickled hemoglobin and prevent it from packing together and crystallizing, averting the shape change of the red cell associated with the sickle crisis. Here is a way of actually modifying gene expression, even when an individual carries the mutant gene associated with the single point gene mutation on the globin molecule involved in sickle cell anemia.

No one, regardless of his or her belief about vitamins, minerals, or nutrients, can underestimate the impact of this emerging understanding of the molecular origin of disease on health care.

In this month's *FMU* I want to talk about the way the environment interfaces with the unique genomic characteristics we all possess to give rise to the expression of various phenotypes. Our Clinician of the Month will talk about autism, one of a spectrum of gene/environment interrelationships. We will also describe Dr. Vera Stejskal's extraordinary work on immunotoxicology.

Folate and Down Syndrome

We have recently begun to see the extension of the Smithells research to Down syndrome. We often think of trisomy 21 and Down syndrome as a genetic condition associated with a mutation of one chromosome about which there is very little we can do. Again, however, the concept of various factors involved in gene expression is coming into play. Recent evidence from researchers at the Food and Drug Administration suggests that folate insufficiency may be associated with the expression of certain types of Down syndrome.

This research concerns methylene tetrahydrofolate reductase mutations, certain genetic aberrations of folate metabolism. Mutation of the methylene tetrahydrofolate reductase gene (MTHFR) may prove to be an action point for an emerging understanding of who is at risk due to folate insufficiencies based on standard dietary intake. The MTHFR gene, which controls the synthesis of that enzyme, plays an important role in the tetrahydrofolate cycle. This gene, in a relative sense, is commonly mutated in such a way that the ability to convert folic acid into 5-methyl-tetrahydrofolate becomes less efficient. The individual might have a much higher need for folate to push that biochemical step to completion through that faulty equilibrium.

MTHFR Gene Mutation

That study on folate and Down syndrome appeared in the *American Journal of Clinical Nutrition* in October 1999.[4] Dr. S. Jill James was the FDA biochemist who led the study. It clearly does not imply that all cases of Down syndrome result from alterations in methylene tetrahydrofolate reductase and folate status. It does, however, point out that a person with this particular genetic mutation of the MTHFR gene is 2.6 times more likely to have a child with Down syndrome if that individual does not get adequate folate intake. This interesting observation ties back to the earlier observations of Smithells, Butterworth, and McCully.

The methylene tetrahydrofolate reductase gene gives rise to the enzyme that converts 5,10-methylene-tetra hydrofolate to 5-methyltetrahydrofolate, which becomes an active contributor in the methyl donation pathway within the folate cycle. If there is a mutation of that gene, an individual will be less able to enter into that cycle through normal folate coenzyme activity. Supplements of 5-methyltetrahydrofolate that bypasses this metabolic block are now available. An individual with the genetic mutation of the MTHFR gene, who require very high doses of folate to stimulate that cycle, may be able to use a supplement of a much lower level of 5-methyltetrahydrofolate. This is another part of our evolving understanding of the mechanism by which wide-ranging conditions are related to a defect in a specific biochemical process. It allows us to see where in that pathway we might intervene with what substance downstream from that metabolic block, to produce appropriate physiological function.

The "Downstream" Concept

I want to emphasize this downstream concept. In molecular medicine, a block can occur upstream, and we have to go downstream to feed the pathway and produce the appropriate later-stage intermediates or products. The use of 5-methyltetrahydrofolate may facilitate intervention at a point downstream from the occurrence of the genetic mutation. Intervention trials have not yet been published using 5-methyltetrahydrofolate in individuals with the MTHFR gene mutation to look at its potential effect on Down syndrome. That study will be very complicated and difficult, given the small gene penetration of the mutation of the methylene tetrahydrofolate reductase gene mutation and the infrequency of Down syndrome. It may be necessary to use some inferential data in individuals with this MTHFR mutation.

It is possible to measure this enzyme activity indirectly through the homocysteine and methylmalonic acid test. Elevation of any of a number of different enzymes can create elevated homocysteine. Although the methylene tetrahydrofolate reductase gene is only one of those enzymes, it may play a principal role. Higher levels of B12, B6, and folic acid or, in this case, 5-methyltetrahydrofolate, can clear those metabolic blocks, or move downstream from them, and then reduce the plasma level of homocysteine and

methylmalonic acid. The homocysteine test, particularly the methionine loading component, may be used to measure all of these gene mutations. In this test you measure plasma homocysteine three to four hours after giving a patient an oral dose of methionine to see if he or she has metabolic insufficiencies in metabolizing these sulfur-containing amino acids. Drs. Smithells, Butterworth, and McCully converge in this unfolding chapter of molecular medicine, which Dr. Pauling described in 1949.

Seventh International Symposium on Functional Medicine

We will discuss this topic in greater detail at our Seventh International Symposium on Functional Medicine, May 24-27 at the Camelback Inn Resort in Scottsdale, Arizona. The topic of this year's symposium is Metabolic Energy, Messenger Molecules, and Chronic Illness—the Functional Perspective. We have pulled together a stellar group of basic researchers and clinicians who will share useful information for moving beyond gene expression to intercellular communicators, biochemical processes, and energy in medicine, and their relationship to physiological function and dysfunction. If you would benefit from a primer course to update your clinical nutrition and biochemistry, we will provide a course called Clinical Nutrition and Biochemistry—a Functional Approach on May 24, 2000, as part of the symposium. That course will provide a good update on the language and some of the things I talk about every month in *FMU*.

We are also excited that, after a two-year process, the Institute for Functional Medicine has been approved by the American Council on Continuing Medical Education accreditation to provide Category I medical education credit. This will be the first symposium for which IFM will provide Category I accreditation. We believe this is another step in the evolution of functional medicine.

Induction of Parkinson's-like Symptoms by Metoclopramide and Other Drug Responses in the Aged

On the subject of neurological problems and interruption of the folate cycle, an interesting paper appeared a few years ago in the *Journal of the American Medical Association.* In relation to molecular medicine, this paper, titled "Increased Incidence of Levodopa Therapy Following Metoclopramide Use,"[5] deserves further comment. This work, by Dr. Jerry Avorn and his colleagues at the Program for the Analysis of Clinical Strategies, Gerontology Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School. Metoclopramide, is the anti-nausea drug Reglan. It is used frequently, sometimes for an extended period of time, by older-age individuals.

