March 2006 Issue | Jacob Kornberg, MD Center for Health Awareness

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Textbook of Functional Medicine

Welcome to *Functional Medicine Update* for March 2006. When we developed the concept of functional medicine nearly 20 years ago, as with any emerging concept, we had little idea how it would evolve. Now, in the year 2006, we are all very excited about how it has caught on. Clinicians and researchers have embraced the concept and have added their own texture and flavor to it, creating what I call "personalized preventive medicine," using functional medicine to personalize therapy to the individual's needs.

The concept is very well described in the *Textbook of Functional Medicine*, published by the Institute for Functional Medicine. I am holding a copy of it in my hands as I speak. It is a remarkable outgrowth of the work of literally hundreds of researchers, clinicians, and multiple authors who have given tirelessly of their time in putting together a true textbook on functional medicine. It is some 800 pages in length, has well in excess of 20,000 references, and has multiple authors, multiple editors, and multiple referees. It presents the best of 20 years in the evolution of functional medicine. This issue of FMU will keep the flame alive and burning, and prepare us in charting the course over the next ten years.

13th International Symposium on Functional Medicine

The 13th International Symposium on Functional Medicine will be held April 19-22, 2006 at the Tampa Marriot Waterside Hotel & Marina in Tampa, Florida. The focus of the symposium is Managing Biotransformation: The Metabolic, Genomic and Detoxification Balance Points, one of the core principles of the functional medicine concept. The time we have spent during the last few issues of FMU in becoming familiar with this concept will pay dividends in both preparation for the 13th symposium, and also to better understand how to properly use what we call the functional medicine matrix, the algorithm that provides patterns from the interconnections between different functions that give rise to personalized therapy.

Over my years as a clinical chemist and laboratory director, I have received periodicals and journals from the American Association of Clinical Chemistry (AACC), including a weekly newsletter magazine, titled *Clinical Laboratory News*. It illustrates how the medical technology of today is emerging, and includes many articles that relate to the functional medicine concept. In the last issue of 2005, the lead article in this journal was titled "The challenges of pharmacogenomic tests: Has personalized medicine arrived?" [1] I found this to be an interesting and different perspective on how we see the functional medicine concept becoming one that provides therapeutic opportunities for doctors and ultimately, for

their patients.

Cytochrome P450 Genotyping Test
Let me tell you how the AACC presents the arrival of personalized medicine. They talk about the fact that in January 2005, the Food and Drug Administration (FDA) cleared the Roche Molecular Systems' AmpliChip® cytochrome P450 (CYP) genotyping test and comment that many experts hailed the approval of this test as the birth of a new era in personalized medicine.

"The first pharmacogenomic microarray designed for clinical applications, the AmpliChip detects specific genetic variations in the cytochrome P450 gene that can provide information on how well an individual will metabolize certain classes of drugs, thereby allowing clinicians to tailor drug therapies to the individual's genetic makeup."

This is a huge breakthrough in the way we view medicine and prescriptions. Rather than just giving a dose of a drug based upon body surface area, we can tailor drug therapy based upon pharmacogenomics and pharmacogenetics-the dynamics of specific drugs and how they pass through phase 1 of the detoxification system. This is what we might call managing biotransformation through detoxification at a very fundamental level-the genomic level. Roche released the chip for sale in the US in June 2005, and labs have now started to use the technology for evaluating specific CYP450 polymorphisms in individual patients.

I recall reading a number of case-precedent examples in the courts over the last two years of patients who brought suits against physicians because of adverse responses to various medications. The patients complained that they had not been tested for specific detoxification abnormalities before the medications were prescribed, and that their unique genetic polymorphisms had prevented them from properly metabolizing the drugs. They ended up having adverse events, which they claimed were the responsibility of the physicians for not having properly evaluated their genetic uniqueness before the medications were prescribed.

The AmpliChip may greatly influence prescribing patterns. It can greatly change the way medicine is practiced. Rather than assuming that all people are within certain acceptable standards of deviation relative to the way they metabolize drugs, a personalization perspective is emerging, indicating that patients need to be evaluated individually because polymorphisms in their detoxification enzymes may result in different outcomes. In a sense, this is another way of going through the door into the room of functional medicine. This new chip is a tool to evaluate patient genetic uniqueness-or biochemical individuality-that ultimately leads to molecular medicine-based forms of intervention, which is the focus of functional medicine. I find this an interesting way that some physicians will ultimately be led to looking at functional medicine concepts.

Obviously, most physicians already recognize that not all patients respond similarly to certain drug therapies, but the label "pharmacogenomic test" may scare some doctors, as well as some patients who might be worried about a test that examines their genetic makeup. We have talked about pharmacogenomics for over 10 years. It is not a new concept; however, when we start talking about its specific application through the use of gene testing chip technologies, like the AmpliChip, it leads to a new, potential generalization of the concept. Pharmacogenomics gets more attention now because it has matured to the point where it can be used in a very practical sense to help ensure that safe and effective

drugs are brought to the market.

"Personalized medicine" is somewhat of a catch phrase for the practice of clinical medicine that relies upon the ever-advancing science of pharmacogenomics and pharmacogenetics. Let me emphasize how I am using these terms: pharmacogenetics relates to the individual characteristics of a patient, whereas pharmacogenomics is the study of how different polymorphisms influence different metabolic outcomes. One is a general theme of the science of biotransformation and detoxification (pharmacogenomics), and the other is evaluation individualized to the patient with his or her own single nucleotide polymorphisms (SNPs). Pharmacogenetics is the study of the role of inheritance in inter-individual variation in drug response. A primary inspiration for this type of research has been the promise of individualized drug therapy.

Adverse Drug Reactions

We are starting to look at this because it has been recognized that there are a lot more adverse drug reactions (ADRs) than perhaps have previously been accounted for. This comes out of the study published in the *Journal of the American Medical Association* in 1998 that reported there are 2.2 million hospital events and up to 100,000 deaths per year annually in the US as a consequence of hospital-based ADRs.[2] If there are that many in hospital environments where medications are administered to patients by professionals at the "right dose," what could be the implication of ADRs in non-hospitalized patients?

"The labs that are bringing the AmpliChip in-house believe that its potential to bolster patient safety will ultimately make it a very marketable test. The AmpliChip uses microarray technology and polymerase chain reaction (PCR) technology to detect variations in the CYP450 2D6 and 2C19 genes."

