# January 2001| Trent Nichols, MD

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Welcome to *Functional Medicine Update* for January 2001. We have an exciting year ahead of us. It will be a year of continuing transformation in medical care, built around some concepts you have heard about in *FMU* over the past three years, focused on three forces of change. The first force of change is the rising tide of health consumer activism. Consumers paying for health care want to get what they pay for. The rising tide of activism and advocacy is creating a force of change in the way health care will be delivered over the next decade.

The second force of change is e-health. Patients are now going to doctors armed with all sorts of information they have gleaned from the Internet. They want to have their questions answered and to be given alternatives to examine. This activism puts pressure on practitioners who are used to giving out information based on selective distribution. Suddenly, they are being asked to pull together various aspects of information into a clinical treatment protocol. Certainly, e-health, as a distributive-information system, is creating a great opportunity to redefine the relationship between health providers and patients.

The third force of change is genomics. We will consider that topic this month, as we focus on gastrointestinal function and biological aging. Genomics is related to understanding the complex pattern of information coded within our 23 pairs of chromosomes and our mitochondrial DNA. That pattern gives rise to our pluripotentiality as individuals, and the way our lives will be explored, discovered, and exhibited in the phenotype—our functional state as we age.

Functional genomics is creating a paradigm in health care that will cause a shift in the way we view the occurrence of disease in midlife and beyond. We are moving from a deterministic, Mendelian model to a less rigid, more plastic model of variability, based on the way a person treats his or her genomic messages. That is, genetic expression is modified by environment. This gene environment duality, I believe, is creating an orchestrated change in the way medicine will be played out over the course of the next century.

Francis Collins, a geneticist and director of the Human Genome Project, was asked recently what ideas he believes will rule research in the next 20 years. He said, "With the sequence of the human genome largely determined, laboratory research of human diseases will shift as researchers adopt a 'genome attitude' toward solving problems. First, there will be increased emphasis on a systems approach. Researchers will examine the integrated function among many genes, gain insight into the web of coordinated interaction among cellular pathways, and determine the impact of external factors. The number of potential therapeutic targets will increase dramatically as a consequence.

**The Effects of Heredity**

"Second, there will be a heavy emphasis on determining the hereditary contributions to common disease. Among the insights with the greatest immediate consequence will be an understanding of individual variability in response to drugs.

"Third, our increasing ability to predict the structure of proteins will accelerate our understanding of how individual proteins work and interact with other proteins and/or DNA elements. This will also contribute to more rapid identification of potential therapeutic agents.

**The Rise of *in Silico* Research**

"Fourth, human genetic and genomic research will become significantly more computational in approach. *In silico* will replace *in vitro* or even *in vivo* for many experiments.

"Fifth, the debate about the ethical, legal, and social consequences of research in human genetics will intensify. While it is hoped that legislative solutions to the problems of genetic discrimination and breaches of privacy will be implemented in many countries, the challenge of educating healthcare providers to be practitioners of this new brand of genetic medicine will be considerable. Furious debates, not all of them grounded in the scientific facts, will rage about the limits of genetic intervention of our own species. To traverse these troubled waters successfully, we will need full and informed engagement by a diverse group of potential stakeholders."

**Biochemical Individuality Comes of Age**

The concept of biochemical individuality, or molecular medicine, which was framed in the 1940s and 50s by Dr. Roger Williams and Dr. Linus Pauling, is being validated. This concept is rooted in the themes of molecular medicine and chemical individuality, which Dr. Archibald Garrod described in his landmark article in the *Lancet* in 1903. It has taken a century for this construct to gain a foothold so it can become part of clinical medicine, and we are seeing it happen as the 21$^{st}$ century unfolds. In this issue of *FMU*, we will apply these concepts to the gastrointestinal system in some clinical ways, to illustrate how genomics will influence the practice of medicine in the next 20 years.

The aging Baby Boomer population has caused us to take a new look at aging and age-related phenomena in our population. We have had to redefine aging and consider how disease is related to chronological age. Must we inevitably get sick as we age? Is illness locked in our genes? What is the nature of the genetic message concerning disease and aging?

**What is aging**

A recent conference sponsored by the National Institutes of Aging and overseen by the National Longevity Center addressed that question and produced a monograph titled "The Aging Factor in Health and Disease." Many questions remain unanswered about what causes the adverse effects associated with aging and even what aging is, including questions about the potential for continuing creativity and contributions to society as we grow older. Our increasing understanding of the human genome and its expression in physiological function is providing answers to these questions. Molecular genetics, or

functional genomics, is contributing a major effort directed toward healthy aging. We want to increase what has been called our health span, compress morbidity into the last phase of our lives, and die a natural death . Dr. James Fries described this concept back in 1980 in the *New England Journal of Medicine*.

Words used to describe the process of aging tend to suffer from imprecision. There are different ways of looking at it. According to Dr. Caleb Finch, professor of medicine at Andrews Center of Gerontology at the University of Southern California, aging refers to changes that occur during the life span, not all of which need to be adverse. Senescence, Dr. Finch points out, refers to age-related changes in an organism that adversely affect its vitality and function.

**Anti-aging versus Anti-senescence**

I believe the distinction between anti-aging and anti-senescence is important. Right now "anti-aging medicine" has become a buzzword phrase. It may be inaccurate to say we are trying to achieve "anti-aging," because some characteristics of the aging process may actually be desirable. The accrual of wisdom over the course of living, for example, is a positive aspect of aging. The other part of the equation, the health decrements and dysfunction that occur with aging, are associated with "senescence," not with "aging" itself. Perhaps "anti-senescence" rather than "anti-aging" should be our objective.

Dr. George Martin, professor of medicine at the University of Washington, and an internationally known investigator in molecular gerontology, suggests the utility of defining a period of life course called "sageing." I like that term. Sageing is the interval between decline in reproductive fitness and the onset of senescence. We would like our sage period, which is associated with wisdom, to be as long as possible. Healthy "sageing" may take place in mid-life, from age 50 to 80, or even longer. I think Dr. Martin has coined a very interesting term.

**Genes versus Environment: Twin Study**

During this period of what Dr. Martin calls sageing, a series of adaptive physiologic and behavioral changes may occur in response to both intrinsic and extrinsic challenges. Maximum life span refers to the empirical value observed for the longest surviving individual in a population. That number may, to a great extent, be genetically determined. But there is evidence that heredity is not everything. In a study of identical twins from twin registries in the Swedish Census Bureau, investigators at the University of Pennsylvania found that only 20 to 30 percent of susceptibility to common forms of cancer, a major cause of death, is determined directly by our genes. In other words, the concept that we inherit our potential for a long life from our parents in "the luck of the draw" is only 20 to 30 percent true. Seventy to 80 percent of that chance depends on what we do to the genes we inherited throughout the course of living, according to this study.

This is a profound change in our view. Most of us have believed that if our ancestors lived to advanced age we can expect to live a long life as well. That does not appear to be as important a factor as what we have done to those genes during our lives. It helps to lack detrimental genes like the apo E4, but if you treat those alleles with respect over the course of living, you may achieve your potential for a long, healthy life, without experiencing Alzheimer’s disease. There is more plasticity in the phenotype, as translated from the genotype, related to aging, than we previously understood. This is good news; it gives

us room for practicing something that will lead to a positive outcome.

**Disease Risk and Aging**

In 1825, Dr. Benjamin Gompertz, an English actuary, observed that human death rates rise exponentially after sexual maturity. He proposed a simple formula to define the relationship between the force of mortality and the age within a population. This "Gompertz curve" implies no finite maximum age for a species, strain, or population, but it does predict the decreasing probability of survival with increasing age. It is true that as individuals age their disease risk increases. Does aging, in and of itself, create more disease? During the last decade investigators trying to answer that question have realized it is extremely complex.

