January 1999 Issue | Jerry C. Kopelson, M.D.

http://jeffreybland.com/knowledgebase/january-1999-issue-jerry-c-kopelson-m-d/

DOWNLOAD AUDIO |

Welcome to *Functional Medicine Update*™ for January, 1999. This will be the year of intercellular communication in *FMU*. We might describe 1998 as the year of nutrient modulation of gene expression. That was the focus of our seminar series and the Institute for Functional Medicine's Sixth International Symposium on Functional Medicine in Hawaii last May. This year, in an extension of that theme, we will focus on modulation of intercellular communication and its relationship to the prevention and treatment of diseases from childhood to adulthood, and age-related diseases. This exciting frontier in understanding the etiology of disease opens new opportunities for therapies that were previously unknown.

As I have often said, the answers to many questions may be contained in the file cards spilled on the floor. All we need to do is arrange those file cards in the right way for breakthroughs in understanding to occur. This year we hope to take another step toward putting the file cards in a logical order that will help us manage the challenges of a complex world filled with complex patients with complex symptoms and diseases.

I believe this discussion will reinforce the concept of the web. Most of us were taught an analytical, *reductionist* model of thinking. True/false, right/wrong, yes/no types of answers to questions enabled us to travel through our academic training with a high degree of proficiency and to be rewarded for our skill if we answered those black-and-white, reductionist questions. When we move into the real world, however, we find the world includes many shades of gray confounded by the lack of blinded, controlled studies, and we have to make decisions based on less-than-perfect data.

As we have begun to learn from chaos theory, pattern recognition, and multivariate analysis, the reality of our world is a time-dependent, nonstatic equilibrium model of function that is constantly changing with chaotic bursts of order and disorder, and patterns of assembly and disassembly. Therefore, the reality of physiology, society, and social network is the web. It is interesting that this is also the age of electronics and the worldwide *web*—web-like thinking, web-like behavior, web-like function. We are certainly seeing web-like interactions in medicine as we better understand the interaction of organs, organ systems, tissues, cells, and even supermolecular biomolecules. Action takes place through a web-like feedback process—feed forward and feed back. This year that theme will be revealed in many ways.

Consider the now-infamous enterotoxigenic *E. coli* 0157 disaster that resulted in the death of a number of children and disabling kidney disease and kidney failure in many others who consumed foods that were contaminated with this bacterium. Where did this bacterium come from? Why did it suddenly appear?

Was it just because we were suddenly cooking our hamburgers at lower temperatures, so the bacterium was living in our hamburgers? The answer that most of us come up with is no. That is not the reason why 0157 suddenly started to become an infectious disease concern in public health. Something else led to the creation of this form of mutant *E. coli*, which is a normal symbiote or, at least, commensal in the human gastrointestinal tract, and caused it to become a stealthy, lethal invader in some individuals.

Looking at this situation from a linear, reductionistic perspective, we can go back through what is called the HACCP Program in food production. This is the *hazard analysis critical control point* approach. We can look at the place where the organism might have sneaked into our food supply system and put thermometers in beef on griddles to make sure the burgers are cooked to a specific temperature to kill all the bugs. This perspective resembles the chemotherapy model for cancer. Make sure every cell is dead. It is saturation bombing, so to speak.

Perhaps, instead of just killing the bug when it exists, a better approach would be to ask where the bug came from. How does it relate to web-like thinking in an ecological system? We know we live within the ecos, the home, and we interact with that home.

An article that appeared in *Science* magazine, titled "Grain Feeding and the Dissemination of Acid-Resistant *Escherichia coli* from Cattle"[1] causes us to think differently about where 0157 might have come from. This article points out that the gastric stomach of humans is a barrier to food-borne pathogens, but *E. coli* can survive at a pH of 2.0, which is reasonably acidic. The *E. coli* presumably passed to human through cattle. Cattle are natural reservoirs for pathogenic *E. coli*. Cattle fed mostly grain are known to have lower colonic pH and produce more acid-resistant *E. coli* by natural selection. Most cattle in a natural ecological system forage on hay, not grain. Grain is "people food." Hay-fed cattle had a million-fold fewer acid-resistant *E. coli* than cattle fed grain. In fact, even a brief period of hay feeding decreased the acid-resistant count in cattle substantially.

The Transfer of Altered Flora from Cattle to Humans

In our web-like thinking model, the implication of that information is that changing the ecology of the way that animals are raised has an impact on bacterial flora in the ruminant. The altered bacterial flora then influences the potential for mutational alteration in these bacteria. Through the food supply system, those altered bacteria are then transferred to humans. And in individuals with compromised immune systems or specific susceptibility factors, those mutant bacteria, 0157, adhere to receptor sites on the unique gastrointestinal mucosa of certain individuals to produce an extraordinary immunological response that jeopardizes the life of the person. It at least causes shock and serious renal failure. By thinking this process through in a slightly different way, we may reach a different perspective regarding management of these kinds of problems, through an ecological, web-like, or interactive model.

The choices available through a linear, reductionist model include killing the bug with radiation of all food, killing it with antibiotic treatments, or, prophylactically, by cooking meat to temperatures that cause it to be damaged. Well-cooked meat leads to the formation of heterocyclic amine compounds that are known carcinogens. With this model we trade the risk of toxic 0157 for potential long-term risk from carcinogen exposure. The web-like model provides a different approach from linear reductionistic method of problem solving in which many of us were trained.

That leads us to another question: How do we evaluate and care for the distressed patient who has

multiple medically unexplained symptoms? These patients do not fall conveniently into ICD9 codes, and their medical taxonomic definition is not so tidy that we know exactly what is wrong with them. Do we just manage their symptoms by individual application of whatever is required from the medical pharmacopoeia of analgesics, antacids, or antidepressants? Or do we look for interacting themes to help us understand the expression of dysfunction, which we can then monitor, measure, or modulate at the causative level?

This was the theme of a recent paper in the *Journal of the American Board of Family Practice*.[2] The article states that although physicians commonly encounter patients with complicated medical problems, some have a mix of unexplained medical symptoms and distress that can seem overwhelming to both physician and patient. We need to develop a model of thinking about and helping these complex patients. That model must move out of the simple diagnostic code system, in which we are looking for "the disease" that results in these symptoms. The article's authors, Drs. Walker, Unutzer, and Katon, have discussed how this model of predisposing, perpetuating, and precipitating factors gives rise to a different way of approaching the patient. It is similar to the model we have discussed for nearly eight years, the patient-centered assessment model using antecedents, triggers, mediators, signs, and symptoms (developed by Dr. Leo Galland) as a way of evaluating complex etiology to understand mechanisms, not just disease. Antecedents, triggers, and mediators result in the signs and symptoms.

We will talk extensively about the mediators this year in *FMU*, because they relate to the intercellular signals that tell cells at a distance what might be going on somewhere else. Those signals tell cells whether to be alarmed or jump into a new state of physiological function, to express genes in a different way, moving from normal, resilient physiology to an active physiology that may produce pathology downstream, a state that later becomes an ICD9 code.

In their article, Walker, Unutzer, and Katon discuss awareness of the factors—antecedents, triggers, mediators, signs, and symptoms—that allow the clinician gradually to unravel the complicated interactions that create and sustain distress in patients with multiple medically unexplained symptoms. This awareness enables the clinician to devise practical and effective management strategies for these complex patients. What an enlightening experience it is when we start thinking web-like, rather than just differential diagnosis.

Discussing function leads to a discussion of a paper that recently appeared in the *Journal of the American Medical Association.* In this paper, titled "Importance of Functional Measures in Predicting Mortality among Older Hospitalized Patients,"[3] the authors explain that functional measures are strong predictors of morbidity and mortality in older patients 90 days and two years after hospitalization. If we can improve function and not just change laboratory signs, the patient has a much better prognosis, with lower utilization of medical services and extension of health span and possibly life span.

This emerging model looks at webs, at antecedents, triggers, mediators, signs, and symptoms, ties them to function, and then relates that information to diagnostic codes without being limited to a single vision of those codes.