These are constitutively expressed genes (not genes with highly inducible characteristics) that are very important in the metabolism in a number of different drug families. We now know that there are over 33 unique alleles, or different potential variations on a theme, for the CYP2D6 gene. The enzyme encoded by the 2D6 gene plays a primary role in the metabolism of drugs used to treat depression, schizophrenia, bipolar disorder, cardiovascular disease treated with beta-blockers, and attention deficit/hyperactivity disorders. This may have a relationship to how some children respond to various medications. The enzyme produced from the CYP2C19 gene metabolizes many proton pump inhibitors used to treat esophageal reflux disorder, anti-malarials, and anticonvulsants. The AmpliChip CYP450 test ultimately provides a predictive phenotype for patients, which ranks them into four categories-poor metabolizers, intermediary metabolizers, extensive metabolizers, or ultra-rapid metabolizers. Obviously, in slow or poor metabolizers, a certain drug dose may build a higher tissue or plasma level and produce toxicity, whereas in ultra-rapid metabolizers, the same dose may be rapidly cleared from the body and have no therapeutic outcome of importance. We need to be looking at how these agents might be transiting through the CYP450 systems of patients. This is an exact application of what we will be speaking to at the 13th International Symposium on Functional Medicine-managing biotransformation-because of the wide range of genetic characteristics associated with detoxification.

We are looking at the development of an effective means of therapeutic drug monitoring and individualizing patient therapies. That leads to predictive testing, as contrasted to pathology testing. For years, we have talked about the use of the laboratory for evaluating patient status. Tests that have traditionally been used for multiphasic screening are designed to evaluate pathology, and include such tests as SGOTs (aspartate aminotransferase) and PTs (prothrombin time) to evaluate liver enzyme

profiles, glucose tolerance tests to evaluate the presence of diabetes, cholesterol and/or triglyceride levels to evaluate lipid disorders, or blood urea nitrogen and creatinine levels to evaluate kidney disorders. In these cases, we are talking about the use of the laboratory for identifying the presence of an existing disorder. To some extent, cholesterol testing is a predictive analyte, because it focuses on understanding the prognostic potential for later-stage vascular events. This may be considered the first predictive analyte that arrived on the multiphasic screening profile, having more preventive, rather than disease diagnostic capabilities. CYP450 genetic polymorphism testing would not necessarily be called prognostic, but would certainly be considered predictive, because these tests tell us a little bit about how that individual, based upon his or her genetic uniqueness, will respond to certain exogenous and endogenous agents that require detoxification through specific enzyme pathways.

This is the birthing of a new concept that goes beyond psychiatry and clinical pharmacology into looking at how people respond to their environment in general. The same detoxification enzyme systems used for the metabolism of specific drugs are also those used for the detoxification and clearance of environmental toxins, as well as some endogenous substances. It will be exciting to see the emergence of a new science developed around pharmacogenomics, which is part of the functional medicine model.

The Question of Insurance Reimbursement for Pharmacogenomic Testing

There are a few hurdles that will challenge the rapid spread of pharmacogenomic testing. Not unexpectedly, one is the reimbursement issue, because there has been a question as to whether there should be insurance reimbursement allowed for the evaluation of CYP450 polymorphisms. It is interesting that we are very quick to reimburse for pathology-based tests, but very resistant in reimbursing for a predictive test, even when that test may allow for the prevention of a disorder that would result in very expensive evaluations, treatments, and potential high hospital costs.

These are philosophical questions that need to be addressed so that functional medicine and predictive and personalized medicine will ultimately find their places as important parts of the healthcare delivery system. Obviously, we have a highly evolved disease-care delivery system. Almost all the incentives and motivations are to financially and physically support the disease-care delivery system. We have a much more primitive predictive, prevention-oriented healthcare delivery system. We have discussed that in previous issues of FMU, when we talked about chronic disease and the need for new clinical education and assessment technologies for evaluating individuals who are on a trajectory toward later-stage, more acute disease.

There is certainly no lack of excitement among those who design and perform these pharmacogenomic evaluations. As the testing expands and focuses on more application-specific panels that include genes beyond metabolism-like genes associated with drug transport-enthusiasm will likely rise outside of the larger labs that do most of the current testing. I believe that, ultimately, pharmacogenomics will be a big driver for converting medicine into a predictive, personalized form. Ironically, that will be one of the ways that biochemical individuality and the concepts of functional medicine will become incorporated into a more traditionally-based, pathology-focused medical practice.

There will always be syndromes that do not fit nicely into a tidy diagnostic category, and may be relegated to the borders between various disease diagnostic criterions. Three of those are chronic fatigue syndrome (CFS), fibromyalgia syndrome (FM), and multiple chemical sensitivity syndrome (MCS). The reason we add the word "syndrome" rather than disease to these conditions is that they do not fall into a

nice, clean fit with the diagnostic criterion of an ICD9 diagnostic code. Does that mean they do not really exist? Are they not real clinical entities just because we cannot get our arms around them and cleanly define them based upon pathophysiological assessment? If we cannot define it, we cannot name it, so we think it does not really exist.

Patients with CFS, FM, or MCS would say that these syndromes certainly do exist. Physicians who have seen patients with these syndromes are aware of the fact that they are real clinical entities. It does not mean that we understand their origin. In fact, these disorders may be models for 20th century dysfunctions of a chronic nature, because they are multifactorial in origin. They do not have one specific etiology. They are related to imbalances in the neuroendocrineimmune system, as are many of the immunological problems we see today that ultimately may be called autoimmune diseases of various types, such as thyroiditis, inflammatory bowel disease (IBD), colitis, and systemic lupus erythematosis.

There is a complex milieu of dysfunctions related to the nervous, immune, and endocrine systems that have inflammatory relationships, and we are not exactly sure what to call them because they do not fit into clean, tidy diagnostic criterion.

