

August 2000 Issue | James Goodwin, MD

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Welcome to *Functional Medicine Update* for August 2000. This issue is dedicated to the promotion of healthy aging. We will examine medical progress in the field of geriatrics and what we can do today to promote healthy aging. These considerations are at the forefront of medicine as aging Baby Boomer reach senior citizen status in the next 10 or 15 years, We will examine how medical services will be utilized and what the supply and demand curve will be.

Francis Waickman, MD, from Akron, Ohio, a diplomate of the American Board of Internal Medicine, and the American Board of Allergy and Clinical Immunology, is a highly regarded member of the functional medicine community. An *FMU* subscriber for many years, Dr. Waickman is a lecturer, teacher, and clinician par excellence. He recently commented on my January 2000 overview of the emergence of functional medicine and its contributors—the pioneers. Dr. Waickman, a senior member of our community who exemplifies healthy aging as he has moved on in his career, had the following to say about the December 1999 issue:

"I've known you for a long time and from afar, I have enjoyed your tapes (*Metabolic Update*, *Preventive Medicine Update*, and *Functional Medicine Update*) for the last 18 or 19 years. I think your intellect, knowledge, your ability to remember, and your ability to have rapid-fire thoughts, and be able to deliver them, are very high skills.

A Pioneer in Food Allergy Testing

"I thoroughly enjoyed the 'History of Peoples through the Twentieth Century in the Medical Arena' that you described in your January 2000 issue. As you look from afar on this, each one built on the other, and there were really very few people who had strictly original ideas. That's why I want to draw your attention to one who was not mentioned. I offer this to you in case you are keeping some major historical sequence.

"Dr. Herb Rinkel is the one who put forth the concept of food allergy as we know it today. If it hadn't been for him, I don't think Ted Randolph would have gotten to the point where he did. Keep in mind that the book, *Food Allergy* was written by Rinkel, Randolph, and Zeller. Randolph was the secondary author. It was Herb who first answered my questions concerning allergy. As I went through my pediatric residency, I had many questions. About 10 percent of the children we saw in the clinics never became well. They always had some chronic symptoms. I did some manipulations of diets on my own when I was first in practice in St. Louis, but I really didn't know what I was doing. Some children improved, but I was not smart enough at the time or logical enough to put two and two together.

Dr. Rinkel's Influence on Dr. Waickman

"I was then taken into the Korean War and was at Scott Air Force Base for two years. There we had six board-qualified pediatricians and we had a very good time pulling each other's leg as well as trying to help each other in our thirst for knowledge in helping people. One of the pediatricians had some pediatric allergy training, such as it was in those years. I milked him for all the information I could, but it still did not answer my questions. When I left the Air Force in 1955, I opened a practice in Akron, Ohio, on February 1, 1955. Dick Stahl signed me up and took me to my first real allergy course, in Cleveland, Ohio, entirely put on by Herb Rinkel. At that course I learned more about allergy and how to help people than I had in the previous eight years of my training. We learned about inhalants and how to do skin testing by EndPoint Titration. I only knew about Prick Testing or Scratch Testing up to that point and never had any real instruction as to how to desensitize. Herb taught Serial Dilution EndPoint Titration and presented absolute guidelines for immunotherapy.

He devoted an entire day to diagnosing food allergy. It was he who brought medical students into his home and gave them free room and board with two requirements: 1) they had to have allergy problems; and 2) they had to allow Herb to experiment on them as he wished. At that time he developed the 1:5 dilution for inhalant skin testing. More important, he also perfected the Oral Provocative Food Test. He put down rigid rules of omitting the food for four days and then challenging on the fifth day.

Masked Food Allergy Concept

"It was he who really developed the so-called 'masked food allergy' or the term 'food addiction' as Randolph applied it in the 1960s. During medical school, Herb was financially strapped. Members of his family, who were farmers, sent him a crate of eggs once a month. He literally lived on bread and eggs. Between final exams and graduation, he and a group of friends went camping for three days and did not bring eggs with them. He did not have eggs for four or five days. After graduation, there was a party at one of the fraternity houses. It was Herb's birthday, and someone had made an angel food cake. He had ingested approximately one-half piece of angel food cake when he became unconscious. Fortunately, another physician did have some adrenaline in the house and he was revived after a couple of doses of adrenaline.

"Herb reasoned that he had this severe reaction to the egg white because he had been so addicted or masked to the egg sensitivity while he ate it, but then having omitted it he then challenged himself with this. From that, he discovered masked food allergy.

Using Dilute Immunotherapy

"When Herb finished his allergy training on the East Coast, he went to a clinic in Kansas. He was seeing many severe reactions with immunotherapy, and he had heard about a different approach put forth by an ear, nose and throat physician in St. Louis. Herb spent some time with him and saw where he was using a 1:10 dilution and using extremely weak dilutions for immunotherapy, from 10^{-7} to 10^{-10} . There is a comment in *The Pediatric Clinics of North America* for 1954, and the statement was basically that this therapy would be better for the patient if the syringe was simply passed under the patient's nose. I have paraphrased this because I don't remember the exact quotes, but it was really a pot shot against the very dilute immunotherapy. However, Rinkel saw that patients getting these doses did have improvement of

symptoms. These were the same people who had severe reactions when they were getting strong dilutions of the antigens. Therefore, he had a built-in skewed practice in using the very dilute solutions.

"After this, Dr. Rinkel went to Kansas City and opened his private practice. That's when he started to take medical students into his home. Using them as 'guinea pigs,' he proceeded to show that a dilution of 1:2.5 was the most accurate way to pick up and treat a patient, but when you made the dilutions at that amount, you had to work with too many bottles. He saw that 1:10 was not accurate enough and showed that the dilutions of 1:5 were the ones that really had the most efficient help for office procedures and gave the best results.

Educating Physicians

"Bear in mind, Dr. Turkerltaub at NIH is now trying to standardize antigens at a dilution of 1:3. He is using erythema as the item to measure, however, and not the wheal. In my opinion this is an inappropriate evaluation. At any rate, people were coming to Dr. Rinkel's office and getting very good results with food elimination and/or immunotherapy inhalant allergies. Other physicians heard about this, and several went to his office and would spend a week with him to learn the techniques. There were several physicians in the Akron area and one in Cleveland who did this.

"Dick Stahl convinced Herb it was ridiculous to educate one physician at a time and that he should give instructional courses. Dr. Rinkel's first course was given in Akron in 1954. The next course, April 1955 in Cleveland was the one I attended. He gave a course in 1956 in Pittsburgh and continued to give yearly courses. Dr. Russ Williams from Cheyenne, Wyoming encouraged him to give similar courses out at Jackson Hole, which he did until the time of his death. He so enjoyed the country and the people that he had a yearly course over the July 4th weekend. Russ Williams, Jim Willoughby Sr., Dick Stahl and myself, and a few other people continued to put these courses on yearly in Jackson, Wyoming. I can remember a program in 1972 when there were 190 physicians attending a single course for allergy instruction.

Carrying on the Legacy

"Herb Rinkel knew he was dying when he put on his course in Jackson Hole in 1962. He had liver metastasis, was jaundiced and was becoming fairly weak. At the break on the last day, he asked that all speakers come to his room in the Wort Hotel. When everyone was present and seated, he asked for their attention and explained that he knew he was ill and these courses must be continued. He asked that each of us continue to give of our time and talent to teach this material. Nearly in unison we answered 'yes'. This was not satisfactory to Herb. He pointed his finger at each of us and made us say, 'yes' individually. It was a very emotional time for many of us.

