January 2002 Issue | Mary Bove, ND

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Welcome to *Functional Medicine Update* for January 2002. This is an auspicious year for the Institute for Functional Medicine and *Functional Medicine Update*. My colleague Jay Johnson and I are beginning our 20th year of producing *FMU,* and we are proud to have provided this service throughout the years. We have learned through the last 19 years and listened to our contributors and participants. We have shaped this product into something we hope you will find useful in improving patient outcome and helping your patients in the management of chronic illness.

2002 is also the year of our Ninth International Symposium on Functional Medicine. This symposium will focus on disorders of the brain and emerging therapies in the complex neurologic and psychiatric areas. It will be held in Fort Lauderdale, Florida, at the Westin Diplomat Resort. The program begins with pre-courses on May 25 and 26. The May 25 topic will be on making a functional medicine clinic work. This pre-course for office staff and doctors will cover the implementation of functional medicine in clinical practice and making the business of it work. On May 26, a second pre-course will cover managing a functional medicine clinic, Part II, for office staff only. This is the first time we will invite staff to attend for training. While staff members are taking advantage of that educational opportunity for enriching their understanding of implementing functional medicine, I will be a principal in leading a pre-course for practitioners, titled "Brain Biochemistry and Nutrition." Drs. Coralee Thompson, Robert Lerman, and David

Perlmutter will join me in presenting this overview of brain biochemistry and nutrition.

Symposium Topics

The symposium officially starts on Monday, May 27. We will talk about the GI tract and functional neurology, with a keynote speech by Dr. Michael Gershon on the second brain. Dr. Sidney Baker will discuss on how GI dysfunction can affect the brain and its function, and Dr. Mary Megson will speak about her work on autism.

Plenary sessions on Tuesday, May 28 will feature Dr. Robert Hedaya speaking on functional medicine approaches to depression. Dr. Abram Hoffer will talk about the extraordinary contributions he has made to orthomolecular psychiatry over many years.

On Wednesday, May 29, the topic will be psychoneuroendocrinology, with Dr. Richard Wurtman from MIT, and Dr. David Perlmutter. We will also announce the winner of the Linus Pauling Award that day. Workshops and discussions of clinical applications will follow these sessions. I hope you will put these dates on your calendar. You can get more information by contacting the IFM staff at 800-228-0622

2002 is also the year the curtain comes up on functional medicine and it becomes a reality on the scene of practicing physicians around the world. The publication of the November 14, 2001 issue of the *Journal of the American Medical Association* marked what I consider the official curtain raising. It marked the time when the focus of medicine changed from managed care and treating average humans to individual intervention and personalized medicine. The new medicine will provide greater effectiveness, fewer side effects, improved efficacy, and greater gratification at a humanistic, altruistic, and professional level for practitioners and providers. Medicine of the 21st century is functional medicine based on functional genomics and functional proteomics.

I have been speaking about this topic for several years. You may have assumed it was only wishful thinking on my part. You may never have expected to see it in your lifetime, but it is happening. It began on November 14, 2001, with the publication of a whole issue on functional genomics and proteomics in the *Journal of the American Medical Association*. With numerous citations, publications, clinical work, and fundamental bioscience research, this issue paints a picture of the early phases of this new medicine. We are moving from medicine whose principal focus was on medical taxonomy and differential diagnosis, to a medicine of patterns, individual recognition, and personalization. In the new medicine we sometimes find the truth resides in the interaction of variables rather than in the evaluation of a single data point that indicates pathophysiology. That new medicine is functional medicine.

Headache and Gluten Sensitivity

I begin this month's discussion with a citation from a recent issue of the journal *Neurology*, which illustrates this dawning of a new medicine. The title of this paper is "Headache and CNS White Matter Abnormalities Associated with Gluten Sensitivity."[1] This work was done at the Department of Clinical Neurology and Neuroradiology and Neuropathology at the Royal Hallamshire Hospital in Sheffield, England. The authors begin by saying that gluten sensitivity is a state of heightened immunological responsiveness triggered by the ingestion of gluten, or alpha gliadin, a family of proteins found in pulses or grains. This immunological response occurs in genetically susceptible individuals, those who have a specific human lymphocyte antigen, HLA-DQ2. Gluten sensitivity includes a spectrum of manifestations; there is no single disease we can call gluten sensitivity. It cuts across a range of variables and medical specialties, including gastroenterology (celiac disease), dermatology (dermatitis herpetiformis), and neurology (various neurological dysfunctions). Neurological manifestations and dermatitis herpetiformis can occur without histologic evidence of bowel involvement, so a person can have gluten-related symptoms without even showing a gastroenterological problem. The most common neurological manifestations are cerebellar ataxia and gluten-related peripheral neuropathies. In this paper, the investigators studied 10 patients with gluten sensitivity and abnormal MRIs.

Gluten Sensitivity Case Histories

One case history these authors described was a 49-year-old woman with episodic unilateral headache, visual aura, and unsteadiness. She had normal intestinal symptoms, an abnormal duodenal biopsy, anti-gliadin IgG antibodies, and low serum vitamin B12. Her MRI revealed extensive confluent areas of high T2 signal in white matter of both hemispheres, and she had a complete remission in response to a gluten-free diet.

A 37-year-old male with episodic unilateral headache and visual disturbances had intestinal symptoms, an abnormal duodenal biopsy, anti-gliadin antibodies of the IgG family, small foci of high T2 signal intensity in white matter of both hemispheres on his MRI. He, too, had a complete remission in response to diet.

A 42-year-old female with episodic unilateral headache with nausea and transient hemianopia had normal intestinal function and a normal duodenal biopsy. There was no evidence of abnormal gluten immunological function. She did, however, have anti-gliadin antibodies of the IgG family and also a low serum B12, scattered foci of high T2 signal in white matter of both cerebral hemispheres. She had a complete response to diet.

A 73-year-old female had unsteadiness of gait, falling, and episodic unilateral headache with visual aura and gait ataxia. She had a normal intestinal symptom profile, meaning normal GI function. She had a normal GI mucosal biopsy, but numerous foci of high T2 signal intensity in both cerebral hemispheres. She had a complete response to diet with remission of her symptoms. The authors reported the same outcome with a 61-year-old male and a 61-year-old female with extensive T2 signal hyperintensities in white matter of both cerebral hemispheres. All had complete remission in response to diet.