At first we all believed that chronological aging necessarily causes biological disease. It is true there is a strong correlation between decreased life expectancy with increased chronological age, but we cannot conclude that disease incidence need necessarily increase if the genes are treated right. We get back to the molecular gerontology construct of how the human genomic message gets translated into phenotype over the course of living during which our experiences wash over our genes. Some experiences bring out the good in the expression of our genes. Other experiences cause suppression, inhibition, or activation of specific processes in the body associated with premature senescence. These processes may include apoptotic cell death in the neurons, chronic inflammatory processes, glycation of proteins, altered phosphorylation, differences in detoxification ability, or oxidative upregulation. All of these enhance the events associated with premature senescence. Consideration of these events will frame a new medicine in the 21$^{st}$ century, giving us room, through intervention, to create an environment that will maximize the best expression of our genomic potential.

**Evolving View of the GI System: Immunity and Messaging**

We will focus on translating that broad philosophical discussion into practical reality in this first issue of 2001 in *FMU*. The gastrointestinal system is one of the premier messaging systems for the body. It transmits messages which originate outside of the body to internal receptors and results in function, which may control some aspects of senescence or its prevention.

The gastrointestinal tract represents a sophisticated piece of plumbing that connects our mouth to our anus. More than 20 feet in length, the GI system has often been thought of as a digestive organ. It breaks down large molecules to small molecules so they can be absorbed and utilized as a source of energy. I would like to dismiss the view of the GI system as complicated plumbing apparatus as a relic of the past. That is not the GI system as we know it today. The studies and our Clinician of the Month, Dr. Trent Nichols, will describe the GI system as a chemical and electrical messaging system. It is a biochemical messaging system that translates information from outside our body to our internal systems and results in characteristic responses. Those responses, related to the up- and downregulation of gene expression, can be associated either with the achievement of healthy aging and increased health span, or with its decreases, depending upon the way we translate and respond to the messages.

**Communications Role of the GI System**

Dr. Sidney Baker effectively described the tremendous surface area of the GI system. He explained that,

when it is flattened out, the convoluted surface of microvilli represents an area about the size of a singles tennis court. That membranous structure plays an important role in communicating messages to the body from the 50 tons of food we ingest over the course of a lifetime. The substances that make up our food contain information expressed in a foreign tongue, and we have to desymbolize and translate that information and make it understandable to the messaging system of the rest of the body. The digestive system is responsible for translating the foreigners of the food into friendly messages to the body. That is what the secretory IgAs do. That is what the mucus that lines our GI tract does. They help communicate the right messages to the body.

We have a tremendous number of bacterial species and parasitic potential within the GI tract. There are, in fact, 2½ to 3 three pounds of living organisms residing principally in the large intestine, the colon, but also to some extent in the small bowel. These several hundred species of living organisms have different personalities, different genes. They produce different molecules. They communicate different messages. As such, we are in a constant communication with this very complex ecosystem called our bacterial flora.

**Bacterial Flora: The Body's Second Largest Organ**

In fact, the organ called the bacterial flora, which is connected not by the blood supply but by absorption across the GI lumen and delivery through the portal blood to our liver, probably represents the second largest organ in our body. In fact, there are more bacteria in our colon than there are human cells in the whole body, by several orders of magnitude. They are constantly turning over, metabolizing, dying, releasing contents that need to be catabolized, and having an effect on the gut-associated-lymphoid-tissue (GALT), which is about 60 percent of the immune system clustered around the GI system. The GALT helps translate the message of this complex milieu of food, bacterial metabolites, and bacterial messages to the body in a friendly way. The wrong message received or an inappropriate response given can be a message of hostility to the rest of the body. It can result not just in localized GI inflammatory response, but also in systemic messages of inflammation.

Rather than being confined to the secondary lymphoid tissue of the spleen and lymph nodes, large numbers of lymphocytes are intrinsically associated with the epithelial surfaces of the body, of which the major one is the GALT. Distinct epithelium-associated lymphoid tissue exists in the reproductive tract, as well as the lungs and skin, and all of these tissues communicate with one another. The body's various immune systems—in the liver as the Kupffer cells, in the brain as the microglia, and in the circulating lymphocytes—are all part of the messaging or trafficking system. They receive messages that may have been initiated in the gut and translate them to the rest of the body.

**Understanding Immune Responses**

The immune system at body surfaces like the GALT has become a contemporary paradigm for understanding systemic immune function. Local and systemic immune responses are probably connected by an informational relay system. There are various runners, each carrying a baton and passing it to the next runner. A message might start in the GALT, be transmitted to the liver, and be passed on to the circulating white cells. The white cells then pass the message to the peripheral tissues such as the microglia of the brain, which are embryologically derived from the same type of cell as the GALT, the white cell, or the Kupffer cell. This informational relay is an important part of the messaging of inflammation/anti-inflammation—friend or foe—in the body.

The relay starts locally, as in the GALT, where antigen-presenting cells such as dendritic cells, can be provoked to take up, process, and present antigens locally, or to differentiate and to migrate to draining lymph nodes to present antigen to systemic T cells. The same relay system may be operational for systemic B cells. Indeed, systemic tolerance to body surface antigens like those of the GALT can be so durable that antigen delivery by oral or nasal routes has been actively pursued as a way of reducing pathogenic autoimmunity and immunizing an individual to "foreign" agents.

**Gut-Associated Lymphoid Tissue (GALT)**

The GALT inherently limits infection. Absorptive mucosal epithelia are covered with a thick electrostatically charged glycocalyx, a collection of secreted glycoproteins that play important roles in defending against the attachment, adherence, or transport of toxic or foreign information to the rest of the body. Essential absorptive functions preclude epithelial layers from being totally impenetrable. However, a breakdown occurs in this barrier function, you get what we call increased mucosal permeability, i.e., leaky gut in the case of the small intestine. A leaky gut allows larger molecular-weight substances to be transported by passive diffusion across the epithelium, providing access to the GALT and imprinting the immune system with a message.

The epithelial cells and intraepithelial lymphocytes play an important role in this relay system. We are just beginning to understand the profoundly diverse system that is the informational relay in the gut. The correlation, or interrelationship among food antigens, commensal flora, harmful pathogenic bacteria, and mutational damage creates pressure on the local response in the GALT. The GALT then can develop local low-zone tolerance. This is like developing immunization against some of these messages. It can have a suppressive effect. It can have an activation effect, producing a response leading to systemic intolerance.

**Messages of Inflammation/Anti-inflammation between Gut and Body**

We now understand that the relationship between the gut and the rest of the body is an important part of the overall body messaging system related to inflammation and antiinflammation. The mucosal surfaces of the gut are exposed to a myriad of antigens and toxins that require different types of responses, ranging from tolerance to suppression to active immunity. The nature of the response required is primarily determined by whether the antigen is likely to be beneficial or detrimental to the body and the way the genes of that unique individual see this message. We get remarkably different responses from person to person based upon his or her genomic uniqueness.

Intestinal dendritic cells are capable of taking up soluble protein antigens that may not be completely broken down into their requisite amino acids. These soluble protein antigens may still contain information, because they are protein fragments, or perhaps even intact proteins, and they therefore prime naïve T cells. Conversely, the dendritic cells may have taken up apoptotic enterocytes and shown to be poor at T-cell priming. This may lead to altered T cell activity.

