March 2002 Issue | Michael D. Gershon, MD Columbia University

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Welcome to *Functional Medicine Update* for March 2002. This issue will be a preview of our Ninth International Symposium on Functional Medicine, to be held in Ft. Lauderdale, Florida, May 25-29, 2002. The Symposium will focus on Disorders of the Brain: Emerging Therapies and Complex Neurological and Psychiatric Conditions. We will approach that topic this month in *FMU* by focusing on the part of the program that looks at the enteric nervous system, the gut/brain connection. It should be a good review of basic principles of the gut/brain connection, in preparation for the more exhaustive information and the workshops in this area at the symposium. I hope you have made plans to attend the symposium. The curriculum and faculty are superb. It is going to be another great meeting. We will look forward to seeing you in Ft. Lauderdale in May.

I begin this discussion of the complex area of the enteric nervous system with a question. What are we trying to accomplish in functional medicine in this area that differs from pathophysiology-focused medicine built around differential diagnosis and compartmentalization of disease? An answer to this question appeared in a recent paper by Paul Plsek and Trisha Greenhalgh in the *British Medical Journal*.[1] The introduction to this article, which is titled “The Challenge of Complexity in Health Care,” describes the transition in health care in the year 2002, and in this third millennium.

“Across all disciplines, at all levels, and throughout the world, health care is becoming more complex. Just 30 years ago the typical general practitioner in the United Kingdom practiced from privately owned premises with a minimum of support staff, subscribed to a single journal, phoned up a specialist whenever he or she needed advice, and did around an hour’s paperwork per week. The specialist worked in a hospital, focused explicitly on a particular system of the body, was undisputed leader of his or her ‘firm’ and generally left administration to the administrators. These individuals often worked long hours, but most of their problems could be described in biomedical terms and tackled using the knowledge and skills they had acquired at medical school.

ATeam Approach

“You used to go to the doctor when you felt ill, to find out what was wrong with you and get some medicine that would make you better. These days you are as likely to be there because the doctor (or the nurse, the care coordinator, or even the computer) has sent for you. Your treatment will now be dictated by the evidence—but this may well be imprecise, equivocal, or conflicting. Your declared values and preferences may be used, formally or informally, in a shared management decision about your illness. The solution to your problem is unlikely to come in a bottle and may well involve a multidisciplinary team.

“Not so long ago public health was the science of controlling infectious diseases by identifying the “cause” (an alien organism) and taking steps to remove or contain it. Today’s epidemics have fuzzier boundaries (one is even known as “syndrome X”): they are the result of the interplay of genetic predisposition, environmental context, and lifestyle choices.”

Post-Genomic Medicine

This is the new, post-genomic medicine.

“The experience of escalating complexity on a practical and personal level can lead to frustration and disillusionment. This may be because there is genuine cause for alarm, but it may simply be that traditional ways of 'getting our heads round the problem' are no longer appropriate. Newton’s 'clockwork universe,' in which big problems can be broken down into smaller ones, analyzed, and solved by rational deduction, has strongly influenced both the practice of medicine and the leadership of organizations. For example, images such as the heart as a pump frame medical thinking, and conventional management thinking assumes that work and organizations can be thoroughly planned, broken down into units, and optimized.

“But the machine metaphor lets us down badly when no part of the equation is constant, independent, or predictable.”

Systems as Holographs

Rather, we find that systems work as holographs. The new medicine of complex, adaptive systems may provide new metaphors that can help us to deal with these issues better. It is this, then, that leads the science of complex adaptive systems—clinical practice, organization, information management, research, education, and professional development are interdependent and built around multiple self-adjusting and interacting systems, not stand-alone and compartmentalized.

“In complex systems, unpredictability and paradox are ever present, and some things will remain unknowable. New conceptual frameworks that incorporate a dynamic, emergent, creative, and intuitive view of the world must replace traditional “reduce and resolve” approaches to clinical care and service organization

This article provides an eloquent review of what we have been trying to accomplish in the developing epistemology of functional medicine, looking at complexity. Even in unknowingness come patterns of understanding you cannot get by reductionist approaches that look at individual pieces apart from the whole.

This theme frames the discussion in this month’s *FMU.* We will look specifically at the interaction of the gut, the brain, and the immune system. A complex interplay of forces, factors, mediators, and modulators in these systems create the rhythmic outcome we call function or dysfunction, disease or health. That is a new model of medicine.

New Thought Patterns

The challenge of complexity in health care requires us to develop different patterns of thinking from what we might have learned. Formerly, we memorized facts to be recited on a test. If we did a good job at giving recitation, we were rewarded with a passing grade and a move forward, as if that was the way the world would work when we went out as practitioners.

Now, we recognize there are “fuzzy” rather than “rigid” boundaries, that the actions of agents are based on internalized rules relating to how they function, one to the other, in patterns or systems. These systems are adaptive. They vary due to environmental conditions imposed by time and space reflecting changes in gene expression and ultimately the warp and weft of life, or the tides of circadian rhythms.

A Systems Approach

Systems are embedded within other systems and therefore co-evolve. In this complexity we begin to understand the reality of the system, rather than in a contrived, constrained reality. When I learned chemistry, it was equilibrium chemistry. We assumed that when we got out into the real world, we must see equilibrium as the principle in chemistry.

In reality, unless you are involved with a very structured chemical system, i.e. closed, that may exist in a test tube , most of the chemistry in real life, whether biochemistry or clinical chemistry, is that of non-equilibrium dynamics. Interaction leads to continually emerging novel behaviors. The system is inherently non-linear. Instead, we are looking at complex geometric patterns of interaction.

Cytochrome P450

This leads to some of the aspects of unpredictability. We have seen this in the example of cytochrome P450 with regard to the way drugs are metabolized. One size does not fit all in the complex interplay of genetic predisposition.
These variables affect the way drugs, environmental chemicals, and endogenous molecules cycle through our bodies and are ultimately detoxified and eliminated in individuals.

In this complexity and the tendency of these chaotic systems for self-regulation, we start to see some answers coming out of the new healthcare paradigm. It is an exciting but daunting challenge for the 21st century.