Let's look at CFS, FM, and MCS. You may recall that we interviewed Dr. Martin Pall on FMU in March 1999. Dr. Pall is a professor of biochemistry and basic medical science at Washington State University in Pullman, Washington. He described the work he had been doing in trying to put together a comprehensive understanding of the etiology of MCS, FM, and CFS, knowing that they share much in common (as was reported by Dr. Debra Buchwald in an article that she and one of her colleagues published in the *Archives of Internal Medicine*in 1994).[3] We also interviewed one of Dr. Buchwald's colleagues, Niloofar Afari, in the August 2003 issue of FMU, and she described patients with CFS who present with an overlap of both FM and MCS symptoms, suggesting that there is a common etiology among these syndromes. Dr. Pall brought this to our attention in 1999 and now, some seven years later, we are starting to gain a better understanding of how things like Gulf War Syndrome, MCS, CFS, and FM are interrelated through a common paradigm-a feed-forward cycle.[4]

This feed-forward cycle has to do with activation of the nitric oxide (NO)/peroxynitrite/oxidative stress pathway. Activation of the immune system produces inflammatory mediators, including interleukin-1 beta (IL-1β;), IL-6, tumor necrosis factor alpha (TNFα), and interferon gamma, that interrelate (like a dog chasing its tail) with the stimulation of the production of NFκB as a transcription factor, and the controlled gene expression patterns associated with upregulation of these inflammatory mediators. All of those feed onto themselves to keep perpetuating the problem. It is different than an infectious disorder where, when a person gets over the infection, the body's immune system has successfully won the battle with that organism and he or she gets well. In the case of CFS, FM, or MCS, there is a re-initiation and a re-stimulation of the condition through the feed-forward cycles that occur through oxidative stress-related mediation and upregulation of the immune system.

Diagnosing FM, CFS, and MCS

When we look at how to diagnose and treat FM, CFS, and MCS, it leads to the concept of neuroendocrineimmune functional medicine web-like balancing. It requires a complex approach that deals with the hypothalamus/pituitary/adrenal axis. It deals with detoxification, gut function, oxidative stress, and immune stabilization of thymus dependent-1 (Th1) and thymus dependent-2 (Th2) activities. It is a classic example of personalized medicine, focusing on the web, which is the algorithm that is taught

as the central teaching and therapeutic clinical tool in functional medicine by the Institute for Functional Medicine.

There are various receptors that have been identified as being associated with activation of these complex immune, endocrine, and neurological conditions. These receptors become activated by their ligands under conditions associated with chronic inflammation and oxidative shifts in physiology. In a recent paper in *Free Radical Biology & Medicine*, investigators from the Vascular Diseases Research Unit at Ninewells Hospital and Medical School in Dundee, Scotland, reported that the etiology of CFS, although unknown, is emerging as being related to oxidative stress kinds of phenomenon, because one sees fairly high levels of 8-iso-prostaglandin α-isoprostanes in these patients.[5] These isoprostanes are related to the free radical oxidative injury that occurs to unsaturated lipids, and is a measure of real-time oxidative stress. CFS patients had very high levels of these isoprostanes. In fact, the degree of CFS symptoms correlated with the level of isoprostanes. This is the first time a strong clinical association between *in vivo* oxidative stress and CFS symptoms has been seen.

What is the origin of CFS symptoms and oxidative stress?
They come from the feed-forward cycle that Dr. Pall spoke about, as it relates to the activation of the immune and neurological systems through various receptor-ligand interactions. Some of these reactions are precipitated by the production of various types of secondary metabolites through inappropriate detoxification. One of those is activation of the vanilloid receptor as a putative target of the first chemicals in MCS. As reported by Dr. Pall and his colleague, Julius Anderson, in the *Archives of Environmental Health*, we are starting to see that activation of specific receptors can, in fact, induce some of these reactions that lead to feed-forward cycles of oxidative stress, immune upregulation, inflammation, and perpetuation of the symptoms of MCS.[6] The vanilloid receptor can be activated by things like mycotoxins, for instance, which may account for the sick building syndrome associated with MCS, and various other types of volatile organic solvents and chemicals. Endogenous chemicals can also activate the neurological system through NMDA receptor activation.

This may be why we see such diffuse symptoms in CFS, such as neurological symptoms, immunological symptoms, cutaneous symptoms, and endocrine symptoms. These are all interrelated to the alteration of physiology that occurs by teasing the web, pulling the web into states of chronic inflammation, oxidative stress, immunological imbalance, and endocrine disturbances. Now, we start to see that it does not look like a disease; it looks more like a syndrome. It presents in multiple ways in multiple forms in different patients.

Treatment of CFS, FM, and MCS
What is the treatment of choice? That is a good question. Obviously, because there are multiple etiological components, a single drug is probably not going to be the answer. In fact, what we would think about from a functional medicine perspective is personalizing therapy to the individual's need based upon the perturbation of their own individual web by looking at the matrix, a teaching tool in functional medicine. We would look at gut-related immune function, oxidative stress, neuroendocrine function, immunological function, and how the body/mind relationship was influencing the neuroendocrine immune system. Ultimately, from this, a personalized treatment, based upon both the genetic uniqueness of the patient and his or her antecedents and personal past history, would be developed to manage their CFS, FM, or MCS.

This leads us to recognizing that the functional medicine approach for the management of CFS, FM, MCS, and what has euphemistically been called Gulf War Syndrome, would be specifically focused on the algorithm that derives out of their web, out of their matrix. We would focus on GI function, and immune function as it arises out of GI disturbances. We would look at the effects on oxidative stress, effects on neuroendocrine function, effects of the body/mind factor, and how stress may play a role in the symptoms of the individual patient. We would recognize that there are common themes that would emerge by asking the right questions about the patient's story to design a personalized program for intervention. It does not fit into a specific singular intervention. When a person asks to be given *the*algorithm for the treatment of CFS, there is not *a* treatment. There is a general principle, and it relates to the etiology and the mechanisms of action in these feed-forward cycles, for which a specific treatment plan would be designed for the individual patient, based upon evaluation of their matrix.

These are the tools of the functional medicine model. These are the outcomes described in the *Textbook of Functional Medicine*. It is a very different model than that which results in a tidy diagnosis of a disease using a singular treatment algorithm for that diagnosis. It requires a more thoughtful approach toward patient management. We need to listen to the patient's story and develop a response to it. The outcome of these complex symptom-related clusters called syndromes, may be much more profound in positive outcome than just trying to pound a round peg in a square hole and get a singular diagnosis.