This paper explains that certain individuals who have taken this medication for a period of time began to report what appeared to be Parkinson-like symptoms. Because no direct evidence linked the drug with Parkinson's disease, the symptoms were frequently diagnosed as Parkinson's disease, and these individuals were started on L-dopa therapy. Levodopa is not an innocuous agent. It is known to increase oxidative stress by the formation of free radicals and by so doing, increases the risk of neural damage. Failure to understand the cause of the initial symptoms can result in inappropriate drug use, which actually amplifies the initial problem.

This paper asks why some individuals have adverse side effects to this anti-nausea drug and develop neurological symptoms. Why were these listed in the *Physician's Desk Reference* as adverse side effects for this medication? What does this research imply for drugs with central nervous system activities when

those drugs are used for an extended period of time?

The Many Uses of Metaclopramide

The authors of this article point out that metaclopramide is widely used, not only for nausea but also for the treatment of gastroesophageal reflux, an increasingly common problem in our society. The drug has also been used for dysfunctions of gastric emptying, including diabetic gastroparesis, and as an antiemetic following chemotherapy. Its adverse antidopaminergic effects, which have long been recognized, include unwanted extra-pyramidal signs and symptoms. Little information is available, however, to quantify the risk or frequency of such adverse events in clinical practice.

The authors point out that according to one standard reference work, the Parkinson-like symptoms "rarely occur in patients receiving metoclopramide." Another states, "Extra-pyramidal symptoms occur in 0.2 to 1 percent of patients treated and are more common in children and young adults."

The frequency and intensity of adverse drug reactions in older patients may be substantially greater than those reported for the overall patient population, however. Older patients are generally underrepresented in premarketing clinical trials, although they may be the major target population for use of the drug. As a result, available information often underestimates the likelihood or intensity of adverse effects in this age group following use of a given therapy. The older-age group was not used in testing of the medication; the medication, which has central nervous system impacts, wins approval. It is used for some time by an older-age population that was not a major component of the study population. It produces untoward neurological symptoms. When these symptoms occur in the elderly, they are not connected to the medication.

According to the authors, drug-induced symptoms in older people are more likely to be misconstrued as indicating the presence of a new disease or attributed to the aging process itself. They are unlikely to be seen as an adverse response to the medication. This misinterpretation is particularly likely to occur when the symptoms resemble those of an illness like Parkinson's disease, which occurs frequently in older patients. The authors found that patients who receive antipsychotic medications often have anti-Parkinson drugs prescribed simultaneously. This again indicates a crossover between a drug used to treat depression and the appearance of Parkinson-like symptoms that may have been induced by the drug itself.

Hepatic Detoxification and the Elderly

We do know that older-age individuals have different hepatic detoxification effects from certain medications, as well as different phase I and phase II first-pass drug detoxification. They may be more sensitive and susceptible to specific agents that require certain types of detox pathways. Their plasma or tissue levels may therefore be higher at a specific standard dose level than those of a younger individual or one with higher levels of detoxification ability. The authors believe this fact may contribute to the increased risk of central nervous system symptoms seen in older individuals who took metaclopramide. They conclude the following:

"Metaclopramide use confers an increased risk for the initiation of treatment generally reserved for the management of idiopathic Parkinson's disease. Such polypharmacy may represent the misdiagnosis of Parkinson's disease in patients with drug-induced parkinsonian symptoms, which should be ruled out

before starting dopaminergic therapy for this condition."

Questions for Drug Testing and Approval

That observation leads to a number of questions. How should we test drugs prior to their approval? What impact do those drugs have in a study population that is different from that which was initially evaluated? What is impact of the medication when that population takes it for a long period of time, when chronic use was not examined in the study? What is the impact of differences in detoxification of medications and the overall body burden of those substances?

We will discuss that theme in relation to environmental conditions and autism in children in this month's Clinician of the Month interview. We are changing our view of the relationship between genes and environment and aging. The onset of symptoms traditionally associated with aging may be accelerated by adverse environmental influences such as the medications themselves.

The Changing Healthcare Sector-Price Waterhouse Coopers Report

A report by the Price Waterhouse Coopers consulting group, called "Healthcast 2010—Smaller World, Bigger Expectations," has just come out.[6] The authors of this report describe some interesting trends for the next 30 years in health care based upon their evaluation of experts around the world who are involved with different aspects of health care and biomedical research.

Through their evaluation, they come up with what they call 3 forces of change, 4 future trends, and 12 implications that will guide the way that health care emerges over the next 20 to 30 years. I believe the three forces of change and the four future trends apply to our discussions in *FMU*.

Three Forces of Change

They believe the following three forces of change will shape health care:

1. An empowered consumerate creates impatient patients—empowered consumers recognize they ultimately control the dollars that fuel the healthcare system. Dr. Regina Herzlinger, a former Clinician of the Month (she was actually a professor at Harvard Business School), focused on the healthcare sector. She discussed her book, "Market-Driven Health Care," in which she explains that we are witnessing a shift in the way the business of health care is run. Consumers are rising up to recognize they control the purse strings, and they will get what they will pay for. Ultimately, consumer activism will make the healthcare sector a much more dynamic system of supplying consumers with what they want, rather than what third-party decision-makers have decided. Health expectations of aging Baby Boomers are higher than those of their parents or grandparents. They want to remain vital and capable throughout their middle and later years. They are examining the way their dollars will be spent to deliver care. They will have more discretionary dollars to spend because they may be the wealthiest generation of older people the world has ever seen.
2. The second force of change in this report states that e-health adaptability equals survival (of health institutions). We recognize the internet, as a democratic source of information, knows no boundaries. Consumers have the same access to health information as health professionals, the

providers. The information trough, from which we are all feeding, is creating an extraordinary rate of change. Individuals who do not have access to that available information, do not share it, and do not make it accessible and user-friendly, will not survive, according to this report. Impatient patients who are empowered consumers with access to health information over the web are creating a dynamic and vital system of information delivery. Healthcare providers will be part of that system as esteemed individuals who can impart information that will serve patients. If they do not understand the electronic age in which we live, the web and all of its opportunities, and how e-commerce is going to shape the business of health care, they may be left behind as society evolves.

3. We have spoken often on *FMU* about the third force of change, the shifting of health care from cure to prevention made possible by genomics. Within the last 10 years the Human Genome Project has gotten us to recognize that our genes tell us not how we will die, but how we will live. They tell us what we need to do to promote health. We now regard human genes not as rigid, deterministic, and cast in stone, but as plastic and pleomorphic. Their expression depends on the way they are treated and the elements to which they are exposed. Within the next two decades doctors will be delivering individualized therapies that will be molecular-medicine-focused and based on function. We will be able to rectangularize the survival curve and compress morbidity, to use the term James Fries coined. Individuals will be able to live to the full extent of their genomic life span.