Complexity is revealed even in answering simple questions, such as choosing the best nutritional supplement program for an individual. What levels, what range of nutrients is justified? What is evidence-based? What is built around belief systems that are not factual in nature? What adverse side effects might occur? What degree of polymorphism and differentiation do we see from individual to individual? What is the range, according to Roger Williams, of biochemical individuality? What is the orthomolecular nature of our environment that creates our health and disease patterns, a question raised by Linus Pauling?

The simple question of whether or not to take a vitamin supplement becomes, in this new model of complexity, a lot more daunting. By raising these questions, however, may come remarkable new answers to achieve people's expectations of long life and good health by matching their environment with their

genes to produce positive outcome.

Vitamin Supplementation

“What Vitamins Should I be Taking?” is the subject of a recent editorial in the *New England Journal of Medicine*, by Dr. Walter Willett and Dr. Meir Stampfer from the Departments of Nutrition and Epidemiology at Harvard School of Public Health, Channing Laboratory, Department of Medicine at Harvard Medical School.[2] Drs. Willett and Stampfer are considered two of the premier epidemiologists who look at nutrition and health-related issues. They have an extensive publication record and a tremendous ability to help us understand how these patterns of complexity might produce principles that result in value-added therapy.

In this article, Willett and Stampfer wrote," A healthy 54-year-old, nonsmoking, omnivorous woman presenting for a routine examination asks about vitamin supplements. She expresses confusion about conflicting reports and recommendations. She currently uses no supplements."

Does this sound like a pattern you have heard about before? The patient is not sure what to do. She knows supplementation sounds good, but it is so confusing with conflicting information that she concludes the best approach is to do nothing. Let's talk about that for a moment, from the perspective of Drs. Willett and Stampfer.

Choosing Nutritional Supplements

Ideally, we would like all nutritional supplement programs to be randomized and evaluated in prevention trials, with measurable clinical endpoints. We would like to individualize to specific biochemical or clinical markers in the patient. We would like answers to a myriad of questions. Unfortunately, we have to make a number of decisions in life based upon best guesses.

This is true to some extent with regard to vitamin supplements. Today, we can make better-informed decisions about the question of what vitamins to take than we could have 10 years ago. Considerable new research has come about, both clinical and experimental, and as a consequence of that research, we are much better able to answer that particular question from a perspective of pattern recognition complexity theory. Let's look at some of things we have learned.

We have learned from epidemiological studies that low levels of folic acid intake during the periconceptual period are associated with increased risk for various types of birth defects, including neural tube defect, the most common birth defect in Western cultures. An association with folic acid intake and inadequacy appears in relation to risk of heart disease, stroke, certain forms of cancer, diabetes, and arthritis, as well as bone mineral metabolism conditions.

This risk is associated with genetic uniquenesses of folate management, such as polymorphisms of the methylenetetrahydrofolate reductase enzyme (MTHFR). Roughly thirty percent or more of Caucasians have at least one copy of the T677 allele, and these individuals appear to be more at risk for problems associated with folate deficiency that their homozygous wild-type (C677) counterparts.

Variations in Folate Digestion

Research has found specific genetic polymorphisms in the gut enzyme system, that hydrolyzes the polyglutamate component of food folate and provides folic acid for absorption across the GI lumen. Some people are poor digesters and absorbers of folate, further amplifying concerns about folic acid, even at amounts that would be adequate in the diet of most individuals.

Folic acid, therefore, would certainly be on the list of supplements to take. This is a case where a supplemental form of folic acid appears to be preferable to a food form in increasing plasma folate and improving physiological function. Many people believe food is always preferable to supplements, but this is a case in which the evidence suggests supplemental folic acid or other forms of folic acid, such as 5-formyltetrahydrofolate or 5-methyltetrahydrofolate, are preferable to food polyglutamyl folates for absorption.

Higher intake of folic acid is associated with lower risk of colon and breast cancer, particularly in individuals who possess specific polymorphisms like the C677T polymorphism in methylenetetrahydrofolate reductase. Therefore, we might say optimal intake of folic acid for the individual is important, but we are not sure what that specific level is. A daily intake of 400 mg minimizes blood homocysteine levels in most people, but more may be needed to reduce the risk of cancer. Some individuals with genetic polymorphisms associated with homocysteine accumulation may require several times that level to manage the metabolic pathways controlled by folate.

Other Nutrients in the Folate Cycle

Folate does not work in the absence of other nutrients. It is part of the folate cycle. Completion of the folate cycle also requires nutrients like vitamin B6 (pyridoxine+), vitamin B12 (cobalamin), and even other methyl donors like betaine (trimethylglycine). All are important parts of the family of nutrients necessary for delivering the one-carbon units necessary for normal cell physiology.

Vitamin B6 intake below the U.S. Recommended Dietary Allowance of 2 mg, is associated with increased risk of coronary disease. Meats and legumes are the major food sources of B6, and people who reduce their consumption of red meat without increasing their consumption of legumes, may have low vitamin B6 intake.

Similarly, low blood levels of vitamin B12, caused primarily by reduced absorption in elderly people with low gastric acid output, are associated with higher blood homocysteine levels. Individuals taking certain types of acid-suppressing drugs are known to have lowered serum B12 levels. Twelve percent of elderly people may have inadequate vitamin B12 stores. Marginal B12 status may have neurological implications and produce depression and cognitive dysfunction in these older individuals, so B12 supplementation may be desirable. Crystalline B12, the form used in supplements, does not require gastric acid for absorption, so a multivitamin can ensure that intake is adequate for most people and is preferable to the food form, in those cases

We used to think vitamin D was a bone-related nutrient. Now we recognize it is a prohormone, modified by hydroxylation in the kidney and liver to produce 1,25-dihydroxycholecalciferol. This nutrient, in turn,

is an immune-modulating hormone with effects on gene expression through the cholecalciferol receptors capable of forming dimers with retinoic acid receptors. The resulting heterodimer can regulate gene expression and have great influence on cellular development. Therefore, the importance of vitamin D extends beyond bone to the support of immune function.

Elderly individuals, who may receive inadequate exposure to sunlight and whose skin may have lost some of its ability to synthesize vitamin D from its precursor, frequently have vitamin D deficiency. Therefore, sun exposure alone may not provide adequate vitamin D in certain individuals, particularly during the winter months.