Let me use one more example that I believe illustrates the matrix in the functional medicine model. It is related to the auditory system and hearing loss. We are an aging population, and hearing loss is becoming more prevalent in our society. Also, in younger people we are starting to see hearing loss as a consequence of sensory trauma to the auditory system through things like listening to very loud music with head phones, and continued over-stimulation of auditory tracts. What is emerging through a basic understanding of the mechanism of hearing loss is that there is a functional medicine connection. Some drugs are now available to ameliorate predictable damaging effects of excessive noise and ototoxic substances, but the real question is: where does hearing loss come from? What is the actual physiological source of hearing loss? These are interesting questions, because what has emerged is that part of the problem is related to the activation of the oxidative stress machinery in the very sensitive organs of the auditory neurological system.

Noise-Induced Hearing Loss (NIHL)

Let me review some of the recent findings. Noise is the greatest environmental causative factor among the defined etiology of hearing loss.[7] Traditionally, prevention of noise-induced hearing loss (NIHL) has been addressed by providing wearable hearing protection and reducing noise emissions. According to the National Institutes for Deafness and Communication Disorders (NIDCD), the American Speech, Language and Hearing Association (ASHA), and the Occupational Safety and Health Administration (OSHA), >30-40 million Americans are exposed to hazardous sound or noise levels on a regular basis. NIHL affects ~10-15 million people, of all age groups in the USA. There are many noisy occupations, including construction, manufacturing, mining, forestry, farming, aviation, trucking, military, and recreational exposure to high noise levels through music and other types of auditory stimuli.[8] The prevalence of this problem-which is very high-can be thought of as a functional condition. What is its pathogenesis?

"In response to sound waves traveling through the cochlea, the auditory hairs in the organ of the Corti depolarize following the opening of the mechanotransduction channels caused by the physical deflection

of the stereocilia on their apical surface. The organ of Corti contains two types of auditory hair cell: inner and outer hair cells (IHC and OHC, respectively). These cells are organized into three rows and are usually the first hair cells affected. Healthy hairs contract in response to acoustic stimulation, resulting in an increase in sensitivity at about 40-50 decibels."

Here is where we get into some interesting functional medicine physiology.

"Mitochondria are some of the first and most affected intracellular organelles in models of NIHL. IHCs are predominantly sensory in nature and are heavily innervated by the eighth cranial (auditory) nerve. The constitutive array of IHCs and OHCs is dramatic given our noisy environments. The amount and type of hair cell damage depends on the frequency, intensity and duration of the noise exposure. Above a specific intensity level, OHCs show signs of metabolic exhaustion with the accumulation of reactive oxygen species and reactive nitrogen species (ROS and RNS, respectively)."

Over a long period of time, this results in an oxidative stress situation that leads to apoptosis, and death of the cell neuronal reserve associated with proper reserve for hearing.

"Over the past decade, much progress has been made in our understanding of the cellular and biochemical basis of NIHL."

We now recognize how these are associated with the formation of free radicals, particularly the reactive oxygen and nitrogen species that ultimately overwhelm resident detoxification and antioxidant mechanisms, showing that even in hearing, antioxidation and detoxification become very important as control points for resistance against environmental pressure, in this case, noise.

"A major intracellular antioxidant pathway that can detoxify free radicals and attenuate ROS and/or RNS involves the tripeptide glutathione (GSH). Loud noise can reduce GSH and increase the level of oxidized glutathione in the inner ear, leaving it prone to ROS- and/or RNS-mediated cell damage. GSH interacts with glutathione peroxidase, which catalyzes the ability of GSH to act as an antioxidant.
...The additive effect of increased ROS and/or RNS and depleted antioxidant capacity can lead to cell injury or death."[9]

The buildup of peroxynitrite is seen, which is the same chemical I described earlier when I was discussing CFS, FM, MCS-a toxic byproduct of activation of the immune system and oxidative stress.

"These free radicals degrade lipids and damage membrane-bound organelles such as mitochondria and nuclei. ...Excess ROS and/or RNS generated by elevated hair cell metabolic activity during intense noise exposure could overwhelm the antioxidant buffering capacity of the cell, leading to permanent loss or injury of hair cells."[9]

That leads to the question of otoprotection. What would be a functional medicine approach, other than just removing the noise, which is obviously a part of the reduction of the antecedents? What may also be some of the other things that could lower injury?

"Recent studies with antioxidants, N-methyl-D-aspartate (NMDA) antagonists, caspase or cell death inhibitors, and growth factors have some significant design limitations that restrict their direct clinical

application."[9]

However, the part of this research that seems most interesting is about the compounds that influence GSH, such as the GSH precursors-N-acetyl cysteine (NAC) and methionine (MET).

"NAC is a GSH prodrug that, upon de-acetylation to L-cysteine by the liver and local tissues, enhances GSH production. High-dose oral NAC is FDA-approved as a mucolytic agent for respiratory diseases and can reverse acute hepatoxicity following acetaminophen overdose. It is given orally or intravenously (i.v.) at 70 mg/kg for 24-48 h."[9]

This can enhance GSH levels, and is under investigation for ability to attenuate NIHL.

There are compounds that accentuate NAC activity, including N-acetyl carnitine, magnesium, and methionine-oral agents for helping to protect against NIHL. In a double-blind, placebo-controlled study, 300 young, healthy military recruits were supplemented with 4 grams of oral magnesium per day and showed significantly less noise-induced injury than those who were exposed to the same noise who received placebo.[9]

I have already talked about the NAC relationship. Similarly, CoQ10 has been shown in a few studies to have some potential protective effects from hearing loss.

We are starting to see that the functional medicine model, at the cellular physiological level, comes to what we might consider a strict environmental problem-NIHL-and that we have to go back to fundamental mechanisms and understand physiology and cellular activity. There is a further review in the journal DDT, of a number of approaches toward reduction of ototoxicity, with a principle focus on lowering oxidative stress and increasing detoxification of free radicals.[10]

I hope you can see from this discussion that our topic at the 13th International Symposium on Functional Medicine is not singular in its focus. When we talk about managing biotransformation and the detoxification balance points, we are looking across many different clinical conditions. We are tying together genomics with environmental exposures and trying to design a personalized program for individuals who may not even understand that they have symptoms related to alteration, biotransformation, and detoxification.

That is a nice lead-in to our Clinician/Researcher of the Month and I think you are going to find the interview very exciting. Our guest has a broad range of over 30 years experience in medicine that speaks to this specific topic

INTERVIEW TRANSCRIPT

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JB: It's time for our Clinician/Researcher of the Month. I look forward to these interviews each month,

because I learn so much from the experiences of these experts in applying the concepts of functional medicine. Our guest this month is Dr. Jacob "Jack" Kornberg. Jack has been a good friend and colleague for the last several years through interactions at functional medicine events and trainings. He has an extraordinarily interesting background, both personally and professionally.