When we begin to look at medicine, health, and disease from this perspective, new opportunities open up. One example is a recently published paper on acute renal failure in an alcoholic patient taking therapeutic doses of acetaminophen.[4] The authors of this paper confirmed what had been reported in the *Journal of*

the American Medical Association a year ago (reviewed in *FMU* 12/97). They confirmed that some individuals who were taking the dose of acetaminophen suggested by the label may risk acute renal and hepatic failure. The risk is not just liver dysfunction; it is also kidney dysfunction, which can result from their unique metabolism of acetaminophen or paracetamol, producing NAPQI. NAPQI is a toxic liver and kidney metabolite that depletes glutathione reserves and increases the risk of exposing the liver and kidneys to oxidative stress and apoptotic cell death.

When we examine unique biochemistry and individual susceptibility and put them in the context of family history, we are led toward the concept of personalized medicine, a theme that will advance as we move into the new millenium. It will become the watchword of a more tailored, effective, and cost-efficient form of health care—personalized medicine.

Variations in the ways individuals metabolize acetaminophen or any other substance or xenobiotic agent depend on unique genetic responses in their detoxification enzyme systems and receptor sites to the messages of toxins. A paper published in the *American Family Physician* discussed genetic polymorphisms of the cytochrome P450 detoxification systems and their relationship to different drug sensitivities and potential reactivities. Those reactions depend upon whether a person has a genetic weakness in cytochrome P450 CYP3A. This enzyme affects the metabolism of amitriptyline or benzodiazepines, such as Xanax, Halcyon, or calcium-blocker drugs.

Altered detoxification may make these individuals more susceptible to adverse effects from those drugs.[5] Some individuals have altered cytochrome P450 CYP2E1, which impacts acetaminophen or ethanol in conjunction with acetaminophen. Many people can drink ethanol and take acetaminophen concomitantly with no potential risk, but those who have a genetic uniqueness of cytochrome P450 CYP2E1 may have a much higher risk of renal and hepatic damage as a consequence of concomitantly consuming acetaminophen and drinking alcohol.

In addition, individuals' genetic uniqueness in cytochrome P450 CYP2D6 may interrelate with Prozac and SSRI drugs. Some genetic characteristics are inducible, and diet, lifestyle, and nutrition can influence their function. It is not just the genes, but also their induction from the genes that relates to their function. These considerations are starting to frame a new, personalized medicine built around pharmacogenetics, the interrelationship between the genetic uniqueness of the individual and the way he or she metabolizes certain materials. In the case of toxins, it affects the way they convert them into detoxified materials that can be excreted or substances that are better used downstream in secondary metabolic pathways.

This concept is an extension of Dr. Roger Williams's concept of biochemical individuality in the 1950s, and what Dr. Linus Pauling described as molecular medicine in his landmark article, "Sickle Cell Anemia—A Molecular Disease," in 1949. In 1999, we are just beginning to witness the emergence of a medicine based upon these principles. The Human Genome Project will help us understand how this model is applied by new diagnostic tests that will evaluate genetic uniqueness at the gene level. Through these tests we will be able to determine which characteristics are modifiable by nutrition and lifestyle, and how we can reduce the risk of diseases including heart disease, cancer, diabetes, arthritis, and autoimmune disorders that occur in later life. This emerging medical paradigm is supported by the increasing weight of evidence from basic science.

A paper in the *New England Journal of Medicine*, although it might appear esoteric, relates to this

emerging theme. The paper is titled "High Risk of Cerebral-Vein Thrombosis in Carriers of a Prothrombin-Gene Mutation and in Users of Oral Contraceptives."[6] The editorial that follows, titled "Venous Thrombosis—The Interaction of Genes and Environment," also conveys the message.[7] Some women taking oral contraceptive drugs, the authors state, carry a specific gene uniqueness: a prothrombin gene mutation that makes them much more susceptible to clotting problems. When these women use oral contraceptives, they run the risk of cerebral-vein thrombosis.

Much of the medical research conducted over the past 50 years has been based on the law of averages, the gaussian curve of statistical variation. That curve is symmetrical about midpoint, but it may shift slightly nonparametrically to the upper end. Normally, however, research was based on normal parametric statistics, standard deviations from the mean, and statistical significance was ascribed based on the data. Unfortunately, we are learning that correlates within these gaussian curves have unique susceptibilities that were lost in the noise of the data, lost in the law of averages.

If we went back and reevaluated the data from all the published studies, many of which concluded that certain things were not true, we would find they *were* true for certain subgroups. There were cohorts within the whole that did respond or had high risk. An example is women who smoke and go on to get breast cancer, who have poor acetylator status. When those women smoke they have much higher risk of breast cancer than women who do not carry the poor acetylator status gene. Yet studies published in medical journals before this observation was made found no real relationship between smoking and breast cancer in women, because these subtypes were washed out in the law of averages. This is another application of the principle of personalized medicine—the right thing for the right individual.

Fortunately, with new diagnostic tests available in the clinical laboratory, we will be able to determine individual characteristics, so therapies can be personalized. In the future, physicians may be legally liable if they fail to screen a patient before giving a drug that causes an adverse drug reaction. Physicians may be expected to ask questions about how a patient metabolizes medications. Is he or she susceptible to adverse reactions? Is he or she someone whose detoxification systems cannot effectively manage a particular medication? The burden of proof shifts when we begin to talk about personalization of medicine. An evidence-based medical approach is emerging based upon this model of antecedents, triggers, mediators, signs, and symptoms—the web-like approach and its relationship to personalization of medicine.

The authors of an article titled "An Evidence-Based Approach to Interactive Health Communication," in the *Journal of the American Medical Association* discuss the impact of the worldwide web, electronic information exchange, and the explosion of information about how individuals respond to their environment. Communication of these concepts to individuals, they suggest, should be based on evidence/empirical observation, not just theory. How did it actually work?[8] What were the results?

Instead of being so tightly tied to a logical, linear, analytical, information-gathering and decision-making tree, information should be based on a web-like decision-making tree. We should look at the strength of evidence from clinical experience, animal studies, epidemiological work, and clinical case management studies, come to a decision around risk and benefit, and make decisions to move ahead based on that information.

A good example of this approach is homocysteine. Based on the extraordinary discovery Kilmer McCully

made some 39 years ago, medicine now recognizes that homocysteine in marginal elevations in plasma is a risk factor for various vascular disorders. Based on Alzheimer's research published in more recent literature, we now know it is a risk even for dementia-related disorders. In a recent feature called "STEPped Care: An Evidence-Based Approach to Drug Therapy," Abby, Harris, and Harris described how one can develop an evidence-based, decision-making tree for the situations like that described in their paper on homocysteine and cardiovascular disease.[9] They call it STEP, which stands for safety, tolerability, effectiveness, and price. S: How safe is the particular therapy that is suggested? T: What are the dropout rates from clinical trials? (Will people tolerate the therapy?) E: How well does the drug or therapy work, and in what patient population? P: How accessible is the price to individuals on that particular therapy? STEP care represents an evidence-based assessment of the applicability of a particular approach.

When one applies the STEP concept to the homocysteine theory of cardiovascular disease, the authors point out, one quickly sees its merit. First, it is very safe. We are talking about B6, B12, and folate supplementation, which, at the doses required, has few or nonexistent adverse side effects. Tolerability—people can take those supplements each day with no problem. It has high compliance. You can fortify foods with these nutrients in the diet. Effectiveness—the data are quite convincing that it is effective. Price—the price is pennies per day.
Homocysteine Passes the STEP Test

Homocysteine supplementation, therefore, although medicine resisted it as a concept for 39 years, fulfills all the criteria of an effective, evidence-based medical approach to reduce risk of a major killer disease—cardiovascular disease. A new decision-making tree results in a different outcome decision.

The blinded, placebo-controlled trial mentality is very good for drugs, but it is not so good for multifactorial contributions to complex illnesses. Using the STEP approach we might make decisions in a different way. It certainly is true of homocysteinemia and its relationship to vascular disease.