Genetic Polymorphisms and Response to Gluten

Each of these individuals had a specific genetic polymorphism, a uniqueness in genetic susceptibility that was determined in part by their lymphocyte antigen (HLA) determinants.. Not everyone, therefore, has an adverse response to wheat or gluten-containing grains. For most people, in fact, wheat is considered "a good food." For individuals with this susceptibility factor, however, based on genomic medicine, what for most people is a high-quality food contains a constituent that for them may become a neurotoxin. It produces neurological abnormalities as a consequence of activation of the immune system to produce distant symptoms, a long way removed from the GI tract.

The authors point out that these associations may be purely coincidental, but the complete resolution of headaches and EEG and MRI patterns in seven of nine patients on the gluten-free diet and partial improvement in the remaining two suggest a strong link between gluten sensitivity and migraine-like headaches. In one case, relaxation of the gluten-free diet resulted in recurrence of headaches with some progression of the white matter abnormalities on MRI. That is a pretty strong association. Perhaps we cannot leap to an unequivocal association of causation, but certainly it is a strong association implying causation.

Systemic Role of Anti-Gliadin Antibodies

Intestinal mucosal damage in celiac disease results from both humoral and T cell-mediated inflammatory processes. Such inflammation is not confined to the gut. Activated HLA-restricted gliadin-specific T cells and antigliadin antibodies are found systemically. They travel beyond the gut.

The gut is not an impenetrable barrier that keeps those reactions localized. Anti-gliadin antibodies have been found in the cerebral spinal fluid, indicating blood/brain transport, or transmittal of the message. CD4 and CD8 T-cells have been shown to infiltrate the cerebellum in patients with gluten ataxia. In

addition, antibodies against Purkinje cells have been found in some of the patients with gluten-induced ataxia. Both humoral and T-cell mediated mechanisms are thus implicated in neural damage. The gut communicates with the brain through the immune system

The example above demonstrates the emergence of functional medicine that is rooted in functional genomics and functional proteomics. In earlier issues of *FMU* we discussed seizures after vaccination for measles, mumps, and rubella (MMR). Researchers in England observed this extraordinary association between MMR vaccination and autism in some children. This observation has caused great controversy, invectives, and emotional counterclaims that vaccination is not associated with autism.

A recent issue of the *New England Journal of Medicine*, however, summarized results from a large retrospective cross-clinic study. The paper, titled "The Risk of Seizures after Receipt of Whole-Cell Pertussis or Measles, Mumps, and Rubella Vaccine," was a cohort study conducted at four large health maintenance organizations and included reviews of the medical records of children with seizures.[2] The investigators calculated relative risks of febrile and nonfebrile seizures among 679,942 children after 340,386 vaccinations with DTP vaccine, 137,457 vaccinations with MMR vaccine, or no recent vaccination. Children who had febrile seizures after vaccination were followed to identify the risk of subsequent seizures and other neurological disabilities. The study concluded the risk of febrile seizures after DTP or MMR vaccine rose significantly, but these risks do not appear to be associated with any long-term, adverse consequences.

Seizure Risk in the Genetically Predisposed

My question is, what about those individuals who carry specific types of genetic markers related to susceptibility? What will we learn in a few years as we continue to study these children with autism, in relation to their unique genetic susceptibility? Perhaps we don't have genes for autism; perhaps we have genes for susceptibility to factors that enable complex immunological mechanisms to influence brain chemistry in such a way as to produce autism. This is the weblike model of functional medicine, rather than the simplistic pathopneumonic model of single agent for single organ pathology, in which the agent works directly upon the affected organ.

Dr. Mary Megson, our Clinician of a Month in September 1999, talked about the extraordinary results she observed in managing autistic children. She instructed the parents to give these children cod liver oil as a source of vitamin A and vitamin D. Photophobia, night blindness, and other kinds of retinoid-related dysfunctions the parents have seem to be manifested as autism in children, once they had received the MMR vaccinations. Genetic variation influences the prevalence of dysfunction.

Autism and Supplementation

In a paper that appeared in *Medical Hypotheses* in July of 2000, Dr. Megson described her work from a clinical perspective. She told of remarkable "awakenings" she observed in children with autism, by giving them vitamin A, vitamin D, and omega 3 fatty acid supplements in cod liver oil.[3] We may be witnessing the dawn of a new era in the evaluation of disorders like autism. Although individuals may not carry a hard-wired genetic determinant for autism, they may carry susceptibility factors that translate, through complex physiochemical mechanisms of different control, into expression of a dysfunction at the

nervous system level that we label autism.

That possibility is quite interesting in relation to a conclusion in this paper in the *New England Journal of Medicine,* which says that the risks do not appear to be associated with any long-term adverse consequences. We should extend the studies and include cohort analysis. What about that small fraction of individuals who carry unique genetic susceptibility factors? That is the essence of functional genomics.

A paper on neurological function and inflammation appeared in 2000 in the journal *Neurology*. The authors found a reduced incidence of Alzheimer's disease in patients who had been taking either nonsteroidal antiinflammatory drugs (NSAIDs) or H2 receptor antagonists regularly.[4] The results suggest that Alzheimer's has an inflammatory component.

The authors of a more recent paper, published in the *New England Journal of Medicine*, titled "Nonsteroidal Antiinflammatory Drugs and the Risk of Alzheimer's Disease," confirm that long-term use of NSAIDs may protect against Alzheimer's disease, but not necessarily against vascular dementia.[5]

Alzheimer's Pathogenesis

An editorial following this paper asks about the possible mechanism by which Alzheimer's disease occurs. Could it be a complex set of events that relate, from many different variables, through genetic translation of risk or susceptibility, into an inflammatory process? The dementia of Alzheimer's has an insidious onset and a gradually progressive course, suggesting that it is a chronic dysfunction. The pathogenesis of the disease remains controversial. The process, however, is widely thought to begin in midlife or earlier, decades before the appearance of symptoms, as a consequence of some change in physiological function.

At some point, largely unknown genetic or environmental factors interact to initiate a cascade of events marked by the accumulation of extracellular b-amyloid plaques and intraneuronal neurofibrillary tangles. These changes result in gradual loss of synapses and subsequently of nerve cell bodies in the hippocampus and cortex, which we later diagnose as the memory loss of Alzheimer's. Eventually, the losses overwhelm the capacity of compensatory or redundant pathways in the brain circuitry ("cerebral reserve"), and symptoms appear. That is the organ reserve concept of Dr. James Fries that underlies the whole construct of functional medicine.