A report from a Boston hospital found 57 percent of individuals age 60 or older were clinically deficient in vitamin D.[3] This deficiency resulted in subclinical effects associated with vitamin D insufficiency. Vitamin D from diet or from skin synthesis does not guarantee proper vitamin D physiology. The effects of vitamin D must be fully realized through hydroxylation at the kidney and liver with specific enzyme systems whose effectiveness may be impaired by adverse kidney or liver physiology. Thus vitamin D is another important nutrient to consider in a supplement

Vitamin A is a fat-soluble vitamin. We think of beta-carotene or the carotenoids as precursors of vitamin A and assume it can be manufactured from beta-carotene by an endogenous enzyme that cleaves to the central carbon atom in the beta-carotene to produce two molecules of retinol. As long as we eat dark red-orange vegetables, we believe we are getting adequate vitamin A. After all, we've all heard "carrots are good for the eyes."

Because of unique differences among individuals in the metabolism of carotene molecules in retinol, however, vitamin A is not always delivered from carotenoids. Vitamin A is more than a vision-related nutrient. Like vitamin D, it is also found in the form of its metabolic byproduct, all-trans retinoic acid. This nutrient is important in binding to the retinoic acid receptor (RAR) and co-hybridizing with other receptors, such as the more general retinoid receptor (RXR) or the vitamin D receptor (VDR), to regulate gene expression and epidermal differentiation.

The availability of retinoic acid affects a number of cell signaling functions. Synthesis of retinoic acid comes from retinol vitamin A. Therefore, because vitamin A helps regulate cell differentiation, adequate intake is an important factor in preventing some forms of cancer and participating in cell differentiation that controls healthy aging or enhances health span. Vitamin A may be another nutrient whose use depends on the genetic make-up of individuals

Vitamin E should certainly also be on the list of nutrients for which supplementation may be required. Increasing evidence indicates that although no deficiency disease in adult humans arises from a lack of vitamin E, it has a varied impact on the regulation of cell redox potential. It helps protect against lipid peroxidation in the cell membranes.

If these oxidants are part of the cell regulating machinery that controls intracellular communication and apoptotic cell death, vitamin E may really live up to its early description as an "antiaging nutrient." It may have this effect at the cellular, by helping to regulate intracellular redox, or reduction/oxidation potential. According to Drs. Willett and Stampfer, although the data are not complete, 400 IU per day of vitamin E may help reduce the relative risk of coronary artery disease and other aspects of unhealthy aging

In the 1970s, Linus Pauling, PhD, raised people's awareness of the importance of vitamin C with his discussion of colds and flu. Vitamin C is more than just an antiscorbutic nutrient. Approximately 3500 biochemical reactions in human physiology depend on a cellular redox potential that is maintained in a large part by the ascorbic/dehydroascorbate oxidoreductive couple. Thus it plays a principal role in many cellular functions. It is concentrated in white cells and plays a major role in the cytosolic reduction/oxidation machinery.

Controversy has arisen regarding whether vitamin C at very high doses is beneficial for all individuals. Dr. Mark Levine has done extensive work with vitamin C at the National Institutes of Health. He found that intake of vitamin C at or slightly above that which would prevent scurvy is far less than what is necessary to optimize *in situ* kinetics, enzyme function associated with vitamin C, and ultimate physiological function. Vitamin C is another nutrient to add to the list of potentially important supplemental nutrients

Drs. Willett and Stampfer provide the following answer to the question regarding what vitamins an individual should take:

"Substantial data suggest that higher intakes of folic acid, vitamin B6, vitamin B12, and vitamin D will benefit many people, and a multivitamin will ensure an adequate intake of other vitamins for which the evidence of benefit is indirect. A multivitamin is especially important for women who might become pregnant; for persons who regularly consume one or two alcoholic drinks per day; for the elderly, who tend to absorb vitamin B12 poorly and are often deficient in vitamin D; for vegans, who require supplemental vitamin B12; and for poor urban residents, who may be unable to afford adequate intakes of fruit and vegetables.

"Education regarding nutrition is vitally important, but it has been far less effective than supplementation or the fortification of food in raising blood folic acid levels.

"We also believe that vitamin E supplements are reasonable for most middle-aged and older Americans, who are at increased risk for coronary disease. We would offer a vitamin E supplement in a dose of 400 IU as an option to the patient in the case vignette, with the suggestion that we review this practice annually as more information becomes available."

Bridging the Gap between Nutrition and Traditional Medicine

What we are seeing for the first time is a bridge crossing a chasm that seemed to be impassable. On one side was medicine; on the other side were nutritional supplements, and it seemed the two would never meet. Suddenly, the importance of functional physiology is emerging from the research . Researchers are discovering how many ways we depend on specific nutrients to promote functional physiology. If we expect to live healthy lives for 8, 9, or 10 decades, we must heed the specific nutrient requirements of our bodies.

I urge you to consider the importance of this article, "What Vitamins Should I Be Taking, Doctor?" It represents a transition from old thinking of the last 30 years about medicine and nutritional supplements and the new thinking regarding the function of complex systems over decades of living

HIV treatment provides another example of the changes in the field of medicine. Not long ago I discussed a paper in the *Lancet* that examined an HIV patient treated with an antiretroviral cocktail that included nucleoside analogs and the protease inhibitor indinavir who presented with of fatigue and acidemia.[4] The article asked about adverse effects of other drugs that produced similar symptoms, fatigue, fibromyalgia, and acidemic conditions. The researchers discovered several of these drugs act as inhibitors of the enzyme flavokinase. Flavokinase is an important enzyme that converts riboflavin, vitamin B2, into the flavine adenine dinucleotide (FAD) cofactor necessary to promote energy metabolism through mitochondrial electron transport and glycolysis effects.

One might wonder if it is possible to overcome the block imposed on the synthesis of the coenzyme flavokinase by administration of riboflavin. The interesting outcome is a direct application of Linus Pauling's thinking from nearly 40 years ago. He believed you can overcome metabolic blocks if they are part of Le Chatelier's principle and equilibrium dynamics, by putting a stress on the equilibrium and increasing the level of one of the reactants to push the equilibrium toward completion.

Overcoming the block

If we can't change the genes, and we can't take away the therapeutic drug, we might be able to overcome the block on that enzyme by giving more of its substrate, which in this case is riboflavin. The question is whether you could increase the production of FAD by giving supplemental riboflavin, increase the production of flavin coenzymes and reduce the side effects of acidosis, fibromyalgia, and fatigue. Clinically, the answer was yes. By giving daily doses far in excess of the RDAs or RDIs, (i.e., not 2 or 3 mg., but 100 mg. per day) the patient had marked clinical improvement. Measures of her blood lactate levels revealed that lactate went down, indicating increased aerobic metabolism, oxidative phosphorylation.