The STEP approach might also apply to the role of B12, folate, and B6 in conditions other than homocysteinemia and vascular risk. We have talked in *FMU*, and earlier in *PMU*, about the role of vitamin B12 and folate in cognitive function in older individuals. Older people who got intramuscular B12 shots reported feeling much better, but their serum B12 was normal both before and after the shots. Therefore, the B12 injections were said to have a placebo effect, since these individuals clearly had no evidence of B12 deficiency. From the work of Dr. John Lindenbaum at Columbia University, Department of Neurology, as well as many other investigators, however, the B12 connection to cognitive function, particularly in older individuals, is beginning to emerge as a significant issue, even in the face of normal serum vitamin levels.[10] I commend Dr. Lindenbaum's studies.

Another paper on the same theme, which meets the criteria of support from an evidence-based medicine perspective, appeared in the *Journal of the American Geriatric Society*. In this paper, titled "The Effect of Vitamin B12 Deficiency on Older Veterans and Its Relationship to Health," the authors found a very much higher level of vitamin B12 insufficiency than had been previously thought in older-age individuals, on the basis of functional improvement when they received vitamin B12.[11] It could not be measured just by positive Schilling test or the absence of a positive Schilling test by a low serum vitamin B12 level. You had to look at functional measures of vitamin B12, such as homocysteine levels in the urine, or methylmalonic acid excretion levels, or plasma methylmalonic acid. These measurements are

more reflective of functional insufficiencies of B12 and correlate very closely with cognitive function in older individuals. This is another confirmation of this theme we have been describing for some time in *FMU*.

That leads us to consider how we can modulate these intercellular communication agents, the cell mediators of signs and symptoms that lead to altered cell physiology—the pain, fatigue, and dystonia that occur when the physiology has been shifted to a new point of equilibrium. That topic will be the focus of our Sixth International Symposium on Functional Medicine, to be held May 23–26, 1999, in Tucson, Arizona. I encourage you to attend this symposium, which is titled "Disorders of Intercellular Mediators and Messengers: Their Relationship to Functional Illness.

We will have an extraordinary conference this year. Dr. Candice Pert and Dr. Michael Ruff will speak about their pioneering work in the discovery of the binding sites for neurotransmitters on the surface of white cells, which gives rise to the mechanistic understanding of the mind/body connection. Dr. Russell Reiter, professor of medicine at the University of Texas, will explain how melatonin serves as a seminal molecule in cell signaling and how it exemplifies a more general theme related to modification of intercellular communication and mediators, and signs and symptoms of various disorders.

On the second day, the keynote presentations will focus on modulation of oncogenes and cytokine expression. Dr. Vincent Castronovo, former National Cancer Society and National Institutes of Health investigator, who is now head of the Metastasis Research Unit at the University of Liege in Belgium, will speak about modification and nutrient modulation of oncogenes. Johanna Lampe from the Fred Hutchinson Cancer Research Center in Seattle, Washington, will discuss her work on soy isoflavones and modulation of intercellular communication and effect on health and disease. Dr. George Zabrecky, medical doctor and chiropractor, will talk about zinc fingers, their relationship to cellular oncogenesis, and the influences of diet and lifestyle on those phylogenetic effects.

On Day 3, we will look at messengers and stress-related illnesses. Dr. Robert Sapolsky from Stanford University School of Medicine, author of *Why Zebras Don't Get Ulcers*, is an investigator who has been given considerable credit for developments in the understanding of stress-related illnesses at the mechanistic level. He will talk about stress modulators and messengers and their mediation through lifestyle and diet. Dr. Robert Lerman, associate clinical professor of medicine at the Boston Medical Center and Boston University School of Medicine, is an expert in fatty acid biochemistry, cardiovascular disease, and metabolic obesity. He will speak about intercellular communication through essential fatty acids and their relationship to chronic degenerative disease. Dr. Kilmer McCully, past recipient of the Linus Pauling Award, will return to give us an update on homocysteine and present the 1999 Linus Pauling Award.

Each afternoon, workshops given by some extraordinary clinicians will take us through the clinical applications of the concepts of disorders, mediators, and messengers in relation to functional illness. Please put the Sixth International Symposium on Functional Medicine on your schedule. You will be receiving a brochure with the full program and confirmation of the accreditation for post-graduate continuing medical education. A basic nutrition workshop will help those of you who might want to tune up your nutrition skills, and workshops will present the fundamentals of functional medicine. I hope to see you at the symposium on May 23–26.

I move now to the concept of intercellular communication and will describe some things we all know, but perhaps in a slightly different context. The objective is to help you develop your own web when you see a patient, begin to analyze complex symptoms, and wonder how to fit them into a treatment program.
Steroid Hormones

First, consider the steroid hormones—cortisol, testosterone, estrogens, DHEA, and pregnenalone. What are these molecules? How do they influence function? How are their levels and activity modified? When we ask those questions, we begin to follow a path of discovery that I believe is never-ending. We will probably never be completely able to answer all of those questions. There is always something more to know, something more to learn.

We have learned, however, that these molecules are derived from cholesterol through a series of extraordinary metabolic transformations that occur in various tissues, like the adrenal glands, the ovaries, or the testes. Those molecules go on to elaborate various signaling molecules whose structure and functional activities can vary remarkably through simple changes in the molecular personality of these molecules.

In a steroid molecule, there is the nucleus (a tetracyclic triterpenoid nucleus), and then we put a hydroxyl group at a certain position on the A ring or the C ring; it changes its activity. We isomerize that from a beta position to an alpha position, and we get different activity. We add a methyl group here; we subtract a methyl group there, and we get a different activity. The body, in terms of these mediators, has exquisite selectivity and sensitivity. Very small shape changes in molecules can make extraordinary differences in the way they fit on the receptor sites and influence function.

Something that at one time was producing male-like symptoms (using the stereotypical connotation of *male*), can, by slight modification in the form of a testosterone dehydrogenation or a desaturation, produce female-like characteristics. Just taking a few hydrogen atoms off the A ring of the tetracyclic triterpenoid molecule converts a testosterone to an estrogen. The effects are quite obvious. The structural changes are very small.

These mediators of function are very carefully controlled. If we start playing around with these mediators by throwing in a typical chemical soup of new exogenous agents, like hormone replacement therapy or xenoestrogens that come from the environment, we can really jam the communication system of our body, producing a wide variety of symptoms. These molecules do not interact with just a single organ. Receptor sites for these hormones appear on the surfaces of cells as far ranging as the heart, the brain, the liver, and the muscles, not just the target tissues of the reproductive glands. We have aldosterone, cortisol, DHEA, and hundreds of different steroid-related molecules that can influence function.

I bring that up because we now recognize that these feedback pathways work in webs. Women whose estrogen begins to diminish have changes not just in reproductive patterns, but in skin texture, immune defense, cognitive function (memory), blood coagulation parameters, and lipid profiles. Lots of things change as a consequence of modification of these signaling molecules. Dysfunction really occurs by alteration of mediator molecules that produce wide-ranging symptoms in distant organ systems. The challenge for the diagnostician/clinician is to start assembling patterns of understanding, clusters of understanding. The steroid molecules, as described in the *Annual Review of Physiology*, are an extraordinary family of molecules to understand.

The vitamin D family, cholecalciferol is a vitamin family that is very similar in structure to the steroid molecules, the hormones. We make vitamin D from our skin because sunlight somehow activates a process to convert provitamin D into vitamin D. That is why people who do not get outside have vitamin D insufficiency. Their steroid hormone molecules are converted into vitamin D molecules by light of a particular wave length exposure.

The functions of vitamin D, in part, also mimic the steroid hormones. Vitamin D is not just a calcium hormone that produces this hormone through cholecalciferol and its hydroxylation into 1,25-dihydroxycholecalciferol as a consequence of liver and kidney hydroxylation. It does not influence only calcium-binding protein expression in the gastrointestinal mucosa, which then allows calcium to be better taken up from the gut into the blood; it also has an effect on the immune system. It has an effect on cognitive function. It has a broader activity than just a single calcium activity. Think of vitamin D insufficiency almost as a consequence of (or interrelated with) the nature of the steroid molecules. Interestingly, if you drove cholesterol levels very low by cholesterol-lowering therapy in a person who didn't get outside much (like many older individuals), you might produce an insufficiency in vitamin D. This could have adverse immunological consequences. Again, it is web-like thinking, not just single-activity thinking.