"Dr. Rinkel had a saying, which he wanted us to continue. 'When you leave this program, if you can't go home and help a minimum of one patient, I have wasted your time.'

He never wasted my time or anyone else's time, because if you paid attention, you always picked up some new thoughts, new ideas in relation to how to help people with allergies. The interesting thing he said on the last hour of the last day was always to evaluate your failures. He always brought up some cases he had not solved and wanted everybody to offer an opinion about what else should be done. He was trying to emphasize that failures should never be looked on as failures until you have reviewed,

analyzed, and thought through the patient's problems for the second or third time. Usually, it was something that had been missed and that the patients could be helped further if you picked up these little nuances."

Sublingual Provocation Neutralization and the Evolution of Medicine

I thank Dr. Waickman for providing this annotated history of the sublingual provocation neutralization concept. It is a specific example of a more general theme of the evolution of medicine. We go from empirical observation to scientific understanding and ultimately to mechanistic explanation. That process leads to a functional medicine. We learn through the wisdom and experiences of our elders in the field.

Wisdom is our most precious reserve and resource. If you are not healthy, it is hard to bring the full weight and benefit of your wisdom to bear on problem solving. When I look at Dr. Waickman, I say Alleluia and celebrate. Here is perpetuation of a great idea, training new generations with the transfer of information and continued evolution of our field, thanks to individuals who have made discoveries. An idea lives on beyond the individual.

An example of this concept is Arnold Beckman, who just celebrated his 100th birthday. Many of you know him as the man who developed Beckman Instruments, one of the premier scientific instrument companies in the world. His life as an inventor and philanthropist was a century of quality. Not long ago he said, "Whatever you do, be enthusiastic about it." That affirmation itself could be part of healthy aging—the ability to wake up every morning and to affirm your value and your contribution.

In the 1920s, Arnold Beckman owned a Model T Ford. In those days, the automobile's gas tank was situated below the level of the carburetor. That made driving up hills difficult, since gravity would prevent fuel from feeding to the engine. When one encountered steep grades, a common practice was to turn the car around and drive backward. Arnold Beckman, a young and inventive chemist, thought this was rather silly, to say nothing of dangerous. He installed a bicycle valve in the auto's gas cap, pressurized the gas tank with a bicycle pump, and sailed up hills facing in the right direction.

How One Views the World

That is an interesting metaphor for the way one views the world. Some people view it differently. Maintaining a problem-solving world view, in the case of Arnold Beckman for 10 decades, can only be achieved through the promotion of healthy aging.

We could celebrate a number of people. We often don't look at those success stories. We look at the people who got sick and died at a younger age. They become our mortality statistics and we evaluate their sickness. Often, we don't review those who not only survive to a ripe old age, but who also make contributions, compressing morbidity, bringing the weight of their wisdom solve problems throughout their lives. These successful individuals then just fall asleep. This is what Dr. James Fries calls "natural death." That is the theme of this month's *FMU*.

A recently published monograph was titled "Why the Elderly Need Individualized Pharmaceutical Care." We have learned through the human genome project that individuals respond uniquely to their environment based on how their genes are expressed, encoded, and influenced by the environment. We

now recognize that medicine is for real people; statistical humans are of little interest. This report discusses the increasing understanding of the differences among individuals in the detoxification of agents such as pharmaceutical drugs.

If we have a one-size-fits-all mentality and give medications on the basis of body surface area, we face problems. We used to call these problems unexpected adverse drug responses, or side effects. Now we realize these reactions are not unexpected. If you ask a different question about how that individual detoxifies or metabolizes medications or substances, you will learn that those adverse reactions in that individual are reproducible every time you administer that drug. That is how his or her body is predisposed, based on unique pharmacogenetic detoxification patterns, to manage those specific compounds.

The Problem of Multiple Medications

These problems become more confusing when one takes multiple medications and drug effects overlap. Examples include a NSAID with Digoxin, a NSAID with an ACE inhibitor, tricyclic antidepressants with blood thinners like Coumadin, NSAIDs with beta-blockers, Digoxin with calcium channel blockers, and diuretics with Digoxin. All of these combinations affect the way the liver detoxifies agents and can alter the pharmacodynamics and pharmacokinetics that determine, in large part, how an individual will respond to a given agent. Given the complexity of these interactions, it is not surprising that adverse reactions occur.

Consider that people 70 years of age or older are, on average, taking three medications. We often know little about their pharmacogenetics, or how they metabolize substances. It is not a wonder that we have so many adverse drug reactions. An article in *JAMA* some years ago reported that 2,216,000 patients in hospital situations experienced diverse drug reactions. More than 106,000 deaths were believed to have been caused by adverse drug reactions. Because we did not ask the right questions before administering the drugs, no one knew exactly how those patients would respond to the drugs. We looked at their reactions after the fact, which may have been too late for those individuals. Personalized medicine is an emerging theme.

I saw a recent report about St. John's Wort. Interest in St. John's Wort, or hypericum, is increasing in its role as an agent to manage depression and act as an immune modulator. Some people have considered it an alternative to Prozac. It is being used in greater frequency in different age groups. According to a report in *Clinical Pharmacology and Therapeutics*, the metabolism of St. John's Wort induces one of the cytochrome P450 enzymes in the liver—CYP3A4. This isoform of cytochrome P450 is clinically significant because it is a detoxification enzyme used for the metabolism of other drugs, so it may induce a drug/drug interaction. By upregulating that enzyme, it may cause greater first-pass clearance of specific medications and alter their therapeutic window and effectiveness.

We have only considered differences in drug detoxification for about 10 years, since we began to understand more about individual genetic uniqueness. An article in *JAMA* not many years ago reported that adverse effects of Reglan (metoclopramide) in some older-age individuals produced Parkinson-like symptoms. Many practitioners diagnosed these extra-pyramidal neurological symptoms as Parkinson's disease because they did not realize the symptoms may have been due to the adverse neurological side effects of this medication in some people. The practitioner may have introduced L-DOPA replacement

therapy, assuming the patient had Parkinson's. As a result, the patient did get Parkinson's, because the continued use of L-dopamine replacement therapy causes loss of dopamine-secreting ability in the nigra striatum. It becomes a self-fulfilling prophecy.

Metaclopramide Testing: Implications for Geriatric Medicine

That unfortunate mistake occurred, it seems, because the drug metaclopramide was tested on younger individuals, whose detoxification mechanisms for the drug differ from those found in the elderly. When you give metaclopramide to an older individual with a depressed first-pass detoxification, a dose which produces no adverse response in a young person may produce neurotoxicity that resembles Parkinson's disease. This story has implications beyond the specifics. Geriatric medicine is now medicine for the individual, not just medicine for the statistical human.

Genomic medicine is the medicine of the future. You have heard that recurring theme in *FMU*. In a recent report in *Science* magazine, titled "Genomic Medicine and the Future of Health Care," Dr. Chris Sander explains that genomic technologies and computational advances are leading an information revolution in biology and medicine. That revolution allows us to understand, through diagnosis, the unique genetic characteristics of a patient's detoxification abilities or first-pass drug detoxification and immunological responses. Therapies then can be matched, in type and amount, to the individual's own need. Medicine of the future will include personalized treatment for individual needs. Drugs, prognostics, and diagnostics will all be tied to the genetics of the individual and his or her environment. This practice will improve decision-making and match the phenotype with the genotype to improve patient health outcome.

