July 2000 Issue | Dr. Robert Sapolsky, PhD

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Welcome to *Functional Medicine Update* for July 2000. What are functional medicine and functional somatic syndromes? Let's discuss a review contained in the *Lancet*, titled "Functional Somatic Syndromes: One or Many?"

Patients seek help from doctors for symptoms, and doctors diagnose diseases to explain them. Symptoms are the patient's subjective experience of changes in his or her body. Severity is a function of intensity, duration, or frequency of these changes. Most patients do not seek the care of a health provider when they feel good. They do so because they are experiencing some threshold of discomfort, seen as subjective symptoms of increasing duration, frequency, and severity.

Diagnosing Disease

Diseases are objectively observable abnormalities in the body relative to some standard. These standards are called ICD9s in today's medical parlance. This relative scale has changed with time, however, as diagnostic procedures have changed. Back in the 18th and 19th centuries, diagnosis of what we now call diabetes was accomplished by tasting the patient's urine to see if it was sweet, a very simple analytical system. Today we have more sophisticated means of analyzing aberrations in insulin and blood sugar control. New technologies, including finger stick techniques, have given us a different set of diagnostic lenses with which to evaluate what we call diabetes. As Dr. Robert Sapolsky states, however, the basic diabetic condition of "feeling crummy" has remained pretty much the same for the patient despite changes in diagnostic techniques. "Feeling crummy" may stay the same, but the way we assess it, language it, and ultimately define it has changed relative to our perceptions. Diseases are objectively observable abnormalities in the body, as contextualized at a particular time in history.

Difficulties arise, obviously, when the doctor can find no objective changes to explain the patient's subjective experience of discomfort of pain. The symptoms are then often referred to as medically unexplained or functional, giving a negative spin to the words "functional medicine." A number of functional syndromes have been described. In fact, each medical specialty seems to have at least one. For rheumatologists, prominent muscle pain and tenderness called fibromyalgia has often been called a "functional disorder," indicating it has a psychosomatic component. For gastroenterologists, abdominal pain with altered bowel habits called irritable bowel syndrome, or IBS, has traditionally been called a "functional disorder," again meaning that a lot of it is psychosomatic in origin. Chronic fatigue, or postviral fatigue syndrome, has also been defined as a "functional disorder."

Defining "Functional" Disorders

As we in the biomedical sciences have looked more deeply into the origin of these conditions, we have found a discrepancy in these definitions. What may have appeared on the surface to be "functional," meaning psychosomatic, is really functional, meaning that a functional change in physiology can be identified when we look in the right places and ask the right questions.

The authors of this *Lancet* article on functional somatic syndromes postulate that the existence of specific somatic syndromes is largely an artifact of medical specialization. In other words, the differentiation of specific functional syndromes reflects the tendency of specialists to focus only on symptoms that are relevant to their specialty that have organic relationships, rather than on any real symptoms and differences in those symptoms between patients. In an exploration of this hypothesis, the authors reviewed the research literature with regard to three questions. First, do the published diagnostic criteria for each of the specific functional syndromes overlap in their constituent symptoms? Second, do patients identified as having one functional somatic syndrome also meet symptom criteria for others? And third, do similarities exist across syndromes in the non-symptom characteristics of sex, coexisting emotional disorder, proposed etiology, prognosis, and response to treatment?

Explaining the Stigma Related to "Functional" in Medicine

The answers to those questions led the authors to draw a very interesting conclusion. Similarities are apparent in case definition reported symptoms and in a non-symptom association such as the variability in demographics I described.

They conclude the existing definitions of these syndromes, in terms of specific symptoms, are of limited value. They believe a dimensional classification related to functional characteristics at a physiological and functional level is more appropriate. The fact that each medical specialty defines its own syndrome or syndromes in terms of its inability to understand physiochemical or biochemical mechanisms has tended to place a negative stigma on the term "functional" in medicine.