Antecedents, Triggers, and Mediators in Alzheimer's Disease

Some researchers have proposed that inflammatory mechanisms are important mediators in the pathogenic cascade that results in Alzheimer's disease. Such mechanisms are indicated by the activation of the classical complement pathway and by the presence of reactive microglia and numerous immune-associated proteins in the brains of patients with Alzheimer's. Many papers published in the last few years confirm this hypothesis. Clinical studies on the use of NSAIDs provide another insight on this subject, suggesting there are factors that initiate inflammatory conditions in the brain, such as carrying certain genotypes in the presence of susceptibility initiators.

Now we go back to the functional medicine model of antecedents, triggers, and mediators, resulting in later signs and symptoms. More than diagnosis, it is the prognosis. It is the progression. It is the mechanism. Antecedents are affected by triggers, such as infection or trauma. It could be brain trauma caused by accident or repetitive concussion injury. It could be a chronic inflammatory condition initiated by a chronic viral infection. It could be a gluten-induced inflammation and immune upregulation, as we discussed earlier.

Numerous events work on susceptibility factors to give rise to the appearance of this condition. The editorial that appeared as a companion to the *New England Journal of Medicine* article on NSAIDs related to Alzheimer's reduction is titled "Do Nonsteroidal Antiinflammatory Drugs Reduce the Risk of Alzheimer's Disease?"[6] These editorials usually conclude citing the need for more studies to confirm a particular association. However, the referred-to report does indicate another clue in our advancing knowledge of the relationship between inflammatory conditions and Alzheimer's disease, and initiators of inflammation and susceptibility genes

The relationship does not stop with neurological disorders. We can take the same model and apply it to coronary heart disease, cerebrovascular disease, maturity-onset diabetes, rheumatoid arthritis, and even the metastatic events of cancer. The underlying mechanisms provide threads of continuity connecting many of these compartmentalized diseases that end up as ICD9s. There are common threads of susceptibility and common threads of initiation or triggering.

The Virchow theory in the 19th century suggested heart disease was an inflammatory condition, not a cholesterol problem. We are now relearning old things in new ways. This is back to the future with the functional genomics model. Three back-to-back papers in a recent issue of the *Journal of the American Medical Association* show once again how this field is evolving. One article is titled "Relationship between Interleukin 6 (a proinflammatory cytokine) and Mortality in Patients with Unstable Coronary Artery Disease."[7] The authors conclude that circulating IL-6 is a strong marker—independent of cholesterol and other heart disease risk factors—of increased mortality in unstable coronary artery disease (CAD). It identifies patients who benefit most from a strategy of early invasive management (to lower inflammatory mediation).

Myeloperoxidase (MPO) and Heart Disease

A related companion paper in the same issue of *JAMA* is titled "Association between Myeloperoxidase Levels and Risk of Coronary Artery Disease."[8] Numerous epidemiological studies have evaluated inflammatory markers for their association with coronary heart disease. These markers include C-reactive protein, various cytokines like IL-6 that we just mentioned, adhesion molecules like intracellular adhesion molecule 1, or ICAM-1, and even white blood cell counts for their clinical usefulness in predicting risk of cardiovascular disease. More recent investigations, however, have suggested that myeloperoxidase (MPO), an abundant enzyme secreted from activated neutrophils, monocytes, and certain tissue macrophages, such as those found in atherosclerotic plaque, may be involved in the development of CAD. In this *JAMA* paper, the investigators point out that elevated levels of leukocyte and blood MPO are associated with the presence of CAD. These findings support a potential role for MPO as an inflammatory marker in CAD and may have implications (as a cholesterol-independent risk factor) for atherosclerosis diagnosis and risk assessment (along with things like high sensitivity C-reactive protein).

Inflammatory Markers in Screening for CAD

According to the authors of a companion editorial that appeared in the same issue of *JAMA,* inflammatory markers are without a doubt an important as part of the CAD profile.[9] "Atherothrombosis is increasingly recognized as a dynamic chronic inflammatory process of the vessel wall, in which phases of inflammatory and thrombotic activity underlie the clinical presentations of acute coronary syndromes. There is also evolving evidence that circulating monocytes and white blood cells may be involved in a proinflammatory or prothrombotic circulatory state."

These two mechanisms—inflammatory involvement of the vessel wall and of the circulating blood—are not mutually exclusive. They are triggered by signals, i.e., mediators, that upregulate the expression of genes to produce these inflammatory substances. Therefore, MPO and its association with CAD, C-reactive protein elevation and its association with CAD, and elevated IL-6, as a risk to CAD, are not mutually exclusive. They are related through gene expression, amplification of inflammatory mediators, and the relationship to dynamics in the artery wall, the intima. Various types of white blood cells are converted into foam cells, which can then activate the peroxidation or oxidation of LDL and initiate monoclonal hyperplasia and an atheroma. Therefore, the same type of model we talked about in relation to Alzheimer's disease, with glial activation of the immunological system, may also pertain to atherosclerosis and activation of the immune system and its participation in arterial dynamics

For years investigators have been looking for the genetic link to Parkinson's disease (PD). Recently discovered gene products like parkin have been associated with PD. A recent study, published once again in the *Journal of the American Medical Association*, described a complete genomic screen for PD. The investigators found no single gene that codes for Parkinson's. They found that multiple genes work together in combination to create an environmental, physiological state function we call PD.[10]

Parkinson's is not a disease with one cause; rather it is a disease resulting from the amplification and modulation of various genes that may result in niagra striatal loss and dopaminergic neuronal dopamine secretory loss over time. The data suggest the parkin gene is important in early-onset PD. A number of genetic factors, however, may be important in the development of idiopathic late-onset PD. Eighty-five percent of patients with PD develop the so-called idiopathic (“of unknown origin”) form of PD, which is related to oxidative stress, inflammatory mediation, and gene regulation through environmental factors such as susceptibility and exposure to petrochemical hydrocarbons or toxic substances. Exposures to volatile chemicals, ingested chemicals, or immunological upregulation may induce the production of destructive substances within the niagra striatum

Functional genomics and the concept of genetic susceptibility are moving into the medical mainstream. In an editorial in the *Journal of the American Medical Association,* titled "Genetics Moves into the Medical Mainstream," the authors state the following:[11]

"Queried at the turn of the millennium about the relevance of genetic diseases to medicine, a primary care physician might well have replied 'not in my practice.' After all, for most of its history, medical genetics has been devoted largely to the study of relatively rare single-gene or chromosomal disorders. Patients with these disorders were mostly cared for in tertiary care medical centers by specialists. But all of that is changing.