In this example a nutritional supplement was given at high doses as a molecular antidote to an iatrogenic metabolic dysfunction. This process of overcoming a metabolic stress on a physiological process may illustrate another role in medicine of nutritional intake in increasing doses. It could be called nutritional pharmacology.

Tryptophan

A similar report was published in the journal *Nutrition.* Investigators looked at HIV-infected individuals being treated with pharmacological substances. These substances are known to cause a significant reduction in plasma tryptophan in these individuals.[5]Tryptophan is an important essential amino acid that is a precursor to many secondary substances, including serotonin, melatonin, picolinic acid, and niacin.

What happens if a disease process is altering the immune system and funneling off a lot of tryptophan into secondary metabolites limiting its availability to be incorporated in muscle proteins? The result is induced sarcopenia. You have actually changed muscle function, or enzyme function, because you don't have as much tryptophan available for incorporation in protein synthesis. Decreased plasma tryptophan is commonly seen in individuals infected with HIV. More than a decade ago researchers reported the effect appears to be a consequence not of inappropriate protein in the diet, but of increased metabolic turnover

of tryptophan

Driving the Equilibrium with Niacinamide

What would you give as an antidote to counteract this problem? The authors of this paper recognized that if they gave one of the nutrients being utilized rapidly by an HIV-infected person who was being treated with anti-viral medications, they might be able to drive the equilibrium back toward tryptophan so it wouldn't be as rapidly metabolized. The substance I am talking about is niacinamide.

Niacin and niacinamide are derived metabolically from tryptophan. We consider niacin to be a vitamin because we assume it can't be synthesized in the body. It actually *is*synthesized in varying degrees in individuals, depending on their biochemical individuality. It is synthesized from tryptophan. Higher doses of niacinamide can help block the wasting that occurs through the activation of the PARS enzyme system. This system is activated when immune upregulation occurs. You get oxidative injury to DNA. You get an upregulation of PARS, which starts utilizing more niacinamide. By giving more niacinamide, you basically fill the pool, the reserve, and demand less metabolic conversion from tryptophan.

Preventing Tryptophan Wasting

When the researchers did this, they administered therapeutic doses of niacinamide to individuals and got an average 40 percent increase in plasma tryptophan within a period of two months. This result indicated they were able to stop the drain of tryptophan being converted into other metabolites, particularly niacinamide. This is another example of an iatrogenic stressor, antiviral medications used to treat HIV patients, that caused wasting of a specific substance. The researchers prevented that wasting by giving a downstream metabolite, in this case, niacinamide.

You will notice there are many roles for nutrients other than just for "proper nutrition" and the prevention of scurvy, beri beri, pellagra, xerophthalmia, and rickets

Another area that demonstrates the same theme is bone loss. Results from the National Osteoporosis Risk Assessment Study (NORA), the largest U.S. study of osteoporosis conducted to date, have recently come in. Commenced in 1997, it was a longitudinal observational study involving more than 200,000 postmenopausal women. The first report from this study was recently published in the *Journal of the American Medical Association.* That report, by Siris, et al, is titled "Identification and Fracture Outcomes of Undiagnosed Low Bone Mineral Density in Postmenopausal Women."[6],[7]

Osteoporosis Study Results

Some interesting conclusions emerge from this study. A total of 200,160 women underwent peripheral bone densitometry, or ultrasonography of heel, finger, or forearm in the physician's office. They were also asked to complete a questionnaire assessing risk factors and, approximately one year later, new skeletal features. Overall, approximately 40 percent of the women tested had a peripheral bone mineral density (BMD) measurement denoting osteopenia, or low bone synthesis, and approximately 7 percent, or 1 in 15, had bone mineral density in the osteoporotic range, according to the World Health Organization.

At baseline, 11 percent of the women reported at least one fracture after age 45. Among the 163,979 participants with follow-up information, a BMD classification of osteoporosis was associated with a fracture rate approximately four times that of women with normal bone mineral density. This study clearly confirms previously noted risk factors for osteoporosis including age, history of previous fracture, smoking, and glucocorticoid use.

Preventing Bone Loss in Women and Men

Where does this take us in terms of some of the other interesting features of preventing bone loss and bone fractures in women? The NORA study confirmed what many clinicians and osteoporosis researchers have long suspected. A significant number of postmenopausal women in primary care practices have clinically significant low bone mineral density, and these women have an increased risk of incident fracture within one year.

When we look at this connection, we recognize that it is not just women, although the NORA study was in postmenopausal women. It also relates to older men. U.S. epidemiological studies suggest that about 1.5 million men over 65 years of ago have osteoporosis and another 8-13 million have osteopenia. The calculated lifetime risk of fracture for men is 13.5 percent at the age of 50 years and 25.6 percent at the age of 60.[8]Although women have a higher overall prevalence of fracture, the increase in fracture risk for each standard deviation decrease in bone mineral density (BME) seems to be higher in men. Moreover, mortality associated with hip fracture is two to three times higher in men than in women.

Preventing Osteopenia and Reducing Osteolysis

We ought to be looking at another factor, which is how do we prevent osteopenia? How do we reduce osteolysis? How do we improve BMD and reduce fracture incidence? It is not just calcium. Calcium alone does not provide all the nutrients and other factors necessary to stimulate bone. We recognize that calcium hydroxyapatite, the microcrystalline hydroxyapatite from bone, differs in its effect on bone remineralization than asked bone; in the latter case you have burned away the protein fraction of the bone leaving only the calcium phosphate matrix or mineral.

Peptide growth factors have now been found in bone that may be helpful in inducing bone remineralization and utilizing calcium more effectively.

Microcrystalline Hydroxyapatite

The clinical response to calcium hydroxyapatite, or microcrystalline hydroxyapatite, is different from that seen with ashed bone. Calcium and vitamin D, when taken together, have been shown in a number of studies to reduce fracture rate. Selective estrogen response modulators (SERMs) like raloxifene used for the prevention of osteoporosis, although they stimulate bone remineralization, do not appear to reduce the fracture rate as effectively as calcium and vitamin D, the right kind of calcium, microcrystalline hydroxyapatite.