A major advance in cell biology will significant implications for geriatric medicine. There is growing recognition that pleotrophic cells called stem cells reside in our adult bodies, even in aged individuals. These stem cells may be awakened and be stimulated to regenerate, at least on a theoretic level, organs and organ system function. These cells that are not fully differentiated and exist in a clonal state can be manipulated to create juvenile or youthful cell function. It is not like replacement of organs or tissues; it is calling forth the action of these pleotrophic stem cells.

Stem cells found in adults can show surprising versatility. They may not be able to match the power of the pleotrophism of cells from embryos, but they represent a frontier level for medicine in the aged. It may be possible to encourage the body, through a stem cell modification program, for instance, to generate new cartilage-producing cells, bone cells, muscle cells, hematopoietic cells, or even astrocytes, to improve central nervous system function. Maybe the brain can regenerate to a greater extent than we recognize. These are fascinating examples of what may arrive in our future to change the nature of what we call geriatric medicine.

Stem Cell Capabilities

Another article on stem cell opportunities in medicine and biology, titled "Out of Eden: Stem Cells and Their Niches," by Fiona Watt and Brigid Hogan, appeared in *Science* magazine. Stem cells are in the news for two reasons. First, we now have the ability to cultivate human embryonic stem cell lines. It has been reported that adult stem cells can differentiate into developmentally unrelated cell types, such as nerve cells into blood cells. Second, both intrinsic and extrinsic signals regulate stem cell fate. Some of

these signals have been identified and may be subject to manipulation by exogenous factors. Environmental factors, for example, may encourage stem cells to differentiate into new, less senescent tissues and organs. This exciting view of where medicine may be going gives more plasticity and a less deterministic view of the aging process.

Our Clinician of the Month, who is eloquent in his description of geriatric medicine, will point out where we are today and share some thoughts about aging and ultimate death. One condition that occurs with aging is increased risk of disease. As Dr. Goodwin points out, the single highly correlated variable is increasing chronological age and increasing risk of disease.

Cancer is one disease associated with aging. We have had a number of discussions in *FMU* of chemoprevention and chemotherapeutics in the last several months. One was an eloquent discussion by Dr. Daniel Labriola (June 1999) from the Seattle, Washington area, co-author of a paper that appeared in *Oncology* on nutritional modulation of the effects of chemotherapeutics. Dr. Labriola received many comments and questions from the *FMU* subscribers. He wanted me to clarify four points so they would not be misconstrued from his or my comments regarding this important area of nutritional modulation of the effects of chemotherapeutics. I will go through those four points to summarize what you heard on the previous discussions on the tape.

First, Dr. Labriola wanted me to point out that only certain chemotherapeutic agents use reactive oxygen species (ROS) as their cytotoxic agents. Different classes of chemotherapeutic agents have different mechanisms. If you are giving antioxidants concomitantly with a drug whose specific mode of cytotoxic action of which is to increase ROS and induce apoptosis, you may be uncoupling some of the therapeutic benefit. Not all chemotherapeutic drugs work in that capacity, however. Last month in *FMU*, we discussed a review article on the different classes of chemotherapeutic drugs, their mechanism of action, and the influence of nutrition. I recommend it as a good reference point. Again, only certain chemotherapeutic agents use the increased production of ROS to induce cytotoxicity. For these agents, giving antioxidants simultaneously might not be advisable.

Specific antioxidants/Certain Types of ROS

Second, specific antioxidants quench only certain types of ROS. You cannot, for example, take vitamin E, alpha tocopherol, and assume it quenches all types of radicals and ROS with equal efficiency. The effect of glutathione is different from that of lipoic acid, which is different from coenzyme Q10, which is different from vitamin C, which is different from vitamin E. You have to look specifically at the antioxidant relative to the species you are trying to quench in the specific cell or tissue type you are talking about.

It is much more complex than the one-size-fits-all mentality of antioxidants. As we gain more precision and understanding of the mechanisms of action of these various drugs and the ROS they initiate, we will understand how to use antioxidants selectively to ameliorate some of the adverse side effects of chemotherapy without uncoupling the chemotherapeutic implications of the drug.

Third, the mechanisms of action of chemotherapeutics for different tumors have different effects. You might say that for one tumor type, one type of chemotherapeutic drug would work differently from another. Does the drug act systemically? What is the effective half-life of the drug? In most cases,

chemotherapeutic agents are metabolized and excreted within 12 to 24 hours, and their pharmacokinetic profiles reveal biphasic clearance. We need to be aware of the relative kinetics of these drugs, as well as their mode of action, as we try to determine the nutritional support programs we offer the patient.

Fourth, Dr. Labriola recommends using antioxidants at a time that would be outside what we would call the clinical window, that period of time the drug is having its influence and highest residence in the body. That will require knowledge pertaining to the rate of drug clearance, as well as dose.

Dr. Labriola was not saying there was no value to nutritional support or that one should not use it during chemotherapy. Instead, he was cautioning us to be mindful of the various aspects of the action and to use these agents outside the clinical window when the medication was working by way of increasing oxidant reactions within cells and enhancing apoptotic cell death.

In a recent issue of *FMU*, Dr. Nicholas Gonzalez discussed the use of pancreatic proteolytic enzymes to treat adenocarcinoma of the pancreas in combination with nutritional support and detoxification. Together, Dr. Gonzalez and Linda Lee Isaacs wrote an article that appeared in *Nutrition and Cancer*. In it they review their own two-year, unblinded treatment with 10-patient, pilot prospective case studies assessing survival in patients suffering from inoperable stage II-IV pancreatic adenocarcinoma. The patients were treated with large doses of orally ingested pancreatic enzymes, nutritional supplements, and a detoxification procedure, along with a balanced organic diet. These were results from January 1993 to April 1996 in a private practice setting.

Ten patients who had the inoperative, biopsy-proven pancreatic adenocarcinoma were entered into the study with appropriate informed consent. One patient dropped out and an 11th patient was added to the study. All 11 patients are considered in the data tabulation. Patients followed the treatment at home under the supervision of the authors. As of January 12, 1999, of the 11 patients who entered into the study, 9, or 81 percent, survived one year; 5 or 45 percent survived two years; and at this time, four have survived three years. Two patients are alive and doing well, one at three years and the other at four years. These results are far above the 25 percent survival at one year and 10 percent survival at two years for all stages of pancreatic adenocarcinoma reported in the National Cancer Data Base from 1995. Although this is a pilot study, it does suggest that an aggressive nutritional therapy with large doses of pancreatic enzymes may significantly improve survival over normal expectations for patients with inoperable pancreatic adenocarcinoma.

Dr. Gonzalez is putting these preliminary observations to the test in a NIH-sponsored clinical trial. He will soon have data available on the more comprehensive experiment to compare the value of this technique to other therapies. We will have a chance to speak with Dr. Gonzalez when the results of that study are complete.

Liver function and liver disease are other areas of concern with aging individuals. The liver is a busy metabolic organ. It is an immunological organ. It has a lot of work to these days. As a consequence, loss of liver function can cause problems across many levels. Its functions include globular and albumin protein formation, metabolism of isoprenoids that lead to cholesterol and its elaboration into other secondary metabolites of cholesterol, regulation of amino acid metabolism through transamination/deamination reactions, metabolism of glucose, triglyceride synthesis, and detoxification of hormones and exogenous substances, bile acid formation, and urea metabolism. Those functions are only

part of its responsibilities.

After the gastrointestinal tract, the liver is the first-level organ to receive a lot of the stuff that comes in through the digestive system. The changing quality of diet and other environmental exposures present the liver with a lot of metabolic and immunological responsibilities.