"Once hereditary contributions to disease are identified, it is potentially only a short step to the possibility of predictive diagnostics." That's where functional medicine has been and is continuing to take us. "Premature introduction of predictive tests, before the value of the information has been established, actually could be quite harmful."

That's why we have to make sure we have good clinical studies that tie together with these predictive gene markers. We also need to know that we can modify the expression of these genes. It's one thing to know that you've got the genetic linkage. It's another thing to know that you can do something about it.

Understanding Molecular Pathogenesis

"&ldots;The greatest payoff from understanding the human genome is likely to be an illumination of the molecular pathogenesis of disorders that are currently poorly understood, and for which treatments are largely empirical and frequently suboptimal. By identifying susceptibility genes&ldots;genomics offers a powerful opportunity to illuminate the pathogenic pathways involved in illness, and thus may provide the greatest opportunity for development of targeted therapy since the development of antibiotics."

"If genetics is about to move into the mainstream of medical practice, are primary care physicians prepared?

"For family practitioners, general internists, surgeons, and many other specialists with more limited exposure to genetics, the mainstreaming of genetics will be even more of a challenge&ldots;." Understanding how the genetic factors are modified by the environment is a big step from looking at pharmacotherapy..

Improving Prevention

"&ldots;Genetic medicine will ultimately improve prevention initiatives, leading to greater emphasis on maintaining wellness and a reduction in health care costs over the longer term."[11]

This will occur if we can appropriate this understanding and utilize it effectively.

Focus Shift in Research and Clinical Medicine

In an article titled "The Anatomy of the Human Genome," Dr. Michael McKusick recently stated:

"Since 1956, the anatomy of the human genome has been described on the basis of chromosome studies, gene mapping, and DNA sequencing. The gross anatomy of Andreas Vesalius, published in 1543, played a leading role in the development of modern medicine. The objective of this article is to show that knowledge of genomic anatomy is having a comparably strong and pervasive influence. The research revealing human genome anatomy is reviewed. The insight provided by genome anatomy has brought about shifts of focus, both in research and in the clinic, e.g., from genomics to proteomic and from the individually rare, single-gene disorders to common disorders (associated with age such as heart disease, cancer, diabetes, and arthritis). Genomic anatomy permits medicine to become more predictive and preventive. At the same time, diagnosis and treatment are rendered more sensitive, specific, effective, and

safe. Hazards in misuse and misunderstanding of the information exist. Education of the public and the health professionals is vital if the full benefits of neo-Vesalian medicine are to be realized."[12]

We need to appropriate this tremendous opportunity to use our capacity to modify the environment in order to manipulate genetic expression in such a way as to give a healthy outcome.

Diversity of Expression in Human Genome

The implications of the human genome for understanding human biology and medicine are extraordinary. The Human Genome Project has revealed that, comparatively speaking, humans have fewer genes than we would have expected. Humans appear to have only about 30,000 genes, while the fruit fly has 14,000 genes, the roundworm (*Caenorhabditis elegans)* has 19,000 genes, and the mustard plant has 26,000 genes.[13] We have only 4000 more genes than the mustard plant. The important difference between humans and mustard plants is not in the number of our genes. It is in the way they interact that sets us apart.

The human genome is filled with blocks or elements of repetitive nucleotide codes whose function is still a mystery. At one time, unfortunately, they were called "junk DNA." They're not junk. They appear to have important regulatory functions that insure that related genes can be expressed in a coordinated fashion. Therefore, we as humans have a unique way of expressing these elements thus guaranteeing the human condition.

Repeat Elements and Human Diseases

"Such elements have previously been characterized as "selfish" DNA (i.e., DNA whose existence seems to be related to replication purposes only), having no direct impact on medicine or natural selection. The availability of the human genome sequence suggests that this view should be revised since it appears possible that such repeat elements may indeed contribute to the causation of human diseases."

We now recognize that these genetic components contribute to age-related susceptibility to disease. The environment plays a major role. We modify the expression of these genes through nutrition and other factors to which we are exposed in our environment. A review paper, titled "Functional Genomics and Proteomics Applied to the Study of Nutritional Metabolism," describes the dawn of this new era. Nutrition will play a fundamental role in modifying genetic expression and proteomic expression into function, and it will become a major tool in medicine.[14]

INTERVIEW TRANSCRIPT

Clinician of the Month:

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JB: We come once again to the Clinician of the Month section of FMU. This year we will focus on nutrition and functional medicine throughout the developmental cycle, starting with the periconceptual period and moving through the whole of development—gestational development, neonatal, infant/toddler, pediatrics, and adolescence. Our clinician this month is Dr. Mary Bove, a naturopathic physician, clinician, teacher, and scholar. She started her professional career as a licensed midwife, working extensively in natural childbirth. She pursued her naturopathic degree and has been in practice for a number of years. She is intellectually skilled in combining traditional botanical approaches with a modern appreciation of standardized phytobotanical extracts.

Midwifery and Naturopathic Medicine
Welcome to Functional Medicine Update, Dr. Bove. Thank you for being with us today. First, has your move from the area of natural childbirth and midwifery into naturopathic medicine represented a logical transition in your career? And how did you bring some of those elements into your naturopathic practice?

MB: Thanks for having me on FMU, Jeff. I did study as a naturopath and a midwife together, so I was looking at midwifery through naturopathic eyes right from the beginning. Midwifery stands on its own because it has always been its own profession. Whether you're a naturopathic midwife, a lay midwife, or a nurse midwife, there are certain things that are the same. As a naturopathic midwife, being able to look at health care in the ante-natal period, the intrapartum into partum, and the post-partum period of time by using good nutrition and naturopathic therapies, a lot of times you can enhance the outcome of a pregnancy. Being a naturopathic physician gives me the advantage of being able to use some of those modalities.

Botanical Medicinals
JB: I know you have deep respect for and expertise in botanical medicinals. Some people believe we should avoid those substances in pregnancy or in the ante-natal or post-natal period, because their safety and efficacy have not been demonstrated. Would you speak to your experience in using botanical medicinals throughout that process?

MB: You brought up a good point. Certainly, safety and efficacy are important. Not a lot of studies have been done on the population of pregnant woman. We can rely on some historic information on herbs that have been used in midwifery birthing and post-partum or prenatal care. I feel it's important to make sure the pregnancy is healthy before you start giving too many things of a botanical nature. I emphasize good eating, exercise, health, water, and getting out in the fresh air in the first trimester.

