

June 2000 Issue | Robert Rountree, MD

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Welcome to *Functional Medicine Update* for June 2000. It is a month since the Seventh International Symposium on Functional Medicine in Scottsdale, Arizona. Thank you to those who were a part of that symposium. If you missed it, you may want to order the tapes and syllabus.

This month in *FMU* we will focus on functional medicine in the real world, emphasizing tools and techniques you might use in managing problems in the complex patient. We begin with a *Journal of the American Medical Association* article titled "Relationship between Modifiable Health Risks and Short-term Care Charges."¹

Is there a difference between modifiable health risks and short-term healthcare charges? Do the costs of medicine change as a consequence of making modifiable health risk changes, or it is just conjecture? Most of us have heard that we will save money in the long term by doing something to promote health and reduce the risk of disease on the front end.

A study which addresses this issue was performed by the HealthPartners Center for Health Promotion and Research Foundation in Minneapolis. The three most obvious factors that increase the risk of morbidity include sedentary lifestyle, obesity, and tobacco. The authors looked at a cohort study of a stratified random sample of 5,689 adults, aged 40 years or older, who were enrolled in a health plan in Minnesota and who completed a 60-item questionnaire. The authors used this retrospective information on how these individuals lived their lives related to their physical activity, eating habits, general health habits, and smoking status. They then asked how that relates to healthcare charges and health risks.

"The mean annual per patient charge in the total study population was \$3570 (median, \$600), and 15 {56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} level of patients had no charges during the study period. After adjustment for age, race, sex, and chronic disease status, physical activity (4.7{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} lower health care charges per active day per week), BMI (1.9{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} higher charges per BMI unit), current smoking status (18{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} higher charges), and history of tobacco use (25.8{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} higher charges) were prospectively related to health care charges over 18 months. Never-

smokers with a BMI of 25 kg/m² and who participated in physical activity 3 days per week, had mean annual health care charges that were approximately 49{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} lower than physically inactive smokers with a BMI of 27.5 kg/m²."

The results are compelling. These three gross evaluators of locus of control over health—lifestyle (sedentary versus active), obesity (related to body mass index), and tobacco use—create a profile of an individual with a much higher use of the healthcare system demonstrated by healthcare charges. The authors go on to say:

"Health plans or payers seeking to minimize health care charges may wish to consider strategic investments in interventions that effectively modify adverse health risks."

Unfortunately, what many plans do is establish exclusion criteria for high-risk individuals so the numbers look better and the profits are higher. In other words, they maximize the value obtained from each healthcare dollar. They exclude high-risk individuals from the plan rather than invest in helping them make changes that would result in lower charges.

How can we translate these concepts to individuals so they can be implemented without great departure from the person's past lifestyle, and ultimately produce not only a higher degree of health and lower utilization of medical services, but extended health span over many more decades of living? We will discuss this question in this issue of *FMU*. The first place to apply functional medicine may be with individuals with chronic disease who are actually prepared to make changes. As we heard from Drs. Trilling and Jaber, along with Dr. Jones at the Seventh International Symposium on Functional Medicine, the willingness-to-change concept is an important part of knowing where to focus our energies and our intentions.

An individual who is a heavy smoker, alcohol consumer, and non-exerciser, who loves his lifestyle and is addicted to it, is highly unlikely to change. Even the most persuasive education program will not get him or her to make meaningful changes. If, however, the individual is willing and ready to change, assisting and supporting him or her through those changes will bring about a tremendously successful outcome. That outcome, as pointed out in the *JAMA* article, can save money and improve life span and life vitality or health span. One focus of *FMU* should be on how to identify individuals who are in a state of readiness to change and support them properly, as opposed to those who just want a quick fix or have a -fix-me-when-I'm-broken mentality. We could focus services more effectively on individuals who will take best advantage of them.

A recent article in *Harper's Magazine* was titled "Let Them Eat Fat. The Heavy Truths about American

Obesity."² This article, by Greg Critser, gives some disturbing statistics. "Today, one fifth of all Americans are obese, meaning that they have a body mass index, or BMI, of more than 30. The epidemiological figures on chronic corpulence are so unequivocal that even the normally reticent dean of American obesity studies, the University of Colorado's James O. Hill, says that if obesity is left unchecked almost all Americans will be overweight within a few generations. 'Becoming obese,' he says, 'is a normal response to the American environment.'

"Children are most at risk. At least 25 percent of all Americans now under age 19 are overweight or obese. In 1998, Dr. David Satcher, the new U.S. Surgeon General, was moved to declare childhood obesity to be epidemic. 'Today,' he told a group of federal bureaucrats and policymakers, 'we see a nation of young people seriously at risk of starting out obese and dooming themselves to the difficult task of overcoming a tough illness.'

"Even among the most careful researchers these days, 'epidemic' is the term of choice when it comes to talk of fat, particularly fat children. As William Dietz, the director of nutrition at the Centers for Disease Control, said last year, 'This is an epidemic in the U.S. the likes of which we have not had before in chronic disease.' The cost to the general public health budget by 2020 will run into the hundreds of billions, making HIV look, economically, like a bad case of the flu."

We are seeing some trends of extraordinary concern, like maturity-onset diabetes, which is now called type II diabetes because it is not confined to mature individuals. It may be seen in adolescence and young adults. Therefore, the loss of eyes, kidneys, and gangrenous limbs, which we used to relate to older-age diabetics, may begin to occur in individuals in their 30s. Therefore, there is extraordinary concern about how we eat, how we act, how we think, and how the healthcare system communicates its message, to introduce patterns of behavior that help us express our genes in ways that lead to health, not dysfunction.

The processed-food industry prepares and sells food under a low-profit margin. Individuals who consume those low-profit-margin products then drive the high-profit-margin pharmaceutical products. Therefore, in some sense, the processed food industry acts as a friend and recruitment arm for the pharmaceutical industry. The pharmaceutical industry owes the food industry a debt of gratitude for providing patients to use their products.

This is a radical view of the system, but it is becoming clear it is not outside the boundary of reality. We are feeding our genes with substances that express not long-term good health and function, but increased risk of the disorders of overconsumptive undernutrition—consuming too much of too little. These disorders include cancer, heart disease, stroke, diabetes, arthritis, and hypertension.

I wrote a paper titled "New Functional Medicine Paradigm: Health Problems Associated with Dysfunctional Intercellular Communication," which was recently published in the *International Journal of Integrative Medicine*.³ I described the earliest markers of dysfunction that will later be expressed as heart disease, cancer, arthritis, maturity-onset diabetes, and digestive disorders. These earliest markers, seen as altered intercellular mediators, sometimes precede the onset of diagnosable pathophysiology by decades. Through these markers we can recognize that the body is trying to compensate for exposure to things that are not in the best interest of its function. It does so by releasing different kinds of mediating molecules that communicate the relationship of that diet and lifestyle to the rest of the body—so-called action at a distance. The ability to read these molecules provides much earlier warning signs of the

dysfunction that will precede the onset of pathology.

Ten years ago we talked about prevention, which included cholesterol screening, weight management, and smoking cessation. Now we are moving toward more personalized preventive medicine, built around recognizing the body's expression, by altered intercellular mediators, of the first signs of dysfunction. If nothing is done about these early signs, they will progress to pathology. Let me give you an example to describe what I am talking about.