These three forces of change combine with the following four trends:

1. Health insurance trends are converging in the U.S., Canada, and Europe. People will be paying for more and more of their discretionary healthcare expenses out-of-pocket. Crisis care will probably be covered by insurance, but other forms of health care will be covered out-of-pocket as a discretionary expenditure for individuals who have more liquid capital. This trend is in operation in Canada. Twenty years ago approximately 3.6 percent of the population was paying for health care out-of-pocket. Now nearly 30 percent are now buying the services they want beyond the crisis service Canada will provide.
2. Health processes are becoming standardized. We are getting into protocols, algorithms, and outcome-based procedures that are successful and reproducible. Some will incorporate nutrition, lifestyle, and environmental characteristics as major gene-response determinants. These characteristics help modify gene expression to produce a phenotype of health rather than disease. I think we will see integrated standardized therapies that involve this complex array of intervention tools.
3. Work forces will adapt to technology and consumerism. Healthcare workers will become much more a part of a team with the patient, rather than diagnosticians standing at arm's length and giving assessment and intervention. Providers and consumers of health care will work together to

develop appropriate therapies to improve individual patient outcome. Again, it is the personalized medicine approach.

4. Aging technology and consumerism create difficult choices. People might want all things, and the question becomes how much can they afford and what is the most efficient. How is technology to be used to improve quality as well as the quantity of life?

The Price Waterhouse Coopers Healthcast 2010 report clearly speaks to the empowered consumerate, the genomics, the information driver through new biomedical research that has been made available through the web, creating a fascinating change in the way health care will be practiced.

Genomic Study Ahead of Predictions

In the 1970s, the Baby Boomer generation witnessed one of the most remarkable events of their young lives—a man landing on the moon. The cost was about 25 billion dollars in 1960 uninflated dollars. Thirty years later, we are now involved in the Human Genome Project to decode the whole of the chromosomal information that leads to the template of the human. This is a 3 billion dollar international endeavor. Although we were told it was going to take quite a while to get this done, entrepreneurial spirit from private enterprise has accelerated the process of deciphering the genome. The entire genome may be deciphered by 2002. Completion of this project will provide an incredible array of information from which personalized medicine may be developed. By 2010 there may be 20 to 30 treatments that emerge in terms of the traditional medical approach from the genomics.

I think we will learn much more about how modifying function in individuals based on specific genetic characteristics well before we are treating only crisis disease. For example, we have learned with the apoE genotypes that there are apoE2, 3, and 4 variants. The individual who carries the double E4 allele, from both the mother and father, has an increased risk of heart disease, Alzheimer's disease, and perhaps even certain forms of arthritis. Evidence suggests we can modify the expression of the apoE4 by practicing the right things. By eating a diet that contains less fat and more polyunsaturated omega-3 oils, being sensitive to certain kinds of antioxidants, and keeping homocysteine levels low by higher intake of folate nutrients, one can lower the risk and incidence of heart disease and Alzheimer's.

Genomics and Intervention Potentials

We are starting to see tracking of a genetic marker against intervention potential for a particular individual. This personalized medicine approach can give a different outcome in the phenotype. We are likely to see more examples of this type of care as genomics becomes part of the average practice of health care.

The Price Waterhouse Coopers paper reported, "Genomics will open markets for diagnostic testing, preventive medicines, follow-up treatments, and even support services such as lifestyle counseling. The business of life sciences and information technology will fuse into a glorious era of biotechnical discoveries in the decades ahead, restrained only by the financial purse strings of government agencies, private foundations, pharmaceutical companies, and equity investors. The human genome map is an

operating system map for the human body, enabling healthcare providers and product companies to customize health care for each individual.

Assessing Immunotoxicology

On side II this month, we will talk about how the environment modifies genomic expression in individuals who may carry autism as a risk factor. To do that, we have to understand something about the interrelationship between genes and environmental factors. At the mechanistic level, a series of studies that can help us understand this relationship is in the area of immunotoxicology. Dr. Vera Stejskal, at the Department of Clinical Chemistry, Karolinska Institute in Stockholm, Sweden, has published several papers in the past five or six years on new ways of assessing immunotoxicology and its interrelationship to the environment.

One of her papers deals specifically with toxic metals, not just lead, mercury, cadmium and arsenic, but nickel, palladium, and platinum. For most people the low environmental levels of these metals would not produce any kind of adverse effects. Using very sensitive immunotoxicology testing, Dr. Stejskal has found that many individuals have extraordinarily accelerated adverse responses through the exposure of white cells to low levels of a toxic metal. It could be a 10^8 acceleration. The effects on that individual's immune system may be 100,000,000 times as intense as on another individual with the same level of exposure to that metal who does not have that same immunological response. This is an exquisitely sensitive measurement of genomic response and individual sensitivity.

The abstract of Dr. Stejskal's paper, "The Role of Metals in Autoimmune Diseases and the Link to Neuroendocrinology," reads as follows: "Current available literature indicates a risk for metal-induced autoimmunity in man. Metal pathology may be due to toxic or allergic mechanisms where both may play a role. The main factors decisive for disease induced by metals are exposure and genetics which determine the individual's detoxifying capacity and sensitivity to metals."

A wide variety of diseases may be threshold diseases associated with heightened sensitivity of an individual's genome to environmental exposure to various metals. Metal-induced autoimmunity can be seen in multiple sclerosis, rheumatoid arthritis, and even amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease), according to papers published over the last several years. Inflammation-induced changes in the hypothalamus/pituitary/adrenal axis may express themselves at a lower stage of severity as fatigue, depression, or other psychosomatic symptoms that are not easily recognized.

"The increased knowledge about individual sensitivity based on genotype and phenotype variability together with the use of biomarkers for the diagnosis of individual susceptibility, seems to be the key in elucidating the operating mechanisms."[7] In the past, the difficulty has been that we did not have good tools for assessing individual response, i.e., the biomarkers. That is currently changing with new immunological testing techniques using cytology and various types of radioimmune assay and blastogenic analysis. We are beginning to be able to evaluate individual sensitivities to various environmental substances that may be immunotoxic to one individual and benign to another. We are more fully recognizing how the environment interrelates with our function.