Dr. Kornberg received his undergraduate degree from the University of California at Los Angeles and his medical degree from the University of California, Irvine College of Medicine, in 1969. After completing an internship at Los Angeles County Medical Center, he returned to the University of California, Irvine College of Medicine, and finished his four-year surgical residency in 1974. He served two years in the United States Navy as a surgeon at the Naval Hospital in Corpus Christi, Texas.

Along with their two children, Jack and his wife, Peggy, moved to Puyallup, Washington in 1976, where he established a successful general surgery practice and became highly respected in the local medical community. He was certified by the American Board of Surgery in 1975 and was elected a Fellow of the American College of Surgeons in 1979. During his years of surgical practice at Good Samaritan Hospital in Puyallup, he served many years as chairman of the Quality Assurance Committee and the Surgical Committee. He was also president of the medical staff for two years. He is a graduate of the IFM's Applying Functional Medicine in Clinical Practice (AFMCP) training program, which led to the incorporation of functional medicine into his surgical practice. I am going to ask him how a surgeon evolves into becoming a functional medicine practitioner. That may seem like an anachronism to some of our listeners.

In 2003, Dr. Kornberg decided to give up his surgical practice, and he created the Center for Health Awareness, an integrated holistic medical clinic, in Tacoma, Washington. This was a big step for a highly respected general surgeon. He has lectured internationally on health and wellness. Since July 2005, he has been seeing patients one day a week as a consultant at the Metagenics Functional Medicine Research Center (FMRC).

JB: Jack, there's much more to you than just those few words, and we welcome you to FMU. My first question is: What led you to make such an extraordinary transition in your career-from highly successful general surgeon to functional medicine physician?

Transition from Surgeon to Functional Medicine Physician
JK: Good morning, Jeff, and thank you. The transition was interesting, because being a surgeon, and especially the "older surgeon" in our community, I used to see a lot of patients who experienced abdominal pain. They were sent to me with a diagnosis of "adhesions." The concept was that they needed another surgery to help them with their abdominal discomfort. As I listened to their stories, it became very obvious to me that this was not a surgical problem; it was a functional problem. However, at that time, I didn't have any kind of framework in which to work them up or to put things into perspective.

One time, when I was at the operating table, I was complaining about how all these patients were being sent back for multiple surgeries. One of our anesthesiologists used to be a student of yours. He told me I had to find you, listen to you talk, and that you would probably be able to give me some insight into what's going on with these patients. That led to my attendance at a couple of your lectures. Once I started to understand the concept of functional medicine and that these patients did not have an anatomical defect that required surgery, but a functional problem with their gastrointestinal tract, I was able to start

incorporating that into my practice. Toward the last year of my practice, I was sending more patients away who didn't need surgery than those who did. That's not very appropriate for a surgeon.

Finally, Peggy and I decided that I couldn't straddle the fence-I couldn't be a functional medicine physician and do surgery. Things had changed in the 30 years I had been a surgeon, and it was no longer much fun. I'm sure a lot of the physicians who have been in standard medicine know things have changed, especially in terms of paperwork and litigation. So, we made the jump and I decided to give up surgery and practice functional medicine. Of course, I had to take lots of classes and courses. I took the AFMCP course twice and now, I love what I do. I didn't want to give up medicine, but it was time to move from surgery into something new and exciting, and it really has been. This practice has grown and the impact we've had is just amazing. We've been able to help guide people back to health in a system that is not geared to do so. Even though we call it a health system, it's not geared to health. The transition has been very rewarding.

JB: That's an exciting story, and the kind we love to hear because it's the raison d'etre for IFM's attempts to provide opportunities for, as David Jones says, "becoming re-enchanted with medicine." Congratulations to both you and Peggy for taking the plunge and thanks, too, on behalf of your patients.

Working a day a week at the FMRC has created an opportunity for you to see patients with what are euphemistically called "autoimmune disorders." That is an interesting stretch for a traditionally trained surgeon-working in the area of autoimmune disorders. Tell us a little bit about the experiences you've had over the last year seeing patients with complex immunological imbalances, and what your perspective is as it has emerged about a category of conditions called "autoimmune disease."

Aspects of Autoimmune Disease

JK: A lot of practitioners are probably overwhelmed by some of the patients' stories and the physical findings of those with autoimmune disease. It encompasses over a hundred different types of diagnoses. When I thought about it, I realized that we learn about a lot of tools in functional medicine that can help us approach autoimmune disease differently than those using the traditional approach. One of the problems with the traditional approach is that autoimmune disease is systemic, yet it has been chopped up into little pieces by the various specialties. The GI practitioner deals with inflammatory bowel disease (IBD); the neurologist deals with multiple sclerosis, myasthenia gravis, and so forth; the orthopedist deals with bone issues, and the rheumatologist deals with lupus. Yet, we've seen that these conditions are all one disease.

I love the story of the blind Chinese man trying to figure out what an elephant is by just feeling one little part. From the traditional perspective, I don't think you get a 10,000-foot view of what autoimmune disease is. But from a functional medicine point of view, you can. We make the assumption that autoimmune disease is a systemic and multifactorial disease. From the functional medicine point of view, we look at chronic disease differently. We look at it from the perspective of what the predisposing factors are, and what things the patient brings from his or her past that create susceptibility to a certain disease. We look at the triggers and mediators going on that keep the disease going. For example, some of these people will have three other people in their family that have had viral infections, yet that patient might be the only one in the group who never got better. They'll tell you that since they expressed that "something," they've never been the same. They appear to have some type of susceptibility that singles them out to become susceptible to autoimmune disease.

The Multifactorial Concept

The multifactorial concept is very appropriate for a functional medicine approach because from our training, we know about the web of connectivity. We believe that all the balances and functions in the body are interconnected. When I approach autoimmune disease, I have that picture in my mind. I try to take the story of the patient and translate it into physiology, biology and what's really happening. I use the tools of functional medicine I learned about to frame what's going on so I can make sense of it. I've found that these diseases don't begin when the patient is diagnosed. Most of the time, the patients we see at the FMRC have had a long history of what I call an "inflammatory process." Their history reflects other family members with different types of (or perhaps even the same) autoimmune disease. But it's interesting that, most of the time, it's not the same autoimmune disease. A relative, for example a sister, might have lupus, and this patient might have rheumatoid arthritis. Or, a family member might have Hashimoto's thyroiditis, and this patient will have some type of IBD. Most of these patients have some type of genetic susceptibility that can be picked up from their history.