**Oral Feeding and Systemic Tolerance/Intolerance**

The relationship of oral feeding to systemic tolerance or intolerance has been difficult to understand. It has been studied extensively. Particularly since the rising concern of HIV and AIDS and its effect on gut immunity, we have seen great breakthroughs in understanding some of these processes. The precise

molecular signals that accompany antigen exposure of body surfaces such as the GALT, however, have not yet been fully identified. What we can say, however, is that there is a tremendous plasticity of responses available from the GALT, based upon how an individual is exposed to his food, diet, and environment. The observed pleotrophy of the epithelial-associated lymphoid tissue explains why dramatic changes in immunological outcome can ensue very swiftly. The process is contingent on the physiological context in which these antigens or other toxins breech these mucosal surfaces through the leaky gut syndrome, and possibly go on to affect the messaging or trafficking system of the whole of the body, producing systemic influences.

Ilya Metchnikoff, director of the Pasteur Institute at the turn of the 20th century and winner of the Nobel Prize in Medicine in 1896, believed that the prolongation of life could be achieved by improving gut flora and administering acidophilus to patients in hospital. At the beginning of the 21st century we are beginning to develop a mechanistic understanding of this simple concept, which started back in the Pasteurian vector disease days in the late 19th century. This biotherapeutic approach toward GI function may have systemic effects that cut across a variety of conditions related to senescence, including heart disease, cancer, arthritis, and diabetes. The fact that the gut can be that signaling tool represents a profound concept.

**Glutamine and Intestinal Integrity**

Scientists have studied the influence of many nutrients on gut mucosal integrity and the cell-signaling system. The results of that research are the basis of the "4R Program™." The four Rs—remove, replace, reinoculate, and repair—are related to therapeutic intervention to improve GI function. Glutamine is one nutrient that has been identified as being very important for GI mucosal integrity. Hundreds of papers published over the past few years have described the therapeutic value of glutamine enrichment in individuals with marked GI permeability problems or GI inflammatory conditions. Glutamine-enriched foods help maintain an intestinal balance of the inflammatory and anti-inflammatory messaging molecules, the interleukins.

A recent paper in the *Journal of Parenteral and Enteral Nutrition* demonstrated that glutamine-enriched foods, when provided to animals with an altered balance between pro- and anti-inflammatory cytokines, could balance the anti-inflammatory cytokines, lower the proinflammatory cytokines in the gut, and result in enhanced mucosal secretory IgA levels. In this case, a single nutrient, glutamine, enhances GI mucosal barrier function with regard to the fourth R—repair. The authors of this paper also talked about this application in humans.

**Glutamine’s Repair Function**

Glutamine plays an important role in augmenting the repair phase of GI mucosal surface barrier function. This study discusses glutamine’s role in balancing these inflammatory messaging substances, lowering the proinflammatory cytokines, and enhancing the anti-inflammatory cytokines in the human gut mucosa.

For follow-up reading on GALT immunology and the important role of body surface GALT function in immune trafficking, I recommend the October 2000 issue of *Science* magazine for an interesting review on this topic.

**Friendly Microbes in a Hostile GI Environment**

How do we get along with these microbes that are living in our gut as part of our overall signaling system? It sounds like a pretty confused message when you have several hundred species of bacteria and protists living in the gut, all vying for space and resources. The mucosal surface of the GI tract interfaces with the complex environment of the gut lumen. Therefore, we are constantly getting a variety of messages communicated to the receptor sites of our immune system. This environment contains potentially antigenic dietary constituents, a daunting variety of usually harmless microflora (symbiots or commensals), and bacterial pathogens that either directly invade the mucosa or produce toxins that damage it. Bacterial cell wall debris such as lipopolysaccharides (LPS) is known to induce inflammatory response. This is a complex environment.

To withstand this hostile milieu, the epithelial cells of the gut mucosa have evolved features that make the intestinal epithelium an active immunologic as well as anatomic barrier. For example, these non-classical immune cells express major histocompatibility locus antigen (HLA) complex class I and II molecules, an HLA system residing, in part, in the gut. More than 60 percent of our immune system is clustered around the gut. The reason the immune system is so heavily clustered around the gut is probably to defend against the complex foreign messages we get from our food and the bacteria that live in our gut, which must be translated into friendly messages. HLA I and II participate in adaptive immune recognition of pathogenic bacteria and play an important in defending against this complex message from living organisms in our intestinal tract.

**The HLA System**

The HLA system is tightly tied to our genes, which may explain why the immune system varies from person to person. A review article on the HLA system recently appeared in the *New England Journal of Medicine*. The second in a two-part series, it is titled "Advances in Immunology." The article discusses the chemical trafficking and messaging system and its interrelationship with autoimmune disorders and spondlyarthropathies. HLA-B27, for instance, is associated with sensitivity to bacterial epitopes of the species *Klebsiella*. This infection or inhabitation of a person's gut can send a message to the HLA-B27 allele, which has chemical mimicry associated with it, and creates an upregulation of the inflammatory process leading to spondlyarthropathies. This is an interesting example of the way the gut acts as a messaging system for communication between the external environment and the internal portion of our cells.

The capabilities of the gut epithelium result in a continuous, very low level of inflammation in the intestinal mucosa, which is the complex interaction of dietary constituents, bacterial debris, and bacterial metabolism that produces a very low-level of inflammatory mediators in the intestinal mucosa. Those inflammatory mediators can be further upregulated in response to a stronger message from pathogens or toxic substances or antigens. It is this total load effect on various aspects of the GALT that may increase the intensity of the message as transmitted to the rest of the body.

**Nonpathogenic Bacteria and NFk B**

In a recent study published in *Science* magazine, Neish et al. looked at a nonpathogenic strain of salmonella and found could abrogate synthesis of inflammatory cytokines by the gut epithelial cells. They

studied the mechanism by which it was able to downregulate inflammation. (This nonpathogenic strain of salmonella is not associated with food poisoning.) They looked at the relationship between this bacterium in the gut and how it transmits its message to receptor sites in the gut mucosa that then leads to either inflammation or anti-inflammation results.

The bacteria accomplish this by blocking degradation of inhibitory Kappa B (Ik B). Ik B prevents translocation of nuclear factor Kappa B (NFk B) to the nucleus. NFk B is a transcription factor which is mobilized when the cell receives certain messages. NFk B stimulates the transcription of several inflammatory cytokines that ultimately influence what is called cell suicide, cell apoptotic death or apoptosis. NFk B is associated with increased inflammatory response, increased output of tumor necrosis factor *alpha* (TNFa ), increased oxidative reactions in mucosal surfaces, and increased cell death. Ik B keeps that process in check.

**Altering the Inflammatory Response**

When researchers studied the nonpathogenic form of salmonella bacteria in gut lumen physiology, they found it caused tight binding between Ik B and NFk B, preventing the cascade of events that could result in this inflammatory response. The investigators propose that through this method, the normal gut microflora, the commensals or perhaps the symbiots, are able to induce a distinctive form of tolerance in gut epithelial cells. Many drugs used to treat inflammatory bowel disease block NFk B. In fact, corticosteroid drugs work principally by activating Ik B. It may be that some friendly bacteria possess the same biological activity as corticosteroid drugs. Namely, promoting the binding of Ik B to NFk B and reducing this inflammatory cascade.

Most of the bacteria that constitute the gut microflora are commensals; that is, they coexist with intestinal epithelial cells without harming them. However, some are symbionts; that is, both bacteria and the host cells benefit from the association. For example, some symbiotic gut bacteria induce intestinal epithelial cells to express glycans, the complex proteosugars that can help protect gut mucosa against messages that could produce upregulation of inflammation. A molecular cross-talk clearly exists between the microflora and the mucosal epithelial cells of the gut.