Consider a man who is on a trajectory toward heart disease. Well before he gets to heart disease, before he even has any signs of hypercholesterolemia, he has an alteration in the balance of pro- and antiinflammatory cytokines. The white cells begin to shift the way they express their genes to produce new molecules, and you can measure that shift in higher levels of various biological fluids. These molecules may include intercellular adhesion molecule 1, or vascular adhesion associated molecule. The alteration may increase the production of tumor necrosis factor *alpha*, a proinflammatory cytokine. An even more gross state might include increased high-sensitivity C-reactive protein.

These molecules may presage the onset of the actual pathology that we observe, but they actually change the function of the heart and are reflective of altered physiological status. If we fail to recognize those molecular changes because we don't look for them, the man may, after years of experiencing this altered state of declining function with an increased state of inflammatory mediators, experience a cardiac event. A series of events could lead to macrophage conversion to foam cells, oxidized LDL, and atheroma that is produced as a consequence of a monoclonal hyperplasia, which then later becomes infiltrated with cholesterol and calcified, to become stage III plaque. The early event, however, may have preceded this onset of atheroma as a consequence of the molecular message that is transmitted through these altered intercellular molecules.

In my article I point out that virtually every chronic age-related disease is associated with early stages of altered intercellular molecules. Our diet and lifestyle, the air we breathe, and the water we drink all can influence the appearance of these messenger molecules, their relative abundance, their personality types, and which ones are expressed and which ones are not. Our diet contains constituents that create a different response of our genes to our lifestyle. We can use soy as an example.

Soy contains a range of substances, not just protein, carbohydrate, and fat. Soy contains phytonutrients, combination of isoflavones, lectins, and substances related to protease inhibitors and the inositol hexaphosphates, the phytates. All play unique roles in modulating function. In whole soy products are substances that block the dietary absorption of cholesterol. Other substances prevent the enterohepatic recirculation of steroids derived from bile. Still others increase the conversion of cholesterol in the liver to its hydroxylated derivatives and bile salts, which are the major way cholesterol is eliminated from the body.

Soy decreases the absorption of cholesterol and increases the metabolism of cholesterol in the liver. Substances in soy alter LDL sensitivity at the hepatic cell membrane, so it helps to regulate the thermostat for cholesterol *de novo* biosynthesis. Substances like the tocotrienols in soy have been demonstrated to be selected HMG CoA reductase inhibitors with statin-like activities in reducing the biosynthesis of cholesterol.

When you put all those things together, soy appears to be a good food for regulating cholesterol dynamics and potential atherogenic risk. My point is that we do many things to our genes every day, and they respond by producing these messenger molecules. We are just beginning to recognize that these modifiers, over decades of living, have a most significant impact on shaping our health. That is a new model of the origin of chronic illness and the concept of dysfunctional intercellular communication.

In my book, *Genetic Nutrioneering*, I describe the revolution in thinking whereby we now understand that nutrients influence the expression of genes, turning on and off specific characteristics locked within the genome that lead to different phenotypes.⁴ The manner in which the genotype is expressed produces phenotype and is related to environmental exposure to specific nutrients. If I had brought this up 10 to 15 years ago, it would have been considered heretical and antithetical to good thought. The Human Genome Project, which is deciphering the code of the 23 pairs of chromosomes, has permitted us to recognize some unanticipated aspects of molecular genetics and molecular biology. The impact of nutrients on the expression of these genetic characteristics results in our pleotrophism. We do not have just one "us" locked in our genes. There are many "we's," only one of which is expressed at any moment. Exposure to various environmental factors alters the expression of genes producing what we call the phenotype.

In *Genetic Nutrioneering*, I talk about modifying the expression of inherited traits so an individual can live a longer, healthier life. We are clearly not talking about modifying genes by mutational injury. The expression of many genetic characteristics, however, can be modified through various diet, lifestyle, or environmental connections. Once that expression is modified, it alters the molecular milieu as it relates to the intercellular mediators I described earlier. The physiological state then can shift from a potential disease state 10 to 20 years down the line, to a state of homeostasis centered around health, or what we in functional medicine call homeodynamics.

A couple of papers from the recent literature validate or support the concept that nutrients can influence the way genes are expressed. The authors of a recent paper in the journal *Redox Report* describe the effect of various antioxidants on cytokine gene expression in T lymphocytes.⁵ We know that several antioxidant compounds inhibit the proliferation of various types of cells, including human peripheral blood lymphocytes. We know that transcription factors locked within the genes create different phases of cell division and replication. These factors, including nuclear factor *Kappa* β (NF- κ B), and AP-1, are known to be affected by antioxidants. Recent studies using DNA microarray technology have allowed researchers to obtain information about the ability of specific nutrients to change cellular expression in thousands of genes, and how that might influence genes related to things like inflammatory cytokine production.

In this study in *Redox Report*, Kristine Hardy and Nicholas Hunt from the Department of Pathology at the University of Sydney in New South Wales, Australia, used lipoic acid as one of the principal antioxidants to see if it influenced gene expression of proinflammatory cytokines.

The researchers used human peripheral blood lymphocytes as the cell type of choice. They used DNA microarray technology to look at the expression of different genes with and without exposure to added levels of lipoic acid. They looked at approximately 4000 genes that were represented on the gene filter. They found that 457 genes were constitutively expressed and 83 genes were repeatedly upregulated, while 238 genes were down-regulated when exposed to a mitogen.

This is important to recognize. Many genes in our genome work at a standard level, called constitutive expression. They are not very modifiable on exposure to various environmental agents. We are more concerned about the genes that are inducible. About 83 of the 4000 genes represented in this study were upregulated, and 238 were down-regulated, meaning 83 were turned on and 238 were turned off as a consequence of exposure to an exogenous substance, a mitogen. Treatment of the mitogen-stimulated cells with the different antioxidants resulted in inhibition of the induction of many of these genes. This indicates that lipoic acid was actually able to down-regulate the mitogen-induced gene expression. Many of the mitogen-induced genes were associated with the production of inflammatory cytokines and the application of lipoic acid dampened their expression.

This is an example of the theme we are describing. By modulating diet and using specific nutrients in higher-than-RDA or RDI doses (or in the case of lipoic acid, for which there is no RDI, higher doses than one might get in a standard diet), it is possible to selectively influence specific functions related to genetic expression of these mediators.

That theme also occurs in a paper titled "Activation of NF- κ B by Reactive Oxygen Intermediates in the Nervous System."⁶ Individuals with dementia or other types of neurodegenerative disorders, including Parkinson's and Alzheimer's disease, may have increased oxidative chemistry occurring in their nervous system. The initiation of these oxidative chemistries results in disruptions of the cell cycle and cell physiology by the activation of transcription factors such as NF- κ B. Reactive oxygen species like peroxynitrite from the combination of nitric oxide and superoxide, superoxide itself, hydroxyl radical, or oxidized lipids (the peroxy radicals) can activate the expression of substances like NF- κ B. NF- κ B then can accentuate the shift toward peroxidative chemistry in the neuronal cell which often leads to apoptotic cell death. It actually increases the rapidity of biological aging in the cell, leading to its death.

