January 1998 Issue | Mitchell Kaminski, M.D., F.A.C.S., F.I.C.S., F.A.C.N.

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Dr. David Eisenberg recently published a paper in the *Annals of Internal Medicine*(1997;127:61) about complementary medicine therapies and how they serve patients. An earlier study by Dr. Eisenberg and colleagues, published in the *New England Journal of Medicine* in 1995, discussed the use of unconventional medicine in the United States. They found that 10.8 billion dollars would be spent on out-of-pocket services in unconventional medical practice. That information awakened the medical community and third-party reimbursement companies regarding the wide utilization of these services.

In his recent paper in the *Annals of Internal Medicine* entitled "Advising Patients Who Seek Alternative Medical Therapies," Dr. Eisenberg eloquently describes how to counsel patients about what alternative or complementary therapies might be desirable, and where to get more information about these therapies. The goal for physicians is to do a better job communicating what they have to offer.

Dr. Eisenberg discusses various research journals like the *Journal of Natural Products*, *Journal of Ethnopharmacy*, *International Journal of Pharmacognosy*, and *HerbalGram.* He examines professional societies, including the National Certification Commission for Acupuncture and Oriental Medicine, American Association of Naturopathic Physicians, Federation of Chiropractic Licensing Boards, and National Center of Homeopathy. All are sources of information for physicians to learn to counsel patients on referrals to complementary medical practitioners.

Times are changing. We know we are in a state of revolution when the *Annals of Internal Medicine* starts considering referrals to complementary medical practitioners.

Another interesting theme evolving in the primary medical literature is the concept that our environment combines with our genetic predisposition to give rise to the expression of function. One area that is specific to the pharmacology-based practice of medicine during the past 40 or 50 years is the role of drugs and medications on intermediary metabolism and how their reaction is unique to the individual.

The concept of atypical or adverse drug reactions is recast in the light of this new information. Individual reactions are not atypical. They are typical and reproducible in that patient as a consequence of his or her unique metabolic response to that class or family of medications. As we learn more about how to predict patients' specific metabolic personalities, we can define potential for adverse reactions before they occur. We can then avoid those medications in people at high risk for adverse reactions, or we might find ways to ameliorate the expression of certain principles of reaction so the person can tolerate that drug without an adverse reaction.

Over-the-counter medications that have been considered reasonably safe for years are now suspected of causing adverse responses in individuals of certain metabolic types. *JAMA*studies published two years ago described the toxicity of acetaminophen in individuals who had either been fasting or consuming alcohol at the time they took the drug. Their risk of liver toxicity and liver damage was many times higher than those who were not fasting or consuming alcohol when they took acetaminophen.

A recent issue of the *New England Journal of Medicine* (1997;337:1112) contained another report and a follow-up editorial that continues to advance this concept. In this report, the investigators describe adverse responses to acetaminophen at an urban county hospital over a 40-month period. They review the source and cause of these accidental overdoses. These were people who did not, presumably, want to overdose but for reasons beyond their understanding, they had an adverse response. These were individuals who ingested 4 grams of acetaminophen or less per day, implying that their doses were not suicidal.

The researchers found that individuals who, because of their genetic uniqueness and nutritional and health status, have unique hepatic detoxification chemistry and impaired detoxification abilities. This lack of detoxification ability is a consequence of the impairment of phase II enzyme systems in detoxification that are involved with glutathione conjugation.

Acetaminophen is metabolized principally through glucuronidation and sulfation. When the drug is taken at therapeutic doses, only a small portion is oxidized by the cytochrome P450. When ingested levels exceed the capacity of the body to engage in sulfation and/or glucuronidation, another intermediate is produced as a consequence of phase I detoxification reaction. This intermediate substance, called N-acetyl-para-benzoquinoneimine, or NAPQI, is highly toxic to the liver. It forms covalent binding with proteins and DNA, alters gene expression, and can produce apoptotic cell death – cell suicide, so to speak – from oxidant stress-induced damage.

INTERVIEW TRANSCRIPT

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We are fortunate to have as our Clinician of the Month a man whom I professionally and personally admire for his insight, dedication, and clinical acumen, who brings us some insights into the gastrointestinal/hepatic connection to chronic illness and how it can be a useful entry point for nutritional therapy for a variety of problems related to inflammation, atopy, allergy, and degenerative disease risk. Dr. Mitchell Kaminski is certified both as a surgeon in internal medicine, and in nutrition. He is a clinical professor of surgery at the Finch University of Health Sciences, Chicago Medical School. He works at Thorek Hospital outside of Chicago and has a very active practice. Dr. Kaminski combines the inquiring mind of a researcher with that of an astute clinician, and he balances those two worlds very well. On the one hand, he explores the frontiers of new information, and on the other he sieves that information and

delivers it in effective ways to patients so they can benefit from what is both new and reasonable

JB: Dr. Kaminski, it is a pleasure to have you on *Functional Medicine Update.* What drew you into nutrition from your background in surgery and internal medicine?