"Environmental factors that are implicated in the development of autoimmune diseases include bacteria, viruses, and xenobiotics such as chemicals, drugs and metals. Many cases of autoimmunity debut after an

infection. However, it seems that despite persistent research efforts, no conclusive evidence has linked certain microorganisms or viruses to the pathogenesis of autoimmune disease."

The Major Histocompatibioity Complex (HMC System)

Several factors have been studied concerning the induction of autoimmunity. This has to do with our better understanding of the MHC system, the major histocompatibility complex. The HMC system is associated with increased risk of autoimmunity in animal models and in humans. The human lymphocyte antigen, or HLA linkage to susceptibility has only a relative predictive value, indicating that other factors also contribute to the development of autoimmunity. An obvious example is the overrepresentation of female patients in certain autoimmune diseases. In systemic lupus erythematosus (SLE), for example, the female predominance ratio is from 10:1 to 20:1. For multiple sclerosis it is 10:4. This disparity indicates that sex hormones or other gender-specific messenger molecules may play a role in the pathogenesis, separate from the HLA linkage.

Even monozygous twins do not always develop the same disease. Other exposure factors may lead to modification of gene expression. We know about HLA B27 in ankylosing spondylitis. We have discussed Klebsiella's relationship to HLA as one indication of a bacterial epitope that may be influencing cell messaging (perhaps by molecular mimicry) in an HLA B27 mutant that goes on to produce an autoimmune disease. That is only one of a number of substances—bacteria, viruses, and environmental substances like xenobiotics and metals—that may elicit complex immune response based upon the individual's own genotype that translates to autoimmunity.

"Available literature clearly demonstrates metal-induced autoimmunity in animal systems.[10]Reports that link metal exposure to the development of autoimmunity in man include epidemiological studies, occupational exposure to metals, and a high prevalence of side effects following treatment with metal chelators and colloidal gold."[7] Metals are often bound to sulfhydryl groups. They can have that same effect on the body, changing enzymatic function and behaving as haptens that appear as foreign proteins to the body which then responds by eliciting an autoimmune reaction.

"The immunological effects of metals are either non-specific such as immunomodulation or antigen-specific such as allergy and autoimmunity." So not all of this appears as a true allergy and may be missed by an allergist who is just looking for immunoglobulin responses. "

How Metals Affect Immunity

"Metals may act as immunosuppressants (cytostatically) or as immunoadjuvants (nonspecific activation of the immune system). One example of immunomodulation is the ability of metals to modify cytokine production *in vitro* and *in vivo.* The resulting imbalance between Th1 and Th2 activation can result in immunodysregulations leading to impaired cell-mediated immunity and/or aberrant humoral immunity that may culminate in autoimmune disease."[7]

"Heo et. al. found that lead and mercury enhanced IL-4 production by a Th2 clone (and inhibited Th2 proliferation) *in vitro* and *in vivo,* suggesting that these metals may induce an autoimmune response by upsetting the balance between Th2 and Th1, which could enhance the production of antibodies to self-antigens. Another example is the enhancement of the intensity and duration of antigen-specific IgE

responses by gold salts, mercury, platinum, and aluminum."

Something about the association of the environment and the immune system may be mediated through the exposure of genes to certain metals. This variation in sensitivity may vary by a factor of 10^8 from one individual to another.

Dr. Vera Stejskal and her colleagues, including Dr. Antero Danersund and others at the Department of Clinical Chemistry and Department of Clinical Metal Biology at the University Hospital, Uppsala, Sweden, wrote a paper that appeared in *Neuroendocrinology Letters.* They showed that lymphocyte proliferation occurred dramatically in some individuals after exposure to exquisitely small levels of specific metals. This was very individualized. Again, we get back to personalized medicine.

Dr. Stejskal has developed a technique called the MELISA®, the memory lymphocyte immunostimulation assay. MELISA facilitates assessment of these unique sensitivities of white cells or the immune system to metals, again showing the extraordinary range of responses to mercury, lead, cadmium, nickel, or palladium among individuals. This may also influence such things as dental restoration using amalgams. Most patients do not respond adversely to the mercury in amalgams, but mercury-hypersensitive individuals experience extraordinary upregulation of certain genomic responses as a consequence of exposure to mercury. It may present itself as mercury sensitivity, not mercury allergy, seen as immunotoxicology. That is the basis of this paper in *Neuroendocrinology Letters*.

Dr. Stejskal and her colleagues wrote another interesting paper on this theme. In that paper, which appeared in *Neuroendocrinology Letters* in 1999, they looked at mercury and nickel allergy. (Nickel is another of the alloy metals in amalgam.) They connected this allergy to fatigue in autoimmune responses seen in some patients after they had certain dental work.

The patients studied included 22 with autoimmune thyroiditis with or without polyglandular autoimmune activation, 28 fatigued patients free from endocrinopathy, and 22 fatigued professionals without evidence of autoimmunity. The study group was compared to a population control of healthy subjects without evidence of metal sensitivity. This paper indicated that individuals with high sensitivity to amalgam metals including mercury and nickel, presented with fatigue and autoimmune type symptoms.

INTERVIEW TRANSCRIPT

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JB: This month's guest , Dr. Stephen Edelson, was last with us as Clinician of the Month in December,

1994. He is an authority, pioneer, researcher, teacher, and clinician in the area of environmental medicine. Dr. Edelson has been working diligently to understand the autistic spectrum and its relationship to environmental health issues. A medical doctor, he attended the Tulane University School of Medicine. He served his internship at Montefiore Medical Center in the Bronx, New York, and then later at the Albert Einstein University School of Medicine in obstetrics and gynecology. He is a Fellow at the American Academy of Family Physicians and the American Academy of Environmental Medicine and has been a pioneer clinician in environmental medicine for the last 15 years.

Dr. Edelson, welcome to *Functional Medicine Update* once again. Tell us how you got into the field of environmental medicine. I know you've had a lot of experience with xenobiotic influences on hepatic detoxification as well as with silicone breast implants and toxic minerals like mercury, cadmium, and lead.

SE: Thank you very much, Jeffrey, for having me on *Functional Medicine Update* again. It's great to have an opportunity to talk about the autistic spectrum, work that is dear to my heart. In the early 1990s, when there was a great amount of controversy on the subject of silicone and its effects on human well being, I started to look at why some women had problems with silicone breast implants and others didn't. One woman who has had implants in for 15 years may have no symptoms whatsoever, and another woman with implants in place for four or five years can be very sick from it. We now know a lot about the way silicone is detoxified in the body. The liver plays a great role in its detoxification, although in the beginning, we didn't think that was the case. The breakdown of silicone takes place through various hydrolytic processes, and then it is moved out of the body. I think a lot has to do with how the liver detoxifies and how functionally efficient it is in that disease.