More and more evidence is emerging that indicates the quinones derived from vitamin K are important for bone mineral matrices and prevention of bone mineral loss. I cite a paper in *Current Opinion in*

Clinical Nutrition and Metabolic Care[9], and another review in *Nutrition,* titled "Vitamin K and Bone Health. [10]

We are beginning to get a different view of bone. It is not just dead tissue from which minerals diffuse in and out. It is a dynamic, actively metabolizing functional tissue in which growth hormone and other modulators influence protein synthesis and ultimately the mineral matrix. There are better choices for preventing fracture than inorganic calcium salts. Vitamin D and its metabolites, microcrystalline hydroxyapatite, vitamin K, and magnesium, all play an equally important role in maintenance of bone mineral integrity. Don't just recommend 1500 mg. of calcium daily, regardless of the form, and think you will get the outcome is assured. That is absolutely not what is emerging from this complex view of bone mineral metabolism

In applying this concept of complexity to the gut/brain connection, I want to discuss the serotinergic neuroenteric modulators. We will shortly hear from an international expert in this area. We will focus on irritable bowel syndrome (IBS).

IBS affects about one in 10 of the general population, most of whom are women. The typical presentation is recurrent abdominal discomfort or pain associated with erratic defecation, often with bloating. It is estimated that IBS has a direct cost in the U.S. of about 8 billion dollars annually, and although it is not fatal, the morbidity of IBS is significant. Quality of life is impaired to a level comparable with patients who have end-stage renal disease, diabetes mellitus, or depression, according to recent studies.[11]

Most patients have more than one symptom more than half of the time, and the mean duration of symptoms in patients with IBS exacerbation is between one and five days. IBS can be divided into subtypes that include constipation-predominant, diarrhea-predominant, or the most common form, alternating diarrhea and constipation.

IBS as a Neurological Bowel Disease

The understanding that IBS is a neurological bowel disease is gaining ground, thanks to the work of our Researcher of the Month. Food intolerance is implicated in diarrhea, although its exact importance in IBS remains unclear. There is evidence that IBS can occur following infectious gastroenteritis and transient inflammation. For example, of patients admitted to hospital for bacterial enteritis, between 20 and 25 percent developed IBS-type symptoms on follow-up and had pre-existing psychological characteristics.

Increases in inflammatory cells in the terminal ileum or colon, including mast cells and entero-endocrine cells, have also been documented in IBS. It is closely associated with serotonin output in the enteric nervous system. About 95 percent of the body's serotonin is present in the gut, 90 percent of it in the enterochromaffin cells, and 10 percent in enteric neurons. Serotonin has complex actions; it can result in smooth-muscle contraction or relaxation. Mucosal release of serotonin stimulates both intrinsic and extrinsic sensory neurons, modulating sensation via 5HT receptors. Serotonin may play a part in regulating appetite, sexual function, and mood. Higher postprandial serum levels of serotonin have been observed in diarrhea-predominant IBS, although an adequately sex-matched group was not included in this study.

There is a strong correlation between the ecology, environment, and immune system of the gut, the gut-

associated-lymphoid-tissue (GALT), and effects on the reactivity of the afferent or efferent connections between gut and brain. Our expert researcher will help us understand these topics

INTERVIEW TRANSCRIPT

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Origin of Interest in Enteric Nervous System

JB: Once again, welcome to the Clinician/Researcher of the Month section of *Functional Medicine Update*. This month we are fortunate to have as our guest Dr. Michael Gershon, a professor in the Department of Anatomy and Cell Biology at Columbia University College of Physicians and Surgeons. Since 1962 Dr. Gershon has been actively involved in studying the enteric nervous system and the concept of *The Second Brain*, which is the title of his remarkable 1998 book. Dr. Gershon has published than 300 works in this area and is a primary investigator in this evolving field.

Dr. Gershon, welcome to *FMU*. How did you happen into this field, looking at the enteric nervous system 30 years ago or more?

MG: At that time, I was a fledgling neurobiologist. I looked at the brain and found it daunting. In fact, I still look at the brain and find it daunting. I looked for something simpler to investigate and decided I would try to study the enteric nervous system, which struck me as a simple model system. I had the idea that if I could learn how to explain the behavior of the gut in terms of the activities and chemistry of single cells, then perhaps the discoveries would help me explain the behavior of the larger nervous system. Of course, I was wrong, not because discoveries in the gut would not be helpful, but in believing that the gut had a simple nervous system. A simple nervous system is an oxymoron, like jumbo shrimp.

Serotonin Research

JB: As your investigation evolved, did you start out looking at the anatomical relationships, or did you first happen onto some of these messenger molecules, like the serotonin family and the serotinergic component?

MG: Even before I got involved in research myself, I wrote a senior thesis in college on serotonin, which was an exciting new molecule at the time. D.W. Wooley, in fact, had postulated serotonin might be involved in schizophrenia. I became interested in serotonin. When I discovered, not through my own work, but from what I read, that the bulk of the serotonin in the body was actually in the gut, I became very interested in looking into serotonin and what it did for the gut. I assumed that God didn't put it all there for sport; it had to have a reason and I wanted to find out what that reason might be.

Molecular Mimicry

JB: At what stage did you start to make the clinical connections with conditions associated with functional gastrointestinal disorders and this molecular mimicry system in the gut?

MG: The very first investigation I did made me suspicious about it. At that time, I was interested in what would happen if all the serotonin in the gut was released suddenly, and I began to study mice. My idea at the time was that mice were mysterious in that they seem to lack responses to histamine. We now know they have inadequate representation of histamine H-1 blockers. They still died in anaphylactic or allergic shock, but it was prolonged.

That first investigation of mine showed that serotonin was actually the mediator of anaphylactic shock in mice, so that if you depleted the gut slowly of serotonin either by blocking its release or inhibiting its synthesis, mice didn't go into anaphylactic shock. I also showed in that study that serotonin came from the enterochromaffin cells, or EC cells of the gut. While looking at the mice that were dying in anaphylaxis when it was introduced (that is, serotonin-mediated death), I noted that a very prominent feature of it was massive diarrhea from those mice. Their guts really discharged. I began to suspect that serotonin might be profoundly important in initiating gastrointestinal activity.