Hepatitis C and viral Infections

Hepatitis C and other viral infections are major contributors to chronic liver problems. Individuals often wonder if interferon is the only way to improve liver regeneration or liver immune and metabolic function in the case of chronic liver viral infection.

Two recently published reports discuss adjunctive approaches to improve liver function in individuals with various problems. One is a treatment with thioctic acid, or a -lipoic acid, for diabetic-related dysfunctions, both at the peripheral neuropathic level and at the liver level. This treatment was given in a two-year, randomized, double-blind, placebo-control trial. Its acronym is ALADIN. ALADIN looked at the antioxidant thioctic acid given therapeutically at doses of 600 mg per day versus a placebo. There was a very positive outcome on liver function in this study. There wasn't as much positive outcome in maintenance of neurological function in these diabetic patients, but there was some significant improvement in liver function, suggesting that thioctic acid may be a very important contributor toward maintenance of liver function in individuals who have oxidative stress as a consequence of diabetes.

One subgroup in this study experienced a very beneficial effect on several attributes of nerve conduction. Therefore, I don't want to say it had no value in this study on nerve conduction and peripheral neurological function, but it was not as general as the apparent influence on maintenance of liver function.

Alpha Lipoic Acid, Silymarin, and Selenium in Managing Hepatitis C

This is concordant with another study done by Dr. Burton Berkson. In June of 1996, on *FMU's* predecessor *PMU*, Dr. Berkson discussed his discovery of the important role of thioctic acid, or lipoic acid, in protecting against liver injury in individuals who have inadvertently ingested deathcap mushrooms and suffered liver injury through increased oxidative stress. By using lipoic acid, he was able to treat these patients who had inadvertently ingested this hepatotoxic deathcap mushroom.

Dr. Berkson has been focusing his energy and efforts for some time on protecting against hepatotoxicity and hepatic injury. In his recent report in *Clinical Practice of Alternative Medicine*, Dr. Berkson states he has been studying the relationship between thioctic acid and liver function since 1977. Now he has developed an approach in the management of hepatitis C using a combination of alpha lipoic acid, silymarin, and selenium, given concurrently. Silymarin and selenium added to thioctic acid appeared to improve the therapeutic success of the program. He reports on the management of three chronic hepatitis C patients with associated complications of cirrhosis, portal hypertension, splenomegaly, and thrombocytopenia. When these patients were given doses of lipoic acid, silymarin concentrate, and selenium, they underwent a significant reduction in their liver enzyme profiles and serum alanine aminotransferase level, and they experienced clinical improvement.

Hepatitis Case Studies

In one case study, a 57-year-old woman became infected with hepatitis C from a routine blood transfusion about 10 years ago. It had been a continued problem with increasing severity. She was put on this program of 600 mg per day of alpha lipoic acid, given in two daily divided doses of 300 mg each. She was given 900 mg a day of silymarin in 3 doses of 300 mg, and 400mcg a day of selenium. She was also given a B complex vitamin supplement, along with high doses of vitamin C, 2000 mg a day, vitamin E 800 IU per day, and 300 mg of coenzyme Q10. Over a period of about two months, her enzyme levels came down very nicely. After one month, she had lost almost 50 pounds of fluid. She is now working eight hours a day, feels healthy, looks good, and is not tired. That is a pretty remarkable case history.

Another case report is a 49-year-old woman infected with hepatitis C following a blood transfusion during trauma surgery 10 years ago. In 1997, the virus was identified as hepatitis C. A liver biopsy showed moderate cirrhosis with active inflammation. She also developed portal hypertension with esophageal varices. She had not developed thrombocytopenia because she had a splenectomy. The patient did not improve with interferon therapy and she was a candidate for a liver transplant. She was put on the program of 600 mg a day of lipoic acid, 200 mg three times a day; 900 mg of silymarin and 400 mcg of selenium. She was very responsive. Within seven months, she regained her health, and her ALA (ALT?) levels came down very nicely.

Clinical Benefits of Lipoic Acid/Silymarin/Selenium

A final report concerns a 35-year-old woman who developed hepatitis C from a blood transfusion during the birth of a baby 16 years ago. Three years ago, she became very ill and was diagnosed with cirrhosis, portal hypertension, and esophageal varices. As a result of the portal hypertension, she developed splenomegaly and thrombocytopenia. She was transferred to a university hospital for a liver transplant evaluation. She was put on the same program of alpha lipoic acid 600 mg, 900 mg of silymarin, and 400 *ug* of selenium, as well as a low-calorie, insulin management diet. She began to feel better and recovered very quickly. Her blood sugar dropped into the normal range. When first reported, it was 250 mg/dL due to problems with liver glucose metabolism and glycogen management. She became much more energetic and was able to resume normal work. Her serum liver enzyme profiles returned to normal and her viral load, as measured by PCR, went back down significantly.

These are interesting examples of the potential value of a lipoic acid/silymarin/selenium nutritional support program for individuals with chronic liver problems as a consequence of viral infection and inflammation.

Polyphenolic Food Substances

There are also polyphenolic substances in a variety of natural foods and beverages that can work synergistically along with the substances I have mentioned to serve as protective liver antioxidants. An example is theanine, found in green tea. Theanine is one of the polyphenolic family of substances that appears to have specific liver protective effects. Green tea theanine plays an important role in protecting against liver injury. There may be an array of nutraceutical compounds, which are important adjunctive agents for helping to protect the liver against liver inflammatory-induced injury associated with viral infection.

In addition to the liver, the gastrointestinal system is an important contributor to healthy aging. The gut is the largest immunologic tissue in the body. The host is continuously exposed to the environment via the mucosal surface. A large number of infectious agents, allergens, and foreign proteins enter our bodies orally and through the nasal and upper respiratory tracts, intestines, and reproductive tracts. The total area of these mucosal surfaces, which cover these tube-like tissues, is at least 200 times larger than the skin. The gastrointestinal system, therefore, plays an important role in distinguishing self from non-self, injurious agents, and protecting the internal milieu of the body. Dr. Sidney Baker, fourth recipient of the annual Linus Pauling Functional Medicine award, pointed out that maintenance of these barriers of defense is critically important in a program of health promotion and healthy aging.

The authors of a paper published in the *Journal of Parenteral and Enteral Nutrition* discuss the importance of maintaining the gastrointestinal mucosal surface area function as an immune organ called the gut-associated lymphoid tissue (GALT). Activation of the GALT is associated with increased inflammation. This is seen as altered secretory IgA and increased proinflammatory cytokines and TNF α . The authors of this article talk about the GALT's role in gut inflammatory conditions and their relationship to systemic inflammation.

Effects of Proinflammatory Cytokine Release

The increased release of proinflammatory cytokines by the GALT participates in regional GI inflammatory conditions like IBD or Crohn's disease. It may also act at a distance through cell signaling effects that enhance arthritis-like complaints. A discussion of this topic appears in a review article on cytokines and inflammatory bowel disease.

To manage these types of conditions, we employ the 4R Program™ which stands for remove, replace, reinoculate, and repair. The four Rs represent an algorithm for managing patients with altered gastrointestinal, immune, or digestive function.

Example of a 4R Program™ Approach

A recent paper titled "Case Problem: Medical nutrition therapy for a patient with Crohn's disease," which appeared in the *Journal of The American Dietetic Association* titled, focused on a program like the 4R Program™. The authors described a case history of a 59-year-old man with an eight-year history of Crohn's disease. He had been treated over the years with several courses of steroid therapy with initial benefit and subsequent relapse as the steroids were reduced. He had experienced weight loss and weakness and, when he presented at the gastroenterologist's office, he appeared gaunt and wasted. Symptoms included several months of diarrhea and blood in the stools. A flexible sigmoidoscopy showed severe inflammation of the colon.