**Pathogenic versus Nonpathogenic Bacteria**

We generally hope to have only a small number of pathogenic bacteria in our intestinal tract, less than $10^4$ per gram of stool as contrasted to $10^9$ per gram of stool for friendly and oxygen-tolerant bacteria. The pathogenic bacteria have evolved strategies permitting them to colonize and invade the gut mucosa. By utilizing these attachment procedures and processes, the bacteria can inject proteins with what are called type 3 translocation proteins. They may use the same apparatus to secrete proteins and molecules that block the phagocytic cells from functioning. They chemically uncouple the normal immune balance and tolerance of the gut.

The study Neish published on nonpathogenic salmonella is among the first to report that normal microflora of the gut is able to exploit the molecular pathways of intestinal epithelial cells and prevent a host of inflammatory responses. This is a dramatic step forward in our understanding of our complex relationship to our gut flora. It gets down to the molecular level, looking at the role of molecular regulatory factors, these gene transcription factors, on the cellular process that can result in premature cell

death or cell senescence through the apoptotic process. This process occurs in the gut mucosa, and it also occurs in other mucosal cells or other places where chronic inflammation is going on. The same physiological process goes on there as well.

**Bacterial Pathogens and NFk B**

A number of bacterial pathogens have evolved strategies to commandeer NFk B activation and accelerate this oxidative stress apoptotic damage. For example, YOP protein of the bacillus *Yersinia enterocolitica* directly interferes with the activity of Ik B, thereby enhancing NFk B activity. It is the exact opposite of what I talked about with the nonpathogenic salmonella.

The physiological significance of these commensal bacteria on NFk B activation is related to what Metchnikoff talked about 100 years ago. Two reports, one by Rembacken in the *Lancet,* the other by Gionchetti et al. in the *Journal of Gastroenterology & Hepatology*, have recently appeared. Both suggest that oral administration of nonpathogenic bacteria (i.e., probiotics) may be effective in the treatment of patients with inflammatory bowel disease. These bacterial species may be able to abrogate NFk B activation, quell the TNFa response and the host inflammatory medication. That mechanism seems to explain how certain probiotics work in this capacity. We have entered an extraordinary new chapter in understanding how to manipulate the gut flora therapeutically and send the right message to the rest of the body related to the balance between inflammation and anti-inflammation.

**Inflammatory Bowel Disease--Ulcerative Colitis and Crohn's Disease**

This same concept relates to inflammatory bowel disease, a collective term embracing both ulcerative colitis and Crohn's disease. These significant health problems affect between 0.1 and 0.2 percent of the population in developed countries. These disabling conditions are characterized by diarrhea, pain, bleeding, and other intestinal symptoms, and by lifelong relapses. Ulcerative colitis is confined to the mucosal layer of the large bowel, whereas Crohn's disease can affect any portion of the intestinal tract. The pathogenesis of inflammatory bowel disease is complex, but it appears to involve interaction among three essential components: host genotype (functional genomics), intestinal bacteria and the environment of the intestinal tract, and the gut mucosal immune response.

How amplified or balanced is that response? Once we understand these things, we can deal with the problem. We can't change the patient’s genes, but we can deal with the other two factors—the host GI environment, bacteria, and the mucosal immune response, i.e., NFk B-mediated TNFa -related functional oxidative stress reactions.

**Colitis Research**

Steidler and colleagues recently addressed both of these concerns in reporting on a therapeutic approach for local delivery in an animal model to reduce colitis. The results of this study were discussed in *Science*. The investigators showed that dietary administration of a recombinant strain of *Lactococcus lactis*, which was able to produce and secrete high levels of interleukin-10 (an antiinflammatory cytokine), was able therapeutically to balance inflammation and antiinflammation in the gut and treat colitis in these models. By giving the mice an oral supplement with this strain, they were able to balance the inflammatory and antiinflammatory messages.

The immune response in the intestinal mucosa is conditioned by the indigenous bacterial microflora, which affects the regulatory network within the GALT. In susceptible individuals, inflammatory bowel disease arises when the immune system misperceives danger within the normal gut microflora and interprets the harmless enteric bacteria as pathogenic invaders. This leads to a breakdown in normal regulatory constraints and mucosal immune function, enhances NFk B and TNFa function, and activates oxidative stress inflammatory damage.

Crohn's disease is associated with the predominance of type I helper T cell activity, associated with the elaboration of cytokines such as TNF, interferon gamma, and IL-1. As contrasted with the thymus-dependent 2 response (TH-2) of cytokines, which are generally considered to be more antiinflammatory, like IL-10, the specific interleukin I just described, it helps to balance the inflammatory message.

**Therapeutic Manipulation of Gut Flora**

The concept of therapeutically manipulating enteric microflora by feeding nonpathogenic bacteria has been a fundamental tenet with in functional gastroenterology and functional medicine. Manipulation of the microbial flora includes the use of nonpathogenic bacteria (probiotics) and the companion prebiotics that selectively feed the beneficial bacteria. Prebiotics include oligosaccharides of a specific chain length and molecular weight distribution. They selectively feed the friendly rather than the unfriendly bacteria. Probiotics are live microorganisms that confer this health benefit by altering the indigenous microflora and may shift the balance of Ik B and NFk B toward the inactive complex of Ik B and NFk B, downregulating the message of inflammation in the cell. Lactobacilli, bifidobacteria, and other members of the resident microflora, with no apparent capacity to induce mucosal inflammation, are commonly selected as desirable probiotics. Specific strains may have improved effects. Probiotic therapy given certain bacteria enhances the anti-inflammatory gene expression of cytokines such as IL-10. Probiotics might alter the gut microflora by competitive interactions with indigenous bacteria, production of antimicrobial metabolites, or modulation of the local immune response in a favorable way. I believe this lowers the inflammatory action and produces a much more favorable reaction in individuals who are genetically susceptible or prone to these types of inflammatory shifts.

**Nitric Oxide and GI Inflammation—Lactoferrin and COX-2**

As the inflammatory pathways upregulate in the gut, more nitric oxide is produced. The nitric oxide combines with superoxide to produce peroxynitrite. Peroxynitrite, a reactive chemical produced in inflamed tissue, influences gut permeability and increases absorption of macromolecules. It creates a situation much like a dog chasing its tail; it establishes a positive feedback trap and perpetuates the problem by increasing the inflammatory response. A recent article in the *American Journal of Medicine* discusses nitric oxide and intestinal inflammation, and explains how cyclooxygenases, lipoxygenases, leukotrienes, and peroxynitrite are interrelated in this cascade of events triggered by the relationship of the messaging system to immune function.

That may explain why the oral administration of lactoferrin can help in some of these GI inflammatory conditions. It is a very powerful antiinflammatory substance. I am citing an article appearing in *Arthritis and Rheumatism*.

Side II

N-acetylcysteine, coenzyme Q10, vitamin E, and carotenoids and flavonoids may also play roles as gut inflammatory substances. Selective antiinflammatories, such as NSAIDs have been associated with lowered incidence of colitis, Crohn's disease, and colon cancer. The selective COX-2 inhibitors will be shown to reduce colon cancer based on the model I am describing. A recent report in *JAMA* discusses GI effects of the selective COX-2 inhibitors. They appear to have lower production of the proinflammatory prostaglandins and therefore lower gut inflammation. In addition, they have potential for lowering TNFa production and NFk B liberation in the colon associated with lowered incidence of damage and mutagenesis.