Serotonin and the Gut

That led me to select Oxford as a post-doctoral place to work, where Edith Bülbring had been making landmark discoveries along those lines. I began to work with her to test the idea that serotonin might be important both in initiating reflexes in the gut and in the nervous system of the gut.

When I came back from Oxford, I did some experiments that turned out to be a large but important tangent for me. They suggested that serotonin was actually a neurotransmitter in the gut. It was not present just in enterochromaffin cells. It was also present in the nervous system, in much smaller, but still respectable, quantities when compared to the brain.

Reception to Serotonin Research

When I published that initial bit of evidence in *Science,* my colleagues in the field reacted as if I had committed blasphemy. My reception was not very different from that of Salman Rushdie for the book he wrote and his suggestions in Iran. They didn't put a contract out on my life, but I felt that was the next step! Anyway, we had a long battle, and I spent many years investigating the role of serotonin as a neurotransmitter.

I'm happy to say that battle is now over. It is now old hat that serotonin is one of four different transmitters, but at the time I made the suggestion, serotonin became the first transmitter other than acetylcholine and epinephrine, or norepinephrine, in the peripheral nervous system. It was very much "two's company; three's a crowd," and people were objecting to serotonin. They thought it was immoral.

Cold Reception to Early Research

JB: I've had the privilege of reading a number of your papers. The science is beautiful. I compliment you on your approach to this whole field. Do you feel the negative bias you received was a consequence of preconceptions, that people wanted to individualize and compartmentalize the anatomical and physiological systems, or were there other reasons for this cold reception?

MG: I don't think there was any personal animosity in it, or anything like that. I'm not a big conspiracy theorist. The major reason I think people objected so strongly is that scientists, like other people, like simplification and order. Entropy is everybody's enemy.

There was a very nice order in systems then. There were two divisions that everybody thought of in terms of the autonomic nervous system, the sympathetic and the parasympathetic. Therefore, it was nice to have two transmitters, one for each in terms of the post-synaptic response. People are now saying that if we've got a simplifying assumption, we know it's wrong. Biology is not simple, and that's a good thing because if it were, those of us who do research would be out of business.

Langley's Nervous System Classifications

We now know, of course, that even when Langley first classified the autonomic nervous system, he knew there weren't two divisions, so even that part of the simplification was wrong. Langley, who was a difficult sort, said there were three divisions. He was known to be an imperious editor of the *Journal of Physiology*, and he was not well liked during his lifetime. I thought it was ironic that shortly after his death the imperious editor got edited. They dropped his third division, which was the enteric nervous system. It took a long time for those of us who worked on the enteric nervous system to go back to first principles and prove that poor old Langley was right.

Serotonin, Peptide Hormones, and Catecholamines

JB: When we look at the messenger molecules related to gut function, the second brain, the obvious focus is on serotonin. But there are also peptide hormones and catecholamines in the system. What roles do they play, or how does this relate to the serotonin story?

MG: Let's go in order. Serotonin plays an important role, first of all, as a sensing cell in the epithelium of the gut. For the enteric nervous system to be able to function as it does, independently of input from the central nervous system, which it can do, it has to know what's going on inside the lumen of the gut. So it needs a detector system.

The Enterochromaffin Cell

The enterochromaffin cell, which is where most of the serotonin of the body is, is a detector cell. In some parts of the gut, it functions as a glucose receptor. In most parts, it's a pressure receptor, so it detects those changes in the lumen of the gut. In the duodenum, it's also an acid receptor. Serotonin is released in response to increases in pressure, glucose, or acid. That serotonin goes primarily into the wall of the gut and stimulates the intrinsic primary afferent neurons, the sensory neurons of the gut, initiates intrinsic reflexes within the gut, and also sends signals back to the central nervous system (CNS).

None of those signals going back to the CNS mediated by serotonin coming from the enterochromaffin cells is pleasant. I like to say that the gut is not an organ from which you wish to receive frequent progress reports—pain, bloating, nausea, and so on. So that initiates peristaltic and secretory reflexes.

Interneurons, Peptides, and other Transmitters

But within the nervous system, serotonin is present in a very complicated system of interneurons, which are long and descending. They deal with the propagation and coordination of the activity of the enteric nervous system. Peptides are also involved in other detectors in the epithelium of the gut. They function as endocrine signals, putting peptides into the bloodstream and activating nerves, and they also function as serotonin does, as interneurons within the system, or as transmitters to the smooth muscle, in the case, for example, of the neurokinins. Peptide substance P can be excitatory to smooth muscle.

The gut uses other transmitters, as well, including acetylcholine, which is involved in ganglionic transmission and in motor neurons to smooth muscle, and in secretion, and it involves catecholamines. Norepinephrine is present in extrinsic nerves, the sympathetic nerves, which can inhibit secretion or GI motility. We've recently found that, like the brain, the gut also has dopaminergic neurons, whose function is yet to be determined. Right now every single class of transmitter that has ever been found in the CNS, has also turned up in the gut. So you can think of the enteric nervous system as "the second brain," as you've said, but another way of thinking about it is just simply as "the brain gone south."

Serotonin Metabolites

JB: When we look at serotonin specifically, are there metabolites of serotonin? In the CNS, metabolic byproducts such as serotonin can have neurological messaging effects, as well.

MG: All of the byproducts of serotonin that we know about that are formed naturally in the gut are inactive. But you raised an interesting question with regard to the irritable bowel syndrome with respect to getting rid of serotonin or the metabolites. Serotonin is a curious molecule in the sense that it has a very high pK, that is, at physiological pH, it's charged. It's really soluble, and it's charged, so it exists with a net positive charge on its amino group. That means it is a molecule that cannot cross the lipid bilayer of a cell membrane, the plasma membrane.

To get across into a cell, serotonin has to be transported. If it's not transported by proteins in a cell, it can't enter. All of the enzymes that turn off the action of serotonin, without exception, are intracellular. It's not like acetylcholine, which has acetylcholinesterase attached to basal membrane. The only way serotonin can be metabolized at all after its release is to take it back up into some cell or other, and that requires a transporter.

SERT

There's a very famous transporter for serotonin called SERT. This serotonin transporter is best known as the target of Prozac and the other SSRIs. When you inhibit the serotonin transporter, you potentiate serotonin by interfering with its inactivation. That accounts for the GI side effects of the SSRIs and other antidepressants. They are not side effects; they are direct effects. They lead to nausea, diarrhea, and ultimately to constipation, all coming from direct effects on serotonin.