Defining the "Functional" in Functional Medicine

In the practice of functional medicine, we use the term "functional" to refer to the early prognostic changes that occur at the level of cellular function. Those changes then affect over time with increasing duration, frequency, and severity until they finally effect a tissue/organ system problem and finally, a whole-body problem. These particular sequences of events that give rise to increasing severity are eventually seen as warning signs to take action, to do something. The body is out of balance. Some people get a warning sign at an early stage of the development of their symptoms. Heeding these signals, they can recognize where these functional disturbances are originating or pinpoint their locus of activity.

Using our definition, functional medicine cuts across and precedes diagnostic medicine. It looks at the physiological, emotional, and cognitive changes that occur prior to the onset of disease. It opens up a broader area of exploration for the clinician in evaluating this "crummy" feeling Dr. Sapolsky describes. Dr. Sapolsky, author of *Why Zebras Don’t Get Ulcers* and *The Trouble With Testosterone*, will be our Clinician of the Month. He will share visionary concepts, insights, perspective, and guidance as to where medicine may be traveling over the next decade.

In our discussion of function, let me revisit something we discussed in *FMU* several months ago. That is

the report in the *New England Journal of Medicine* of an evaluation of chiropractic manipulation as an adjunctive treatment for children with asthma. In evaluating this work, I believe I did the investigators some disservice that I now want to correct. The principal investigator, Dr. Jeffrey Balon, is a medical doctor and chiropractic physician I have known for a number of years. This study attempts to understand, using metric evaluation, the effect of chiropractic manipulation in reducing symptoms of childhood asthma compared to more traditional medical intervention.

This report described 80 children, 38 in the active-treatment group and 42 in the simulated-treatment group. Evaluation of outcome data revealed small increases—7 to 12 liters per minute—in peak expiratory flow in the morning and evening in both treatment groups (the group that received chiropractic treatment versus those that did not). No significant differences appeared between groups in the degree of change from baseline. Symptoms of asthma and use of b -agonists decreased, and quality of life increased in both groups, with no significant differences between the groups. No significant changes appeared in spirometric measurements or airway responsiveness between the children who received the active chiropractic treatment and the simulated treatment group. The authors conclude that in children with mild or moderate asthma, the addition of chiropractic spinal manipulation to usual medical care provided no benefit.

Importance of Therapeutic Touch

I criticized that conclusion by saying it did not seem to derive fully from the study data, nor the inference of that data. Using straight statistical normative evaluation, their conclusion that chiropractic manipulation of the spine provides no benefit to children with mild to moderate asthma does stand the test of that evaluation. However, what also emerges from the data is the possibility that doing something—a laying-on of hands, being present with the patient, having some relationship to that patient—which occurred in both the simulated-treatment group and the active-chiropractic-treatment group, had a positive benefit.

This benefit causes one to wonder about the importance of having one’s hands on a patient in a way that is therapeutic, developing a powerful relationship. What is the connection with the exchange between provider and patient? How does the system change as we increasingly move to white-coat, laboratory medicine that distances the practitioner from the patient and never makes the patient a human being insentient contact with their provider? I believe we can conclude from the study by Dr. Balon and his colleagues that this collaborative study seems to indicate the importance of a sentient patient/practitioner interaction. Something profound, regardless of the specific technique used, occurs that enhances function on a number of levels. Perhaps that should be woven into our treatment protocols in a more real way and not discounted as a placebo effect or as an outlier relative to the overall success of any therapy.

A repeated theme in *FMU* and its predecessor *PMU* over the years has been the question of how the environment influences the expression of genes to give rise to function in the course of living over decades of life. How do we accumulate this message of interaction between the environment in which we live and ultimately our preprogrammed genetic code? That concept has been receiving much more interest in medicine recently. It emerges from Dr. Linus Pauling’s concept of molecular medicine. A recent paper titled "Association Studies of Genetic Polymorphisms and Complex Disease" appeared in the *Lancet.* The authors examined the increasing awareness on the part of geneticists of the limits of investigations based on the association of polymorphisms, meaning genetic differences from individual to

individual.