The Role of Stress in Autoimmune Disease

Stress seems to play a large role in autoimmune disease, so I place it at the top of the list. The mind/body connection appears to be really important. In our stressful lives, we are not smart enough to stop behaviors that are destroying us, but the body is smart enough. A lot of times, the body will stop the patient from engaging in an activity that is extremely stressful. It might be work; it might be being a "super Mom," and so forth. When patients come to the clinic, we have to recognize that. If we don't change the environmental inputs, we probably will not have an impact on changing the disease.

Examining the Antecedents, Triggers, and Mediators

We look at the antecedents, things the patient has in his or her past. Then, we look at the triggering episodes, and they can be anything. The same autoimmune disease can have multiple triggers. A lot of people will swear their problem started after a viral infection. Some people say the problem started after some kind of trauma, such as an automobile accident, or even a mental trauma, such as a divorce or a death in the family. Onset could occur after taking a certain medication. The stories are just as varied as the number of people. As a functional medicine physician, that doesn't bother you. You put the pieces together. You "peel the onion" down to the core thing that's going on. Eventually, you get to the mediators, or the processes that are going on in the body that maintain the disease.

Autoimmune disease is very complex. You can get into CD4 versus CD8 ratios, and Th1 and Th2 ratios. I love that quote about the patient saying he doesn't really care about the science; he just wants to know if he can be cured. From a functional medicine point of view, the intricacies of all the various processes going on are interesting, but the key is, what can we do to impact the disease?

JB: That's a great segue, because you've defined a different playing field and a different domain from the functional medicine perspective. What would you call the perimeter goal post? From a clinical perspective, what types of things became part of your tool kit?

The Functional Medicine Practitioner's Tool Kit

JK: It's as varied as the web. All of the areas we look at can have an impact on autoimmune disease. We know a few of them. As a surgeon, I always go to the gut. We've been taught that the gut is responsible for a large percentage of the body's immune function. One of the things that I immediately evaluate is GI function and balance. In a study of 20 patients we've done at the FMRC, four of the patients had celiac

disease and didn't even know they had it. They had no symptoms, but they had some of the highest antibody numbers to gliadin and transglutaminase that we've seen. The gut is a very important place, and it's where I start my evaluation. I use the stool analysis, food, antibody panels, and now, we're doing a celiac panel on almost every patient because it has cropped up so many times. It's kind of hit us from the side, because there were no GI symptoms leading us to believe the patient had celiac disease. But all these things upregulate the patient's immune system.

Estrogen Metabolism

In the FMRC study, I believe we only had one male with Crohn's disease. All the other patients were females. That brought up the concept of where estrogen metabolism fits into autoimmune disease. I use some of the tools we have to look at the ratio of metabolism of the 2- and 16-hydroxyestrone as an indicator of whether there's something on the estrogen side that's stimulating the disease process. Studies have shown that patients with autoimmune disease tend to have higher 16-hydroxyestrone, and patients that do not seem to have these diseases have a higher 2-hydroxyestone. Therefore, the concept of estrogen metabolism is very important, and I use these tools in my office to measure this. Most of my patients have a problem. About 75 of the patients appear to have a high 16-hydroxyestrone level and we needed to address that and modulate their metabolism.

JB: That relates to the concept of altered detoxification because estrogen is metabolized principally through the cytochrome P450s in the liver. I'm wondering if you see any correlations with other types of imbalances of detoxification capability?

Imbalances in Detoxification

JK: Yes, we have seen that, especially from the perspective of the gut being one of the largest containers of toxic material. We look at bowel function, constipation, and methylation. We look at a lot of the parameters in our workup and use the data to try to tailor specific things to each patient's needs. I usually do these things after the initial evaluation. In the research center, it's really neat, because we have a fairly nice budget. We have a long list of tests that we can do that would usually end up costing the patient several thousand dollars. In real practice, you have to pay attention to where you're going to get the biggest "bang for your buck." The framework of functional medicine allows you to go through the patient's history and figure out where you think you're going to achieve the most influence on this complex physiological system. Using that approach, which I learned in the AFMCP course, sometimes makes it very obvious that the problem is in the GI tract. In other patients, it will be obvious that they're toxic. I've had several patients who became toxic from exposure to heavy metals. In my practice, it hasn't been a common thing, but you have to be aware of it.

Vitamin D Deficiency

It's interesting. Most of these patients have a vitamin D deficiency problem. There is literature discussing that vitamin D is a very pivotal, important component in modulating and slowing down the autoimmune response. We're finding that most of our patients have vitamin D levels in the 20s, with some even in the teens. That's another important tool that is part of the picture.

JB: I want to comment for the listeners that when you're talking about vitamin D levels, I presume you're talking about 25-hydroxy vitamin D3, just so people will know what to order to assess vitamin D status.

JK: I'm even using that in my private practice. It's almost like a standard test now. It's a little pricy, but it's amazing how many times it's abnormal. I've used it as almost a base test for people with autoimmune

disease.

JB: I know that you've had extraordinary experiences with some of your patients. Perhaps you could tell us about one or two of them.

An Extraordinary Case History

JK: I'd love to. It's amazing how all these things come together. For instance, there was an article that appeared in the Tacoma newspaper about a rare disease called erythromyalgia. It's a disease that's exactly opposite from Raynaud's syndrome, in which you get constriction of the blood vessels resulting in cold hands and the fingertips turning white. In erythromyalgia, there is dilatation of the microvasculature resulting in very hot and painful hands and/or feet. The newspaper article on erythromyalgia was published during the same week that a patient came to me suffering with that condition. In the article, the disease was described as one that caused the kind of pain that nobody can really deal with, and there was a picture of a lady and the 20 or 30 pills she took to try to alleviate the pain, the constancy of which continued despite all the medications.