When I first looked at that, I wondered how animals or people survived treatment with antidepressants, or a bout with cocaine, which blocks the action of the serotonin transporter. It turns out that animals have backup systems; there are other transporters called organic cation transporters that can also take up serotonin, and they're present in the gut with very high capacity.

IBS and the Knockout Mouse Model

Interestingly, if you look at a serotonin transporter knockout mouse, it doesn't have it. It's a genetically engineered transgenic animal without the transporter. Those animals go through life with what looks to be something very similar to the irritable bowel syndrome (IBS). That is, they have alternating diarrhea and constipation. I don't know if they have bloating; I can't ask them. But if you look at their stools, you find that they put out big heavy stools most of the time and have increased, very rapid colonic motility. The stool doesn't last long enough in the colon to get the water out so that's why they put out so much.

Periodically, serotonin receptors desensitize. There's so much serotonin release without an ability to get rid of it efficiently. The other transporters aren't adequate for the animal to survive (if the animal survives), but the receptors desensitize. They go through bouts of terrible constipation and then back to diarrhea, so they just alternate. They look like a model of IBS.

Fecal Flora Effects on Serotonin

JB: That's fascinating. Does fecal flora have a relationship or an impact on this cycling, or on the serotonin—microbiological organisms and their secondary metabolites, like polyamines?

MG: That's a very interesting question. I have no idea how to answer it at the moment, but I'm going to look. IBS in people is very often precipitated by infection. Somebody takes a trip to Mexico and has IBS for the rest of his life. I wonder, for example, what would happen if you infected these animals with trichinosis, which causes an inflammation of the bowel.

IBS Treatment with Bacterial Cultures

JB: In some of the more recent clinical work, some publications suggest that at least certain forms of IBS have been ameliorated by supplementation with oral cultures of bacteria, like bifidobacteria or lactobacillus acidophilus species. I wonder if there's a connection between the floral population and some of the intercellular messages that go to the EC cells.

MG: As I stated earlier in regard to the study of anaphylaxis, an immune response caused the serotonin

to be released from the EC cells. It doesn't take a lot of speculation beyond that to wonder whether a more minor immune response to flora, less severe than anaphylaxis, might alter bowel habit just through this mechanism that is releasing serotonin abnormally. It would be interesting to look to see whether the alternating diarrhea and constipation of mice with this SERT knockout is changed by acidophilus.

Alarm Molecules and Interleukins

JB: It would also be interesting to know how, if at all, that relates to these alarm molecules from the GALT that you're describing, like TNFa, or some of the interleukins, whether that may precipitate some of this, and how it's related to the bacteria.

MG: It makes sense that there would be a relationship. Clearly, the ENS system is vital to protection of the body against the flora in the gut. Chloride secretion in diarrhea has a purpose. It's not just there to ruin your trip to the tropics or some other salubrious location. It's there to protect you, to clean out your gut. This is why, when I have the problem, I find Pepto Bismol is a much better alternative than paregoric or Immodium.

Alosotron

JB: I'd like your view, in hindsight, regarding why the enteric serotonin-inhibiting medication alosotron ran into the problems it experienced.

MG: If you watch politicians at work, it should come as no surprise that medicines, even good ones, run into difficulty. Alosotron was the first drug introduced that took on the placebo in an FDA-approved, double-blind controlled fashion, and won. No other drug had ever done that before. There is some evidence that the antidepressants, in low doses can help, but there's nothing quite like alosotron. The shock, in fact the rage, that patients exhibited when it was withdrawn from the market is wonderful testimony to its efficacy.

Constipation Problems with Alosotron

It was withdrawn because it had two untoward effects, both of which were known. One was that a certain percentage of the patients who took it became constipated. You can explain that through the physiology of the 5HT3 receptor, which the drug acted on. The percentage was rather low, had been apparent, and was known to the FDA when the drug was licensed. Nothing new came up in use that wasn't known about constipation before. In most of the people, the constipation abated after they used the drug for a while, discontinued its use, or the dose was lowered. Then therapy could be resumed. If it occurred early, or it didn't reoccur, many patients could take the drug afterward.

Alosotron was prescribed improperly for some people. That is, they had terrible constipation before they were given alosotron. And they had difficulties; nothing fatal, but they had difficulties. Misuse can cause difficulties for any drug. Digitalis is a good example. Too much digitalis can kill you, but that's not what you're supposed to do with it.

Alosotron and Ischemic Colitis

The other problem with alosotron was that it was associated in some patients with ischemic colitis, which is a much more severe problem. However, studies do not indicate that the incidence of ischemic colitis in patients who received alosotron is any different from IBS subjects who don't receive alosotron. It is clear that a major risk factor for ischemic colitis is IBS.

Patients with IBS get ischemic colitis at a much higher rate than the general population. Whereas alosotron didn't protect from ischemic colitis, I don't think it caused it either. In summary, I think it was withdrawn for no good reason in response to a political campaign by those who believe IBS is a state of mind, the raving of hysterical women, and not a real disease.

Gender and Alosotron

JB: I find this gender connection interesting, knowing that serotonin and estrogen have interrelationships. Is the reason alosotron was only approved for women with diarrheal-predominant IBS related to this interaction of estrogen?

MG: No. IBS is, particularly where people are studying it, in tertiary centers, a female-predominant disease. There just weren’t enough male patients available initially to know whether the drug was effective. In terms of anecdotes, it certainly seemed effective in a subset of males as well as females. Very likely, if the studies had been conducted in a sufficiently large population of men, it would have been effective in them, too. Men pretty much hate to admit to having IBS.

Gender and IBS Reporting

JB: So do you think the frequency of the disorder is probably comparable in both genders and the difference is only in reporting frequency? Are women more sensitive and feel more comfortable about reporting it than men, rather than its being an endocrinological difference between the genders?

MG: I would not use the phrase "rather than." I think there may very well be a female predominance of IBS that is real, but it is certainly aggravated by the macho tendency of men.

Schizophrenia and the Gut

JB: I'd like to go back to one other point you made. You talked about the fact that the EC cells are the major cells secreting serotonin in the body. Then you discussed how you started down this path initially, looking at schizophrenia and certain mental illness and its tie to the molecule for schizophrenia. Do you believe, some 30 years later, there is some relationship between certain forms of schizophreniform and the gut?