MK: Thank you, Jeff. It's a pleasure to be here. Although I've been accused of being an internist, people forget that I am a board-certified surgeon and that I also have my Boards in nutrition. I am not a trained internal medicine fellow, although in the way things function, looking at the patient holistically, there has to be a lot of medicine practiced on the part of any surgeon.

I got into the nutrition area by a series of accidents. I took my residency at Walter Reed during the Viet Nam conflict, with every intention of becoming a plastic surgeon, but I became impressed with a very new technique. In fact, I was involved in the care of the first patient in the department of surgery that eliminated malnutrition from disease and trauma. That technique is called intravenous hyperalimentation, or TPN.

As time went on, it became evident that the gastrointestinal tract is God's way to feed and that if you have a patient who cannot eat, but has a gut that works, it was wiser, just intuitively, to use the intestine to deliver the nutrients via a tube being placed either nasogastrically or by other surgical means. And that's how we got into it.

When we eliminated malnutrition from disease and trauma, none of the young men who came to us with severe war wounds who were expected to die did so. We applied that technology to people with other very serious conditions that were potentially reversible or treatable. When we eliminated malnutrition from that algorithm, they didn't die, although they had been expected to die. One thing led to another, and I set aside the idea of becoming a plastic surgeon and devoted my time to understanding the link between nutritional support and outcome. It's been a lot of fun. It's led me down the yellow brick road; I'm still clicking my heels and enjoying every minute of it.

JB: One way you have really assisted me and countless others who have been fortunate enough to be associated with you or listen to your lectures, is in the way you have developed the concepts of gut function, immunological function, and the inflammatory cascade. From a clinical perspective, how do you see the gut and the immune system as being interrelated, and how do you communicate that relationship to patients and put together treatment programs based on that model?

MK: My earliest appreciation for the interlink of the immune function of the gut also stems back to my Army days. I spent nine years in the Army. The last year I was assistant chief of the Physical Sciences Division out at Fort Dietrick and our job there was biological war defense. A coworker had discovered small molecules released by monocytes that had hormone-like effects, apocrine-like effects, and paracrine-like effects.

At the time we called it LEM -- leukocyte endogenous mediator. Today they are called cytokines. The link to the intestine became heightened when, using my interest in feeding the gut, I began to contribute to the literature that clearly showed that if you did not use the gut, you had problems systemically and globally with decreased immune function and the appearance of deep sepsis in organs remote to the intestine. When you did use the gut, even at a very minimal rate, you maintained immunity globally.

That science has progressed quite a bit now, and it has proved to be absolutely true. Looking at it in a more focused way with the HIV problem, doing reading around that, employing the background knowledge and then updated knowledge of cytokines, it became apparent that the gut is the center of the immune system. In fact, there are more immune cell elements in the intestine than in the bone marrow, liver, spleen, and Kupffer cells combined. It is a very exciting and very dramatic center of your immune system.

JB: You are now referring to what has been abbreviated in the literature as the GALT, the gut associated lymphoid tissue, how that is modulated, how it relates to dendritic cell activity and mucosal cell activities. That is becoming a fascinating story. Some of those messenger substances are even interconnected with brain neurohormones. It is hard now to partition our physiology into specific subcategories. Using this model, it appears to me that as a surgeon you are addressing the patient as an interconnected whole being rather than just dealing with organ parts as isolated pathology events.

MK: Absolutely. Dr. Leo Galland, one of your previous contributors, enlightened me to the fact that there is not a single neurotransmitter or receptor in the brain that you do not also find in the intestine. Even more important is the area you and your group have so eminently contributed to, namely dysbiosis. Dysbiosis leading to adhesion of pathogenic organisms to the mucosa, causing inflammation and leaky gut, is real. I am very fond of testing that. I have found a link between dysbiosis and the exacerbation, or worsening, of virtually any other condition the patient has, from AIDS to arthritis. This is something that you and your group have put out over and over again, and it is slowly working its way into the allopathic thinking. The contribution of Great Smokies Diagnostic Laboratory, in giving us the tools to objectively measure it, to correct it, and objectively measure it again is beautiful. That's the allopathic system. Now we can bring all of this wonderful nutrition into this arena.

JB: It seems the body is triggered by a balance of effector molecules, activators, and inhibitors. When we look specifically at the inflammatory markers, the so-called TH1 and TH2 system, how do you see the relationship of the gut to the cytokines of the proinflammatory and anti-inflammatory systems?