That brings us to another disease I'm interested in—autism. I'll get into that in a minute. In addition, I've just completed a study on Lou Gehrig's disease that I'm about to publish in one of the neurological journals showing clear-cut evidence that every patient with Lou Gehrig's disease suffers with detoxification aberrations of various kinds, in addition to being loaded with toxic chemicals and heavy metals. I think there is a general scheme of things that runs throughout the chronic disease spectrum that has to do with the ability to detoxify. The individuals who develop chronic illnesses of various kinds are those who have some sort of dysfunction in detoxification. They may also have some specific genetics that lead them to develop Alzheimer's, multiple sclerosis, scleroderma, or another disease, but the basic environmental influences and the liver detoxification abnormalities play a major role in the onset of the chronic disease per se.

JB: The hypotheses you have offered to clinicians through your work at the Edelson Center for Environmental and Preventive Medicine have been supported by the whole concept of genomics and the research coming out of the Human Genome Project in the past five years. It is interesting that a new word has been coined—genomics—to talk about what you and your colleagues have been addressing for some time. It is a mixture of environmental exposure with genetic susceptibilities to give rise to a phenotype that shows signs of dysfunction. I think that takes us very nicely into the whole concept of the autistic spectrum.

SE: In 1994 I was presented with a patient who had a lot of allergic problems. The parents brought the patient to me primarily because of allergies, not realizing that I might have an interest in trying to help them figure out why the child was autistic. This was the first autistic child I had a chance to work with. At

the same time, I had heard about Rimland's work related to nutritional biochemistry in these children. I heard him lecture and explain that most of these children have allergies.

I began to wonder what might be related to 100 percent of these children having allergies of some sort and also having injury to the brain. What came to mind was that toxins will damage the immune system and the brain and result in both of those patterns. I decided to put together a study to look at all of the potential immunotoxicological, nutritional biochemical, gastrointestinal, and detoxification characteristics of these children. I contacted various laboratories to help support this research, and they were very helpful. Great Smokies, Specialty, and Doctor's Data helped with support of the initial study we did on about 30 autistic patients.

At that time, we were looking for all of the characteristics, all of the issues that might be involved in these children, not specifically what I know today. We found that every one of these children certainly had an allergic diathesis. Every one had an immune dysregulation. Something was abnormal about every one of the children's immune systems. They either had low natural killer cell activity, elevated CD4/CD8 ratios, or myelin basic protein abnormalities.

Then we found their livers were not detoxifying normally. This was true across the board, 100 percent. It was interesting that the type of detoxification in about 80 percent of these children was pathological. They had very high phase I detoxification levels, much higher than I had seen in the average adult population. We saw elevated levels of toxic chemicals in almost every child. In a percentage of these children, we also found elevated levels of heavy metals. The three heavy metals we usually found were mercury, tin, and lead. That was very interesting since all three are neurotoxins.

The types of chemicals we found were common things of our world—hexane, the pentanes, the aromatic hydrocarbons, benzene, trichlorobenzene, trichloromethane. Occasionally we would find organophosphates and the chlorinated hydrocarbons as well. In looking at all of this as a total picture, we decided there were certain things that were 100 percent in every one of the children. Their liver detoxification was abnormal, and they were all toxic. We decided that we would try to publish a paper looking at those issues since those were the most prevalent (obviously at 100 percent) whereas the other characteristics were found in smaller percentages. I found, for instance, 50 percent of the autistic children had maldigestion. Fifty percent had malabsorption. Eighty percent had zinc deficiency. Sixty percent had magnesium deficiency. There was probably a 30 percent Candida overgrowth phenomenon in their gastrointestinal tracts.

We found all sorts of systemic manifestations of a toxic situation, and I put together a flow chart showing how all of those interrelate. The basic premise I thought I had to get across to the public was that this was a genetic and an environmental illness. Both pieces of that puzzle had to be present for these children to become autistic. I think it also showed up in the past with studies of twins showing that identical twin concordance rates with autism is in the 95 percent range, whereas in fraternal twins, it's more like 25 percent.

I published a paper in December of 1998 in the *Journal of Toxicology and Industrial Health*showing these characteristics—the abnormal liver detoxification and the toxic chemical issue. Recently, we submitted to the same journal a study on an additional 50 children showing the exact same thing. Now, we're talking about somewhere in the neighborhood of 70 autistic children, 100 percent of them having

abnormal liver detoxification; 100 percent having a high level of toxic chemicals; and a large percentage also showing high levels of heavy metals.

I am having an unbelievably difficult time getting this message across to the people who are interested in autism. The DAN Group (Defeat Autism Now), the CAN Group (Cure Autism Now), and all of the groups that are interested in autism are completely putting aside the unbelievable statistics I have found. They're not paying attention to it. Back in 1994, prior to the DAN Group's coming out with their protocol, I had already put together this study and presented it to John Pangborn. He told me I didn't have to do any study, that they were going to take care of the study, and that they were doing it with a group of people called the Dan Group. I told him I'd have my study published before they even got their computers online.

In fact, that's what happened. I sent the material to Bernie Rimland and Sid Baker, and a few weeks later I found my material was in the DAN protocol. I called them and asked what was going on, and later on they added me to the DAN protocol. It was way before they even got started.

The big problem with the DAN Group is that everybody they call to speak talks about his or her own individual issues. Shaw, for example, for whom I have a lot of respect, talks about organic acids and their relationship to Candida. Not that this doesn't play a role or that there isn't this characteristic in autistic patients, but it's a secondary one. Wakefield talks about finding measles virus in the gastrointestinal tracts of these children. Sure, they're immune deficient. You give these children vaccines and they're not going to kill off these viruses; you're going to find them all over the body. Martin found the stealth virus in the brains of autistic children. That's not difficult to believe when you're looking a child who's immunotoxic and who has an immune system that doesn't function normally.

I've forgotten who did the work, but back in 1993 it was shown that these children have natural killer cell difficulty. It makes sense they're going to have overgrowth of these viruses. Reichelt is looking at the peptides and their effect on the brain. These children do not have excellent abilities at breaking down proteins. They have problems with digestion. I showed that early on. Some of it is pancreatic malfunction. I proved that with para-aminobenzoic acid (PABA) testing.