MG: I don't know about schizophreniform. Autism in children has a very high incidence of accompanying GI symptoms, which has become controversial because of the potential link to measles, mumps, and rubella vaccine. I don't think measles, mumps, and rubella vaccine have anything to do with either autism or the problems these kids have in the gut. A very high incidence of GI problems associated with autism in these children, however, could be explained by serotonin, because the children with autism do have an elevated serotonin level. Since 100 percent of blood serotonin is derived from the gut, that

observation alone shows they have defective serotonin behavior in the gut. I think autism is probably a disease of both nervous systems, the CNS and the ENS.

Managing ENS Disorders

JB: We have all watched the emergence of mind/body science and have started to gain some more footing in basic research. Do you feel this will lead us into new ways of managing disorders of the ENS?

MG: You have to think of the ENS and the brain functioning as a combined unit. I have been talking about the ENS and its ability to function independently, but of course it doesn't normally do that in real life. It functions together with the brain. In fact, when you look at the vagus nerve connecting the gut with the ENS, the bulk of the fibers in it, surprisingly to many people, are not descending fibers carrying information from the brain to the gut, but ascending fibers carrying information from the gut to the brain. So the ability of a disturbed gut to disturb the brain is highly developed.

When I was a student ulcerative colitis was thought to be a psychosomatic disease. We now know ulcerative colitis and Crohn's disease are autoimmune diseases. There was something called the ulcerative colitis personality, which I think was real enough, but it wasn't that thinking bad thoughts put holes in your colon so much as having holes in your colon caused you to think bad thoughts. The gut has a real ability to cause mental disease. When you look at studies that show one form of anxiety or another, depression, or other psychoneurotic conditions in patients with IBS, you really wonder about the relationship. Is it primarily in the head or is it primarily in the bowel? It could be either. If your entire life is devoted to pain from your gut and intestinal agony, you can become crazy from it.

Future Clinical Applications

JB: That concept certainly mirrors the changing view of anatomy and physiology, looking at systems approaches rather than portions of the anatomy in isolation. If you were to look forward, where do you think this field is going? Do you have any vision about how this will apply clinically?

MG: Right now, I think the field is in a very difficult position because for one reason or another, mostly another, virtually all effective drugs for the treatment of motility disorders of the GI tract have been removed from the market. Cisapride affected a cardiac potassium channel, so we don't have Propulsid. Alosotron was removed because of a political campaign directed against it, so you can't treat the diarrhea of IBS. Novartis is trying to get Tegaserod approved by an extremely reluctant FDA, which is putting up all kinds of nonsense obstacles to try to prevent its approval. Tegaserod is a 5HT4 receptor agonist and is useful for just the opposite of alosotron for constipation-predominant IBS and of constipation.

I think the first thing we can look forward to is the development of either a serotonin-based pharmacology or peptide-based pharmacology to get at the ENS and give physicians who have to deal with these problems something to use in treating it, other than their good wishes for their patients. I think enhanced understanding of IBS as a real disease, and not the ravings of hysterical women, will ultimately get through to the public consciousness and allow some good to be done for the mass of people who suffer from that condition. We're talking about up to 20 percent of Americans. I'd like to see something done for them.

IBS a Common Functional Disorder

JB: I think that's an extraordinary message to close on because this is one of the most common functional disorders that we see in the American public.

MG: Yes, and it should be a treatable one if the politics can be resolved.

Conclusion

JB: Your research has been a beacon of light to help us understand where the fact and fiction meet, and how to move from fact. We appreciate your spending time with us and your years of contribution in opening up this field.

erotonin receptors and transporters are connected to the emerging understanding of brain function as well. A recent *Journal of the American Medical Association* paper titled "Similar Effectiveness of Paroxetine, Fluoxetine, and Sertraline in Primary Care,"[12],[13] looks at SSRI drugs (serotonin re-uptake inhibitors). The paper describes the work of Kroenke et al. In this study, the investigators found all three commonly prescribed SSRI antidepressants appeared to have similar effectiveness clinically.

It is important to recognize that just because SSRI drugs are equally effective on average, they may not be equally effective for individual patients. Among patients who do not respond to one SSRI, half or more will derive benefit from others. Significant differences exist in the polymorphism of the enzyme cytochrome P4502D6, which is involved with SSRI metabolism. During the next decade, selection and prescribing of antidepressant drugs or serotonin modulators will come to depend on knowledge of these drug/gene interactions. Both the doses of specific antidepressant drugs and the potential of drug interactions may be predicted by genetic variation or single nucleotide polymorphisms (SNPs) in the cytochrome P450 system.

Selecting an SSRI Drug

Randomized, controlled clinical trials offer clinicians little specific guidance regarding initial choice of SSRIs for how individual patients will respond to them. Complexity in health care and individualization of treatment represent a recurrent theme in the functional medicine model. The gut of every patient is different. These differences include the way an individual metabolizes protein, fat, and carbohydrate, the way those substances nourish the more than 100 separate species of microorganisms in the gut, the production of substances due to the metabolism of those organisms, and the subsequent influence on the GALT.

This may explain why probiotic supplementation in infants with atopic disease was able to lower their allergy and atopy by improving the communication of the friendly bacteria to the GALT and the subsequent influence on the inflammatory cascade.[14] This process involves both macronutrients and the resulting fermentation products, organic acids and gases. The resulting biochemical cauldron activity influences the enteric nervous system and impacts upon conditions like IBS. These, in turn, influence brain chemistry and mood, as Dr. Gershon explained in his discussion of autism.

The authors of a recent article in the *Journal of Fertility and Sterility* discuss the relationship of endometriosis and neuromuscular diseases and the GI tract. They conclude:

"This study suggests that endometriosis and gastrointestinal tract symptoms are a result of the dysfunction of hollow organs. Correction of the biochemical imbalance of the eicosanoid system (the fatty acid inflammatory modulating system) and the hypersecretion of insulin that results from excessive intake of glycemic carbohydrates and lack of essential fatty acids significantly decreases symptoms in patients with endometriosis and associated neuromuscular disease of the gastrointestinal tract."[15]

We are looking at a holographic web of complex interacting systems, not just single diagnosis. We will continue discussion of this theme in the next issue of *FMU*.

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