MK: T-helper cells can be in different states of activation. First, they may be in a TH zero, or a resting state, in which they put out a little gamisch of cytokines and are not particularly oriented in one direction or another. Second, they may be stimulated to a lower state of readiness. The TH1, or some people might even call those the anti-inflammatory or idling up-stage set, produce predominantly interleukin 2 and INF gamma. That is the state of readiness in which most of us find ourselves now.

If there is a persistent antigen load, however, whether it is an infection, inflammation, radiation, or a state of gut dysbiosis or leaky gut, with organic molecules and other protein peptides coming across, constantly bombarding this set with other cytokines, the T-helper cells switch into what you might call a pro-inflammatory state. It is as though they say, "I've got to find the invader. I've got to mobilize myself and destroy this invader." That state is characterized by IL 4,5,6,8,10, tumor necrosis factor alpha and so on. That kind of a cytokine set gives you, in effect, a chronic state of subclinical endotoxemia. People in this condition are, as you have fondly pointed out, our "walking wounded." You can find that walking-wounded set linking back to what I said earlier as part of the pathology. This makes conditions, which should respond to treatment, very difficult to treat.

I would like to use one example. A good friend and colleague of mine, Dr. Raja Atiyah, is a well-known

head and neck cosmetic surgeon who is a big name in allergy. He and I have been collaborating on several small projects. He found a paper describing research on resistant-to-treatment, chronic allergic sinusitis in patients who had a nose job, sub-mucous resection, to correct a cosmetic defect. The study looked at the mucosa there for free radical scavengers like glutathione, uric acid, vitamin C, vitamin E, and so on. They found they had adequate tissues.

Then the tissues of people who were not responding to any form of treatment in the allopathic system were biopsied and found to be deficient in free radical scavengers. So, on his own, without asking me, Dr. Atiyah went ahead and loaded up his patients with vitamin A, vitamin C, glutathione, selenium, and CoQ10. He has had 27 patients now, all in a row, about whom, in his own words, he has said, "They're not improved, Mitch; they're cured!" That antioxidant link to the TH1/TH2 profiles is clear in regard to the perpetuation of the chronic illness. Free radicals are produced which then stimulate NF-*Kappa* B, I-*Kappa* B to separate. The NF-*Kappa* B goes to the nucleus, tells the nucleus to make more TH2 cytokines, which then produce more free radicals, and unless you intervene with a nutritional therapy to stop that link, you are going to have this ongoing problem.

JB: That is a beautiful segue into very exciting work you have been doing as a pioneer in the area of HIV/AIDS, looking at that, again, as an inflammatory and noninflammatory-modulated immunological problem and how it relates to the gut. Could you tell us how you are approaching that?

MK: That is, in fact, how I came to know you. I was the national medical director of a company that was interested in HIV. I took it upon myself to do a little reading, and I discovered several papers that clearly said HIV is a TNF (tumor necrosis factor) disease. TNF is the signal to the virus genome to begin replication.

I said, "well, fine. Where does TNF come from?" Let's just not have any TNF around. And TNF, of course, is the principal inflammatory mediator. It kicks off the other mediators, making you ill, anorexia prostration and the whole TH2 cytokine set, and so on.

People normally do not have this inflammation going on. So where is it going to come from? You have episodic surges of TNF when you get a cold. Or if you eat a bad bug, and you have a little period of diarrhea. But those can be controlled. Where does the TNF chronically come from?

Once again, you look at the intestine. We have ambulatory people with dysbiosis who are putting out the inflammatory mediator tumor necrosis factor (and, by the way, there are several others). It goes to the cell and, as we mentioned, it's not actually TNF that tells the genome of the virus to replicate. It's free nuclear factor *Kappa* B. So NF-*Kappa* B not only kicks off the cytokine set to make you ill, but NF-*Kappa* B also tells the genome of the virus to replicate most efficiently. Obviously, the next strategy would be to do things to preserve the intestine and maintain the strength of the intestine as the focus of the immune system.

How it links to you is that, I had learned this, and I wrote a paper called "The gut hypothesis," about HIV. A representative from an organization with which you are familiar walked into my office, and I thought I would challenge his mind. Well, he knew everything I knew; and he knew things I wanted to know. Then he told me about you and your work several years ago, now, and you really are my teacher in this.

It became apparent that you have to defend against episodic surges of TNF. You have to repair any dysbiosis. Then you have to take a look, as we mentioned, at the free radical issue. You have to quench those free radicals and then support the tissues to repair the damage that has been done.

One thing we haven't mentioned yet, of course, is hepatic detoxification pathways. Does that sound familiar? Sounds like the 4R program to me! As I began to understand what you were saying (and it took a year and a half of listening to the *PMU* and *FMU* tapes over and over), I finally said, "oh, a common pathway." If you understand what we're talking about today, it is finally a common pathway for everything from allergic rhinitis to AIDS. It is a very exciting time in my life, and I think a very exciting time for you, too, because look at how what you've pioneered is now moving into the allopathic consciousness

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