Some of it has to do with zinc deficiency. About 80 percent of these children are zinc-deficient, so they have problems with the intestinal peptidases. They are going to have peptides that are secondary causes of problems in the brain, but everybody is missing the root cause of this problem. The root problem is that these children are toxic. Their livers don't work normally. If I have anything to leave with the public, it is that these children need to be detoxified. They need to have their liver function upregulated.

I'm not saying you're not supposed to deal with these other pieces of the puzzle. If you deal with the other pieces of the puzzle, such as diet and treating Candida, and forget all about the fact that the cause of this process is the toxins, you will miss helping these children to survive.

JB: The incidence of autism over the last 10 years seems to have increased dramatically. Is this a result of more sensitive diagnosis, or is it an absolute number?

SE: In the last year, a publication came out of the U.S. Department of Education that studied the incidence of autism across all the states in our country between 1992 and 1997,. The national increase

over those five years was 178.86 percent. In Illinois alone, there was an increase of 21,000 percent. States that had over 1000 percent increase in autism over those five years were Maryland, Nebraska, Nevada, Ohio, Oregon, South Carolina, and Wisconsin.

These are actual absolute increases, not earlier diagnosis. Some of the other states had no significant change. Every state had an increase. There is no question about that. School systems have to report autism. That's how they get extra money from the government for children with disabilities. We are talking about an absolute epidemic throughout the world. I think everybody agrees with that.

JB: Do you feel that this is a manifestation of increased toxic burden the children are experiencing?

SE: As an expert in environmental medicine, I believe the incidence of chronic diseases across the board, from autism to cancer, relates to curves you can plot of the amount of toxic chemicals that have been dumped on our planet in the last 100 years. These substances are dumped every year. They don't disappear; it's cumulative. They don't leave the stratosphere; they stay within our atmosphere. If every year you dump 40 billion tons of toxic chemicals on the planet, what's going to happen in 100 years of doing that?

JB: That argument is supported by Dr. Sondra Steingraber's book titled, *Living Downstream*, which we reviewed in *FMU*. The book has a 40-page a bibliography that cites hundreds of government studies supporting that position.

SE: I recently heard Nicholas Ashford talk. He is a brilliant man, and he said we're not opening our minds to the new paradigm. Years ago, in the early 1900s, when infections were the major cause of illness in our world, we dealt with that paradigm. We're in the early part of a totally new paradigm, which has to do with low-level chemical toxicity to human beings. All of the chronic diseases are related to these low levels of toxic exposures that people are accumulating because of poor nutrition and the fact that their livers are being depleted of these nutrients and aren't functioning efficiently. They are building up these toxins in their bodies, and by the time they're 40, 50, or 60 years old they come down with some chronic degenerative disease. Regardless of whether it's immune-system mediated or directly related to the central nervous system, it's all due to this new paradigm of disease.

JB: Let me trace back to the autism component by looking at some of the previous people who have spoken on *FMU*. Kelly Dorfman**,** a nutritionist in the Washington, DC/Maryland area was the first to bring to my attention the important role of nutrition and brain biochemistry in autism. We've had Dr. Bernie Rimland, Dr. Sid Baker, Dr. William Shaw, and Jeff Kopelson, who talked about secretin and its relationship to autism. All of these people have started to build a picture that autism is not just a fingerprint one inherits as a child and cannot escape. It is, as you've indicated, a combination of genetic susceptibility factors and environmental factors.

SE: There's no question about it. I'd like to comment on the people you mentioned from the standpoint of their expertise and how it plays in autism. Kelly Dorfman, for example, is a brilliant lady who deals with nutritional biochemistry in these children. There is no question these children are nutritionally deficient. They don't eat very well; they have very limited diets. In addition, their systems are working at 10 times the rate of a healthy individual. They're trying to detoxify. They have problems with maldigestion and malabsorption.

Their bodies are under tremendous oxidative stress. I've studied oxidative stress levels in these children; they're all under severe oxidative stress. No wonder they become malnourished. Between maldigestion, malabsorption, oxidative stress, and the fact that they don't eat well, how could they not be nutritionally deficient? Does that have anything to do with the root causes of the disease? No. It's secondary. I think that people like Patricia Kane and Kelly Dorfman make it sound as though this is the primary problem, but it is secondary to the toxicities these children are suffering with.

With Bernie Rimland it is the same kind of thing. When secretin came along, Bernie featured it on the front page of his newspaper: "Secretin—We've Found the Answer to Autism." He's made a big step when we didn't have any science behind it. A recent article out of Chicago describes a double-blind, controlled study that shows absolutely no effect from the use of secretin in autistic children. A second study from the Northeast indicates the same thing. We're expecting five or six more of these studies. My initial observation was that secretin might help these children with their digestive systems, but that it isn't going to heal their chronic, abnormal brain disease.

Kopelson talked about secretin. A lot of doctors say they are getting results. You and I know that's not science. Mother says the child is doing better, he's speaking, and so forth. That isn't science. You have to wait for the science. The science is starting to come out, and it's showing that secretin is not effective. Dr. Rimland has made a tremendous amount of headway in the biology of autism, but I think we're beyond the B6, DMG, magnesium issues. We now know these children have massive toxins in their bodies. How can we look away from that? How can we acknowledge that they have all these toxins in their bodies, but we're going to deal with their peptide issues?

JB: One of the two papers you referred to with regard to Secretin is titled "A Double-Blind, Placebo-Controlled Trial of Secretin for the Treatment of Autistic Disorder."[18] As you pointed out, this comes from the University of Chicago as part of a multicenter study with the University of California-Irvine and University of Utah. They conclude there was no evidence for the efficacy of secretin in this preliminary randomized controlled trial. You are bringing to our attention a very important point in any kind of clinical observation or basic science. That is, what is cause and what is effect? We often can get an effect thinking it's a cause, but actually it's only a secondary or tertiary manifestation.

SE: I agree with that wholeheartedly. A researcher named Gupta was giving megadoses of IV gammaglobulin to children with autism. He was helping a few children with this treatment. Others repeated this treatment but didn't get such good results. At a meeting at which I was a presenter a few years ago, I asked Dr. Gupta what he thought was causing this autoimmune process that might be going on as part of this illness. He really didn't have an answer. As you and I know, most people in immunology do not understand immunotoxicology. They do not understand how toxins affect the immune system.