According to this report, recently published in *Antioxidants & Redox Signaling*, reactive oxygen species are released in the nervous system by a variety of mechanisms and regulatory pathways. These mechanisms and pathways mediate the activation of NF- κ B in gene expression and create this increased cell senescence or cell death potential. Controlling redox potential in cells (reduction/oxidation potential) has an effect on gene expression and shifts the phenotypic personality of the cell.

One regulatory compound in the shift that occurs as a consequence of oxidative chemistry is 4-hydroxy-nonenal.⁷ That chemical comes from the oxidative damage to long-chain polyunsaturated fatty acid molecules, particularly omega-3 fatty acids found in the nervous system on the 2 position of phospholipids. When a specific oxidation process occurs, there can be a cleavage of a double bond in the omega-3 fatty acid, releasing this aldehyde compound, 4-hydroxy-nonenal. This compound is now recognized as a biological signal modifier. It is a molecular species that is released from the rancidified or oxidized biological lipid. This chemical can then have pathophysiological implications because it is itself a modifier of gene expression. Even at very low concentrations it modulates many cell functions, including signal transduction, gene expression, cell proliferation, and the response of target cells.

You can see that a cascade of events occurs within cells that is directly and indirectly related to antioxidants and oxidants. Antioxidants may have a direct impact on gene expression. On the other hand, they may have an indirect effect by blocking the expression or production of the secondary oxidized byproducts like 4-hydroxy-nonenal, which interacts with the genome to create expression of specific regions of the gene associated with oxidative stress, NF- κ B expression, and ultimate apoptotic cell death.

Hyperinsulinemia

Oxidative stress has an impact not only on gene expression in the nervous system, but also in other cell systems and organs, including the β -cells of the pancreas. That might explain why, over time, hyperinsulinemia (insulin resistance syndrome) is associated with the U-shaped insulin curve. An individual with insulin resistance has increasing levels of output of insulin from the β -cells over time to compensate for the peripheral insulin resistance. The β -cells work harder and harder. It is an example of Selye's general adaptation to stress, which includes arousal, adaptation, and finally exhaustion. Over time, the β -cells work harder and harder, secreting more and more insulin. The person thinks he's fine. He doesn't think he has diabetes. More and more insulin molecules are coursing across his cells and insulin binding sites, however. The increased insulin induces protein tyrosine kinase and other gene-regulatory molecules that affect not only glucose management, but also on gene expression. The person with hyperinsulinemia finds him/herself in a different phenotypic state.

Over a period of time, dysfunction of insulin and its regulation of glucose has its effect. Oxidative stress transitions occur from altered gene expression. That process is described in an article in *Antioxidants & Redox Signaling*. The article, titled " β -Cells, Oxidative Stress, Lysosomal Stability, and Apoptotic/Necrotic Cell Death," looks at the susceptibility of isolated pancreatic cells to transition metal catalyzed oxidative stress. The investigators explain that oxidative stress induces the disruption of lysosomes resulting in the depletion of β -cell insulin secretory ability. This depletion occurs by apoptotic death or necrotic death of the β -cells resulting from a shift toward oxidative chemistry.⁸ Years of hyperinsulinemia can shift the redox balance of B-cells toward one of oxidative stress and result in the ultimate destruction of insulin-producing cells.

In the immune/endocrine connection, white blood cells are related to the integrity of the β -cells of the endocrine pancreas. This relationship also includes oxidants and gene expression, cell cycling, and apoptotic cell death. This type of molecular model is emerging as we begin to understand the origin of many diseases that take decades to progress before they are finally diagnosed as illness. The question for practitioners is to determine the point at which to step in and intervene. What questions do we ask in the functional medicine model? What are the symptoms? Is it reactive hypoglycemia? Is it postprandial two-hour insulin elevation? Do we look at glycosylated hemoglobin or glycosylated albumin? Are there oxidative stress markers? What are the biomarkers for these transitions? Are triglycerides elevated and HDL lowered, which are hallmarks of the insulin resistance syndrome? All these are morphological or gross indicators of what is occurring at the level of gene expression.

A functional medicine practitioner can have a significant impact in the area of gut/immune function, its relationship to overall systemic balance of pro- and antiinflammatory mediators, and the potential influence of those gut-related signals on the expression of modulators and mediators at different organ systems. This is a major breakthrough in understanding.

Mediators traveling through biological systems are the earliest warning signs of later-stage pathology. The more we can read the balance of mediators, the more we know what is going on in the body. That is in contrast to looking at SMAC 24 indicators like elevated SGOT, SGPT, glucose, uric acid, or LDH. These are indicators of damage to organs, and if you could examine the cells of those organs under the microscope, you would undoubtedly see pathology. In the case of these mediating molecules, the cells, tissues, or organs from which they are derived may be morphologically normal. It is only functionally that

they start changing their ability to perform.

Substances in our diet—phytonutrients as well as proteins, carbohydrate, fat, vitamins, and minerals—influence the expression of genes. Lipoic acid, N-acetyl-cysteine, vitamin E, and coenzyme Q10, for example, are known to have an impact on the modulation of gene expression. We are not just looking at the absence of nutrients relative to scurvy, beri beri, pellagra, rickets, kwashiorkor, or marasmus. We are looking at conditions that may occur decades before the appearance of outright disease and its diagnosis. Nutrients might influence the expression of these genes.

Antioxidants in the diet can influence the shift of the redox balance, which secondarily, through molecules like 4-hydroxy-nonenal, can communicate to the genes to create a different personality in the phenotype like that of NF- κ B.

Role of the Gut-Associated Lymphoid Tissue (GALT)

The balance between mediators of the pro-and antiinflammatory pathways are, in part, related to the message of the signal derived from the gut, the gut immune system or gut-associated lymphoid tissue (GALT). "Nutritional Modulation of Gut-Immune System Interactions in Autoimmunity" is the title of a recent article in the *International Journal of Integrated Medicine*.⁹ The author, Dr. Jeanne Wallace, reviews the way the immune system, which is clustered around the gut, participates in the presentation of various types of mediator molecules of the anti- and proinflammatory cytokine family, Th-1 and Th-2. By modulation of the phenotype, it can induce production of substances that upset the balance between anti- and proinflammation, shifting the individual toward a proinflammatory-driven system characterized by things like IL-1, IL-2, and TNF α .

This is an important contributor to the intolerance of inflammation initiated by a d hyperactive immune system. Our Clinician of the Month will discuss this topic in greater detail. Intestinal hyperpermeability contributes to activation of the GALT. This relationship has a systemic effect resulting from an imbalance between Th-1 and Th-2. This takes us beyond consideration of a single disease entity like inflammatory bowel disease. We begin to look at insulinitis and cardiac inflammation due to the release of C-reactive protein and TNF- α as manifestations of the same process.

This interrelationship also, in part, explains the connection between gluten sensitivity and early-stage dementia. A gluten-sensitive individual who continues to eat wheat products for a lifetime can experience symptoms triggered from the gut mucosa to the brain. It raises a different weblike understanding of physiology through these mediator molecules and takes us back to restoration of gut function and the stability of the gut immune function as pretty important for general systemic balance around these Th-1 and Th-2 cytokines.