One other thing we learned about cell signaling in studying intermediary clinical biochemistry was that it is not only steroid hormones that play a role in signaling messages from cell to cell, and tissue to tissue. It is also small molecules like cyclic adenosine monophosphate (cyclic AMP). Cyclic AMP, which has a relationship to gene expression, is one of the principal first-signal messengers. It is a ubiquitous molecule. We actually call it a second-signal messenger. It gets its trigger from first-signal messengers, which I will describe later. It is produced in cells in response to hormones and nutrients. Therefore, steroid hormones may interact with receptor sites on cells to interact with the machinery that converts ATP into cyclic AMP. Some nutrients also do this and can trigger this response. Proinflammatory agents like histamine can have this effect as well.

Production of cyclic AMP depends on the actions of many different proteins that affect its synthesis and degradation. An important function of cyclic AMP is to activate the phosphorylating enzyme protein kinase A, which converts various enzymes from inactive to active forms by phosphorylation. The key roles of cyclic AMP and protein kinase A and the phosphorylation and regulation of enzyme substrates that involve an intermediary metabolism are now well studied. A newly discovered role for protein kinase A, however, is the phosphorylation and activation of transcriptional factors that are critical for the control of gene expression in response to elevated levels of cyclic AMP.

In situations of allergy or alarm, where cyclic AMP level is increased, transcription is upregulated in certain genes, which modifies the way our cells function through modification of gene expression.

This interesting, newly emerging theme that we have been describing is the mechanism by which environment and genes interact to give rise to phenotype of function. That the cell signaling molecules like cyclic AMP (not only cyclic AMP, but *like* cyclic AMP), can then influence functional alteration in gene expression across many cell types. Levels of cyclic AMP increase as a consequence of the interaction of the cell with its environment.

Cytoplasmic ATP-dependent regulation of ion transport and channels is also interrelated with cyclic

AMP. The uptake of magnesium and potassium across cell membranes and the export of calcium and sodium to the exterior of cells through these calcium channel ports (or potassium/sodium ports) are driven by ATP. They are interrelated with cyclic AMP, and also cyclic GMP, and the balance between cyclic GMP and AMP plays an important role in the yin/yang dynamics that gives rise to cellular equilibrium. In a moment, we will learn that cyclic GMP interrelates with nitric oxide production, which is another signaling messenger.

So we get a web of intercellular mediators that are creating different physiological states as a consequence of an individual's exposure to a precipitating trigger, which works on their antecedents, which is their biological genotype. This is a new model of how dysfunction might emerge. You will find this interesting study and review of how cytoplasmic ATP-dependent regulation of ion transport channels works, its mechanisms and its messengers, in the *Annual Review of Physiology*.

Another regulator of this process is cellular reduction/oxidation (redox). This is a new part of the story of what creates messages within cells that regulate their function and gene expression—redox potential. Where does redox really participate in the cell? Its activity comes through the mitochondria, the powerhouse of the cell. Redox regulation of cellular activation is an emerging view of the way certain genes are turned on and off. We now have cyclic AMP, cyclic GMP, steroid hormone activation, and their interrelationships with redox potential across the mitochondria. Growing evidence indicates that cellular reduction/oxidation status regulates various aspects of cellular function.[15]

Helmut Sies has used the term oxidative stress to define a state of intercellular redox that is shifted toward the oxidation side. It elicits positive responses, such as cellular proliferation or activation, as well as negative responses like growth inhibition, or cell death by apoptosis, as contrasted to the chronic cell death.

Thioredoxin is a small protein that has redox disulfide dithiol within the conserved active site sequences. Its function and structure relate to the activity of glutathione in its reduced state and to lipoic acid, dihydrolipoate. Therefore, conversion of redox activity depends on the antioxidant levels and forms of active sulfhydryl-containing materials like glutathione.

Is lipoic acid oxidized or reduced? When the immune system is upregulated and cell messengers like interleukins (particularly interleukin-2 and tumor necrosis factor-alpha) are released, the cellular physiology shifts toward the oxidative state in the redox potential. You start to see an expression of different gene transcription factors like those associated with oxidation, such as nuclear factor *Kappa* B (NF-*Kappa* B). These are signs of increased response to what the cell defines as a hostile environment. Oxidative chemistry shifted in the direction of redox potential may be associated with lowered resiliency and increased cellular death, biological aging.

In cases of infection, trauma, or specific mechanical injury to cells, this shift is very important. Recycling of cellular materials is necessary. It is also important when a cell has undergone a functional mutational injury and needs to be put to death, so to speak, so it will not send its message to other cells. But if it occurs in an accelerated way over long periods of time, increased apoptotic cell death can result in premature cellular loss of function, which we associate with biological aging and age-related diseases. Redox regulation of cellular function and gene expression is emerging as another important tool to help us understand the web of dysfunction. By the way, we can learn about this by using assessment tools for

redox or oxidative stress in the laboratory.

INTERVIEW TRANSCRIPT

Clinician of the Month:
Jerry C. Kopelson, M.D.

JB: The focus of this month's *FMU* is on intercellular communication and its relationship to the emerging view of the etiology of various chronic, degenerative, and age-related diseases. We are seeing applications of this concept in autism, a condition that is not associated with aging. Autism is seen most often in children. Jeffrey Kopelson, MD, this month's Clinician of the Month, will bring us a perspective that is revolutionary in our thinking. He will speak about the new relationship between secretin and its potential use in the treatment of autism.

Dr. Kopelson received his MD degree from New York Medical College and has a background in biological science from Syracuse University. He has been in both family practice and nutritional medicine since 1993, and he has started to integrate many of the concepts we have discussed in *FMU* and earlier in *PMU*.

Dr. Kopelson, what interested you in nutritional medicine or integrated therapies and moved you into this new area?

JK: Thank you very much, Jeff. I feel privileged to be here. Actually, when people ask me that question, I relate what I think is a very funny story, but it was very important to me. About eight years ago, I had a dog that was very sick. We took him to a holistic vet who prescribed vitamins and antioxidants. Lo and behold, several months later, the dog was healthy and happy again. Quite honestly, that impressed me quite a bit, and I started taking vitamins and antioxidants myself. I found I felt better, had more energy, and that is really what stimulated me to move in this direction.

JB: I think it's extraordinary that people have these "aha!" experiences in their lives. A person who is a seeker and is open to new observations can find a path that can embellish past training and provide new opportunities. That seems to be a characteristic shared by almost all of the Clinicians of the Month whom we have had the good fortune to interview for*FMU*.

Let me move to the area of secretin, which I think is an exciting, new advance. Even the MSNBC web page recently contained the headline, "Could New Therapy Cure Autism?" The authors talk about the use of this gut/brain neurohormone to modify autism. It certainly suggests there is something important for us to understand about the gut/brain connection in children who express this condition. Tell us about the history of secretin in autism, and then perhaps we can move to a discussion about how the gut and the brain are interrelated.

JK: Secretin has been around for some time. Gastroenterologists have used it for decades to test for pancreatic dysfunction. As it happens with many of these discoveries, it was completely serendipitous. An autistic child was being examined and endoscoped by a gastroenterologist. As part of the procedure,

the child received an intravenous injection of secretin. Mom noticed in the next several weeks that the child made amazing progress in developing his social skills. It was rather remarkable. We were very fortunate because this Mom happens to have an incredible knack for doing research and making associations. She came to the conclusion that the secretin the child received had caused the advance in his ability to interact with his environment.

I was fortunate to hear about this fairly early on, about a year ago. Because I thought secretin was a nontoxic substance with tremendous potential to help these children, I felt obligated to try it and hope for good results.