Because of the technical simplicity, the polymorphic association is used too much and too extensively, the authors say, without any in-depth knowledge of the underlying theory. Geneticists have written some excellent reviews that address genetic and methodological arguments. They believe some aspects are easily comprehensible. In other cases, it is difficult for the average healthcare provider to understand the interaction between genes and environment and how the polymorphic genes give rise to the expression of the phenotype.

Personalized, Individualized Medicine

One should be very cautious, according to this report, not to generalize to the mean, looking at populations, mean averages, and standard deviations. Rather, this whole model has to be applied to the individual. It is focused on personalized, individualized medicine. We are moving from the consideration of average patients to an evaluation of the unique interaction of an individual's genomic message and epigenetic patterning. We are considering how that patterning interrelates with his or her variables of environmental exposures —stress factors, exercise factors, dietary habits, exposure to electromagnetic radiation—to influence how these chemical and electrical communication systems shape the body and its function.

This theme also appears in an article in *Nature Genetics,* titled "Grass-Roots Genomics. The authors of this paper describes the coming-of-age of genomics. They explain we are a few years away from having the techniques for evaluating multiple gene characteristics in individuals as they come into the routine practice of medicine, interpreting how those genes are being expressed, and understanding the optimal way of modifying their expression to give rise to appropriate function. We are certainly making progress in that direction.

Practical Applications of Genomics

The new technology is moving out of the laboratory of the esoteric research specialist and into the clinical laboratory with DNA microarrays of gene expression. The authors go on to say:

> "Putting the techniques of today's genomicists within reach of the rank-and-file biologist is essential if functional genomics is to fulfill its much-heralded promise. This dispersal is just beginning to happen; a few relatively small laboratories, mostly through independent effort, have acquired the ability to measure gene expression with DNA microarrays, a technology formerly accessible only to genomicists. Advances in DNA microarray fabrication techniques promise to reduce the cost of arrays, which should increase their availability to the general community."

We are witnessing the beginning of a revolution in medicine, utilizing genomics to understand aspects of the complex array of multigenes that give rise to various phenotypic characteristics. We are beginning to understand how environmental modulators of gene expression and the inducible gene array can be constructed in such a way to personalize medicine for that patient.

One aspect of this new understanding of genomics is the gene/environment interaction in cancer risk. An

interesting study published in the *Journal of the National Cancer Institute*discusses the passive smoking relationship to cancer through the genetic polymorphism of an enzyme or a gene called glutathione S-transferase M1. This enzyme is found in high concentrations in oxygen-rich tissue and that is involved with glutathione conjugation reactions. It is found in high levels in the liver and is involved with conjugating glutathione with a xenobiotic or a biotransformed intermediate to produce a mercapturate, a glutathione conjugate. That mercapturate is excreted in the bile if it is a higher-molecular-weight product, or in the urine if it is a lower-molecular-weight product.

Passive exposure to tobacco smoke produces an increased carcinogenic risk if the individual has the null variant polymorphism of glutathione S-transferase M1, according to the authors of this paper. Individuals who are less able by their biochemical heritage to detoxify the same exposure as an individual who might have a higher level of glutathione S-transferase M1, puts them at higher risk.

Carcinogenic Epidemiology

I guess you would call this carcinogenic epidemiology. It is cancer epidemiology at the molecular level, looking at genetic polymorphism. This is another way of restating the "yellow canary" premise. Some individuals carry specific genomic risks, as identified by their unique metabolic characteristics tied to their genes and their environment, that create increased risk of disease relative to someone else.

This concept takes us away from the Mendelian deterministic view of medicine, according to which everything is locked into our genes and we can do little about it. Our parents gave us the sperm and the egg and that is what we have been dealing with ever since. Our understanding has evolved to what I call a plastic, or modifiable, life history. According to this understanding, although we do have certain locked-in principles in our 23 pairs of chromosomes, we can modify the expression of those characteristics through the environment to which we expose them. This understanding that the expression of our genes can be modified extends even to problematic genotypes such as inherited cancer genes. With regard to RAS, p51, and p53mutations, we have heard that if one has those mutated genes, there is little he or she can do to decrease the risk. Another example is breast cancer genes, the BRCA genes.