The 4R Program™—remove, replace, reinoculate, repair—aids in gastrointestinal restoration. Some people call this the biotherapeutic approach toward GI problems. Others call it reflorastation. A number of substances are useful in each of those steps. Remove the unfriendly pathogens, the parasites, and the offending food antigens. Replace digestive enzymes and hydrochloric acid to acidify the chyme in cases in which a person has either pancreatic insufficiency or atrophic gastritis type B (not uncommon in older individuals). We reinoculate by adding back the friendly bacteria—acidophilus, bifidobacteria, and the probiotic materials like inulin and fructose-oligosaccharides. To repair we add appropriate supporting

nutrients like L-glutamine, pantothenic acid, a nonirritating form of zinc, and vitamin E. A variety of nutrients are helpful for establishing proper mucosal integrity.

What happens if an individual sustains prolonged challenge to his or her gastrointestinal mucosa, from dehydration, food antigen exposure, extraordinarily vigorous exercise, or stress? These triggers all influence mucosal integrity. A recent paper in *Medicine & Science in Sports & Exercise* was titled "Gastrointestinal Mucosal Integrity after Prolonged Exercise with Fluid Supplementation."¹⁰ Investigators found heavy exercise could cause breakdown of the GI mucosa. This transmucosal damage may then enhance inflammatory response, increasing the delivery of potential antigenic molecules to the GALT and inducing increased GI and possibly systemic inflammatory conditions. During heavy exercise or times of great stress, one needs to be aware that the GI mucosa, the barrier of defense against these molecules in our gut, is compromised. That compromise may serve to activate the immune system.

GI microbial ecology is very complex. Several hundred types of living organisms inhabit the gut. Proper balance of symbiotic, commensal, and parasitic organisms is important for the health the ecology. These bacteria represent the second largest organ in the body, second only to muscles. This mass of living bacteria, about 1½ kg in some individuals, influences immune function. Mucus formation, secretory IgA formation, crypt cell enzymes, and paracellular junctions keep the integrity of the mucosa in a state that minimizes the absorption of larger molecules from the gut. All of these factors help defend us against the hostile organisms in our GI tract and against other toxic or caustic molecules.

However, when we lose the mucus formation from the gut mucosa, have a breakdown of our secretory IgA system, or develop leakiness between the junctures of the small intestinal mucosal cells, we get an increased potential burden on our immune system from the interior contents of our GI system. Nearly 10 years ago, Dr. JO Hunter discussed this topic in a classic article in the *Lancet*, "Food Allergy or Enterometabolic Disorder?"¹¹ The individual is begins to react to the influence of their bacteria and their secondary metabolites on the immune and cell-signaling systems.

The predominant bacteria of the intestinal flora are bacteroides, which are gram-negative rods, non-spore-forming, which produce succinic, acetic, formic, lactic, and propionic acids from carbohydrates. These are found predominantly in fecal samples. There are bifidobacteria, which are gram-positive irregular rods, non-spore forming, that produce acetic and lactic acids from carbohydrates. In the infant, these are very high in number in the stool, but they decline in the elderly. These particular bifidobacteria may be important for proper function of the GALT.

The clostridial family, gram-positive rods, endospore-forming bacteria, produce butyric, lactic, acetic, and formic acids from carbohydrates. This is a large, but rarely cultured group comprising bacteria that constitute less than 50 percent of human fecal bacteria. Most forms of clostridia are not toxigenic, but some species are. Enterococci are gram-positive cocci, facultative anaerobes that produce lactic acid from carbohydrates. They are generally used as indicators of fecal contamination in nonsterile foods. This is a simple biological test used for the transfer of substances through the fecal material. They are also often antibiotic-resistant and can transfer antibiotic resistance genes in the GI tract.

Eubacterium is a genus comprising gram-positive rods, non-spore forming, which are obligate anaerobes, and produce butyric, acetic, and formic acids from carbohydrates. It is a phylogenetically diverse genus. Lactobacilli are gram-positive rods, non-spore forming, and produce lactic acid from glucose. They are

used widely in probiotic applications, grow best under anaerobic conditions, and have complex nutritional requirements. Among the families of bacteria are many species. This complex ecological community can be disturbed and its function rapidly modified. Instead of the months or years it may take to change human cells, bacterial populations can change in just hours.

An interesting review article on this topic appeared in *Science & Medicine* recently. The authors of the article, titled "Gastrointestinal Microbial Ecology,"¹² describe aspects of inflammatory bowel disease as an abnormal immune response that could occur from alteration of GI flora, producing chemical mimicry or a molecular mimicry that overdrives the chemical communication system.

Chemical and molecular mimicry is illustrated by the implication of *Klebsiella* in ankylosing spondylitis in individuals with the class I histocompatibility gene HLAB27. Individuals with this MHC-I marker exhibit immunological cross reactivity with certain *Klebsiella* serotypes. Reactive arthritis or spondylarthropathies could be associated with a unique genotype that responds to the epitopes from *Klebsiella* bacteria that inhabit the gut. Thus, not everyone has this problem, but those who carry the unique HLA B27 genes may be very susceptible.

We are beginning to understand the importance of the relationship between the living flora of the GI tract and the balance between Th-1 and Th-2 cytokines. We can modify the flora by the way we think, act, and eat. Probiotics, used in the reinoculate phase of the 4R Program™, compete with, push out, and replace parasitic bacteria with friendly symbiotic bacteria. A review in the journal *Food Technology* described probiotics and scientific support for their use.¹³ Even the Institute of Food Technologists is awakening to the use of these substances. An expert panel on food safety nutrition described the scientific status of the support for probiotics and its influence on health and function.¹⁴

Mary Ellen Sanders, a professional member of the IFT, reviewed this report. She talks about a variety of strains of probiotics, including the *Lactobacillus acidophilus* NCFM strain, which has been shown to be stable and have very high adhesion. Adherence is important for maintenance in the gut and for the displacement of potential parasites.

Forms of Probiotics

Lactobacillus DDS-1 is another strain that has been discussed. Dr. Kim Shahani at the University of Nebraska worked on this and another patented form of *Lactobacillus acidophilus*.¹⁵ *Lactobacillus* LA-1, produced by Hansen Labs, is sold as LA-5 in Europe. There are a number of varieties of lactobacilli. *Lactobacillus* KCI has been used extensively in Japan. Probiotics are very commonly used in Japan. *Lactobacillus plantarum* is another lactobacillus used in a product in Sweden, ProBAB. It is another lactobacillus species that inhabits the gut with a different set of metabolic byproducts. A company in Canada, Urex Biotech, uses a rhamnosus species.

Many different forms of bifidobacteria and acidophilus can be used as probiotics with different adherence, replicative rates, and personalities related to survival in the GI tract. They have to be stable. They have to be able to survive GI acid and bile, and they have to be able to adhere to be functionally able to be part of the reinoculation program. I think it is fortunate that products are being made available to deliver these characteristics. If a person does not respond favorably to one acidophilus or bifidobacterial product, then we may need to shift him or her to a different species or product. A unique

personality of bacteria may be required for each individual GI tract.