JB: It's interesting to see how quickly this discovery, has moved into the general understanding and review. It demonstrates the power of the web-like society we now live in, in which information that has value travels at light speed. It's not held in a cloistered environment as it used to be, waiting for peer review and the slow, plodding progress from one individual to another. We are seeing an explosive exchange of information.

To demonstrate that, I was intrigued to see on November 16, 1998, an electronic message on the worldwide web from the National Institutes of Health. Marie Bristol Power, the health scientist administrator for NIH child health and human development, asked for a secretin registry, so that children on this therapy could be monitored, and it now has Compassionate Use status. Clearly, this must have gotten on the radar screen. Do you see more and more individuals starting to use it with autistic children?

JK: Yes. As a matter of fact, there has been pretty much an explosion of its use in this country, with the presentation of the Dateline segment about a month ago on TV, which illustrated how effective secretin can be. That involved the mom and son I mentioned previously. It documented this very nicely and, since that time, the use of secretin has really exploded.

JB: That leads to the question of how a hormone, or a neurotransmitter that has been used diagnostically for evaluating aspects of pancreatic function could, in fact, have an impact on brain chemistry and behavior. It seems almost to contradict the compartmentalization model of the body that many of us learned about in anatomy and physiology. Would you explain the suggested mechanism of how a gut hormone is potentially related to a brain chemical function?

JK: One of the most wonderful things I've experienced in treating autistic children is having my mind opened to this very thing—that everything in our body is related. I know you've mentioned this any number of times. In fact, the gut and the brain are intimately connected. I believe that children who become autistic do so because they develop a certain type of immune dysfunction and that, in fact, autism is really an environmental illness. I believe that some children are born with a genetic predisposition to develop immune dysfunction. What happens after they're born (sometimes purely by chance) when they get a vaccine or are treated with antibiotics has everything to do with creating the immune dysfunction that spills over into the central nervous system. I believe a chronic inflammation of the intestinal tract begins to occur, which leads to intestinal leakage, which then leads to immune dysfunction. If it gets sufficiently severe, it then leads to the central nervous dysfunction that we tend to place in the autistic spectrum.

Secretin has been used in many ways in the past. In fact, in the 1980s it was used in Germany for

gastrointestinal bleeding. I believe secretin is primarily a gut healer. That's probably why it works in autism. When we heal the gut, we are healing the immune system and therefore healing the central nervous system. I know that sounds rather simplistic, but I can't really do very much better than that at this point without further research. Secretin probably also directly affects the central nervous system.

JB: The model you just described ties together nicely with the work that Dr. William Shaw published in *Clinical Chemistry* two or three years ago. He was a researcher who was Clinician of the Month on *PMU* three years ago describing his work with autistic children and showing unique urinary metabolite patterns that reflected gut dysbiosis. There seems to be a connection between the Shaw work and the secretin work.

JK: Actually, dysbiosis has a great deal to do with the production of this syndrome. Dr. Shaw will be one of the first to tell you that the toxic bacteria and yeast that tend to grow in the GI tracts of these children not only cause more chronic inflammation of the gut, but also release toxic substances that affect the way they think and feel. Another issue that develops with autistic children is that as the immune dysfunction progresses, they tend not only to develop food allergies, but they also begin to process proteins differently from the way we normally do. Every time they eat a food they are allergic to—usually foods containing gluten and casein—they cause further damage to the intestinal lining.

In addition, instead of breaking down these proteins into their component amino acids, they break them down into peptides that have opiate activity and are very toxic to the brain. In fact, incredibly, one of the substances they produce in their guts after consuming these foods is actually the same toxin that natives in South America get from the poison dart frog. So the types and amounts of toxins they're producing in their gastrointestinal tracts are amazing and fascinating. Johnson & Johnson today is doing a tremendous amount of research into this topic. They have identified these specific substances.

JB: Could you tell us something about the organization called DAN (Defeat Autism Now)? I know that Dr. Bernard Rimland**,** Dr. Sidney Baker, William Shaw, Dr. Woody McGinnis, you, and many others have been involved with this organization.

JK: When people refer to the DAN Organization, they're usually referring to the DAN protocol. The DAN protocol is actually not a protocol. It's merely a list of various tests that a group of people recommended, which they felt were useful for autistic children. Bernie Rimland**,** as well as the other individuals you've mentioned, has worked tirelessly to further the cause of treatment of autism. I know Bernie has been doing this for at least two decades. Sid Baker and the others you've mentioned have worked with autistic children for varying lengths of time. They deserve a tremendous amount of credit for making autism more of public issue, lifting people's awareness of autism, and leading us to see the connection between autism and the rest of the body—the immune system and the gut. The DAN organization is a group of concerned parents and physicians who work together to further the cause of the treatment of autism.

JB: Recently on the web, I saw a report by Dr. Cindy Schneider, who is both a medical doctor and the parent of an autistic child. She described what she thought was an adverse reaction to secretin in her child. She thought the reaction may have resulted from her use of porcine secretion as contrasted to the synthetic secretin. Could you explain the potential for adverse side effects and whether there's a difference between the porcine and the synthetic form?

JK: Certainly there are a number of differences between the porcine and the synthetic secretin. Synthetic secretin is not commercially available in this country at this time. Human secretin and porcine secretin differ by four amino acids, so it's a slightly different chemical chain. Not only that, but porcine secretin is actually derived from the intestines of thousands and thousands of pigs, so the potential for impurities is certainly there, although it is my understanding that the people who make this do a really very good job in purifying it. However, I would think, based on my experience with secretin thus far, that using the human version, because it's identical to our version naturally and because it would be chemically pure, would be the ideal thing to do.

Regarding adverse effects from secretin, I really couldn't say if the adverse effects we see are due to the porcine-derived variety, or whether we're seeing adverse effects as a result of the secretin molecule. I would say that 60 to 70 percent of the patients I treat with secretin have experienced a beneficial effect as a result of using it. There are certainly children who experience no effect at all. About 5 to 7 percent of the children I've treated have had a temporary regression, which has been described as hyperactivity and some aggression, as well. That's always been temporary. Because this is an experimental technique at this time, we certainly can't be sure that no one will regress permanently, but I'm not aware that that has happened to anybody as yet. Other potential side effects are really the side effects that people experience with any medication. You have to be concerned about allergic reactions and that kind of thing.

JB: Could you tell us what the general dose is in a child and its route of administration?

JK: The route of administration used by those of us who have been doing this is an intravenous route. As far as dose is concerned, most people have been using one vial in almost all of the children, as I understand. Ferring Laboratories, the producer of the product, recommends a certain amount per kilogram. However, I must say that I don't really believe that this is a dose-related effect. When we think in terms of doses and the use of medications, typically we're talking about drugs that suppress symptoms that require a specific serum level to work. I believe that what secretin is doing, actually, is setting up a chain reaction, and the exact dose is not terribly significant.

Keep in mind that in one vial of Secretion, we are only talking about .0025 mg of secretin, and it is certainly not in the bloodstream very long. You can begin to see what I'm talking about as far as dosage is concerned. There are people who are using secretin sublingually as well in very small dilutions—about 1 to 600, and they have been seeing some success with it. I'm really not prepared to comment on it myself because I don't have enough experience, but the comments I've heard have been favorable. Regarding the mechanism of action of sublingual secretin, I really couldn't venture to know as to exactly how it works. Perhaps it sends a message to the brain.

JB: I've heard the cost of this therapy can be quite considerable, and presumably it's not reimbursable by insurance. Has this been a deterrent in its application and evaluation?

JK: Yes, it can be fairly expensive. The drug itself is fairly expensive. With the emerging popularity of the therapy, prices have seemed to skyrocket. However, I will say that it's been so successful that people seem to be willing to bear the expense to get their children treated.

JB: What percentage of the children you've seen do you feel have been good responders to secretin?

JK: I would say about 70 percent.

JB: Does it seem to require repeated administration to maintain higher-level function?

JK: In some children, I have had to repeat administration of the secretin. The effect in some children seems to taper off after three to six weeks. Repeated dosage has restored the effect in a number of children. However, that has not been universal.