The different trimesters of development for the fetus carry different risks. Some herbs that would not be used in the first trimester might be considered in the third trimester. Also, in the breast feeding or post-partum time, any herb or botanical medicine the woman might take can come through into the secretions of the breast milk, exposing the child. It is important to select herbs based on good historical knowledge, knowledge within my own clinical practice, and the Materia Medica. Resources are slim, as few herbs are

felt to be safe in pregnancy. You have to limit what you use. The only study I've seen recently is one on the use of Echinacea to treat colds and flu in pregnant women. That work did show there needs to be more information and more studies done, but it didn't contraindicate or reject the use of Echinacea during that time.

Botanicals in Infancy

In dealing with newborns and the neonatal time, you again need to be as cautious as you would be in pregnancy. I don't necessarily like to see newborn babies given a lot of botanical medicines unless it's absolutely necessary. The form and type of herb one uses is important, as you might not use an extract of a strong basis for something that has weaker attributes. You might use a preparation that would be a tea or a water infusion, rather than a strong extract.

The biggest issue is safety, and there are few guidelines. Experiential data comes from passing information back and forth with other clinicians, through understanding the dynamics of how the herb works, the pharmacology of the herb, and the pharmakinetics of the herb in the body. Sometimes, in working out the pieces, you recognize that even though an herb isn't contraindicated at this point, it would be, because you understand the pharmacology and pharmakinetics of the plant in the body. It does take some study.

Herbs for Pregnancy and Postpartum

JB: What herbs have you found useful in fulfilling these criteria in pregnancy and the postpartum period?

MB: A lot of the herbs I use in pregnancy and the postpartum period are the same types of herbs I might use with pediatrics under the age of five. They tend to be tonic herbs, adaptogenic herbs, or those that work for a particular condition. For instance, everyone knows you can use ginger to diminish morning sickness and the nausea of pregnancy. Many people use ginger for that reason. Or, one might use some bulking fibrous types of mucilaginous herbs like flax and psyllium for helping with constipation in early pregnancy. They tend to be food-grade herbs, or tonic types of herbs.

Later in pregnancy, as complications can become more advanced, you might have hypertension, protein the urine, edema, and you might use plants to treat that. The use of herbs then is not ongoing in the sense that you treat the problem. When the problem is resolved, you stop the medication. They need to be used as medicines. Tonic herbs like raspberry leaf, which has been shown to have a positive effect on the contractile ability of the uterine muscle, does help in toning the uterus through pregnancy. It would be used as a tonifier. But I generally tend to use things for a specific purpose and then discontinue them. If a woman is looking for a tonic type of tea or something she can drink during pregnancy, or herbs to support iron, the herbs are tonic herbs like nettles that could also be considered food-type herbs. In the old days, they would have been called pot herbs because they were put in soups.

Herbs for Pre-Conception

JB: When women are having difficulty getting pregnant because of hormonal imbalances, are there occasions prior to conception when you would use herbs like black cohosh or Agnes phytex castus?

MB: Yes. I use Agnes castus when I'm trying to help a woman get pregnant. I often use the flavonoid or the isoflavonoid-containing leguminacea, such as soy, red clover, alfalfa, or licorice as part of that process of balancing the hormones. Many of the herbs used before pregnancy need to be stopped or the formula

readjusted if the person gets pregnant. Other herbs, like red clover or phytex, if the woman gets pregnant, I tell her to come off of them, although they have not necessarily been shown to be a problem. It's just my own philosophy. If it's not needed, don't give it.

Black Cohosh
JB: What about black cohosh to modulate progesterone/estrogen balance?

MB: Sometimes I'll use black cohosh to help modulate estrogen/progesterone balance. I often find that these women have insufficient progesterone, and I like the vitex because it mostly works on helping the corpus luteum stage to get stronger. As the progesterone becomes stronger in the cycle, often that alone will help the estrogen to balance itself. If I do need something, I will often use the black cohosh in a standardized form for a particular time. Then I back that up with things that tonify the uterus overall. Chamaelirium luteum is the main plant I like to use because it has such a strong effect on a healthy corpus luteum which is so important in the first few weeks of pregnancy.

Herbs for Postpartum Period
JB: What herbs do you use for the postpartum period, when a woman might have depression? Do you use ashwagandha or other types of adaptogenic modulating herbs?

MB: Yes. If a woman is having postpartum depression, first of all, it's important to look at why that's occurring. Sometimes it has to do with hormonal issues based on estrogen/progesterone, or lack of hormones due to the pregnancy change. Sometimes, it has to do with the adrenal pathways, and that's where adaptogenic herbs play a part. I use Ashwagandha withania a lot for that. I also use eleutherococcus.

Typically, I also find those women need to be supported and built up. I have them use some of the Chinese mushrooms and astragulus root in soup forms as a tonic to help build the body back up and the systems in a slow food manner. I typically use ashwagandha in capsulated form because ingestion of alcohol tinctures by my postpartum women can upset the baby’s stomach.

A Summary of Herbs for Pregnancy
JB: To summarize, in preconception hormone balancing is important as you look at overall nutrition and health habits of the woman, and probably also her male partner. You then try to help balance hormones where there might be a progesterone/estrogen imbalance by using things like chasteberry or Agnus vitex castus, soy, or kudzu, red clover family, or licorice. In the first trimester after conception, you use principally nutrition and hygienic methods because you don’t want to subject the susceptible fetus to any risk. In the second and third trimesters, you utilize specific therapeutics to manage symptoms as they develop. You mentioned ginger for nausea, which you may use in the first trimester. After delivery, you manage mood swings by looking at a woman’s overall health status, and you also use specific types of adaptogenic products to try to normalize her hormone and mood affect. Is that a fair summary of what you said?

MB: That was an excellent summary. The only thing I didn't mention is that in all parts of the cycle, preconceptual, prenatal, and postpartum, the other thing I find most important in these women is good essential fatty acid intake. I emphasize DHA, particularly at the beginning of pregnancy.

Types of Fatty Acids
JB: Do you tend to use the non-animal-derived DHA or the algae-derived DHA?

MB: I use the algae-derived DHA. Otherwise, if I'm using EPA and DHA combined, I'll use a fish form. I try to get the women to use raw oils in their diet so they're not just doing it in supplemental form.