INTERVIEW TRANSCRIPT

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JB: This month we are fortunate to have as our Clinician of the Month a great clinical representative of functional medicine, Dr. Robert Rountree. Bob is a long-time friend. Since we met, more than 15 years ago, his practice in Boulder, Colorado has burgeoned. He is considered one of the top people in the country in functional medicine. Dr. Rountree has been a clinical associate professor in the Department of Family Medicine, at the University of Colorado School of Medicine since 1995. He is a faculty member in our Applied Functional Medicine in Clinical Practice training program and is actively involved on the Steering Committee for the Institute for Functional Medicine.

Bob received his BA degree from the University of North Carolina at Greensboro in biology with a minor in chemistry, and his medical degree from UNC at Chapel Hill. His family medicine residency was spent at the Department of Family and Community Medicine at the Milton S. Hershey Medical Center in Hershey, Pennsylvania. Bob stepped out of the traditional insurance/HMO environment to be in private practice serving patients in the functional medicine arena on terms of his own and of his patients.

JB: Bob, what led you to move your practice into functional medicine and out of the third party payer system?

BR: That's a complex question. Right after my residency, I spent a week at the Omega Institute with you, Sid Baker, and Neil Ornstein, so I got radicalized from the very beginning. I think that's part of what influenced my thinking. Right after my training, I was exposed to another way of doing medicine. I think I was pretty idealistic and naïve when I first started practicing. I believed there was a way to take this expanded knowledge of biochemistry, this whole different way of looking at medicine, and integrate it into the conventional way of doing things.

When I first went into practice some 17 years ago, I really did try to make it work within the context and the framework of the health insurance industry. It actually worked for a number of years. I was working in one of the first holistic health clinics in the country, called Well Spring Clinic here in Boulder. We had all kinds of alternative modalities including acupuncture, massage, and nutrition. Back then, you could bill for these kinds of services and the insurance companies didn't bat an eye, but over the years, more and more of our clients were rejected. Lots of questions were being asked, and eventually we got to the place where it was totally untenable. We were spending so much time filling out forms and talking to agents on the phone, begging to get basic things paid for that we finally realized we couldn't do it. Eventually, unfortunately, that clinic folded as a result of what happened in the insurance industry.

JB: The mixture of personalities of the practitioner and his or her patients determines the personality of a

practice. What kind of patients seek your services, and how has that shaped the relationship between you and them?

BR: It has changed a bit since I went off insurance. I started a new clinic about five years ago. We thought if we approached this from a very efficient management perspective, once again, maybe we could make this work in the context of managed care. But it again became untenable. I think the biggest problem was that if someone only has to pay \$10 to see you, he wants to make an appointment to see you every week. If a patient has chronic fatigue syndrome or rheumatoid arthritis, you can't deal with that in a 10- to 15-minute visit.

About two and a half years ago, I decided to completely stop all insurance contracts and go to a cash basis. When I did that, I found I had a lot more time to deal with complex problems in the way they needed to be dealt with. If someone has a problem that has developed over a 5- or 10-year period, there's no way you can deal with that in 10 minutes. I've found that gradually, my practice has gravitated toward more and more complex patients. A huge percentage of my practice consists of people who have seen lots of other practitioners and haven't had any relief or success with those methods. So time is a big factor. Typically, I spend a minimum of 45 minutes with each patient and often it is up to an hour and a half.

JB: When you look at the profile of your patients, the demographics, how would you break down the age, gender, and characteristics that define your patient population?

BR: When I stopped the Medicare coverage, my older clientele dropped off dramatically. I still see some people in their late 60s and 70s, but for the most part, my patients are in their 20s, 40s, and 50s. The community here in Boulder is pretty upscale and generally wealthy. I tend to see more of those kinds of clients.

JB: Several functional medicine doctors express concern that this medicine might become exclusionary or discriminatory because it does require more time to be thoughtful with the patient and that, therefore, demands a different financial relationship. Do you see this as a stepping stone to new medicine? How do you put this in the context of providing care to those in need?

BR: I understand what you're saying, and I grapple with it a lot. For years, I felt my mission in life was to provide holistic health care, complementary medicine, or integrative medicine to the working class. That's part of the reason I stayed with the insurance companies for so long. But I found it to be crippling.

I don't think there's a good answer right now. It's more expensive to practice this kind of medicine. It is beyond the reach of a number of people. However, we have to start somewhere by gathering information and by getting more efficient with this approach to medicine. I believe that the more efficient we get, the more we come to understand how to practice this in a streamlined way, and the more ideas will filter down so they really do work for the general public. I'll give you an example. About five years ago, I spent some time in Ghana, West Africa. When I went there, I wasn't sure if the ideas I'd been working with, using nutritional medicine and so forth, had applicability in that setting. Frankly, I was amazed at how many people there were interested in nutrition and herbology, and how many people wanted a natural approach. I suddenly found this stuff I had been dealing with for years did have applicability in these almost simplistic settings, just dealing with common infectious diseases, for example. So, I do think that functional medicine will get to the point where it's more readily applicable to the particular

population we're talking about.

JB: I share the view that change has to start somewhere. It often starts with the more financially advantaged, and then it becomes more efficient and demanded by all sectors of the socioeconomic strata, so I agree with you.

I'd like to know a little bit more about the kind of patients you are actually serving. What are the problems they come in with? How would you cluster those problems? Where do you spend most of your time in dealing with the things they are interested in having help with?

BR: I'd say about a third of my practice is devoted to cancer. I deal with cancer in a specific way. I'm not an oncologist and I don't pretend that I have a treatment or a cure for cancer, but I've specialized in helping people through the process. As people are getting chemotherapy, for example, and they are going through lots of side effects, the whole system basically gets out of whack. There are a lot of things you can do based on functional medicine tools that can help people tolerate that process better. That's one issue I address with people. I also deal with the issue of secondary prevention.

A typical person diagnosed with cancer, say a woman with breast cancer, will have initial treatment, maybe a lumpectomy and some radiation, and then the doctor will tell her to come back in a year and see if it has come back. I say there are a lot of things we can do in between that we would call secondary prevention. Let's use some of the science that's out there about phytochemicals, using things like green tea or curcumin or soy products, and let's put together a program for you so that we can prevent this cancer from coming back. That's become a larger and larger part of my practice.

Probably another third of it deals with people who have chronic fatigue or fibromyalgia, problems that would fit into the category called hypersensitivity syndrome, which happens to people who have become over-reactive to their environment. They have chemical sensitivities, sensitivity to muscle strain, or even a condition I've come to call irritable mood syndrome.

We get so stuck in diagnoses, and one of those in modern psychiatry right now is bipolar disorder. My sense is that anybody who is irritable, or who has mood swings, or who is uncomfortable in his/her body, is now being told he or she has bipolar disorder. The patient is put on anti-convulsants or other heavy-duty drugs. I'm looking for natural alternatives to that. One example is to use essential fatty acids. You've talked on *FMU* about the research done at Harvard using essential fatty acids for mood disorders. I think this indicates we can be using nutrition for a real wide range of problems.