JB: The mechanism of action you propose is that secretin may relate to gut function and the ecology of flora in the gut. That is related to the mucosal-associated lymphoid tissue, which interrelates with blood/brain barrier communication messages to the brain. Given this understanding, is the secretin administered with some kind of program that is directed toward the gut function as well as the neurotransmitter?

JK: I feel that the frequency of dosage of secretin is probably going to end up being the most significant issue here. As I said before, I believe that it is healing the gut, and it would seem to me that repetitive doses would probably promote that healing. I would hope, in the long term, that the immune system would reach a point where it wouldn't need the boost it's getting, and treatment could be stopped at that point.

JB: I know that part of the DAN protocol Drs. Baker and Rimland use is to look at ways of doing reflorestation of the gut, improving the floral ecology by what we call the 4 R approach—remove, replace, reinoculate, repair. The purpose of that program is to lower the burden the dysbiotic organisms may place on the immune system, while also healing the gut using the secretin. It seems that an integrated approach may be emerging, using a very powerful therapeutic modulator along with an underlying normalizing dietary and lifestyle approach.

JK: I wholeheartedly agree with that, and I'd like to add something. Three or four years ago, when I first became involved with autistic children, I was already treating adults with chronic fatigue and fibromyalgia. I began to see a pattern of immune dysfunction in those patients. At that time I felt I might see the same thing in the autistic children. I believe the immune dysfunction in autistic children is really the same process we see in adults, but the symptomatology differs, based on the maturity of the nervous system. So when I discuss this process in terms of autism, I feel we're just hitting the tip of the iceberg and that there is a great deal of chronic illness in this country that has the same cause. To me, that's a very fascinating thing.

JB: I appreciate that insight. I think we're all looking for those interconnected understandings. According to David Deutsch in his book, *The Fabric of Reality,* emerging from our understanding of the evolution of medical science are central principles of disease that may allow us to predict the success of therapies before they are even administered. That's different from the medical taxonomy approach most of us learned in our schooling, which is that each individual disease stands alone. From your experience with secretin and autism, could you provide some insight for practitioners who have not crossed that bridge yet and still feel bound by their traditions to the double-blind, placebo-controlled trial? How can responsible practitioners make decisions regarding therapies?

JK: The secretin experience, and working with autistic children in general, has been the most exciting

thing I've ever done in medicine. It has rejuvenated my interest in medicine. Today, I'm happy to say that I love what I'm doing. I've not always been able to say that. I think one just needs to be open-minded. His or her heart has to be in the right place. Practitioners have to want to help people.

I believe I am using more of the basic science I learned in medical school today than I've ever used. I always loved the basic sciences, Jeff. That's another wonderful feeling about pursuing this type of medicine. It's been one of the most fulfilling things that's ever happened to me.

JB: That's an exciting affirmation of what I think medicine is all about—using knowledge to put together programs that will help patients. I appreciate your sharing that insight. Dr. Kopelson, if people want to follow up with you, is there a place that they can write or call to learn a little more about your experience?

JK: My phone number at the office is 914/278-6800. My fax is 914/278-6897. I'd be happy to speak with anybody who would call.

JB: Thank you for providing this information and for your willingness to have people follow up with you. We will make sure those phone and fax numbers appear on the summary cards at the end of this month's session.

JK: Thanks for the privilege, Jeff.

I want to thank Dr. Kopelson for this extraordinary application of the principles I described on side I of this tape, related to intercellular communication and its relationship to the web of dysfunction that later appears as disease. He has put meat on the bones, so to speak, of this understanding.

On side I, I talked about oxidative stress. Dr. Orville Levander and his colleagues at the USDA Research Center in Beltsville, Maryland, have been looking at oxidative stress and the potentiation of viral infection, particularly various types of infections, such as the relationship of coxsackievirus with selenium status. We have discussed Dr. Orville Levander's research in *FMU* for more than 12 years. He did some of the early pioneering work on lead and oxidative stress, and how vitamin E helps to protect against lead impairment. More recently, he has been looking at selenium.

> "Oxidative stress is implicated in the pathogenesis of several viral infections, including hepatitis, influenza, and AIDS. Dietary oxidative stress due to either selenium or vitamin E deficiency increases cardiac damage in mice infected with a myocarditic strain of coxsackievirus B3. Such dietary oxidative stress (concomitant with a viral infection) allows a normally benign (i.e. amyocarditic) coxsackievirus B3 to convert to virulence and cause heart damage."

This means low antioxidant status of vitamins E and selenium increases the mutational rate of a virus when it infects an individual, and produces a more virulent strain. This is powerful when we start to think about the interrelationship of genes, environment, and function.

> "This conversion to virulence is due to a nucleotide sequence change in the genome of the benign virus, which then resembles more closely the nucleotide sequence of virulent strains. Although it has been known for many years that poor nutrition can affect host

> response to infection, this is the first report of host nutrition affecting the genetic sequence of a pathogen (and modifies the expression of the organism in a more pathogenic form)."

This indicates that we need to be very concerned about nutritional status and maintenance of redox potential for the prevention of and defense against chronic viral infections. Redox potential may influence the residence of a virus within our system for some period of time. If not properly defended against, such a virus can result in mutational injury and more active virulence. If you would like to read more about this, I suggest you read the excellent review on the Levander work in the *Annual Review of Nutrition.*[16]

Antioxidants play a role in protecting against vascular disease. The mechanism by which that occurs is still being studied. One suggestion is that antioxidants help protect against the conversion of monocytes and macrophages in the endothelial space into foam cells; that relationship to the oxidation of LDL may be what initiates monoclonal hyperplasia of the artery and produces the atheroma. Antioxidants help defend against one of the angiotoxic injuries that may initiate atherosclerosis, although there may be other mechanisms by which antioxidants play a role in modifying the expression or the appearance of vascular disease.

The authors of a recent paper in the *Journal of Pediatrics* talked about the occurrence of endothelial dysfunction in children who have genetically related hyperlipidemias.[17] In this trial, children ranging from 6 to 21 years of age were given antioxidant therapy, using in this case ascorbic acid (500 mg twice a day) and tocopherol (400 IU twice a day). The trial involved 18 children with familial hypercholesterolemia, 15 with combined hyperlipoproteinemia, and 12 control subjects. They were studied with high-resolution, two-dimensional ultrasonography. The researchers found that when they received antioxidant therapy, the children who had these genetic uniquenesses with hyperlipidemias experienced significant improvement in vascular reactivity. They wrote:

> "The improvement in vascular reactivity observed during supplementation with antioxidant vitamins suggests that reactive oxygen species derived from oxidized lipoproteins may be responsible for the impairment of vasoregulation in subjects with hyperlipidemia."

This seems to confirm the preliminary conclusions of Steinberg and others that oxidized LDL may be atherogenic. They believe that if you can prevent the oxidation of LDL, you can help defend against these conditions in individuals with specific genotypes, i.e., those who are susceptible to hyperlipoproteinemias who may be more responsive to these types of antioxidant therapies. So *one size* does not *fit all*. Again, it is personalized medicine. This was not a dose-maximized study. It simply used a level that was far greater than the RDI to study the effects of antioxidant supplementation on vascular function and lipoprotein oxidation.

Added Effects of Vitamin E

Vitamin E does more than just block the oxidation of LDL. It also influences immune function and reduces the expression of the proinflammatory cytokines. These cytokines, like interleukin-6, interleukin-2, and tumor necrosis factor-alpha, are related to cortisol release from the adrenal glands and to the shift of cellular redox toward an oxidation potential. I refer to a study in which pigs were exposed to endotoxin to upregulate their immune system. This caused them to express more of the proinflammatory cytokines, which was related to lipoprotein oxidation and vitamin E protection against it.18

In this study, investigators showed that vitamin E supplementation helped these animals resist the oxidative stress that occurred from exposure to lipopolysaccharides, with their influence on cardiovascular risk factors. Lipopolysaccharides represent an inflammatory component related to cardiovascular risk factors that go beyond the oxidation of LDL.