Standardized versus Food-Grade Herbs
JB: Let's talk about standardized versus more traditional decoctions or food-grade deliveries or powdered forms of herbs. How has this field evolved as it has moved more into the pharmaceutical model of standardization of herbs? The European imports have gotten us thinking about extracts or standardized extracts.

MB: I've worked in the herbal world for two thirds of my life. I have come from a grassroots place and then studied in England where I saw how European standardized extracts have come into popularity. I see there's a place for all of that. Standardized extracts offer people who are not necessarily trained in traditional herbal medicine a method for using botanical medicine. They can depend on this dose to get a particular type of response. I think a lot of manufacturers are seeing the benefits of having a range of standardized extracts so they may still be standardizing to a particular constituent. They may be standardizing to a particular constituent, but insuring inclusion of all the constituents in the product. I think this is a better route than just working with a particular active constituent.

Ashwagandha and Standardization
Standardized extracts have led to the discovery of new herbs. You mentioned ashwagandha. Traditionally, in American herbology, we don't have a lot of tradition around ashwagandha, but if we look at Ayurvedic tradition, we find information. A lot of the scientific studies on ashwagandha have been done on a standardized extract, and the traits and activities we are seeing in this plant are measured by those studies. I think it's important to make sure that if we are claiming to use traditional medicines in traditional forms, that we're not saying their activities are those that we've discovered through using, measuring, and researching standardized forms. I think that's an important piece that we sometimes forget and we expect that if it's a particular herb, it's going to do the trick, no matter what. I don't necessarily think that's so.

Sometimes, powders, teas, and food-grade sources are an easier and better way, or they are financially easier for a client to do. There are other times when those won't cut it, and you need to work at the standardized dose and the standardized preparation. That's where the beauty comes with having so many preparations available. There are times when one type of preparation is much more effective than another.

St. John’s Wort
JB: I think you are making an important, insightful, and wise observation. An example might be St. John's Wort, hypericum. For many years we assumed the biological activity came from the hypericums that were standardized. Recently, however, a group of investigators from Italy published papers showing that the flavonoid components, of which there are some 30 or 40 apart from the hypericum-like compounds, have an entirely different effect on the central nervous system. They believe it is the combination of the two families of molecules in the whole herb that gives rise to the remarkable effects. If you use hypericum as the marker compound, the standard might be the more hypericum the better, and you may lose a lot of the other parts of the symphony.

MB: I agree with you.

Aspirin and Willow Bark Salicylates

JB: Another example is aspirin and willow bark salicylates. Willow bark extract has certain effects historically. That is one form. Then there is synthetic salicylic acid and acetosalicylic acid. We use low doses of salicylic acid as baby aspirin for the prevention of heart disease. We use therapeutic dose to treat headaches or fever. And then we use the supraphysiological dose to treat rheumatoid arthritis pain. The risks and mechanisms are different at each of those levels. Willow bark contains a mellow range of compounds. When you can move all the way up to use that same biologically active compound at the arthritis treatment dose, you can get have bleeding complications and other kinds of acute inflammatory potential. It is not just the name of the compound; it's the delivery form and the other molecules in its presence.

Choosing the Best Botanicals

As a professional, how do you decide about what product to select? Various companies produce products. Choosing among them could be overwhelming for the practitioner who is just beginning to use botanical medicine. When they buy an OTC or X drug, that molecule is that molecule and it's supposed to be the same no matter whom they buy it from, but that's not necessarily the case with botanical medicines.

MB: Absolutely. There are many markets out there. I try to consider the needs of each individual when I decide the type of product to use. It might be a liquid extract, capsulated form, or the whole-cut gross herb where they're decocting it from cells.

Typically, I like to know the companies that I buy from so I like to be able to talk to them. I like to know whether they run assays on their herbal extracts, and where their raw materials come from. I feel a lot of the companies are willing to do that. I also like to get recommendations from my colleagues. If someone tells me a certain company has been good or they felt a product is good, I investigate that to see whether or not that's so. Many companies give good information to back up their product.

Seeking Consistency in Herbal Preparations

Traditionally, I like liquid compounds. I buy them from people who can assay their products and tell me I will consistently find these active ingredients in the products. That helps very much. If you're refilling a product after months of using a bottle, you expect the next batch to be the same. If the product is different from one batch to another, it is a problem in the clinic.

When I look at standardized types of extracts that come already capsulated, I tend to buy things that have been substantiated by research articles or if research has been done on that product, then I tend to use that.

Learning about Herbs in a Complex Market

JB: An increasing number of herbal products are now getting into the U.S. market as a consequence of the world’s shrinking. Ethnographic borders used to keep certain indigenous medicines culturally contained; now they are available all over the world. How does a clinician sort out the array of information?

MB: There is an enormous amount of information, and it's not always good information. I personally try to read particular types of journals that report on it. Also, with herbs like kava or withania, herbs that come from different parts of the world, I don't know that tradition so I don't try to use those herbs in

traditional ways. I try to educate myself on the Western way of using herbs that have been substantiated through clinical research that has been done on those plants. Andragraphus, for example, is an Ayurvedic plant that's gaining popularity and it has a similar effect in reducing cold duration and intensity that is similar to the Echinacea species. It has all kinds of traditional use, but I never use it for that. I find it works very well for reducing cold intensity and duration. I limit myself to those uses I can understand, that I can read and learn about in a small amount of time.

Botanicals In Europe
JB: The European tradition of using some botanicals is presumed to be richer or longer than in the U.S. In your experience in Britain, did you see any differences between what you saw there and what's going on here?

MB: My experience was very positive. I felt I got a whole education in the art of herbal medicine, or botanical medicine. Phytotherapy was looked at as a whole theory of medicine. When I came back to the States, it was very much herbal medicine and it didn't have that art to it. In some ways, it was what I call allopathic herbal medicine, or symptomatic herbal medicine.

The interesting thing about the English tradition is that there was a tradition in the U.S. called the physiomedical herbalists who existed at the same time with the eclectics. Physiomedical herbalism fell out of fashion in the U.S., but it was very strong in England, and it lived on there. In many ways, those are the roots of the modern herbal practitioner in England. With that, it did embrace or preserve a few American traditions that we've only begun to realize belong to us as herbalists in America.

Physical Medicalists
Physical medicalists work in polypharmacies so they like to formulate. That means you could do a formula for somebody with hypertension and you might have eight different herbs in it. Formulation is not as strong in the U.S. because it's harder to document a formula than if you're using a single herb. There's a lot more discrepancy around that, and people often wonder which herb is working. In the theory of physiomedical herbalism, it doesn't matter which herb. It is the combination and the way of combining that makes the difference.