While continuing with aggressive pharmaceutical intervention, he was put on a program to reduce exposure to antigenic foods. (This is the remove part of the program; to put the patient on a more elemental type of diet.) He was given nutritional support. The patient was first put on total parenteral nutrition (TPN) to calm his gut. Later he was put on a diet with fundamental enteral nutrition that was less antigenic. He was given appropriate types of dietary products—medium-chain triglycerides, readily digestible protein and carbohydrate, and essential fatty acids, along with added micronutrients known to help replenish and support repair of the GI mucosa.

He had a tremendously positive response. He continued to gain weight, reaching 89 percent of his usual body weight six weeks after the initial assessment. His strength and functional status were greatly improved. He was out of bed all day and was able to walk two miles a day on a treadmill, which he had been unable to do at the start of the program. Nutrition can play a very important role, even in very acute functional disorders of the gastrointestinal tract. Omega 3 fatty acids help modulate proinflammatory cytokines. Many studies have now demonstrated the role of omega 3 fatty acid supplementation in Crohn's disease and colitis.

These may not be better than sulfasalazine, but may be adjunctive. A recent report in the journal *Nutrition* compared omega 3 fatty acid supplementation to sulfasalazine in ulcerative colitis. It was found the supplements were not as good, but the possibility of benefit as adjunctive benefit remains open.

As part of healthy aging, both in prevention and therapy, we have some options. Let's turn to side II and continue our discussion of the healthy aging approaches.

INTERVIEW TRANSCRIPT

James Goodwin
Department of Medicine
Center of Aging
University of Texas Medical Branch
301 University Boulevard
Galveston, Texas 77555-0460

Introduction and Background of Dr. James Goodwin

JB: This month we have another extraordinary Clinician of the Month. Dr. James Goodwin, from the Department of Medicine, Center of Aging, at the University of Texas Medical Branch in Galveston, Texas, was a highly regarded presenter at our Seventh International Symposium on Functional Medicine in Scottsdale, Arizona in May. A graduate of Amherst College and Harvard Medical School, he received further training at UCLA, the National Institutes of Health, and the University of New Mexico School of Medicine. He is a board-certified internal medicine specialist, with an emphasis on rheumatology and geriatric medicine. He has written eloquently over many years. I have enjoyed his articles in a number of journals, on topics ranging from "the tomato effect" to how nutrition is seen as quackery in medicine, to geriatric medicine or chaos in medicine.

Dr. Goodwin is an insightful thinker about medicine. He has a range of experience moving from his NIH days through his medical professorship and geriatric medicine. Welcome to *Functional Medicine Update*, Dr. Goodwin. Please start by telling us how your travels have taken you professionally to where you are today.

JG: I came to geriatrics by accident. In the late 1970s I was at the University of New Mexico, my laboratory research was in immunology, and I was studying how prostaglandins regulate the immune response. One of the findings had to do with the fact that the immune response of older people was depressed because of an increased sensitivity to a certain prostaglandin—prostaglandin E.

Very early on, I wrote a grant proposal to the NIH saying that we now know one of the major causes of depressed immune function in the elderly and, theoretically at least, this has a preventable component. We could inhibit prostaglandins endogenously. The question is, does depressed immune response matter? There is a rather obvious answer, but I was asking this question before AIDS, so it wasn't as obvious as it seems that having a depressed immune response with age might be some homeostatic adjustment that would be good for you.

A Study of Healthy Elderly Individuals

I requested funding to do a longitudinal study of healthy old people. We gathered 300 people over age 70. To get into the study, they had to be in perfect health. They could be on no medication at all. They could never have been given a major diagnosis, and they had to pass a complete history and physical without having any diagnosis such as high blood pressure or diabetes. Many members of that cohort, founded in 1980, are still alive. We followed them asking a very simple question. Does depressed immune response act as an independent risk factor? When we took these 300 people who were perfectly healthy, about a third of them were anergic (that is, they did not respond to skin testing), and their T cells or lymphocytes in test tubes did not proliferate very well. We asked if that was an independent risk factor for future health and survival.

This was back in the early 1980s. I was spending a lot of time with these older subjects, and I became fascinated by them. They were unique in that they were all healthy and on no medication. They all had something they wanted to tell me about how they had stayed healthy. I began to realize I was asking a rather small question for such a big study. I realized there was little information on the natural history of thyroid failure in the elderly. There's little information on hearing and how it affects things. We kept adding more and more clinical studies onto this basic immunology study. Three or four years later, it was primarily a clinical and nutritional study. Immunology was almost an afterthought. That really got me into geriatric medicine. I realized I had a lot more fun being around people in their 80s and 90s than I did working as a rheumatologist. I gradually moved over into geriatrics. There were very few geriatric programs at that time, perhaps only two or three training programs in the country. The dean, who wanted to have a geriatrics program and center on aging, asked me to set one up. At a relatively young age, I was placed in charge of a center on aging and geriatrics program in New Mexico, and I've been doing that ever since.

Autoantibodies and Aging

JB: You mentioned a report in the *Lancet* out of the University of Bologna School of Medicine in Italy. When they contrasted healthy centenarians to unhealthy 60-year-olds, they found one of the principal differences was that these healthy elderly individuals had very low titers of autoantibodies against their endocrine glands, particularly anti-thyroid antibodies and anti-adrenal antibodies. In your immune or endocrine evaluations over the years, have you seen any relationship between how people may develop intolerance to themselves being related to this biological aging process?

JG: I find the body immensely confusing. When you get to the aging body, I'm overwhelmed with confusion in terms of what is a cause and what is an effect. It is clear that as we age, to a certain extent we lose the fine control on autoimmunity. We are born with the ability to make antibodies against essentially every antigen in our body, so we are fully capable of making autoantibodies. Therefore, autoimmune disease is now seen somewhat as a loss of control, just like cancer is seen as a loss of control of proliferation in the cell cycle.

As we age, we lose control somewhat selectively. If you look at autoantibodies, some, like antinuclear antibodies rheumatoid factor, are much higher levels and much more prevalent than other autoantibodies with age. It all seems to be a loss of suppressor cell function. Where I have problems with theories is that we are looking at a very complex organism. We can step in at any one point in that organism, pick a result of whatever the proximal cause is, and say here we have a proximal cause. We know a lot about immune function because it's the most easily biopsied tissue in humans. If we could have gotten liver cells like we were getting white blood cells over the last few decades, I'm sure we'd have all sorts of theories about the importance of liver function in aging. I have tremendous difficulty separating out cause from effect. I don't want to be nihilistic about it, but I do want to be humble in the face of the complexity of the body. Otherwise, you say that autoantibodies are important and, therefore, I have this treatment to lower your autoantibodies, when in actuality, autoantibodies are just a result of some other thing that we don't know about.

Cause or Effect—the Use of Cement Controls in Evaluating Theory

Let me take that a little further. My wife Jean and I wrote an obscure article titled "The use of cement controls in evaluating assumptions about etiology and mechanism of action." I wrote it back in the 1980s when I was tired of people coming along saying they understood why old people have poor immune responses: their white cells don't grow as fast. Then someone else came along and said they understood the basic cause: it's because they don't make enough IL-2. Two years later someone said he understood the basic cause: it's because the gene that makes IL-2 isn't transcribed or translated. With each step more proximal, people really thought they were getting at some sort of core identity.