The authors of a paper in the *Journal of the American Medical Association* talk about life expectancy gains from intervention to prevent contralateral second cancer in women with BRCA1 and BRCA2 mutations. These mutations indicate the women carry the genetic propensity toward breast cancer. For years, we have asked the question, could a person with a genetic risk to cancer create a different phenotypic outcome by modifying her environment? Determinists have said no; if you have that risk, you might as well live with it while you can and pursue whatever lifestyle you want to engage in. If you have that message, there is little you can do to escape it. Medicine is there to rescue you to the best its possibilities from the ultimate cancer.

This paper in *JAMA* discusses something different. The researchers used an intervention—in this case, some chemopreventive approaches to BRCA expressions—in individuals who have various degrees of penetrants of the BRCA mutation. The investigators found that by using things like tamoxifen therapy, they were able to alter the actual phenotypic presence of breast cancer in women who shared risk as a consequence of carrying the BRCA mutation at different levels of penetrants. This paper is interesting, although it is speaking about tamoxifen therapy. One might also consider other environmental interventions that could reduce or alter the expression of these characteristics that give rise to breast

cancer. The more we learn about altering expression of even some fairly severe mutations, the more we will be able to modify or prevent some very serious diseases. In this paper, investigators examined the effect of tamoxifen by lateral prophylactic oophorectomy to change estrogen secretion patterns, and prophylactic contralateral mastectomy in women who had very high incidence and degrees of penetrants of BRCA. Tamoxifen is the most interesting because it is an estrogen modulator with secondary influence to carrying the relative gene risk.

Researchers are now discovering a range of dietary factors that modify gene expression and various oncogenic processes in carcinogenesis. Some of those substances are found in high concentrations in fruits and vegetables. There has been a tendency over the last several years to try to find the single molecule in fruit or in a specific vegetable that is the chemopreventive agent such as beta carotene, even though we know of hundreds of different carotenoids. There has been a tendency to say, let's isolate the chemical. Scientists wanted to purify it, synthesize it; and administer it like a drug to see if it can prevent cancer. When results like those in the Finnish Smokers' Study do not indicate beta-carotene prevents cancer, those same scientists are likely to assume it doesn't work and give up on it.

This is a flawed approach to the problem. We don't eat just beta-carotene in the all-trans form. In orange-red vegetables and fruits, we eat hundreds of different carotenoid isomers and molecules, all of which influence different physiological functions in differing ways. That complex symphony of different phytonutrients influences function.

Fruits, Vegetables, and Bladder Cancer

One of the events associated with carcinogenesis is mutational injury to the cell, causing altered DNA configuration in the genome, DNA adducts, or DNA excision mutants. Would it be better to give a person a few selected supplements of antioxidants instead of giving him or her a whole-fruit and -vegetable dietary intake containing thousands of redox-active compounds?

That is, in essence, what the authors report in an interesting article in *Carcinogenesis.* In the article, titled "White Blood Cell DNA Adducts and Fruit and Vegetable Consumption in Bladder Cancer," investigators looked at white blood cell DNA adducts and mutations in the presence and absence of fruit and vegetable consumption. They correlated their findings with bladder cancer. They looked at various types of genetic metabolism uniquenesses or polymorphisms. One was the N-acetyl-transferase mutation associated with smoking-induced cancers. They found that fruits and vegetables protect against bladder cancer, apparently by inhibiting the formation of DNA adducts perhaps in ways that differ from individual phytochemicals or phytonutrients isolated from fruits and vegetables.