The other big thing I noticed in the way English herbalists practice is dose. Here in the U.S., it was typically 2 or 3 mls less per dose 3X/day than you would see in England. Typically, in England, a dose would be 5 ml/day 3X/day. Here people would dose anywhere from 30 drops to 60 or 120 drops, which is basically 1 to 3 mls. That's probably the biggest difference I noticed.

Dosage and Clinical Efficacy
JB: Do you think dosage has limited some of the clinical efficacy in the States?

MB: Yes, particularly for liquid extract tinctures. I think that's why standardized capsulized extracts often do better, because the dose is standardized and can't be varied. With a liquid extract, one could prescribe 3 drops versus a tsp. That is quite a large range.

Getting Started in Botanical Medicinals
JB: What advice would you give doctors who are just getting into this field of the use of botanical medicinals, in regard to their education and clinical application?

MB: Two things. They should make sure they have not just one, but two or more good reference books, in which they could read about the plant they want to give. Second, they should feel comfortable with that plant and not try to do too many at once. Start with a few, get comfortable with them, read from different sources, start to use them, and watch and observe the effects they get. I think it can be overwhelming if you try to do too much at once. You feel as though you don't have a handle on it or you can't work with it.

Reference Books
JB: Could you advise us of a couple of the top reference books you feel should be in most people's libraries?

MB: The PDR on Herbal Medicine is a good reference book because it's familiar to a lot of physicians and they can work with the format. Principles and Practice of Phytotherapy: Modern Herbal Medicine is another excellent reference book, written by Kerry Bone and Simon Mills. It was published by Churchill Livingstone in 2000. James Duke’s book, Handbook of Medicinal Herbs, and Varro Tyler’s most recent book, The Honest Herbalist, contain good information about plants, and they're very reputable.

The Most Useful Herbs
JB: What do you feel are the herbs that might be most useful for a practitioner just starting in this field, for chronic symptoms of unwellness?

MB: I believe they should certainly look at and understand the effects of Echinacea. I think elderberry would be one they should look into a little bit more. They'd be surprised at what comes from that. Hawthorne and valerian are two I use a lot. They're old standbys. They are out there on the market and there's a lot of good information on them, as well as milk thistle and ginkgo. It's easy to start using them. If they want to look at something that's a little bit unknown, but I would say it's on the up-and-coming list, the plant andrographis, which is an Ayurvedic plant, is going to hit the forefront soon, in the next year, I’d say.

Drug/Herb Interaction
JB: You didn't mention St. John's Wort. Did you avoid it because of the recent publicity about adverse drug/herbal interaction?

MB: No, I'm not swayed much by herbal/drug interaction information yet, because I feel the information contains a lot of discrepancies. I’ve not typically used St. John's Wort for depression. Having been trained in England, I would more likely use St. John's Wort in a combination that I'd mix myself. That's why I didn't mention it.

Acknowledging Dr. Bove’s Expertise
JB: We want to thank you. You've given us a tremendous amount of information on a number of topics. It shows the depth of your clinical experience. We really appreciate your bringing that to FMU for our 20th year anniversary.

Dr. Bove has showed us how these complex elements from our environment—herbal-based products and phytomedicines that contain rich arrays of molecular species—can modify multigene expression and function. These substances can provide an outcome that may be very different from a single molecule against a single function. That may be the difference between traditional pharmacology of isolated, single-

melting-point compounds and the mixtures of compounds found in an herbal extract.

Functional genomics and proteomics applied to the study of nutritional medicine are extremely important. The effects of nutrition on gene and protein expression are extraordinary. We know now that perhaps as many as 3 million single nucleotide polymorphisms, or SNPs, reveal extraordinary variation between individuals. There is no such thing as an average patient.

The concept of genomics and nutrition could apply to gene expression changes resulting from zinc deficiency. By augmenting zinc intake, you could alter transcription that could be determined by the analysis of mRNA, which later shows up as altered protein synthesis.

Another example would be genes regulated by chemicals that activate peroxisome proliferated activated receptors (PPARs). The omega 3 fatty acids, EPA and DHA, and conjugated linoleic acid, CLA, or DHEA, are molecular substances that regulate nuclear receptor expression of the PPAR family that has an influence on insulin sensitivity and blood sugar management.

The protein difference to which I'm referring will be revealed by proteomic methods that are just know being developed. "The cause of most human disease lies in the functional dysregulation of protein interactions. Proteomics, which includes the study of cellular protein interactions, has evolved from advances in scientific knowledge and technology."[15] These applications are being made in the clinical laboratory and will help us understand not only how our genes are being expressed, but also how that genetic message, once encoded in messenger RNA, is translated into active protein that regulates function. It is a combination of functional genomics and functional proteomics that will give the clinician the tools to understand the uniqueness of a patient's specific situation.

"The field of molecular medicine is moving beyond genomics to proteomics. While DNA is the information archive, proteins do all the work of the cell and ultimately dictate all biological processes and cellular fates.

"Genetic defects cause disease because the proteins they encode are unable to maintain normal cellular functions. A primary example is cancer in which activation of oncogenes through mutation causes uncontrolled cell growth because the abnormal protein product stimulates, or fails to suppress, proliferation."[15]

"We are starting to develop proteomics as a tool, the next downstream activity from genomics This will directly change clinical practice by affecting critical elements of care and management. Outcomes may include early detection of disease using proteomic patterns of body fluid samples, diagnosis based on proteomic signatures as a complement to histopathology, individualized selection of therapeutic combinations&ldots;."

These combinations include various nutrients and phytomedicines, OTC and Rx medicines, as well as lifestyle variables including stress reduction, meditation feedback, and exercise, all of which influence the genomic and proteomic profile.

We are starting to see the opportunity to build a safer and more efficient medicine. That opportunity is articulated in an article in the *Journal of Internal Medicine*, titled "Pharmacogenetics: An Opportunity for

a Safer and More Efficient Pharmacotherapy."[16] The author points out that as a consequence of drug therapy in this country, we have an extraordinary number of adverse drug reactions (ADRs). The annual cost in this country is estimated at $100 billion, and ADRs are responsible for more than 100,000 deaths per year, making them between the fourth and sixth leading cause of death. These are drugs administered in hospital under authorized conditions. It doesn't include all the other potential adverse effects out of the hospital.