Natural Anti-inflammatories

A number of natural and selective food-borne substances may act as anti-inflammatories. They include curcuminoids and other flavonoids and terpenoids found in foods, which downregulate the inflammatory message in the gut over and above changing the gut flora. This may explain the efficacy of Ayurvedic Indian spices which are nitric oxide synthase inhibitors. Curcuminoids, turmeric, and ginger constituents may have anti-colon cancer effects because of their downregulation of inflammatory messages at the colon epithelium. That also relates to lipoxygenase inhibitors like omega 3 fatty acids, which help downregulate production of these proinflammatory leukotrienes. A paper in the *Journal of the National Cancer Institute* recently discussed inhibitors of lipoxygenase that can help prevent colorectal cancer and may work by the same mechanism by which NSAIDS work.

Sulfasalazine works as a drug to treat colitis because it has also been found to be an anti-inflammatory that downregulates TNF expression in macrophages. It may have the same mechanism of action. This is from a paper in *Arthritis and Rheumatism.* A new science is being born out of functional genomics and its relationship with the immune system. It relates to anti-senescence, using the gut as one of our cell trafficking or signaling systems.

**Dietary Fiber and Colon Cancer**

I want to thank Dr. Nichols again for the overview and synthesis he has given us so we can understand this web of genomics in a clinical way. It is another indication we are witnessing a revolution in medical thought comparable to what occurred at the beginning of the last century, when the vector disease model of health and disease emerged from the Pasteurian constructs.

The molecular medicine/functional genomics model helps us understand things that were formerly confusing. One difficulty individuals have in implementing some concepts clinically is apparently contradicting information supporting their use. One month we hear something is good in the diet; the next month another esteemed investigator says it's bad. We go back and forth. Is high-protein better than low-protein? Is a high complex carbohydrate diet better than low? Is it better to have high or low intake of vitamin C? Does vitamin C cause mutagenesis or carcinogenesis, or does it not? The list of these controversies goes on and on.

One controversy that exemplifies why our understanding at the human genomic level will help to tell us where the answer might lie around specific genotypes is associated with dietary fiber. Is it good, and does

it lower the risk of colon cancer? Or is it bad? Does it increase the risk of colon cancer? Does it lower, increase, or have no effect on the risk of heart disease?

**Conflicting Information and the Genomic Solution**

You may remember the oat bran craze. Everything had oat bran in it, even candy bars. It was touted as the protector against everything. Then two negative papers appeared in the *New England Journal of Medicine* and *JAMA*, which I reviewed in *FMU* several years ago. They said oat bran doesn't actually reduce heart disease; it has either no effect or perhaps even an adverse effect on GI function. Sales of oak bran plummeted.

Why do we have those great shifts in knowledge or understanding? Aren't there some facts we can glean? The answer to those questions, and fiber is one example, comes from our better understanding of molecular and functional genomics and the influence of individual constituents in our diet on individual genotypes or classes of genotypes. Let's look at the dietary fiber and colon cancer story.

**Definitive Fiber Studies**

Colon cancer is the second leading cause of cancer death in the U.S. Its development is highly responsive to modification of dietary principles or constituents. The number of papers on fiber and colon cancer published around animal models or around human epidemiological studies seemed to grow exponentially during the last decade. With the important exception of the most recent of data from the Nurses' Study, which found no relationship between dietary fiber intake and colon tumor incidence, most of the epidemiological studies have shown a protective effect of dietary fiber against colon cancer.

Randomized controlled trials (RCTs) of a prospective nature that are now ongoing are the definitive studies of how fiber will or will not affect colon cancer. A few, which have reported either a decrease in colon cell proliferation or a decrease in polyp recurrence as endpoints, have shown at best only modest protective effects with fiber supplementation.

**An Answer from Functional Genomics**

In sharp contrast, virtually every study in experimental carcinogenesis in animals, particularly rodents, has reported lower numbers of tumors with supplementation of specific fibers; in particular, oat bran as compared with fiber-free diets. So why is there such a lack of agreement across these different studies? Functional genomics and an understanding of functional physiology can play an important role in answering that question.

First of all, fiber is not a homogeneous, inert substance. It is a class of various interacting substances of non-digestive carbohydrate that have different effects, both physicochemically and biologically, on the way our bodies function. For some reason, we have not fully appreciated that the word "fiber" refers to this class of compounds, each with its own particular property. Fermentability, according to most of the recent information, as dietary fiber’s most important property, as it relates to the prevention of colon cancer and cell signaling to the colonocyte. Fermentability is more closely associated with soluble fiber than insoluble fiber, yet many human trials are done with insoluble fiber-rich fibers.

## The Importance of Fermentability

By definition, fiber is not digested and absorbed in the upper GI tract. It passes relatively unchanged into the colon as an intact, non-digestible carbohydrate. There, the colonic micro flora can ferment this fiber because they have the digestive enzymes to chew up the carbohydrate linkages that are non-hydrolyzable by humans. The net result is the production of carbon dioxide, methane, hydrogen, and short-chain fatty acids such as acetate, butyrate, and propionate. This is an important role and property of dietary fiber interacting with gut flora. The amount of these metabolites and their fermentability can be from almost 0 for certain types of cellulose to nearly 100 percent for fibers such as pectin and guar, which are highly soluble. You can get a wide variety of different fermentability. The resistant starches, which are less able to be digested and broken down in the upper bowel, are those that increase the amount of these fermentable byproducts of certain bacteria, which are the butyrate and propionate byproducts.

Two main points apply to the protective abilities of fiber. Fiber fermentation results in a lower colonic pH, which is seen to be protective. Fiber fermentation at the right time can result in the production of short-chain fatty acids like butyrate, which we know is the primary energy source of the colonocyte. It also has an effect upon genetic expression through butyrate’s role in histone metabolism and the regulation of gene expression within chromatin. Fermentable fibers lower colonic pH, which protects against colon cancer. That has been discussed since 1981 when it was hypothesized that dietary fiber was protective by amplifying/acidifying colonic contents.

## Butyrate

Butyrate appears to be the second most important part of the emerging story. It plays a role as a gene response element in the colonocyte and serves as an "anticarcinogen," allowing colonic microflora and the gut mucosa to interact in an appropriate way, so damaged colonocytes can be moved toward death by apoptosis. You don't want a damaged mutational injury of a colon cell to sit there and not be excised from the population. In this example the occurrence of apoptosis at the right time is desirable for the host. You want to the body to recognize the damaged cell and get rid of it. That apoptotic, pruning process is augmented by the fermentation of dietary fiber into butyrate.

Fermentable fibers are protective against colon cancer, but this effect may depend heavily on the amount and type of dietary fat. This is the other variable, again demonstrating, as Dr. Nichols pointed out earlier, it is a web of interacting variables, not a single thing.

## Fiber and Fat Interaction

Fiber and fat interact. Fish oil, for instance, in animal experiments, is more protective than corn oil against colon tumor development, and the relationship of oils to fiber is an important synergizing or amplifying factor in the way these two work together to prevent colon cancer.

It is a major surprise to learn that the most protective diet in studies on fiber is one that combines fish oils and soluble fiber pectin. Here is a breakthrough as we understand the molecular biology of the colonocyte, its gene expression elements, and the influence of butyrate, and the genetic polymorphisms that relate to expression of different oncogenes in the colon that may be linked back to colon cancer risk. Dietary fish oils and soluble fiber work together to provide much more benefit and protection than just

fiber generically and fat.

**Apoptosis**

We are moving to an understanding of the programmed cell death method of pruning damaged cells, the apoptotic method. The possibility of the interaction of the two relates to apoptosis enhancement through the selective COX-2 inhibition effect, just like the COX-inhibitor drugs we talked about earlier. Fish oils and fibers seem to have that same influence on colonocyte function, thereby allowing for proper pruning, apoptotic cell death, of damaged colonic cells. We are getting NSAID-like effect.