My thesis was to take either a human or a white blood cell and for the human, drop a block of cement on them. For the white blood cell, we just add cement to the test tube. Then we look and wonder about the cause. We find this human under a block of cement, and we wonder why this person is splashed on the highway. If we look, we're going to find that his lymphocytes don't proliferate very well. We are going to find that he doesn't make much IL-2. Or, in the test tube, we find that as those cells are dying or getting sick from whatever cause, there's going to be the same final common pathway of proliferation going down. There is the same pathway of IL-2 production going down, and receptors going down. We find all of those things that, when people get hold of them, make them think they've finally achieved the answer. I see most of them as epiphenomena, because the human body is so complex. Just because we can measure something very carefully doesn't mean it has a critical proximal, causative role in what's going on.

Evaluating the Whole Organism Approach

JB: That's very insightful. It takes me to a whole organism level. This was actually first a hypothesis by Dr. Fries in the *New England Journal of Medicine* back in 1980 about compression of morbidity. Later, in

1998, there was a follow-up of 17-year studies of Stanford alumni. Do you feel the whole organism approach toward healthy aging is real, even though we can't really understand the mechanism?

JG: As a physician, I've got to stay with the whole organism. You give me your finding, you tell me what you found empirically, and I'll be able to explain it to you with a mechanism. The hero of a Walker Percy story reads his horoscope, which says he's kind to a fault, he's shy, and other people think such and such. The hero says, yes, that's me. Then he realizes he's reading the wrong horoscope. When he reads his proper horoscope, it says he's selfish and willful, and the hero says, yes, that's me. It's sort of a metaphor for the fact that we're very complex and we don't understand ourselves, so we're going to identify with any description. For any empirical finding you bring me, I can find a theory to explain it. If you come the next day and give me the exact opposite empirical finding, I can find a theory to explain that. I have a deep distrust as a clinician in theories. I have much more trust in looking globally at the individual patient.

The nice thing about Fries is that he started with a theory, but what Ken Manton did in the *Proceedings of the National Academy of Sciences*, was to test that theory empirically. He used national data and showed that, indeed, the period of time between when we become disabled and when we die is shrinking, even as our life expectancy is increasing. I wasn't sure about the Fries theory, even though it drove a lot of good research on compression of natural morbidity. I must admit, I was rather skeptical. His reasoning did not resonate with me when he first published his theory. I thought, well, with a lengthening life span, why wouldn't there be an expansion of morbidity, but indeed, he turned out to be correct, at least in the first good test of it, which was this article in PNAS by Manton.

Chronological and Biological Aging

JB: There has been considerable discussion recently about the difference between chronological aging and biological aging. Do you sense an emerging view in geriatric medicine that there is a difference between biological and chronological aging? Are there some variables that can influence the biological aging process?

JG: There definitely are factors that can influence the biological aging practice. I'm sure you could list them quicker than I. They include antioxidants, exercise, or other interventions. These have clearly worked in experimental animal models, and epidemiological studies now indicate these factors appear to be important in humans. I don't want to get too far into this biological versus chronological issue because I distrust some of the motivation behind it. I think there's too much death denial in our society. One fact I point out when I get into these chronological versus biological arguments is that in any longitudinal study of aging, you cannot find a factor as strong as chronological age in terms of predicting survival. Examples include the huge EPESE studies, in which they follow 3500 older people for 15 years, and HANES and all big longitudinal studies of aging.

The strongest factor in predicting your survival is how old you are. That's stronger than cigarette smoking and stronger than all the health indicators. Indeed, there are huge differences in biological aging. We should not, however, allow our patients or our society to kid themselves that somehow if we do the right things, we're not going to get old or die, because chronological age is still the biggest determinant of life expectancy.

Anti-Aging Medicine and Hormone Replacement

JB: That leads to an interesting area of controversy. It has been called anti-aging medicine, as if we somehow were fighting against an incurable disease called aging. The lowest common denominator is hormone replacement therapy. If you measure something and it's low, that must mean if it's high in youth and low in older age, you give it. Do you have thoughts about hormone replacement anti-aging strategy?

JG: I have thoughts, but they're confused. I have biases. I think most physicians have a strong bias that you don't mess with Mother Nature. I remember 15 years ago I would confidently tell postmenopausal women that if Mother Nature shuts off their estrogen, I don't want to replace it. I'm coming from a sort of *primum non nocere* perspective. I don't do that any more. Now I'm a big fan of postmenopausal estrogen replacement. I think it's a wonderful idea. It took a lot of evidence to convince me because I think *primum non nocere* is a good idea, and we shouldn't mess with Mother Nature. I start with a fundamental bias, and there has to be a fair amount of evidence, not just theory, to take me over the other way.

From a theoretical perspective, we have all the motives in the world to have a lot of true believers out there. No one wants to die; no one wants to get old. In science, you're not supposed to study a disease that you have because you lose perspective. You lose the ability to be disconnected from the process. I worry about things under the heading of anti-aging medicine. My initial bias is negative because I see the enormous incentive for people to believe these things work. On the other hand, I started off by saying I think I was wrong about estrogen. In 10 or 15 years, if there's a lot of evidence that says yes, indeed, you routinely to give x and y to your patients, I will do that. Until then, my bias is on the side of conservatism. If I have a skinny old guy who's falling, then I'm treating a disease. Then I can look at anything hormonally and give him androgens or whatever I think is going to work, because I'm treating a disease. If I have someone who's doing okay, it seems to me there has to be a much higher burden of proof before I give them a potentially harmful thing in order to keep them okay.

The State of Geriatric Medical Intervention

JB: There is confusion in this field right now. I think to have an expert kind of acknowledge the state of confusion is helpful as part of our process. How does this translate, in the clinic and in the practice of geriatric medicine? We often hear there is overutilization of services provided to older patients. There is a difference between controlling the supply of services and controlling the demand for services. We often emphasize the control of the supply of services by some kind of rationing or managed care, rather than teaching patients about the demand for services, or the need for services. You wrote an editorial in the *New England Journal of Medicine* presenting your view of the state of geriatric medical intervention. Would you bring our listeners up to that understanding?

JG: One of the problems in talking about medical care right now is that we're really in a revolutionary state. You cannot overemphasize the importance of going from fee-for-service medicine to managed-care medicine. There are obviously many incentives that drive medical care, but one of them is financial incentive. Marx taught us that financial incentives are important in all aspects of life. Whatever financial incentives there are, they are switched 180 degrees when you go from one system to the other.

When we're sitting in the middle of a system, as we are today, which is in part managed care and partly fee-for-service, what you get is chaos. My feeling has been that traditionally, since Medicare was the traditional fee-for-service practice, older people tended to be overtreated. They tended to be overtreated because they were treated the same way that younger people were, where studies had shown that yes, this might be an appropriate way for treating younger persons. In other words, someone comes in with a stomach complaint. It might be appropriate to stick a tube down their throat and look in their stomach. This may be the best way to handle it to prevent problems later on. But it isn't at all clear to me or to other geriatricians that it is the most appropriate way to treat an 82-year-old. A lot of things we do in medicine have unmeasurable toxicities and side effects. It's not a small thing to get an 88-year-old a chest X-ray. You're paying a price for that. You're paying a price for a lot of things in 80-year-olds that you don't even think about when you're treating a 40-year-old. I think that traditional fee-for-service medicine resulted in a lot of over-treatment and a lot of medicalization of normal aging. I think that's bad for our old people.