We know by looking at genetic variability and drug metabolism that the drug level in plasma can vary more than 1000-fold between two individuals of the same weight at the same drug dosage. The human genome contains 30,000 different genes, with a total of 3.12 billion nucleotides. Single nucleotide polymorphisms (SNPs) occur at a frequency about one in every 1250 base pairs. Thus we can expect to see more than three million genetic variations with the potential to influence response to a single substance. The number of reported SNPs has increased dramatically. The more we look, the more we find.

Drug Treatment Efficacy

In general, the efficacy of drug treatment is not very good. The response rates and treatment of different diseases like Alzheimer's, cardiac dysrhythmias, depression, incontinence, high blood pressure, osteoporosis, schizophrenia, and rheumatoid arthritis, not to mention oncology, are in the range of 30 to 60 percent, which means they are 40 to 70 percent ineffective and produce adverse effects. Given this relatively low frequency of responders and the high cost and serious adverse consequences of ADRs, the idea of moving to a new form of personalized medicine based on genomics and proteomics becomes even more attractive.

A recent article in the *Journal of the American Medical Association* was titled "Potential Role of Pharmacogenomics in Reducing Adverse Drug Reactions." Its authors pointed out that we are starting to see that drug therapy based on an individual's genetic makeup, may result in clinically important reduction in adverse outcomes and improve clinical efficacy.[17] The same would hold true for nutrition intervention, phytomedicine intervention, or all other therapies focused on the individual.

A paper published recently in the *Lancet* is titled "Effect of Preoperative Oral Immune-Enhancing Nutritional Supplement on Patients at High Risk of Infection after Cardiac Surgery: a Randomised Placebo-Controlled Trial."[18] The authors of this article showed that when patients facing cardiac surgery were given a supplement containing L-arginine, omega 3 fatty acids, and nucleotides in the form of yeast RNA before surgery, their immunological defense improved, infection was reduced, and their recovery improved.

We are beginning to see that genetic stressors such as surgery change the way genes are expressed as a consequence of the signal of that trauma, creating the need for different types of substances to modify or modulate function.

Genomics, Proteomics, and Breast Cancer

Finally, in regard to breast cancer, some women feel that because they have breast cancer genes, BRCA1 or BRCA2, they are destined to get breast cancer. A recent paper in the *Journal of the American Medical*

Association was titled “Tamoxifen and Breast Cancer Incidence among Women with Inherited Mutations in BRCA1 and BRCA2.”[19] This paper showed that tamoxifen, a selective estrogen response modulator, was able to reduce the incidence of breast cancer in women who carried the breast cancer gene. Therefore, we might say that those things that modulate gene expression and function at the proteomic level, which include things like the natural selective estrogen receptor modulators (SERMs)**;** soy isoflavones, and lignans found in flax, may effect improvement in reduced outcome as the phenotype of a disease called cancer. Therefore, our 21st century medical thinking challenges the concept of a genetically determined death sentence. Instead, we ask what we might use in that patient to modify gene expression to produce a healthy outcome.

We have just witnessed the emergence of a functional medicine.

Biblilography

1. Hadjivassiliou M, Grunewald RA, Lawden M, Davies-Jones GA, Powell T, Smith CM. Headache and CNS white matter abnormalities associated with gluten sensitivity.*Neurol.*2001;56:385-388.
2. Barlow WE, Davis RL, Glasser JW, et al. The risk of seizures after receipt of whole-cell pertussis or measles, mumps, and rubella vaccine.*N Engl J Med.*2001;345(9):656-661.
3. Megson MN. Is autism a G-alpha protein defect reversible with natural vitamin A?*Med Hypotheses.*2000;54(6):979-983.
4. Anthony JC, Breitner JC, Zandi PP, et al. Reduced prevalence of AD in users of NSAIDs and H2 receptor antagonists: the Cache County study.*Neurol.*2000;54(11):2066-2071.
5. Bas A, Ruitenberg A, Hofman A, et al. Nonsteroidal antiinflammatory drugs and the risk of Alzheimer's disease.*N Engl J Med.*2001;345(21):1515-1521.
6. Breitner JC, Zandi PP. Do nonsteroidal antiinflammatory drugs reduce the risk of Alzheimer's disease?*N Engl J Med.*2001;345(21):1567-1568.
7. Lindmark E, Diderholm E, Wallentin L, Siegbahn A. Relationship between interleukin 6 and mortality in patients with unstable coronary artery disease.*JAMA.*2001;286(17):2107-2113.
8. Zhang R, Brennan ML, Fu X, et al. Association between myeloperoxidase levels and risk of coronary artery disease.*JAMA.*2001;286(17):2136-2142.
9. Vorchheimer DA, Fuster V. Inflammatory markers in coronary artery disease.*JAMA.*2001;286(17):2154-2155/
10. Scott WK, Nance RL Watts RL, et al. Complete genomic screen in Parkinson disease.*JAMA.*2001;286(18):2239-2244.
11. Collins FS, Guttmacher AE. Genetics moves into the medical mainstream.*JAMA.*2001;286(18):2322-2323.
12. McKusick VA. The anatomy of the human genome.*JAMA.*2001;286(18):2289-2295.
13. Subramanian G, Adams MD, Venter JC, Broder S. Implications of the human genome for understanding human biology and medicine.*JAMA.*2001;286(18):2296-2307.
14. Guengerich FP. Functional genomics and proteomics applied to the study of nutritional metabolism.*Nutr Rev.*2001;59(8):259-263.
15. Liotta LA, Kohn EC, Petricoin EF. Clinical proteomics. Personalized molecular medicine.*JAMA.*2001;286(18):2211-2214.
16. Ingelman-Sundberg M. Pharmacogenetics: an opportunity for a safer and more efficient pharmacotherapy.*J Int Med.*2001;250:186-200.
17. Phillips KA, Veenstra DL, Oren E, Lee JK, Sadee W. Potential role of pharmacogenomics in

reducing adverse drug reactions.*JAMA.*2001;286(18):2270-2279.
18. Tepaske R, te Velthuis H, Oudemans-van Straaten HM, et al. Effect of preoperative oral immune-enhancing nutritional supplement on patients at high risk of infection after cardiac surgery: a randomised placebo-controlled trial.*Lancet.*2001;358:696-701.
19. King MC, Wieand S, Hale K, et al. Tamoxifen and breast cancer incidence among women with inherited mutations in BRCA1 and BRCA2.*JAMA.*2001;286(18):2251-2256.
20.

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