Humans who take nonsteroidal inflammatory drugs on a regular basis have statistically a 40 to 50 percent lower relative risk to colorectal cancer. We also know that individuals who either supplement their diets with fish oil or regularly consume omega 3 oils in their diet by eating fish, along with soluble fiber, statistically have lower incidence of colon cancer. The mechanism by which this operates is now being discovered as it relates to gene expression in the colon. Fish oil and soluble fiber downregulate COX-2 expression, which may upregulate butyrate-induced apoptosis and reduce carcinogen-related cancers in the colon.

A paper titled "Are Dietary Fiber-Induced Alterations in Colonic Epithelial Cell Proliferation Predictive of Fiber's Effect on Colon Cancer?" by Laurence Whiteley and David Klurfeld appeared in *Nutrition and Cancer*. The authors conclude there is yet a lot to know about how fiber influences colon cancer risk. I would say that's true. As we start to put these dietary variables of fat and fiber together, however—the right type of fat, omega 3 oils, and the right type of fiber, soluble fiber—we recognize their benefit. In genetically susceptible individuals, this combination may help reduce colonocyte mutational injury, increase the pruning of cells that are mutationally injured by apoptotic cell death, and lower colon cancer risk and incidence.

**Eighth International Symposium on Functional Medicine**

A remarkable new model is emerging in medicine. We will consider this medicine in our Eighth International Symposium on Functional Medicine in May 2001. I invite all of you to be participants in this extraordinary conclave in Vancouver, Brtitish Columbia, Canada. It will focus on neuroendocrinology, which also relates to functional endocrinology, because of the gut/brain, brain/gut connection. We will consider neuroendocrinology from a functional medicine perspective at the 5-Star Westin Bayshore Marina resort in Vancouver, British Columbia, right next to Stanley Park. We urge you to put May 22-26 on your calendar now. Come, bring your family, and spend a tremendous week with us in Vancouver, Canada talking about functional neuroendocrinology.

Next month, we will extend this concept of functional genomics into applied clinical areas. I think you will see, as we poise for the endocrine discussion, that there is much yet to learn and apply to improve patient outcome through this model. Thanks for being with us for this first issue of *FMU* in 2001.

**Interview Transcript**

**Clinician of the Month: Trent Nichols, MD**

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**JB:** Our Clinician of the Month for the first issue of *Functional Medicine Update* in 2001 is a fundamental contributor to the evolution of functional medicine. Dr. Trent Nichols, a gastroenterologist in Hanover, Pennsylvania, has been a colleague and friend for a number of years. He has been a principal member of the Steering Board for the Institute for Functional Medicine and contributed to the development of our protocol for treating irritable bowel syndrome. Dr. Nichols is a board-certified gastroenterologist whose rich history in medicine goes back to the 1960s. He completed his medical degree at Northwestern University Medical School. He is currently involved as a staff physician in many clinical teaching situations, and has been assistant clinical professor of internal medicine from 1979 to the present at Pennsylvania State University College of Medicine. He is a member of many professional societies, including the American Digestive Disease Society, American Foundation for Ileitis and Colitis, American Gastroenterological Association, and the American Liver Foundation.

**Optimal Digestion—New Strategies for Achieving Digestive Health**

Trent, it's wonderful to have you on *FMU* this month. You are a principal author of *Optimal Digestion--New Strategies for Achieving Digestive Health*, a book I think should be in everyone's library. It contains chapters by many of your colleagues. What impact do you believe this book is having in the field of gastroenterology?

**TN:** Thank you again for inviting me to be your guest, Jeff. We decided to put this book together about three years ago and were writing it up until the very last moment before it was published in October. One of the reasons we wanted to do it was so that patients would have a good source to read so they could understand their digestive problems on a functional medicine basis. This is somewhat like a functional medicine primer in which we take all the various concepts, such as leaky gut, intestinal permeability problems, liver detoxification, oxidative stress, and the individuality factor of each person having different dietary needs.

Incidentally, you have a wonderful chapter in the book on oxidative stress and free radicals. We have chapters on integrative medicine, how to use nutrition, how to use supplements, and how to use herbals. We have a chapter written by a homeopathic physician, an Ayurvedic physician, and information on some energy medicine, which I've written about. We have chapters on movement therapy, using things like Tai Chi, Qigong, or yoga to increase flexibility and digestive health. There is information on biofeedback and guided imagery. We tried to include everything we could get into the book, and each chapter stands alone on its own merit. We put the book together with 19 different contributors, and I think we did a good job. We have patients calling up from all over the U.S. telling us this is the best thing they've ever read about their problems and how helpful it's been. Readers want to know how they can find a functional medicine physician in their area to counsel them and help them achieve a state of optimal health. I think it's helping to get the job done in that sense.

## Functional Gastroenterology

**JB:** The authors you've selected are people who have been members of our community for the last 10 years or more. They include Scott Anderson, Michael Rosenbaum, Len Saputo, Jeffry Anderson, Elson Haas, Richard Kunin, Michael Lerner, Jon Kabat-Zinn, Marty Rosman, Sid Baker, and Aristo Vojdani. I think you've done a tremendous job. Most of those authors have also been *FMU* Clinicians of the Month. We will provide information on how to order this book on the summary cards at the end of this interview.

I would like to like to move to the concept of functional gastroenterology. It has been suggested that functional gastroenterology represents about 50 percent of patients' visits to gastroenterologists. They don't fit into discrete diagnostic disease codes because they're functional gastrointestinal problems. It appears that most GI specialists don't have much in their bag of tricks to treat these particular problems. Would you tell us about your experience with functional gastroenterology—things like IBS and nonspecific GI dysfunctions?

**TN:** I think you're right about the fact that we don't have very good tools in pharmaceuticals to treat conditions like irritable bowel syndrome, delayed food allergy, or even candidiasis. Most clinical gastroenterologists have no concept that what you are taking in orally has anything to do with your GI symptoms. It's somehow lost on them. They don't understand nutrition; they don't understand that you have another flora in your body that is just as important as the human cells you bring into your being—the gut flora, the gut ecology. Even though it's starting to get out there, they really don't have good tools for diagnosing it, modifying it, and helping the patient get better.

As a result, we see a lot of patients who have failed conventional medical therapy. They've been on anti-spasmodics, proton pump inhibitors, mesalamine for their ulcerative colitis or Crohn's disease, or steroids. They come to us seeking help. They tell us they have been sick for 10 or 25 years, or for six months. They have seen 12 gastroenterologists, 3 internists, and 5 family practitioners. They've done yoga and acupuncture, and they're still not any better. We do a comprehensive stool analysis or a leaky gut test, and we get liver detoxification information. We do some other things and get them on nutrients and probiotics. Not only do they get better, but they also stay in remission. We are so good at doing this that we are having to find other things to treat. Every spring and fall, we used to have a large group of inflammatory bowel disease patients who would relapse. For the last four years, we've had fewer and fewer. They stay in remission. Of course, they're pleased. They don't have to take prednisone; they don't have to be hospitalized; and they don't have to have TPN. It's very gratifying. It's really based on the work you pioneered, Jeff. I thank you again for that. You have opened a new door for us, a new modality of treatment.

## Alosterone and the Pharmaceutical Approach to IBS Treatment

**JB:** The drug of the year 2000 for digestive disorders is the new drug Alosterone, an IBS serotonin-modifying drug. What has been your experience with Alosterone? How does it compare to functional medicine approaches for the treatment of diarrheal forms of IBS?