When the patient came to see me with this disease, I liked the idea of being challenged. (If somebody says you can't do it, of course you have to try.) I decided to take her on because the disease is rare. You wonder why I would want to treat a rare disease, and it was because this lady was in constant pain. She had not been able to wear tennis shoes or other shoes for five years; she had not really been able to walk for two or three years. It had taken five years to come up with her diagnosis. She was positive for ANA (anti-nuclear antibodies) in her workup and there were several other interesting things of note. She was on Neurontin®, Celexa®, and lots of other medications to relieve the pain. Essentially, her physical examination was negative, except for the fact that when she was not experiencing extremely hot fingers and feet, they were actually cool to the touch. It appeared that the entire thermal regulatory system was reversed. She also had a very low vitamin D level. We conducted genetic testing and she had a polymorphism in tumor necrosis factor alpha (TNFa), which meant she probably had upregulation of her immune system. She also had an interleukin-10 polymorphism, which meant there was a probable downregulation in its dampening effect.

She's had different problems with allergies all her life-problems with eczema and problems with one type of inflammatory process after another, because she had carried these polymorphisms since birth. It was interesting to put this all together. She had personal or family histories of multiple surgeries and allergies and she had these genetic polymorphisms. She had an abusive childhood and had a lot of emotional baggage. She had repeated antibiotic use in the past. She did not eat well, so she had nutritional deficiencies. She had some back and neck trauma. What could have been the triggers? Well, she obviously had problems with the antibiotics and gut microbes. She had endogenous toxins. The temperature of the environment was a trigger for her. Then, there are the mediators, of course. You could list all the interleukins, and the signaling molecules and cytokines.

What did we do with this lady? We put her on an antiinflammatory medical food and added a product that had things that we knew help to modulate the immune system-selenium, zinc, and an extract from hops of reduced iso-alpha acids. That's all we did in the beginning. During the first couple of weeks, she reported a 50 percent improvement in her symptoms. She had less fatigue, and she noticed that other pain, for instance in her shoulder, had decreased. We got her lab work back, which reflected that she was low in vitamin D, so we added that, as well as some omega 3 fatty acids. She had an elevated homocysteine and

we thought she might have some problems with methylation, so we added some B12 and folate to her regimen. We put her on an elimination diet. By the fifth week, she had a 100 percent reduction in the pain in her feet and hands. For the first time in three years, she was able to open a jar. Her migraines were gone. She was able to sleep, and she had resolution of her intestinal gas. By the fifth week, we got back her stool analysis that reflected very, very high calprotectin and very, very high eosinophil proteins. That's when we did the celiac panel, which showed some of the highest scores: she didn't know she was celiac, but she was. She was already on an elimination diet. We put her on celiac diet. Her eosinophil proteins were over 31 and her calprotectin was over 250. She had no growth of lactobacillus or bifidobacterium. She had 4+ proteus. We put her on the 4R Program to try to rebuild, to reinoculate, remove pathogens, and replace digestive function. She continued to experience great improvement and, by about the eighth week, she had taken herself off almost all her medications. She was down to only three tablets of Neurontin® per day, rather than nine, and she said: "I feel like I'm 20 years younger." That was really cool, because her disease was the same disease that the article in the paper described as one that nobody could help. Using the simple tools of functional medicine, we were able to make a major impact in this lady's life.

By the 12th week, she was off all her medications. She was able to stand for the first time in a long time, and started to wear shoes. When I saw her recently, she told me I wouldn't believe what she'd done. She went to the mall in tennis shoes, which she hadn't done for six or seven years. She didn't realize how much of the abdominal symptomatology-the bloating and stuff-had been resolved. By the 12th week, her lab work showed that her eosinophil proteins had come down to almost 18; her calprotectin was down to 35 from 250; she had bifidobacteria growing; she had lactobacillus growing; and her intestinal permeability was actually coming back toward normal. Her homocysteine had come down from 9 to 4. Her vitamin D was still a little low, so we increased that. But, here's a lady who was being told by her physician to be prepared for a long life of pain; of not being able to wear shoes; and of not being able to do the things she loved to do. Now, she's a functioning person. She said she knew it was wintertime, but she went out and did some gardening. She hadn't worked in her garden for five years. When she came in, her MSQ scores were way up around 30; they went down to 5. Here's a lady who feels as if we gave her 20 years of her life back. That's very rewarding, and it's done with just the simple tools of functional medicine, approaching the problem from a multifaceted viewpoint and listening to the patient's story. Piece by piece, we separated the environmental influences on her susceptible genes so that we changed how her body responded. To me, this is where it's at.

JB: Jack, that was so compelling. I'm sure anyone listening to this for the first time who has not had any experience with functional medicine is sitting there simply amazed at your story. Of course, those who have been in functional medicine probably have similar case histories to report. It raises a question that may be unanswerable, but I'd like to get your opinion as a practitioner with more than 30 years of experience. Why do you think there's resistance in traditional medicine to this concept? It seems non-toxic; it doesn't necessarily prohibit the application of other intervention modalities, so why the resistance?

Resistance to the Functional Medicine Concept in Conventional Medicine

JK: I think it has to do with perspective. That was one of the biggest things I had to change when I went from surgeon to functional medicine physician. It isn't a matter of changing the science; it's a matter of how you change your perspective and your interpretation of the science. We've all seen that picture that has two faces looking at each other. It's either an old lady or a young lady, depending on how you look at

the picture. It flips back and forth from one picture to the other. Yet, the data in the picture didn't change. What changed is how we look at it, how we perceive the data. That's the problem. People who are doing functional medicine perceive the data with a much broader interpretation. Unfortunately, I think that traditional medicine perceives data from a very narrow point of view, especially within a specialty. Specialists have a hard time adjusting their binoculars for a wider view so they can see outside the box. The funny thing is, this information is in the literature, but traditional medicine is 20 years behind what is coming out in its own literature. I think that's where the problem is. And, not to get into politics, but my own personal opinion is that medicine is now being funded by pharmaceutical groups. That's where the money comes from to run medical schools and to do the research, and it's biased.

The approaches we use are simple. One of our patients is taking the intravenous medication, Remicaid® and I think that's about $3000 per dose. It's a change of perspective. We're giving folic acid, which is about 25 cents a dose. It's amazing. When I talk to physicians about it, they respond with statements like, "Huh! I never thought of that." They've never considered another scenario outside of their little boxes. That's one of the things I've noticed.