Benefits of Geriatric Medicine

The reason I like being a geriatrician is I'm dealing with real illness. When my patients come to me, it's because they hurt; and they have a need. It's not to deal with some sort of theoretical future event. They're right there. When you're 85, you're not concerned with risk factors for theoretical future events. The 85-year-old is concerned about getting up, getting around, getting fed. Spiritual matters are also important, because you know your life expectancy is getting short. It's old-time doctoring; it's real medicine. I'm ashamed to admit that I looked at managed care 15 years ago and said, bring it on. Managed care will reduce some of this over-utilization, and we can spend the money we save on colonoscopies where we need it—on nurse visitors to come out to the house or run exercise programs or things that are helpful.

Unfortunately, because managed care got hooked up with for-profit industry, it hasn't worked that way. I think we're in a revolutionary state. Many physicians and many people worrying about health care feel very uncomfortable. I don't know how it's going to turn out. I think there's a chance there might be some sort of federalization of health. We may go in a lot of different directions, but I tell my medical students that they shouldn't consider this a steady state. We're in the middle of a revolution in a societal organ that is very important.

Revolution in Medicine

Medicine is critical to society, just like religion education are. When you have these large societal organs like medicine, education, or religion, typically they change very slowly over time; typically they're very stable. Then, every once in a while, you get a revolution and the revolution is very ugly. Whether it's the French Revolution or education in the 1960s, or whether it's the revolution in medicine we're undergoing now, a lot of people get hurt. A lot of people are uncomfortable and unhappy. Then, things settle down again and you get back to a stable situation.

So I tell my students they shouldn't have deep thoughts about what's going on now because it's going to be different in five years. In 10 or 15 years we may be back in a stable system where we can just concentrate on giving good care to our patients.

Core Wisdom for the Future

JB: I would like to ask you to leave our listeners with some core wisdom to guide them in their thinking about their practices and their relationships with patients. Is there anything you give your students or your colleagues that you consider very insightful as to how we move forward?

JG: I don't think I can give insight to established practitioners. I think established practitioners have the insights. I think sometimes the systems don't, and clearly, the students don't because we can't expect it of them. The major thing I emphasize to my students is that whether your patient is happy or not is critically important, and you can actually play a role in that. It's not my only goal in life, but I try to have my patients leave my office in a happy state. To the extent that we can validate them and be a witness in terms of what they're going through, that is a major thing a physician can give an older patient. That's not to be dismissed as bedside technique or hand-holding. It is a major component, no matter how many machines we have. No matter how many lives we can save with wonderful intervention, witnessing for our patients, being there, understanding their problems, and listening are still the major things we can do for our older patients.

Conclusion: The Best of Humanistic Medicine

JB: Dr. Goodwin, thank you for doing something quite extraordinary. You started in practice with a reductionistic and analytical perspective with the research you did at NIH. Later, in your medical school appointments and now in your teaching, you have reached what I would describe as the best of real humanistic medicine. It takes a remarkable bicameral brain and being to do that. You have given us all guidance and about forming balances in this complex world of medicine. It doesn't get easier; it gets more confusing each day as we have more tools, but we still have people feeling crummy. So, thanks very much for sharing your wisdom and insight with us.

JG: Thank you very much for inviting me.

To continue with the topic on side I, some factors related to unhealthy aging are subject to remediation through a program like the 4R Program™. We discussed the "remove" phase. The reinoculation phase of the 4 Rs concerns the replacement of friendly bacteria—lactic acid-producing bacteria, acidophilus and bifidobacteria.

Immune function can be improved by yogurt supplementation with live cultures of lactate-producing organisms. A recently published paper in the *American Journal of Clinical Nutrition* describes a clinical study using supplementation with live bacterial cultures and prebiotics with substances (eg, fructooligosaccharides) that selectively nourish these friendly bacteria to improve immune function. Oral supplementation can help improve butyrate production in the colon as a colonocyte fuel and substance that helps regulate cell cycling in the colonocyte. This is the third R, the reinoculate phase.

Reinoculating the Bowel in Managing Ulcerative Colitis

Last year in *FMU* I discussed a *Lancet* study that described using nonpathogenic *E. coli*, rectally instilled or orally supplemented, in the management of ulcerative colitis. This reinoculating of the bowel with friendly bacteria was highly effective. The paper, titled "Non-Pathogenic *Escherichia coli* versus

Mesalazine for the Treatment of Ulcerative Colitis: a Randomised Trial," describes research from the Centre for Digestive Diseases, General Infirmary at Leeds, England. It was a single-center, randomised, double-blind study in 120 patients with active ulcerative colitis. Of the 120 patients invited to participate, 116 accepted; 59 were randomised to mesalazine and 57 to the *E. coli* oral supplementation. All received standard medical therapy together with a one-week course of oral gentamicin

After remission, patients were maintained on either mesalazine or *E. coli* and followed up for a maximum of 12 months. In the mesalazine group 44, or 77 percent, attained remission, compared with 39 or 68 percent in the *E. coli* group. Mean time to remission was 44 days (median 42) in the mesalazine group and 42 days (median 37) for those treated with *E. coli*. In the mesalazine group, 32 (73 percent) patients relapsed compared to 26 (67 percent) in the *E. coli* group. Mean duration of remission was 206 days in the mesalazine group (median 175) and 221 days (median 185) in the *E. coli* group. Results of the study suggest treatment with nonpathogenic *E. coli* has an effect equivalent to mesalazine in maintaining remission of ulcerative colitis. The beneficial effect of live *E. coli* may provide clues to the cause of ulcerative colitis. It may also relate to the importance of introducing a therapeutic program like the 4R Program™.

Irritable Bowel Syndrome (IBS)

Irritable bowel syndrome (IBS) has recently received attention in the medical community as a consequence of the development of the new drug, alosetron. It is marketed for treatment of women with diarrhea-predominant IBS. Alosetron is a very selective drug for a selective type of IBS that influences the serotonin-receptor sites in the gut mucosa. It is a potent and selective serotonin receptor antagonist that modulates the enteric nervous system and may reduce pain and hypermotility in women with diarrhea-predominant IBS. Whenever we modify serotonin receptors, although a drug may be selective for a type of receptor in the GI tract, there will be overlap with other serotonin reactions in other tissues. Therefore, one might expect secondary side effects. The package insert for this drug describes a number of selective side effects that are of concern. It is also important to point out that this medication is very specific for women with diarrhea-predominant IBS. It doesn't appear to work for men.

A paper in the *Lancet* talks about the efficacy and safety of alosetron in women with IBS. This randomised, placebo-controlled trial found that 24 percent of patients in the alosetron group and 16 percent in the placebo group dropped out. The difference in the dropout rate was due mainly to constipation in the alosetron group. More alosetron-treated patients than placebo-treated patients (41 percent versus 29 percent) reported adequate relief for all three months of treatment, a 12 percent difference between the two groups. It is a fairly small difference. We cannot call this an extraordinary breakthrough medication with that kind of statistical improvement. Alosetron also significantly decreased urgency and stool frequency. Constipation occurred in 30 percent and 3 percent of patients in the alosetron and placebo groups, respectively.

Evaluating Alosetron in Treating IBS

The editorial following this article is titled "Neurotransmitter Antagonism in Management of Irritable Bowel Syndrome." The author believes the jury is still out. Although the study has shown some beneficial effect of alosetron, the drug has not yet been compared with existing pharmacological or psychological therapies, and its costs have not been taken into account. Its effect in men is also being investigated. Until

these issues been clarified, the role of alosetron in managing IBS remains unclear.