**TN:** I was a primary investigator for Alosterone. We had this drug about three or four years ago. It takes three to four years before it gets on the market. We did a double-blind, placebo-controlled trial, limited to women with diarrhea-predominant IBS. We chose these women because earlier studies had found that

neither men nor women with constipation respond to it. In fact, that's the problem; it actually can constipate the patient because it's a 5HT receptor.

We deal primarily with two receptors—the 5HT3 and the 5HT4. As a result, constipation is the side effect. It often works very well with someone with diarrhea-predominant IBS, but many times constipation will be the outcome. Of course, the woman isn't very happy about that. Now Alosterone is out on the market, but I wouldn't say we had many patients on it. We haven't needed to use it with patients since we've applied the functional medicine approach. It does help, but it has side effects. It's expensive, and we still haven't had 5 to 10 years' experience with it.

**Prucalopride**

We have had another medication called Prucalopride. I probably have the largest group in the U.S. that has been put on that drug. That is another medication for constipation, a 5HT4. We've had to stop the trial for now because of an animal model that developed mammary carcinomas. That even happened with a proton pump inhibitor many years ago that caused carcinoid in mice or rats. It was never found in humans, but we had to stop the trial.

It's a very effective drug for patients with severe constipation. Some of these patients would have a bowel movement once every two weeks. That's the problem with all these pro-motility drugs. There are sometimes very adverse side effects. They're usually going to be used in patients who have severe derangement of their motility, and I hope they don't fall into what happened with another medication called Propulsid, a pro-motility drug. It started being used but was taken off the market. It was a drug that helped empty the stomach. We used it for nausea and for people with delayed gastric emptying, gastroparesis. They started using it in elderly patients. These patients, who were in their 80s and 90s, had low magnesium and cardiac arrythmias. They also used it in infants under six months old who had gastroesophageal reflux disease (GERD). After some testing, it was pulled off the market. Now, its use is quite restricted and it's only available to gastroenterolgists as a research drug, which they use as a compassionate clearance.

**The Functional Medicine Approach**

**JB:** The nature of pharmaceuticals by their very action is to take charge of certain physiological processes. By taking charge, they have a more dramatic effect on physiological function than nutrition or lifestyle intervention, which may be milder but also can promote more balance in physiological function. That's what I think is the risk/benefit tradeoff one often has.

Using the lower technology as the first step seems cautious and reasonable. We use what we call the "4R Program"—remove, replace, reinoculate, and repair. You undoubtedly have your own approach for functional gastroenterology. How does this program work in your practice?

**TN:** We use that program with almost every patient suffering with fibromyalgia, chronic fatigue, delayed food allergy, headaches, migraine, or musculoskeletal pain. We've found that a lot of our arthritis patients benefit tremendously by doing the 4Rs. They have much less arthralgia/arthritis. Their joint pain is reduced. We start out doing a patient-centered history, which Leo Galland has taught us how to do. We look for precipitating triggers or factors. We try to take the patients back to when they were initially

feeling well and find out what happened to them after that.

**Assessment and Diet**

One of the first tests we do is for intestinal permeability, as well as a Comprehensive Digestive Stool Analysis (CDSA) to find out what gut flora problems they have. There's a lot of yeast out there of various types, Candida and others besides albicans. We try to find an antifungal, neutraceutical, or herbal product that is sensitive to that and takes care of the problem.

Then we put them on a diet. Often, they're eating way too many refined carbohydrates and sugar. Many patients have delayed food allergy. Sid Baker and I worked on that problem in a paper about five years ago. Now the paper is being submitted for about the fifth time. We did a double-blind, placebo-controlled trial with a fairly small group of patients. Forty-eight started, and about six dropped out. We followed 18 patients for 6 weeks, and when we broke the code, the patients who were on the placebo diet didn't do as well. The ones who got the true IgG elimination diet experienced a significant improvement in their symptoms—everything from headache to arthralgia to bloating, gas, IB-like symptoms. I had a number of inflammatory bowel disease patients in the study, too. It's a wonderful paper, but it uses a nonconventional, non-skin test, the IgG and IgE RAST tests, so it has been ignored by conventional allergists, even though the RAST and MAST tests were designed by academic allergists.

**A Multifactorial Approach**

We try to do liver detoxification; that's very important. I have found you have to use every basic tenet we've learned. If you try to get by with just one or two, it may work for one patient, but the majority need the entire program. They need proper detoxification; they have to get rid of toxins. They have to have their gut flora restored. They have to get their gut permeability restored. We're currently working on some double-blind, placebo-controlled trials using a bioactive peptide from whitefish. It seems to be very efficacious. We're also going to be doing a study where we add that plus glutamine. Again, this has an omega 3 fatty acid in it.

We're trying to cover the gamut, but it's more than just one thing. For patients with inflammatory bowel disease, irritable bowel, or delayed food allergies many factors enter in. We are starting to become aware of heavy metals. Some of the patients, until you get the mercury out of the body with chelation and DMSA, will continue to have increased gut permeability, and increased food allergies. It becomes a vicious cycle.

**Functional Testing**

**JB:** You have summarized beautifully the functional medicine approach using the patient-centered assessment model of antecedents, triggers, mediators, signs, and symptoms, and differential diagnosis. This web of understanding of precipitating and antecedent factors that contribute to multiple symptoms is a different strategy. It looks for patterns rather than single definitions, as we are often forced to in diagnosis. There is a place for both, and they interact with one another. They're not completely isolated from one another, but I believe you have described the difference between the two models very well.

You mentioned two assessment tools, the gut permeability test, by which I assume you mean the

lactulose/mannitol challenge test, and the CDSA. Would you describe those tests?

**TN:** I'll start with the CDSA. The patient sends a stool sample to a lab, which does a test for parasites. In the test for gut flora, they culture out what is actually in the stool. They divide it into two types; they have what they call potentially pathogenic bacteria. Often these are things like Klebsiella or pseudomonas in the stool, and *E. coli*, considered a beneficial bacteria, and some others. The concentration of the bacteria is expressed as 4+, 3+, 2+ or 1+ to give an idea about the concentration.

They do bacterial sensitivity tests for antibiotics in which they take the pathogenic bacteria, put it into a Petrie dish, and put on various antibiotic test disks to see whether they're sensitive to that. They also do some nutraceutical testing where they can use things like garlic or *Uva ursi*. They also determine what the sensitivity level is for various fungi—Candida and its allies. I don't like saying that a lot of people have a 4+ overgrowth from antibiotics, NSAIDs, stress, prednisone, or female hormones. They select what sensitivity they have to the various herbals as well as antifungal medication. They do some fatty acid analysis—short-chain and long-chain fatty acids. They look at fiber and blood. There is a new test available now for inflammation, which gives a sort of index of whether the patient has oxidative stress in the bowel. They give you a lot of information. When you use it correctly, it's a wonderful tool.

**Intestinal Permeability Testing**

The other test is for intestinal permeability. The patient takes a cocktail of two non-metabolized sugars: lactulose, which is a disaccharide, and mannitol. After that the patient collects his or her urine for six hours. The whole idea is that these sugars are relatively non-absorbable when you have a normal intestinal mucosa that's very tightly packed. There are either bigger gap sizes, or inflammation that's causing the gaps to open up. Somebody with Crohn's disease or celiac sprue or even intestinal food allergy will have a more leaky gut. As a result, the lactulose/mannitol absorption will be increased. By looking at the ratio between the two, you can get some idea of what's going on. We would take a patient who has increased intestinal permeability and find out what food allergies he or she has, eliminate the dysbiosis, the yeast problem, or the bacterial overgrowth. We would also perhaps put the patient on more glutamine. We would add omega 3 fatty acids. We'd use some trophic factors sometimes, such as the bioactive whitefish peptides, and these patients get better. That's what counts. Those are the two mainstays of the lab testing that I do, as well as the IgG/IgE RAST food allergy test.