JB: This has been one of the most enchanting discussions I've had the privilege to experience on FMU. You've brought clinical insight to our listeners "from the trenches," so to speak. Sometimes we get caught up (I certainly do) in the esoterism of this mechanism and that mechanism, and great technology breakthroughs in our understanding of how the body works. But it all eventually distills down to how that patient behaves in the world in which they live and how they present themselves. I think you've done a magnificent job of making this complex story sensible and understandable. If someone was thinking about functional medicine and they listened to this interview, I have a suspicion they would take the time to gain some mastery of this area, because it's pretty motivating.

Long Latency Period in Autoimmune Disease?
JK: Another thing I want to share is that there's a huge latency period between when patients start having symptoms on the slippery slope to autoimmune disease. This is very similar to what we found with diabetes, and now with syndrome X/metabolic syndrome. There is a syndrome, (I've called it the inflammatory immune syndrome) that begins years and years before they actually get the four criterion of the condition; for example, with lupus. When telling their stories, these patients have gone from doctor to doctor and sometimes they're given Paxil® because they are seen as depressed. As functional medicine practitioners, we have a golden opportunity to intervene in a potentially devastating disease years before there is physiological damage, in a way that actually stops the process. This is a whole new field about how we can get in early, before the patient actually comes in with gnarled up hands or, for example, in patients with sclera derma, with skin that looks like leather. How do we get to these patients early and prevent this whole process from ever happening? That's where the future is going to be exciting.

JB: I can't thank you enough for spending time with us today. This has been very motivational. We'll take the lead and continue to try and inform people about this emerging inflammatory syndrome that you've described. Thank you, Jack, for being part of the functional medicine family. We appreciate it.

JK: Thank you.

The Functional Medicine Assessment

It struck me, in thinking about Dr. Kornberg's extraordinary comments, that when we start looking at the functional medicine model from 30,000 feet in a kind of broad-brush evaluation, the approach is very different from that of the traditional differential diagnosis, which is to try to know more and more about less and less, so that you can ultimately get a specific diagnosis. The functional medicine assessment, so eloquently described by Dr. Kornberg, is to keep moving up to higher levels of organizational perspectives to look at where the interconnections occur, and then to drill down into the individual mechanisms of action related to each of the nodes on the matrix. There is a sense that we are moving back and forth between a telescope and a microscope with the functional medicine model. There is a broader-based perspective and then a very small perspective, and a personalized approach for the patient is developed, based upon the interrelationship between the connection of the whole and focusing therapeutic energies into implementation to the individual components.

Oxygen as a Therapeutic Agent

What is one of the most important elements that all air-breathing organisms need to be concerned with, as it relates to dysfunction? That, of course, is oxygen, which is about 20 percent of the air we breathe. Often, we forget about air and water as being very important parts of therapy. Every traditional form of healing, from the dawn of medicine, had something to do with delivering air or oxygen to tissues. It could be deep breathing, yoga, exercise, various types of physical medicine, or dance-any number of things up through aerobic exercise and later, into mechanical intubation.

I am talking about making sure that oxygen delivery and respiratory gases are properly controlled. Low levels of oxygen in tissues produce oxidative stress, which is associated with inflammation and tissue injury. We want to make sure that tissues are properly oxygenated, and that a person is delivering oxygen to things like the monooxygenase enzymes, which are the cytochrome P450s, the various detoxification enzymes we have talked about that require oxygen for their activity and for proper function to detoxify endogenous and exogenous toxins.

Water as a Therapeutic Agent

Water is also a very important therapeutic agent, because hydration is critically important for establishing appropriate environmental conditions within cells, tissues, and organs for their function. Dehydration increases the solute concentration and changes enzyme function, cellular activity, and membrane transport. Proper hydration becomes an extraordinarily important part of any therapy in making sure that there is proper balance of intra- and extracellular fluids. The nature of the medications many patients take may alter their intra- and extracellular fluid balance and can lead to intracellular dehydration. Anyone who has overdone alcohol sometime in his or her history recalls the effect that it has on intracellular hydration. It produces a dehydration effect and makes one very thirsty because the cells become dehydrated and, as a consequence, there are toxic symptoms. I want to make sure we recognize that sometimes the simplest things become the most important for proper breathing, delivery of oxygen, and proper fluid intake for intracellular hydration.

Again, that obviously ties into the topics that Dr. Kornberg was speaking about as part of the matrix-concepts of GI function, immunological function, hepatic detoxification function, oxidant balance, redox balance, neuroendocrine balance, and body/mind balance. These all interrelate as components of the web in the matrix to things as simple as proper delivery of oxygen and proper fluid intake.

What we have outlined in the course of this issue of FMU is a model that has sprung out of nearly 20

years of the emergence and evolution of functional medicine. It paves the way for increased application of this model to a variety of different complex, chronic disorders that do not necessarily fit into a tidy diagnostic profile. I am holding the *Textbook of Functional Medicine*, which relates to the themes and concepts described in this issue of FMU. This is an 800-page embodiment of the spirit of what we have been talking about for nearly 20 years. I hope you will have a chance to read the textbook and spend some time getting the kind of mastery of these techniques that will allow you to help your patients more effectively.

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

Bibliography

1 Pizzi R. The challenges of pharmacogenomic tests. Has personalized medicine arrived? Clin Lab News. Dec 2005.

2 Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA. 1998;279(15):1200-1205.

3 Buchwald D, Garrity D. Comparison of patients with chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivities. Arch Internt Med. 1994;154(18):2049-2053.

4 Pall ML. Multiple chemical sensitivity: towards the end of controversy. Townsend Letter. Aug/Sept 2005:52-56.

5 Kennedy G, Spence VA, McLaren M, Hill A, Underwood C, Belch JJ. Oxidative stress levels are raised in chronic fatigue syndrome and are associated with clinical symptoms. Free Rad Biol Med. 2005;39:584-589.

6 Pall ML, Anderson JH. The vanilloid receptor as a putative target of diverse chemicals in multiple chemical sensitivity. Archives Environmental Health. 2004;59(7):363-375.

7 Holley MC. The auditory system, hearing loss and potential targets for drug development. DDT. 2005;10:1269-1282.

8 Lynch ED, Kil J. Compounds for the prevention and treatment of noise-induced hearing loss. DDT. 2005;10(19):1291-1298.

9 Attias J, Weisz G, Almog S,et al. Oral magnesium intake reduces permanent hearing loss induced by noise exposure. Am J Otolaryngol. 1994;15:26-32.

10 Rybak LP, Whitworth CA. Ototoxicity: therapeutic opportunities. DDT. 2005;10(19):1313-1321.p>