A large national health insurance agency recently wrote to an FMU subscriber (a physician) concerning reimbursement for the use of alosetron in the management of IBS. This particular agency has determined that alosetron for the treatment of IBS will require prior authorization before it is covered as part of a member's health plan contract. This requirement results from concern about the narrow window of therapeutic efficacy and the value it may or not have in a risk/benefit relationship.

Alternatives to Drugs in Treating IBS

The alternative to drugs like alosetron is nutrition and lifestyle intervention. At the Functional Medicine Research Center we have had remarkable success in managing IBS with nutrition and lifestyle intervention and the 4R Program™. This may be a condition that is not in search of a drug. It may be in search of an appropriate nutrition and lifestyle intervention program that involves lower risk of adverse side effects.

According to estimates of the prevalence of IBS, it may affect 20 percent of U.S. adults and be one of the top 10 reasons for physician visits. Its very prevalence may suggest beginning IBS treatment with a low-technology approach. The *primum non nocere* approach, as Dr. Goodwin pointed out, would be nutrition intervention. IBS provides a tremendous opportunity successful implementation of nutritional strategies in the clinician's practice to lower both the cost and the potential adverse side effects that might occur with pharmacological intervention.

L-Glutamine in the 4R Program™

As part of the 4R Program™, one of the nutrients we have looked at for gut nutrient replenishment of mucosal function or gut nutrient support is L-glutamine. Glutamine is a signaling molecule in intestinal cells. It is a "competence factor" necessary for intestinal cell proliferation, intestinal fluid/electrolyte absorption, and mitogenic response to growth factors. Glutamine deprivation produces apoptosis. Glutamine stimulation of quiescent cells produces immediate early gene expression and activation of appropriate cell signaling.

Glutamine is more than just an amino acid of a nonessential nature. It may play an important role in maintaining metabolic function, cell cycling, and mucosal cells, and interconnecting that with other mucosal-mediated inflammatory conditions. Glutamine can, therefore, be seen as an immune-enhancing nutrient, according to a recent paper in *Journal of Parenteral and Enteral Nutrition*. This review paper discusses its role as both a preventive and treatment-related agent for infection or gastrointestinal inflammatory conditions.

One should not, however, focus solely on glutamine. The amino acid arginine also plays an important role in gastrointestinal inflammatory conditions. Animal studies have shown an arginine-supplemented diet decreases the expression of inflammatory cytokines and improves survival in immune-upregulated animals. Arginine and glutamine may work together through modulating nitric oxide, cell signaling, and the cell cycles. The combination also increases butyrate production in the gut through the glutamine connection, which may have positive benefit on colonocyte regeneration.

Glutamine and Glutamate

Glutamine and glutamate are obviously connected through an amino transfer reaction in which glutamate is amidated to become glutamine. Vernon Young and his colleagues at MIT have been studying glutamate and other amino acids for many years and are experts in protein metabolism. Theirs was the first group to discover the role of arginine-based diets on nitric oxide and, ultimately, on blood pressure. This fortuitous observation led to the real discovery of nitric oxide in cell physiology.

In the *Journal of Nutrition*, Dr. Young and his colleagues recently published a paper titled "Glutamate: An Amino Acid of Particular Distinction." They point out that glutamic acid, or L-glutamate, is an abundant biomolecule. It plays an important role in cellular metabolism. Even though we do not consider it an essential amino acid, as such, it facilitates involvement in a number of metabolic processes, including an interface between amino acid metabolism and carbohydrate metabolism. Therefore, it plays an important role in nitrogen economy of the host, as well as serving as a nutrient and an energy-yielding substrate. It is also a potentially excitatory molecule in the nervous system. It has multiple influences. Glutamate stands at the interface between amino acid and carbohydrate metabolism, or protein and carbohydrate metabolism.

Glutamate Considerations

There are three things you might want to consider with glutamate. A well-described transamination system involves the transfer of the α -amino group of glutamate to an α -keto acid. Glutamate is also a precursor of glutamine. Second, the glutamate family of amino acids, which includes arginine, ornithine, proline, histidine, and glutamine, requires the conversion of these amino acids to glutamate for their metabolic disposal. Last, glutamate serves as a substrate for the synthesis of N-acetylglutamate, an essential allosteric activator of carbamoyl phosphate synthetase. 1, a key regulatory enzyme in the urea cycle. Glutamate should be contrasted to glutamine. Glutamate plays an important switching role between protein metabolism and carbohydrate metabolism and also have some neurological function.

Arginine, Glutamine, and Insulin Sensitivity

Incidence of type 2 diabetes is increasing as we move into the third millennium. According to an article in *Diabetes Care*, cell signaling and the interrelationship with cell signaling molecules that relate to energy economy have something to do with type 2 diabetes, or non-insulin-dependent diabetes, insulin resistance, or hyperinsulinemia. One factor may be the interrelationship between carbohydrate and protein metabolism and signals related to those effects. That may explain why arginine and glutamine both have an effect on insulin sensitivity. Both of these substances improve insulin sensitivity in animal and human trials. These glutaminergic amino acids may play a role in these pathways and relate, in part, to some of the effects we are seeing with insulin sensitivity.

Glutamate as a Neurotransmitter in the Brain

Brain Meldrum from the Department of Clinical Neurosciences, Institute of Psychiatry, London, recently discussed glutamate as a neurotransmitter in the brain. It has an interrelationship with the N-methyl-D-aspartate membrane transport on the neuron and activation. It may be involved with excitotoxicity. Clinical conditions that respond to drugs that act on glutaminergic transmission include epilepsy,

amnesia, anxiety, hyperalgesia and psychosis (perhaps even schizophrenia).

We discussed a report from the *American Journal of Psychiatry* in which researchers gave therapeutic doses of the amino acid glycine (in excess of 0 grams/day orally) to improve schizophrenic response to anti-psychotic medications by managing the glutaminergic pathway more successfully. This is another example in which a little is good but a whole lot more may not be better in individuals who have specific sensitivities.

Monosodium Glutamate (MSG)

Monosodium glutamate (MSG) is a big issue. Some people appear to be more sensitive to MSG, which is a form of delivery of glutamic acid. Individuals who have a low taste threshold to glutamate (the so-called umami taste) may be hypersensitive to glutamate. They may have more of a reaction at the neurological system to glutamate. This evidence emerges from an interesting series of papers, one of which appeared in *Nature Neuroscience*, on the glutamate receptor variant and its relationship to taste reception. This paper suggests that people who are more sensitive to glutamate in a taste test may have a higher response at the neurological system level and may be more vulnerable. The umami taste or glutamate taste enhancement is the reason you put meat tenderizer and flavor enhancers on foods to bring out the flavor. The authors of this article discuss protein-rich foods high in glutamate. A high sensitivity to glutamate, demonstrated by a very rapid reaction to the taste, may indicate an individual has a higher neurological response. Another article, titled "Glutamate Excitotoxicity in a Model of Multiple Sclerosis," appeared in *Nature Medicine*.

Environmental Variables Contribute to Healthy (or Unhealthy) Aging

A number of variables in our environment may contribute to healthy or unhealthy aging. Alzheimer's disease protective factors—the antioxidants, vitamin E, lipoic acid, and N-acetylcysteine—also interrelate to the upregulation of immune function in the brain with glial hyperfunction. All of this information is part of a new view of aging, extending healthy aging, and compressing morbidity. The objective is to get the most out of that wisdom that is resident in individuals who have the fortune of living seven, eight, nine, or ten decades. I think that is a great mandate for functional medicine and certainly a theme we will be discussing in future issues.

I thank you for being with us. Thanks also to Dr. Waickman for his insightful comments.

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