**Allergy and Gastroenterology**

**JB:** Some gastroenterologists might feel that allergy is not related to the field of gastroenterology. As we know, however, the gut is connected to other organs. An example is the gluten sensitivity connection to dementia. How does a gastroenterologist cross that invisible boundary that separates gastroenterology from immunology and allergy?

**TN:** I think it is an essential part of gastroenterology that has been ignored. I'm upset that clinical allergists have actually ignored the gut axis as it relates to immunology. As you know, the Peyers patches are there; you've got more immune-processing cells in your intestine than anyplace else in the body. As a result, allergists concentrate on inhalant and environmental allergies, even though they give some credence to food allergies. That's usually IgE, something they can see immediately that results in a an urticarial rash or anaphylaxis. They do skin testing primarily, patch testing, scratch testing, or prick

testing, and don't seem to understand that what we're really talking about is immune processing and inflammation that's going on in the intestinal tract.

This has been very difficult to do in the past. We've had various studies where they do endoscopic exams. They'll spray various food antigens into the small intestine or stomach and try to wait for a weal. This just isn't practical. As a result, it has never really caught on. My gastroenterologist colleagues have tried to do this.

**Elimination or Rotation Diets**

Often, in the past, the British have done elimination diets or rotation diets, where they'll take patients off things like wheat gluten, milk, and corn, and follow their IBS or IBD for six or eight weeks to see if they get better. You can use an enteral diet, which is refined to a certain extent. It will not contain wheat, gluten, milk protein, or even citrus, and put patients on that type of enteral diet. It is actually just as powerful as using steroids in these patients with IBD, especially Crohn's disease. That has been well known for 30 years.

The British are very good at doing this, but they haven't really gone on to the next step, which is that there are other things out there besides those three factors—citrus, milk, and wheat. Reactions can still be delayed anywhere from 3 to 72 hours. When you remove those items from patients' diets, they stay in remission. They often don't need prednisone or surgery. I think it's a very important principle.

**The Gut/Brain Axis**

The next thing I'd like to get into is the brain/gut axis. Every neurohormone we have in the brain is actually in the gut. We say that the gut is the second brain. This is why patients can have schizophrenia, depression, headaches, migraine, or even bipolar disorder to some extent, directly related to what they're eating. Carl Pfizer was a very famous proponent of this back in the 1970s at the Brain Bioinstitute in New Jersey. Sid Baker has also worked on this concept with autism. There is definitely a direct link between the brain/gut axis.

Dr. Gershon wrote a book titled "*The Second Brain."* It's a good book that everyone should read. I'm currently attending a meeting of at least 22,000 neuroscienctists here in New Orleans. They are becoming even more aware of the brain/gut axis than gastroenterologists, I would say.

**Nervous System Messaging in the Gut or the Brain**

**JB:** I know you're presenting a paper at that meeting. The fact that a gastroenterologist is presenting a paper at the Society for Neuroscience meeting doesn't fit into a linear, reductionistic model of medicine and science. What you are describing, however, is an intimate clinical connection between the gut and its processing of information from food and the environment, and the transmission of that information to the microglia of the brain. There obviously is a chemical and electromagnetic interrelationship between the gut and the brain. You have been interested in other ways of looking at the nervous system, through nervous system messaging in the gut or in the brain, using electromagnetics, or looking on the effects they have on these functions. Can you tell us how that work is going?

**TN:** We presented two papers here in New Orleans on magnetic molecular energizing in patients with three conditions: 17 with Parkinson's disease, 9 with Alzheimer's disease, and 1 with cerebral palsy (presented by Dr. Pierce, a neurologist). Magnetic Molecular Energizing (MME) is an IRB approved, experimental treatment consisting of two strong, non-pulsating direct current electromagnets (5000 gauss) with the patient lying in a focal point between the two magnets.

The patient is placed on an aluminum table that slides in and out. In central nervous system diseases, we're treating the brain. We focus this magnet between the two poles, from negative to positive at the area of the pituitary, and it goes through the hippocampus. The patient remains on the table for 3 to 5 hours, and then we increase it to as many hours as the patient can tolerate, usually between 8 and 12 consecutively, day after day.

**Magnetic Molecular Energizing (MME) Benefits**

We have found that we can improve symptoms in these patients with from 130 to 200 hours of MME. In Alzheimer's patients, I'll start out with 8, 9, or 10 hours and go up to about 12. It improves their mentation and cognition, and they're no longer confused. The patients with Parkinson's will have less rigidity and less tremor. I had a patient who was in a wheelchair. She couldn't walk, couldn't talk, and couldn't swallow. After about 130 hours, she could smile, had no rigidity, could walk with her walker (she hadn't been out of her wheelchair for about a year), and was able to swallow and feed herself. This has been very gratifying. I think it's a tremendous breakthrough.

What we're doing is three things. We're ridding the body of heavy metals; that's the first thing we found out. Most patients with CNS diseases have either pesticides or chemicals stored in their brain plaques or lesions, as well as heavy metals such as aluminum, mercury, lead, and iron.

**The Hall Effect**

Any atom becomes an atomic magnet between 5000 gauss. When you place a strong magnet, you have what we call the Hall effect, actually produced it right in the brain. Unpaired single electrons are usually much more susceptible to this Hall effect. They start going into what we call a precession, by the Lamar frequency precession. It starts to look like a figure 8. As a result, it is energetically causing that electron velocity to be around 1000 times its normal velocity in this strong magnetic field when there's no frequency.

As a result, unpaired covalent electrons can start causing chemical reactions because that's the basic principle of enzymatic reactions, and we're upregulating superoxide dismutase, catalase, and all the good protective mitochondrial enzymes. As Flint Beal pointed out years ago, in oxidative stress we have free radical damage to the brain or to the CNS or even to the peripheral nerves and on a molecular basis, that's the cause of the disease. In other words, they have various genetic problems. For instance, beta amyloid may have caused these problems, but what's happening on a molecular basis is that it's oxidative stress.

**Chemical Damage and Energy Medicine**

There was a paper presented here about Rotenone that made the news. Rotenone is an insecticide that's causing Parkinson's in some mouse models. Again, that is eliminated due to this energetic

electromagnetic field that's causing these heavy metals and toxins to actually be expressed and come out through the skin, breath, and urine of these patients. We're presenting this new, dynamic, novel approach as an alternative to medicine, surgery, and even nutrients. Of course, you have to have all the building blocks in place. This is a new molecular medicine that I think is going to be seen in the future. I'd stake my reputation on it.

I think the next new paradigm of the 21st century will be energy medicine. Healers have been doing it for a long time with electromagnetic fields they set up from their hands. That has now been measured and found to be magnetic. We're actually paramagnetic beings. We're atomic molecules. It's a whole new way of looking at medicine and how we can change function and the approach to disease.

**Conclusion**

**JB:** This has been a good way to start the new year, Dr. Nichols. Thank you so much for sharing all of this. For people interested in following up, we will list your phone, fax, and e-mail address on the summary cards and in the quarterly digital *FMU* so people can communicate with you. Once again, thank you for being with us. I hope many people will be reading your book, *Optimal Digestion*, because I think that's a good place for both doctors and patients to start.

**TN:** Thank you, again, Jeff.

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