That might help us understand other mechanisms by which vitamin E and other antioxidants help protect against vascular disease. A recent issue of the *Journal of Nutrition* contained a paper titled "Vitamin E and Atherosclerosis," by Dr. Alvin Chan at the Department of Biochemistry, Faculty of Medicine, University of Ottawa. Dr. Chan explained that protection against formation of foam cells could be due not only to the prevention of LDL oxidation, but also to the normalization of immune function to prevent the triggering of these oxidative stress reactions.[19]

Where does the inflammatory burst come from? What is the trigger that might upregulate the immune system and express, from the genes, proinflammatory cytokines like TNF-alpha and IL-2? A review in *Science & Medicine*, titled "Chronic Infection and Coronary Artery Disease" discusses this question.[20] The author re-explores the hypothesis of Rudolf Virchow, a German physiologist who, late in the 19th Century, proposed that vascular disease (or coronary atherosclerosis) was caused by infection and inflammation. This was different from the cholesterol hypothesis advanced later by Anichkov**,** the Russian physiologist, at the turn of the century. It now seems there is something to the Virchow hypothesis.

Chronic infection and inflammation due to *Chlamydia pneumoniae* or *Helicobacter pylori* may in certain genotypes be connected to the relative risk of atherosclerosis. This compelling paper presents pathological and histological specimen examples of how infection—not just bacterial infection, but also viral infections like cytomegalovirus—may have resulted in atherosclerosis. You can track this chronic inflammation with markers in the plasma. C-reactive protein, for example, is a marker that tracks very closely with cardiovascular disease risk. Like elevated homocysteine, it is another cholesterol-independent risk factor for vascular disease.

A recent issue of *Clinical Laboratory News* contains a review of the clinical utility of C-reactive protein as a cholesterol-independent risk factor for evaluating the relative risk of cardiovascular disease. Elevation of C-reactive protein shows chronic inflammatory potential, increased oxidative stress, and modulation of gene expression toward this redox potential that we described earlier—NF *Kappa* B upregulation, for instance.[21]

Atherosclerosis and Defective Mannose-binding Lectin Site

Individuals with severe atherosclerosis often have a defective mannose-binding lectin site on the gastrointestinal mucosa, which may then increase the relative risk of inflammatory responses to their environment and to infectious organisms like Chlamydia pneumoniae. That relationship connects the gut to the heart and is another example of web-like thinking. That paper, titled "Association of Mannose-Binding Deficiency with Severe Atherosclerosis," is published in the Lancet.22 Dr. Peter D'Adamo, our Clinician of the Month in August, 1997, talked about the "Eat Right For Your Type" diet. This diet uses the ABO blood group to evaluate how a person would react to certain dietary principles, such as lectins, and how that would influence the inflammatory system through the gut-associated lymphoid tissue. (GALT).

Dr. D'Adamo's suggestions seem to be borne out with more research. *Chlamydia pneumoniae* carries the relevant structure for binding certain histocompatibility locus antigens, which are shown to prevent pneumoniae from getting access to cells, even in the presence of complements. Therefore, it is possible that mannose-binding-lectin protein, which sits on the surface of gastrointestinal mucosal cells, participates in the first-line defense against chlamydia species. If an individual has defective binding, he or she may be more susceptible to infection, which increases the likelihood of upregulation of the immune system. That upregulation sets in motion oxidative stress, increased production of C-reactive protein and TNF-alpha, and increased vascular injury and stickiness of white cells to the vascular endothelium, transmigration, conversion of foam cells, and so forth.

In other words, the gut is connected to the vasculature, which is connected to the heart and coronary arteries. It is a remarkable association, as we start to examine these webs.

The authors of this *Lancet* paper go on to say:

> "If confirmed in prospectively designed studies, our results may provide a genetic explanation of why only a few *C. pneumoniae* infections result in ischaemic heart disease. Our observation could, however, also reflect an association with other pathogens or some unsuspected noninfective mechanism (i.e., gut dysbiosis and toxicity) relevant to the development of atherosclerosis."

This is very interesting. We might look at these stories from a different perspective when we start examining how binding sites, intercellular communication, and gene expression all interrelate.

That leads to a discussion of some newly discovered molecules that are involved in setting up these intercellular signals, the STATs and JAKs. STATs are signal transduction activators of transcription. JAKs are the Janus family of tyrosine kinases.[23] They interrelate to upregulate the expression in the genes of the NF *Kappa* B, interferon-gamma, and the type 2 proinflammatory cytokines like TNF-alpha. They upset the balance between the type 1 and type 2 cytokines, which shifts the body into a proinflammatory state. STATs are in part released by activation of the mucosal-associated lymphoid tissue (MALT), as well as systemic immunological components. Again, the gut is connected to the Kupffer cells of the liver, which are connected to the white blood cells of the vasculature, which are connected to the glial cells of

the brain. These are all derived from similar embryonic cells and can ultimately be seen as having similar responses to the environment and upregulation of the immune system.

Nobel Prize in Medicine Won By Dr. Murad

I was excited to see that these concepts of second-signal messengers, the interrelationship to signal transduction, and how these mediators play a role in chronic illness and function, were the subject of the Nobel Prize in Medicine for 1998. Drs. Furchgott, Ignarro, and Ferid Murad received the 1998 Nobel Prize for Medicine for discovering that the body uses nitric oxide (NO) to regulate blood vessels, that NO serves as a neurotransmitter, and that it plays a role in a number of functions related to the immunological system.24 Dr. Murad was a presenter at our Fourth International Symposium on Functional Medicine in Aspen, Colorado, where he talked about his discoveries of nitric oxide.

Many people who attended that symposium thought Dr. Murad's talk was too scientific, too esoteric, too removed from clinical practice. In retrospect, however, we can see that understanding the implications of nitric oxide and its influence on how we look at webs of disorders to come up with new therapies was an important part of a path of discovery and education for students of functional medicine. We have to push ourselves at times to places of less comfort with our knowledge and open our minds to the thoughts that through these discoveries may come opportunities for growth. Dr. Murad's presentation, which was very elegant science, infected us with thoughts of where this field might take us and new ways of looking at modulation of function.

Nitric oxide is an important molecule for proper vascular tone, proper neurotransmission, and proper immunological defense. It is derived from three isoforms of nitric oxide synthase—an immune-inducible form, a constitutive endothelial form and a neuronal form—so it has poly-organ effects on function. Symptoms of nitric oxide dysregulation can be seen in a myriad of organs and symptoms. We learn that balance is important.

Nitric oxide is not a bad molecule. Like the prostaglandins, it is a very important molecule. But its balance is important. Too little is not good; too much is not good. It must be balanced in various tissues.

One agent that causes alteration of nitric oxide is sildenafil. As you know, Viagra has received a tremendous amount of attention as a drug that modulates nitric oxide production (purportedly just in the penis), causing increased vasodilation, increased vascular profusion of the penis, and improved erection. Because both nitric oxide and the enzyme nitric oxide synthase are nonspecific, however, the relationship to cyclic GMP, which relates to nitric oxide synthase activation, is not found just in the reproductive organs of males. We begin to see side effects appearing elsewhere in the body, like blue vision in some individuals, and headaches. A recent *Lancet* article reported possible risk of acute myocardial infarction in individuals who are not on nitrate-containing drugs who took Viagra. The outcome appeared to be death itself.[25]

Genetic specificity, personalized medicine, one size doesn't fit all. If we start tampering with the web, we get very significant effects on lots of different influences within function. For some individuals, it may be undesirable, so we have to look at effects, not just make assumptions.