Dr. Vojdani, one of the world's experts in this field, is an exception, and there are a few others like him. In autism, the toxic exposure these children are suffering with every day, along with their damaged immune systems, is a major factor. It shows up in many ways. There's a publication out of Washington University in St. Louis this year from Anne Connolly and her group at the Department of Neurology and Pediatrics. She shows autoimmune IGM antibodies to brain cortex that in 36 percent of autistic children, and in somewhere around 20 percent of children with Landau-Kleffner syndrome, a variant of autism. Again, this is not the root cause. It is another secondary issue because of this damaged immune

system.

JB: That is an interesting paper. I agree with the interconnection of neuroimmunology and neurotoxicology. It's interesting that the toxicologists and immunologist go to two different sets of meetings, and speak two different sets of languages, yet they think they're not connected together somehow.

SE: It's quite amusing. I've actually sent at least 20 specimens over the last couple of months, and we've had two patients that turned out positive, which documents that these autistic children, some of them, have an autoimmune component that needs specific treatment. Now, these are the children that do need megadoses of gammaglobulin because that's the only way to shut off the immune attack on the brain.

JB: Dr. Woody McGuiness has also been involved in research into autism. He was the person who first introduced me to Dr. Mary Megson, who has talked about G proteins and the interrelationship with fat-soluble nutrient malabsorption in some autistic children. Have you had any experience with this malabsorption syndrome?

SE: Yes, absolutely. We do comprehensive amino acid analysis on every child who comes into my center. We find malabsorption in a minimum of 50 percent of these children. John Pangborn and John Evans at Great Smokies must have at least 100 of my cases they could pull out of the computer to give you the statistics you're looking for. How many autistic children have malabsorption? How many suffer with maldigestion? I have all those numbers. I just have to get them out of the computer. I think malabsorption in these children needs to be treated very vigilantly.

Identify the areas in the gastrointestinal tract that are damaging the small intestine and remove those. Give these children the things they need to heal–the glutamine, and aloe vera that will help heal the gut. Remove the heavy metals, the toxic chemicals from their bodies, which are probably part of the injuring mechanism of the GI lining, and you'll heal these children. We've healed many of them.

JB: To summarize, how do you approach a child who presents with a component of the autistic spectrum? What's the general strategy?

SE: We have a list of mandatory things we look at—things that I need to help the child. We do a heavy metals challenge so we can see whether or not there a problem with that. We do an amino acid analysis. We do skin testing, ALCAT testing, so we can see what their allergic components are. We do blood testing for both aliphatic and aromatic hydrocarbons and in some cases, organophosphates and chlorinated pesticides (not in all of them). We do the liver detoxification evaluation, looking at phase I and phase II detoxification, as well as oxidative stress characteristics in these children. We do the autoantibody studies at Washington University.

As an option, we also have a panel looking at about 15 different autoantibodies to brain fragments that I've set up in Specialty Labs which, as you know, is one of the best immunology laboratories around. We do a special panel there. That's an optional thing. We don't do it on everybody because it's very expensive. Some patients can't do it because it's so expensive. The treatments are expensive; there's no question about that. We bring in a child who's loaded with toxic chemicals, and the child spends four

weeks, eight hours a day, five days a week, going through a detox sauna depuration program to mobilize these toxic chemicals and get them out of the body. These are expensive treatments, but. the bottom line is saving these children. I'm trying to save as many as I can.

JB: You helped us understand the emerging science of this field. It is more than just keeping the child comfortable and hoping he or she won't deteriorate. It gives an optimistic view of where we're going in better understanding the genetic uniqueness of these children and the how the toxic burdens influence gene expression and produce a phenotype of autism. Putting all the investigators together paints a very different picture. I include Andy Wakefield's work on the ileal lymphadenopathy, Dr. Mary Megson's work on vitamin A, Dr. Baker's work, and certainly the historical work of Dr. Rimland and the work on secretin. It all goes together with your model of the way the environment influences the genes of these children.

SE: How does the environment cause all of these downstream effects in these autistic children? I certainly believe that everything you've mentioned goes on in these children, but we need to concentrate on the root causes if we're going to save the children. Treating these downstream processes without removing the toxins is not going to save the children. We have treated children who were severely autistic and are now normal today. I wish I could show you the videotapes so you could show your listeners the before and after.

JB: One picture is often worth a thousand words. I'm sure if any listeners would be interested in getting more information about those videotapes they could contact you at the Edelson Center for Environmental Medicine. The address is 3833 Roswell Road, Suite 110, Atlanta, GA 30342, 404/841-0088. We'll put that address at the end of the tape as well as your phone number. Do you have an email address?

SE: Yes. Sbedelson@pol.net. We also have a massive web site, 600 pages long, at edelsoncenter.com.

JB: You articulate this complex field in a way that really gets our attention. We appreciate your advocacy.

SE: Thank you for giving me the opportunity to tell this very important story.

JB: As you said in one of your many articles, autism is not a single entity, but a complex, almost wastepaper basket diagnosis for a variety of different neurochemical impairments that end up under the diagnosis of autism. You have eloquently described that today, and I thank you.

A New View of Autism-A Model for the Functional Medicine Approach

Dr. Edelson has improved our understanding of the complex spectrum of conditions under the rubric of autism. I also want to thank many of the other individuals whose names came up in this discussion, including Dr. Bernie Rimland, Dr. Sidney Baker, Kelly Dorfman, Dr. William Shaw, Dr. Mary Megson, Dr. Woody McGuiness, and Dr. Andrew Wakefield and his work on ileal lymphadenopathy published in the *Lancet.* They are helping us develop a new view of autism as a complex mismatch between the nervous system and the internal and external environment of that individual as translated through their own genome. It gives rise to a much more optimistic view of finding ways to ameliorate the expression of this condition in genetically susceptible individuals.

I have seen many autistic children in my experience over the last eight years, working with the Institutes for the Achievement of Human Potential in Philadelphia. I have been amazed at how intelligent these children are, how insightful they are. This biochemical uniqueness they possess is like a double-edged sword. On one side is the unbelievable brilliance the autistic child frequently has. On the other is this biochemical brake pedal that seems to put them into a state of dysfunction as they relate to the world in which they live. If we can keep the accelerator on without simultaneously pushing on the brake pedal, we can help these children grow up to be extraordinary human beings.

Dr. Linus Pauling would be proud of the new paradigm that is emerging. It is built around molecular medicine precepts and the interrelationship of the human genome, the environment of the individual. That environment includes the individual's nutrition, the endogenous environment from the bacterial flora, and the exposures to the external environment, from metals to xenobiotic chemicals that may modify function, burden their detox mechanisms, and create immunotoxicological and neurotoxicological responses.