JB: Last month on *FMU* I cited an article titled "Functional Somatic Disorders," in which the authors talked about the broad range of syndromes that fall outside tidy diagnoses. Illnesses are given diagnoses because we have to find a way to reimburse for services, but often they don't fit cleanly into diagnoses and are more functional in nature. Many deal with central or peripheral nervous system dysfunctions. It ultimately leads to shoot-the-messenger therapy, which basically uncouples the message rather than dealing with the actual problem.

BR: It's amazing to me how much blaming goes on in modern medicine. If a patient comes in and has complex symptoms and the doctor doesn't know what to do, the patient is basically told the problem is psychosomatic. After more than 17 years in practice, I continue to be amazed at how often we find

answers to things that have been labeled psychosomatic. I think it's blaming to tell a person he is a hypochondriac, that it's all in his head; if he'd just calm down, everything would be fine. You and I know that the more we use probes that allow us to look at things like oxidative stress or dysbiosis, the more we learn there is actual physiologic dysfunction going on.

JB: You've talked about two thirds of your patients. Is the last third a collecting ground of all sorts of things?

BR: I still see a lot of typical family practice patients, people who just come in for routine exams or people who want to get healthier.

JB: In the functional medicine training course, you have taught about inflammatory disease. Clearly, you have passion and expertise there. Does that constitute quite a few of the kinds of patients you see that fall under the heading of inflammation?

BR: You could probably say inflammation plays a role in just about any kind of chronic illness. If you look for it, you will find it. I do see a number of patients with classic inflammatory disorders like lupus, or rheumatoid arthritis, allergic disorders, or chronic eczema—things like that. Functional medicine is particularly effective in that area because we have a systematic way of dealing with these conditions.

JB: You have been the principal author of the functional medicine algorithm on inflammatory arthritis. Could you take us through how you approach a patient regarding evaluation and intervention.

BR: If a person with rheumatoid arthritis comes to see me, typically he's been to see a rheumatologist who told him he had some joint aches and put him on methotrexate. And the person believes that surely there's another way of dealing with this. I usually spend quite a bit of time during the first visit with a patient, explaining the theory behind triggers and mediators, and their role in disease. I explain that we're not trying to put that person into a box and put a label on him or her. We are looking at a process that's out of whack. That process clearly starts in the gut.

At that point, I usually talk about the 4R Program™ and how we can institute it. I usually do a stool analysis, even if the person has no symptoms, just because we quite often find pathogens—Klebsiella, Proteus, or things like that—in the absence of intestinal symptoms. Often, we'll do intestinal permeability testing. The jury is still out on how valuable allergy testing is. I think there are still some issues with the methodology. I occasionally do IgG testing if I really think it's warranted, but a lot of times, I will simply run a person through a basic detoxification program with a medical food product. Then I reintroduce foods to see if there's some kind of reaction. Usually, we'll start there.

There are a number of phytochemicals I like to use—extract of curcumin, ginger, and Boswellia. I have certainly found high doses of fish oils to be extremely helpful. The most important thing to tell people when they go through this program is that it's going to take a while. In contrast to methotrexate, it's going to take some patience on their part. That's why I think they really need to understand what we're doing. Some studies on fish oils show it can take up to a year to get the full benefit. So you have to get a patient who is willing to go through this process with you, as opposed to the kind of person who wants immediate results.

Doctor/Patient Relationship

JB: That comes back to your ability to develop a relationship of trust, understanding, and communication with a patient. This form of medicine selects for developing a different kind of patient/doctor relationship, with communication as the key.

BR: It's often been said that people don't care how much you know until they know how much you care. I really have tried to cultivate that with my patients. If you have a relationship like that with people, and you try something that doesn't work, they'll stick with you as you try other things.

One of the principles I put out to people is that in conventional medicine, you basically have a fixed methodology. When you have a fixed methodology, you're going to have a variable outcome. If you always have to do the same thing or the same protocol because this is what the textbook says or this is what the insurance company says, then you're stuck with that and you don't really know what the outcome is going to be. On the other hand, if you have a fixed outcome, then you're allowed all kinds of variability in your methodology. I try to explain this to my patients so they understand we might come at this from as many different angles as possible, but we're not going to stop until we can make a difference.

JB: That raises a question about how to take complex topics about the etiology of a patient's condition and translate them into language the patient can understand. You mentioned *Klebsiella* and its relationship to molecular mimicry, as well as the polymorphism of HLA-B27 and how that could cross-react with ankylosing spondylitis or arthritis. How do you get those are complex concepts across? For example, how would you describe that to a patient about the molecular mimicry issue?

BR: I use a lot of metaphors. I frankly have to translate some of this stuff in my own brain just so I can understand it. You'd be amazed at how readily people can grasp some of these concepts if you just say there are bugs growing in their intestines. I tell them that in a typical thimble full of stool, there are more bacteria than there are stars in the known universe. I explain there are a lot of different kinds of bacteria in the colon. On the surface of these bacteria are some very complex molecules that basically resemble the same surface molecules that are present in the joint or in connective tissue. Sometimes the immune system simply makes a mistake and thinks the lining of joints looks like a bacteria, a bad guy, so it goes on the attack. People usually can understand that kind of concept.

JB: Patients often want a pill that will solve their problem. They want it to be really simple. They want an antibiotic to treat every infectious organism. You've honed your skills in that area. Your upcoming book, *Immunotics*, talks about natural alternatives to antibiotics. How do you explain the antibiotic story to your patients, and what use do you have for those compounds in the kind of medicine you are now practicing?

BR: My task may be a bit easier in Boulder because the people who come to see me usually have a negative attitude toward antibiotics in the first place. It's almost to the other extreme. When a person needs an antibiotic, I almost have to beg him or her to take it because people here are pretty biased toward natural medicine.

I do think there are some natural compounds that share some degree of potency with antibiotics. One

example is olive leaf extract, which has been around for a long time. It's just gotten popular in the last year or so and has become available in health food stores. I've been amazed sometimes at how effective compounds like that can be, or herbs like astragalus, which the Chinese have used for thousands of years and which appears to be quite effective against colds and flu.

In the book I tried to summarize a lot of data from different sources so it's all in one place. Then people can pick and choose and decide if they're sick enough to take an antibiotic. What's in between? What can I do that's one step beyond taking vitamin C, for example? I do think antioxidants make you healthier in general. Sometimes, you need to get a little bit more specific. It's amazing how much is out there in the herbal field that can really be helpful and powerful.

JB: From everything I've heard, Bob, it sounds as though you are having a good time, that you're finding joy in the relationship with your patients, and they are responding positively by getting well and giving you positive feedback. Is this correct?

BR: It has taken years and years of learning how to work it my way. I tried for so long to fit into the context of the health insurance model. It was quite liberating to break loose from that. I have something worthwhile to offer, and I had to trust that if I simply put it out to the world, people will come and see me whether I'm on their insurance plan or not. It really has worked that way, and it's made me much happier.

JB: In your experience, do patients assume a different level of responsibility for their health when they're paying out-of-pocket, as opposed to relying on insurance companies? Do you think that's changed the relationship at all?