Obviously, the way this web is modified is through things we do every day, such as the way we eat, think, and behave. Individuals who do not get enough B12, B6, and folate in their diets, for example, have

different gene expression and modulation. Elevated expression and altered patterns of the activity of DNA methyltransferase were seen in livers of animals that were fed diets deficient in B6, B12, and folate.[26] Eating soy, which contains the isoflavones genistein and daidzein, will modify the risk of disease. It does so by modifying signal transduction and intercellular communication. These isoflavones influence kinase enzymes, protein tyrosine kinase, as discussed in the *Journal of Nutrition*.[27]

Humans who consume soybeans with isoflavones have increased plasma, urine, and fecal levels of these agents. Some difference in absorption can occur from one person to another, based on their digestion, assimilation, and tissue distribution. The same amount of soy in the diet may have different effects from individual to individual on digestion, absorption, and tissue response at the receptor site levels of these signal modulators like the soy isoflavones.

Many other nutritive agents influence intercellular communication. An example is a lycopene, the red pigment found in tomatoes, which is better absorbed from tomato paste than fresh tomatoes, and better absorbed when given along with olive oil. Lycopene influences various aspects of cellular differentiation and expression in the prostate in males. It may, therefore, be the cause of the reduced prostate cancer seen in individuals who consume a lot of pizza and tomato sauce.[29]

Broccoli, broccoli sprouts, and other members of the cruciferous vegetable family contain glucosinolates that upregulate the expression of various detoxification enzymes that influence intercellular activity and the mediators that help balance the internal and external environment. Talalay et al. at Johns Hopkins School of Medicine conducted research on broccoli sprouts as inducers of enzymes that protect against chemical carcinogens.[30]

There is also ongoing work with green tea and its constituent epigallocatechin gallate, which is a very powerful gene response modulator, antioxidant, and redox potential agent.[31,32]Numerous papers support the protective effect of this tea. Even the *Journal of the National Cancer Institute* recently had an article, titled "Tea Therapy? Out of the Cup, Into the Lab," which described extensive study of epigallocatechin gallate and its potential in chemoprevention.[33]

We are witnessing the emergence of a new paradigm in health that is web-like rather than linear and reductionistic. It uses the environment as a tool rather than as a hazard and starts to construct a personalized medicine, which will be the focus of *FMU* as we move through 1999.

Bibliography

1. Diez-Gonzalez F, Callaway TR, Kizoulis MG, Russell JB. Grain feeding and the dissemination of acid-resistant *Escherichia coli* from cattle. *Science.* 1998;281:1666-1668.
2. Walker EA, Unutzer J, Katon WJ. Understanding and caring for the distressed patient with multiple medically unexplained symptoms. *J Am Board Fam Pract.* 1998;11:347-56.
3. Inouye SK, Peduzzi PN, Robison JT, Hughes JS, Horwitz RI, Concato J. Importance of functional measures in predicting mortality among older hospitalized patients. *JAMA.*1998;279(15):1187-1193.
4. Maze GL, Lee M. Acute renal failure in an alcoholic patient taking therapeutic doses of acetaminophen. *JABFP.* 1998;11(5):410-413.
5. Cupp MJ, Tracy TS. Cytochrome P450: new nomenclature and clinical implications. *Am Family*

Physician. 1998;57(1):107-116.
6. Martinelli I, Sacchi E, Landi G, Taioli E, Duca F, Mannucci M. High risk of cerebral-vein thrombosis in carriers of a prothrombin-gene mutation and in users of oral contraceptives. *N Engl J Med.* 1998;338(25):1793-1797.
7. Bertina RM, Rosendaal FR. Venous thrombosis—the interaction of genes and environment. *N Engl J Med.* 1998;338(25):1840-1841.
8. Robinson TN, Patrick K, Eng TR, Gastafson D. An evidence-based approach to interactive health communication. *JAMA.* 1998;280(14):1264-1269.
9. Abby SL, Harris IM, Harris KM. STEPped Care: an evidence-based approach to drug therapy. Homocysteine and cardiovascular disease. *JABFP*. 1998;11(5):319-398.
10. Stabler SP, Lindenbaum J, Allen RH. Vitamin B-12 deficiency in the elderly: current dilemmas. *Am J Clin Nutr.* 1997;66:741-749.
11. Bernard MA, Nakonezny PA, Kashner TM. The effect of vitamin B12 deficiency on older veterans and its relationship to health. *JAGS.* 1998;46:1199-1206.
12. Wehling M. Specific, nongenomic actions of steroid hormones. *Ann Rev Physiol.*1997;59:365-393.
13. Daniel PB, Walker WH, Habener JF. Cyclic AMP signaling and gene regulation. *Ann Rev Nutr.* 1998;18:353-383.
14. Hilgemann DW. Cytoplasmic ATP-dependent regulation of ion transporters and channels: mechanisms and messengers. *Ann Rev Physiol.* 1997;59:193-220.
15. Nakamura H, Nakamura K, Yodoi J. Redox regulation of cellular activation. *Annu Rev Immunol.* 1997;15:351-369.
16. Beck MA, Levander OA. Dietary oxidative stress and the potentiation of viral infection. *Ann Rev Nutr.* 1998;18:93-116.
17. Mietus-Snyder M, Malloy MJ. Endothelial dysfunction occurs in children with two genetic hyperlipidemias: improvement with antioxidant vitamin therapy. *J Pediatr.*1998;133:35-40.
18. Webel DM, Mahan DC, Johnson RW, Baker DH. Pretreatment of young pigs with vitamin E attenuates the elevation in plasma interleukin-6 and cortisol caused by a challenge dose of lipopolysaccharide. *J Nutr.* 1998;128(10):1657-1660.
19. Chan AC. Vitamin E and atherosclerosis. *J Nutr.* 1998;128(10):1593-1596.
20. Muhlestein JB. Chronic infection and coronary artery disease. *Sci Med.* 1998;5(6):16-25.
21. Tracy RP. C-reactive protein and cardiovascular disease. *Clin Lab Rev.* 1998;24(8):14-16.
22. Madsen HO, Videm V, Svijgaard A, Svennevig JL, Garred P. Association of mannose-binding-lectin deficiency with severe atherosclerosis. *Lancet.* 1998;352(9132):959-960.
23. Leonard WJ, O'Shea JJ. JAKS and STATS: biological implications. *Ann Rev Immunol.*1998;16:293-322.
24. Three Americans share Nobel for medicine. *Ashland Daily Tidings.* Oct 12, 1998.
25. Feenstra J, van Drie-Pierik RJ, Lacle CF, Stricker BH. Acute myocardial infarction associated with sildenafil. *Lancet.* 1998;352(9132):957-958.
26. Lopatina NG, Vanyushin BF, Cronin GM, Poirier LA. Elevated expression and altered pattern of activity of DNA methyltransferase in liver tumors of rats fed methyl-deficient diets. *Carcinogenesis.* 1998;19(10):1777-1781.
27. Lichtenstein AH. Soy protein, isoflavones and cardiovascular disease risk. *J Nutr.*1998;128(10):1589-1592.
28. Watanabe S, Yamaguchi M, Sobue T, et al. Pharmacokinetics of soybean isoflavones in plasma, urine and feces of men after ingestion of 60 g baked soybean powder (Kinako). *J*

Nutr. 1998;128(10):1710-1715.

29. Gartner C, Stahl W, Sies H. Lycopene is more bioavailable from tomato paste than from fresh tomatoes. *Am J Clin Nutr.* 1997;66:116-122.
30. Fahey JW, Zhang Y, Talalay P. Broccoli sprouts: an exceptionally rich source of inducers of enzymes that protect against chemical carcinogens. *Proc Natl Acad Sci USA.* 1997;94:10367-10372.
31. Witschi H, Espiritu I, Yu M, Willits NH. The effects of phenethyl isothiocyanate, N-acetylcysteine and green tea on tobacco smoke-induced lung tumors in strain A/J mice. *Carcinogenesis.* 1998;19(10):1789-1794.
32. Suganuma M, Okabe S, Oniyama M, Tada Y, Ito H, Fujiki H. Wide distribution of [^{3}H](-)-epigallocatechin gallate, a cancer preventive tea polyphenol, in mouse tissue.*Carcinogenesis.* 1998;19(10):1771-1776.
33. Vastag B. Tea therapy? Out of the cup, into the lab. *J Natl Cancer Inst.*1998;90(20):15041505.

p>