In talking about immuno- and neurotoxicology, I may be saying the same thing with different words. The immune system is the nervous system and the nervous system is the immune system. We recognize that through the work of so many investigators who have been uncovering the chemical messenger substances and receptor sites that tie together nervous and immune function through mediator molecules. Dr. Candice Pert, at our Sixth International Symposium on Functional Medicine in May of 1999, described her work on the receptor sites for neuropeptides that are derived from the central nervous system. The receptors on the surface of white cells caused us regard the body as an integrated holograph. Receptor sites are present not only on the surface of white cells, but also on virtually every organ for these endogenous opioids called endorphins.

We are interconnected, hard-wired together, and holographically disposed to interface with our environment in a resonance that is very different from the analytical reductionistic model taught in anatomy and physiology textbooks. The discussion with Dr. Edelson helps us understand the combination of genes and environment that give rise to the outcome we call autism. How can we work through a differential set of evaluations to recognize how to modify that child's phenotype so the brilliance exists without the burden of having the foot on the brake pedal?

There is no single answer. We have to look at the external environment of the child, his or her detoxification ability, and the gut-associated lymphoid tissue and bacterial flora. We have to examine the metabolic function of the mitochondria and look at immunological function as it relates to the expression of some of these reactive messenger molecules, the inflammatory mediators. We have to try to rebuild the basic biochemical patterns of detoxification and immune integrity, and rebalance the proinflammatory and antiinflammatory cytokines.

We have discussed these skills and tools for years in *FMU*. It is the basis of the functional medicine model of looking at the interface between the outside environment and the genes.

On a practical, assessment level, it would be useful to learn something about the gastrointestinal environment. Are the bacteria in the gut producing secondary byproducts that might be damaging to the immune system of a child with a certain level of sensitivity? We look at things like digestive stool analysis. We look at immunochemical markers associated with upregulation of the immune system.

This takes us into immunological assessment. We ask what about the detoxification processes and how that interrelates with oxidative stress. Are the phase I and phase II detoxification pathways balanced? Does the child digest and assimilate nutrients appropriately due to changing functions in the gastrointestinal digestive system? Does the child absorb fat-soluble nutrients? Dr. Mary Megson explained that G protein deficits may cause some children to be unable to absorb or utilize essential fatty acids like EPA, or vitamin A or D, all of which are prohormones and immunomodulators.

We would consider improving the absorption and the uptake and status of essential fatty acids, the omega-3 fatty acids. Docosahexaenoic acid (DHA) plays a very important role in the nervous system. DHA is a major component of the neutral lipids in the myelin. DHA is really an essential fatty acid that comes either from EPA or is consumed directly from the diet.

The essential fatty acid gamma linolenic acid plays (GLA) is an omega-6 fat that is a precursor of the antiinflammatory prostanoids, the 1-series prostanoids. GLA from primrose or borage oil, EPA from fish oil, DHA from fish or algae-derived oil, and alpha-linolenic acid, ALA, from flax oil are part of the balancing of the essential fatty acid components we have been describing.

Detoxification

In considering detoxification ability, we need to supply adequate levels of the phase II detoxifying nutrients like glutathione, which plays an active role in detoxifying heavy metals because of the binding capacity of its sulfhydryl moiety. Dihydrolipoate, or lipoic acid, thioctic acid, plays another important role in protecting mitochondria against dysfunction, improving hepatic detoxification, and also serving as a metal chelator because of its dithiol characteristics. It's almost like British anti-lewisite, the medication that was used during World War I to treat toxic gas poisoning, because it binds very nicely with its thiol residues, the heavy metal or the mineral, and prevents neurotoxicity. So lipoic acid is another good detoxifier for metal toxicity.

Glycine is an amino acid that helps with phase II conjugation. Taurine is an amino acid that helps with phase II detoxification. N-acetyl-cysteine, a precursor to glutathione, is another very important nutrient or substance that can help stimulate hepatic detoxification.

In detoxification and establishing gut flora integrity, we recommend the 4R™ Program for individuals with imbalanced gastrointestinal integrity. This remove, replace, reinoculate, repair program has almost become a mantra for us. Remove the toxic substances. Replace the digestive enzymes and acid where necessary. Reinoculate the gut with the friendly bacteria, acidophilus and bifidobacteria. Repair the GI mucosa so it is not permeable to middle molecular weight molecules. L-glutamine, inulin, fructooligosaccharides, vitamin E, zinc, and pantothenic acid are very important for the fourth R.

If you are not familiar with the 4R™ Program and its clinical applications, I urge you to call our functional medicine staff, at 1-800-843-9660. They can send you a clinical protocol on the 4R™ Program.

Balancing the pro- and antiinflammatory cytokines comes down to utilizing the appropriate type of diet that does not accentuate inflammation, knowing that various types of food antigenic materials can induce upregulation of inflammatory cytokines. We want to use an oligoantigenic diet. We want to use immune function-supporting nutrients like quercetin, vitamin C, vitamin E, and zinc. We want to be very cautious

about certain botanicals that might produce benefit. *Boswellia serrata* is a natural antiinflammatory that helps modulate nitric oxide synthase. Curcumin and the curcuminoids from turmeric are another important part of the antiinflammatory phytochemical pathway. Limonene helps upregulate phase II of detoxification and affects antiinflammatory mediators. These are important contributors to the formation of balance between the Th1 and Th2 cytokines.

We have a series of opportunities for detoxifying, rebuilding immune function, renourishing the gut so the flora becomes friend rather than foe, and improving digestion. These are primary tools in the management of this complex spectrum of disorders called autism.

Will this cure every autistic child? Obviously, not. If so, someone would undoubtedly win the Nobel Prize for this approach. It can make an extraordinary contribution toward the improvement of health in many children whose function is compromised by the overlay of these molecules that are causing mimicry and disturbance of brain biochemical patterns, resulting in outcome that we call autism.

It's like putting cheesecloth over the bright light of good health. The radiance and the brilliance of these children cannot fully radiate through because their brain biochemical pathways are covered with these other molecules that confuse the coherence of the information.

In this month's *FMU* we have continued our theme of genes and environment—genomics that have pleomorphic functional capability as modified by the exposure to the environment. An example is the use of the appropriate nutrient tetrahydrofolate, 5-methyl-tetrahydrofolate, for individuals with methylene tetrahydrofolate reductase deficiency. These individuals require it to improve their handling of homocysteine and methionine. Autism is involved in this complex interweaving of the brain with function. Thank you for being with us in the February issue of*FMU*.

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