BR: It's changed 100 percent. One of the most discouraging things about working with people in managed care is the sense that they would spend more money fixing their cars than fixing their bodies. Something goes wrong, and an invisible entity out there is responsible; the individual is not responsible. If people are paying for health care themselves, they feel totally responsible. What that means is when you make suggestions to them about lifestyle changes, for instance, if you're saying they need to exercise more or lose weight or even go on a restrictive diet, they're much more willing to comply with your recommendations.

JB: Many of your colleagues may feel their needs as physicians are not being met right now, and they would like to relate to their patients in a different way. They may, however, be afraid to break away from the tradition of having insurance companies provide their support. What would you say to them, both encouraging and sobering?

BR: I can say it's the only way to go. We doctors have had our hands tied by this insurance situation for way too long. I'll be blunt. I think the whole health insurance industry is a scam because it basically promises people they'll be taken care of when they need it. What's happened is that it has really restricted doctors from practicing good medicine. It's gotten in the way of good medicine. The first thing I would say to doctors is that if you want to practice the kind of medicine you went to medical school to learn, this is the only way to do it.

The sobering thing is that you'll probably go through a phase after you drop your contracts—and I

recommend this whenever possible. Your income does take a dip, and you're going to have to learn how to float for a while. What's going to happen is that patients are going to realize they will get really good quality care from you. They will get care and attention, and you'll be willing to deal with their problems in a way that nobody else does. What will happen is you'll get so busy, you won't know what to do with yourself. That's clearly what's happened to us. We turn people away all the time because we just don't have time to see everyone who wants to see us.

JB: Would you recommend that anyone considering this change develop an area of expertise in a certain area or condition, or do you feel it is just doing good medicine across the board?

BR: I do think being a functional medicine practitioner is being a kind of specialist. I wouldn't say there is a general area of competence. If they make it known that they can deal with complex problems that nobody else can handle, they will definitely have their hands full.

JB: Your upcoming book—*Immunotics*—will provide both patients and practitioners with a sense of antibiotics in context and what other kinds of agents might, in fact, be available. Is that book going to be widely available?

BR: Putnam publishes it, so it's going to be all over the country. I'm sure Amazon.com will have it.

JB: Bob, it's been a treat sharing thoughts about the 17-year evolution of your practice. You are a model for others who aspire to break free from the constraints and practice the kind of medicine that, as you said, they went to medical school for. You have given us a very forward-looking and optimistic perspective.

BR: Thanks, Jeff. It's a pleasure working with you.

Relationship of Autism to MMR Vaccine

I will finish up this month's *FMU* with a recap on a controversial area, the connection between autism and vaccination for mumps, measles, and rubella. In the September 1999 COM interview, Dr. Mary Megson, a pediatric developmental specialist, told us about the use of cod liver oil in managing children with pervasive developmental disorders and autism.

This follows on the heels of Dr. Andrew Wakefield's landmark 1998 paper in the *Lancet* in which he described autism as being associated in some children with the MMR vaccination.¹⁶ Although he did not arrive at a specific cause-and-effect conclusion, he implied we should look more closely at this area. In children and infants who are immunologically at risk, the MMR vaccine may trigger a series of events that lead to a heightened state of inflammation. He talked about ileal nodular hyperplasia in these children in their gut and its relationship with brain chemistry.

Cod Liver Oil and Remediation of Inflammation

Dr. Megson described how cod liver oil containing vitamin A could possibly, through G protein signaling, remediate some of these cases. If you did not have a chance to listen to the September 1999 *FMU* interview with Dr. Megson, you should get hold of that interview. It is a powerful interview

with some very good information.

Since Dr. Wakefield's paper was published, other published studies have followed up. One, in the *Lancet*, was titled "Autism and Measles, Mumps, and Rubella Vaccine: No Epidemiological Evidence for a Causal Association."¹⁷ In that paper, the authors reviewed, statistically in retrospective analysis, a large sample of children. They concluded no statistical evidence indicated there was an increase in autism as a consequence of MMR vaccination.

Dr. Wakefield has responded saying this is true—you will not see it statistically because the prevalence increase is still buried in the mass of data for children who do not adversely respond. It is an individualized low-frequency response, but for those children who get autism and their parents, this concern is real. You will notice that as we get into the "ghost of Gauss," how statistics are used and what precision and power we have in statistics, and how can we tease out low-frequency prevalence of various occurrences from a broad statistical sample. It is an interesting statistical question.

Recently the *Lancet* carried another follow-up series of discussions on autism, measles, mumps and rubella. Dr. Dan Altmann from the London School of Hygiene and Tropical Medicine has questioned why there is so much discussion about MMR vaccination and neurological risk. The data do not seem to argue for this at all, and the risks from not vaccinating are substantially higher than those from vaccinating, according to his review.

On a broad statistical basis, this is probably correct. Vaccination does, in fact, reduce the relative risk of a condition that, in some children, may be very threatening. Measles, mumps, and rubella are not benign conditions in some children. The question that has been raised is not whether vaccination in general is a good idea. What neurological risk does it impart to certain infants with certain immunological genotypes or phenotypes?

The management of autism is in a state of extraordinary dynamic reevaluation. We heard about it from Dr. Sidney Baker in a COM interview in *FMU* in August 1999. He spoke about the work of the DAN group (Defeat Autism Now) in looking at a comprehensive approach toward minimizing risk in treatment of autism. In the February 2000 issue of *FMU*, Dr. Stephen Edelson, an environmental medicine practitioner in Atlanta, Georgia, spoke about his experience with the management of autism as an environmental disorder. In January 1999 we interviewed Dr. Jeffrey Kopelson, a physician experienced in the treatment of the symptoms of autism with secretin injections. He talked about the positive benefits derived from that therapy.

How do these viewpoints wrap together with Dr. Megson, Dr. Wakefield, and these other critical reviews? The *New England Journal of Medicine* last December featured a paper titled "Lack of Benefit of a Single Dose of Synthetic Human Secretin in the Treatment of Autism and Pervasive Developmental Disorder."¹⁹ The authors stated that when they gave a single dose of synthetic human secretin, they found it was not an effective treatment for autism or pervasive development disorders. This study involved 60 children, four of whom could not be evaluated. Two received secretin outside the study, and two did not return for follow-up. Therefore, 56 children, 20 in each group, one half on placebo and one half in the secretin group, were evaluated, using the Autism Behavior Check List at base line after treatment.

The researchers did not find any difference between the two groups in terms of outcome after either

placebo or secretin administration. They gave intravenous infusion of synthetic human secretin, 0.4 mg per kg of body weight versus a saline placebo. The editorial that followed this paper was titled "Lessons from Secretin."²⁰ Its author pointed out that we should avoid jumping to conclusions about new therapies for complex disorders like autism. The severity and social anguish of these conditions create pressure to accept new, positive outcomes. Thus we may rush to judgement too quickly without having all the information and data.

After talking with capable clinicians, I believe secretin administration has had a positive influence on the developmental status and symptoms of autism in a number of children. The difficulty was that it didn't last, and it may have been more of a symptom treatment. You have to ask, how does a gut-related neurotransmitting hormone interrelate to a brain chemistry function? Do we not know about all of the multiple effects of secretin? Or is there is a gut/brain connection to the disorder that has to do with altered gut permeability and messenger molecules that induce molecular mimicry and create an environment in the brain that alters its chemistry and induces the symptoms of autism or developmental disorders in genetically susceptible children?

These are complex but important questions. We should not be too quick to conclude that secretin is an ineffective remedy and the whole concept we have been describing is wrong. I believe it suggests there is something about altered gut function, the gut/immune function, and brain chemistry that interrelates with these possibly in children, and perhaps even in adults. I have described a similar situation with the gluten sensitivity question and dementia in older-age adults.

We know the measles virus induces changes in the GI mucosa. In adults who have gotten measles later in life, there is a very high likelihood of triggering Crohn's disease, small-bowel immunological dysfunction. Information on this was published in the *Italian Journal of Gastroenterology* in 1999, demonstrating an association between measles infection and the onset of Crohn's disease.²¹

In children, there also seems to be a relationship between measles and immunological events that may resemble allergy, atopy, eczema, or asthma. The emerging view has been that by immunizing children in an attempt to prevent their getting childhood infectious diseases like measles, mumps, or rubella, we have lowered their immune system's response and made them more sensitive to their environment.

That is an interesting precept in environmental medicine or what is sometimes called Darwinian medicine. The belief is that it is okay for a child to get an infection with a childhood disease like measles because the child's immune system will then be protected against other things in his or her environment. This theory was recently tested and an article published in the *Journal of the American Medical Association* titled, "Measles History and Atopic Diseases: A Population-Based Cross-sectional Study," The article describes the association between measles history and atopic disease.²²

The authors of this paper came to a different conclusion, which contradicted the previous belief that measles infection in children may reduce the risk of atopia and asthma. In this study they found that measles and atopia occur together more frequently than expected, which did not support the hypothesis that experiencing natural measles infection offers protection against asthma or atopic disorders.

The editorial following that article describes the central point of the discussion of the relationship of immune function, GALT, and the microglia of the brain with external agents.²³ The two writers, Dr. James

Gern and Dr. Scott Weiss, pose a major question that faces medicine. Why have atopic diseases like asthma, allergic rhinitis, and dermatitis, which have in common the overproduction of allergen-specific or total IgE, increased in prevalence? Atopic diseases are environmental disorders associated with the genetic predisposition and environmental exposure we described earlier. Since spontaneous genetic mutation rate is quite slow, it is not clear why we have seen so many more of these conditions in the last couple of decades. If the genes have remained the same, it is the environment that is changing. The authors ask what environment factor could be the culprit.

Many theories based on epidemiologic or experimental data have been advanced to explain the increased incidence of asthma and other atopic conditions. Those factors include improved hygiene, changes in diet, changes in intestinal microflora due to increased use of antibiotics, and altered patterns of infant feeding, greater exposure to allergens, obesity, reduced physical activity, and changes in the prenatal environment. Like autism, this may be another example of a very significant disruption or maybe a high genetic susceptibility, coupled with a disruption through environmental triggers.

The atopic disorders have to do with the balance between the T helper cells, the Th-1 and Th-2 expression of these intercellular mediators—the cytokines, the interleukins, the chemokines, which then alter function at a distance in the body and are associated with allergen-specific IgE and eosinophilic inflammation. According to the hygiene hypothesis, infection with virus and perhaps other intercellular organisms at an early age influences the developing immune system and changes the way these Th-1 and Th-2 mediators are produced throughout the rest of one's life.

Gern and Weiss continue:

"The theory is attractive for several reasons. First, the increase in allergic diseases and the decrease in childhood infectious diseases have occurred during roughly the same period. Second, the worldwide prevalence of atopic diseases is unevenly distributed: the United States, Western Europe, Australia, and New Zealand have high rates of atopic disorders, whereas atopic diseases are less common in developing regions such as Eastern Europe, China, and India. In contrast to the low prevalence of atopic diseases, these developing countries have relatively high rates of serious infections in infants and children. Moreover, several epidemiological studies demonstrated inverse relationships between certain childhood infections, such as measles, mycobacteria, and hepatitis A, and the risk of atopic diseases."

A study of the relationship of measles infection and subsequent atopy in a village of Guinea-Bissau stimulated considerable debate and demonstrated that as there was increased measles infection, there was a much lower rate of atopy. This *JAMA* paper, which seems to find the converse, is something of an outlier and deserves more attention.

Epidemiological studies comparing family size and infectious diseases with the prevalence of atopic disorders have initiated new areas of research. These research areas examine relationships among

lifestyle, the immune system, the gut flora, and developing atopic disorders. If we recognize there is a brain connection to the gut, we know the gut is interrelated to the mediating molecules of the inflammatory pathway. In some immunologically susceptible children, immunization might activate this pathway. This activation would produce the ileal nodular hyperplasia observed by Dr. Wakefield. In this small cohort of individuals, immunization, lack of natural development of the immune system, and exposure to the viruses in their natural cycle may precipitate these disorders.

I raise this as a question. I am not giving an answer. Some individuals have spoken out very strongly. Dr. Wakefield was asked to come from Britain to give a presentation before a subcommittee panel of Congress regarding his thoughts on his research and his recommendations. The dialogue that was televised on C-Span during these hearings was very interesting. Dr. Wakefield eventually said that if we are going to immunize children, why do we need to do it so early in their lives? Why do we need to do it when their immune systems may be at greatest risk, in the first few months of life? Why don't we wait until they have gotten a bit of immunological maturation that occurs perhaps in the second, third, or fourth year, before they get into public school? We could start at that point to consider immunization. By doing it so early we are asking for problems in the immune systems of sensitive individuals who are not yet "mature enough" to handle that load.

These are all interesting questions. As healthcare practitioners giving counsel to patients and parents of children, you are continually asked about immunization. It appears that even these attenuated viruses have some potential adverse impact on a very sensitive immune system. If an infant is showing atopy very early, one should be very cautious about introducing these particular antigens. Waiting for the child to develop a bit more mature immune system before immunization may be the way to proceed.

I urge you to look over these papers that appeared in *JAMA* recently and make some decisions based on your interpretation of this emerging literature. I think Dr. Wakefield's observations and those of Dr. Megson are going to prove to be very prescient and guide us in new ways of both preventing and possibly treating disorders associated with the gut/brain connection.

This concept of genetic uniqueness is giving birth to the field called pharmacogenetics. Certain drugs, when given to individuals who have bad detoxification pathways for that particular medication, can produce adverse side effects. They used to be called atypical side effects, but now we realize they are not atypical. They are reproducible in that person. Some time ago I made a prediction, based on the evolution of this information and the discovery of how to analyze unique detoxification genotypes. Physicians of the future, I said, would be held medically and legally liable for their patients' adverse reactions to medications they prescribed. This liability would occur if the doctors didn't determine how that patient would detoxify the drug and if he or she had a polymorphism of poor detoxification like cytochrome P4502D6 problem for an SSRI drug. Believe it or not, according to the *British Medical Journal* within the last month, this is starting to happen.²⁴ In the wake of new pharmacogenetic information, physicians will have to ask questions about the relative detoxification patterns of their patients based upon their genotype. This is true for chemotherapeutic drugs, as well. So hold tight. The gene/environment connection we have started to expand, which is the root of functional medicine, is evolving, in both strategy and tactics.

Thanks for being with us. We will see you in July.

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