I want to emphasize the synergy that comes into play when you start using whole, natural foods such as fruits and vegetables that are minimally processed, rather than giving single nutrients, one at a time, and then using a pharmacological model to look at endpoints of cancer. It is a very different study with a very different outcome. This is the kind of thing people have generally done over millennia. Our ancestors ate foods. They didn't eat single nutrients, one at a time. Our protection systems evolved in that matrix of complex nutrients.

Reviewing the Ameliorating Role of Antioxidants in Cancer Therapy

Dr. Davis Lamson and Matthew Brignall, ND, wrote a review article on antioxidants and their role in helping to ameliorate the secondary side effects of cancer chemotherapy and radiotherapy. The review, which appeared in *Alternative Medicine Review*, is titled, "Antioxidants and Cancer Therapy II: Quick Reference Guide." The authors have assembled nearly 100 references at the back of this paper, describing research on the amelioration of various aspects of chemotherapeutically induced cell damage, without uncoupling the therapeutic potential of the drug. They broke it down into human studies, animal studies, and *in vitro* studies. Then they made comments. They look at vitamin A, beta-carotene, vitamin C, vitamin E, selenium, coenzyme Q10, melatonin, N-acetylcysteine, glutathione, green tea, and quercetin. They break these substances down into different types of chemotherapeutic agents—alkylating agents like cyclophosphamide, antibiotic agents like doxorubicin or bleomycin, antimetabolites like 5-fluorouracil or methotrexate, platinum compounds like cisplatin, and radiotherapy. They describe a variety of effects of each family of substances. I urge you to take a look at this paper, which includes a tremendous amount of information. I think it summarizes a vast amount of information in a readily available form.

A great number of studies appear to demonstrate the value of specific types of nutrients in the amelioration of the adverse side effects of cancer therapy. In humans undergoing radiotherapy, the list of nutrients includes vitamin A, the carotenoids, vitamin C, selenium, melatonin, N-acetylcysteine, and glutathione. With platinum compounds, the list includes selenium, melatonin, and possibly N-acetylcysteine. If we look at antimetabolites like 5-fluorouracil, the list includes vitamin A and coenzyme Q10. The toxicity associated with doxorubicin, cyclophosphamide and 5-fluorouracl is reduced by glutathione. Basically, evidence indicates that without interrupting the therapeutic benefit of these medications, certain nutritional follow-up strategies might be considered desirable. I urge you to read this review article.

An individual’s response to a chemotherapeutic drug will be related to his or her detoxification pathways and the way the body is programmed to detoxify, the genomics of the person’s detoxification. This new approach in pharmacology tries to understand something about a person’s phase I and phase II detoxification activities by assessing the activities prior to the administration of a medication. Then, if you know the method of metabolism and detoxification of that medicine, you can predict how that person might respond to it based upon his or her genetic uniqueness. Such is the case for mercaptopurine. By taking pharmacogenetics into account, the dose can be optimized based on how a person is expected to metabolize the drug.

This approach is very different from just determining the dose based simply on body surface area, and not taking into account some of the differences in metabolism. You can see the transition to personalized medicine based on genomics. Individuals given mercaptopurine therapy can exhibit intolerance as a consequence of heterozygosity in the S-methyltransferase gene locus. One can actually look at the methylation reactions and predict how a person will respond to the therapy and what dose is necessary to get positive response. We are starting to see some extraordinary progress in converting the philosophy of genomics into an actual diagnostic and treatment application concept.

Glucosamine and Chondroitin Treatment of Osteoarthritis

Traditional medicine in the United States has for some time discounted the benefits of oral glucosamine sulfate and chondroitin in managing degenerative joint disease or osteoarthritis as having no basis in good science. Observational studies in which a valuable response was seen were thrown out because it was not

supported by an underlying mechanism, nor was it a randomized clinical control trial. Medicine is only based on scientific principles. American medicine, which tends to be parochial and provincial, has not accepted the conclusions of European studies, particularly in Italy, which have suggested or even demonstrated benefit in osteoarthritis with glucosamine sulfate supplementation. It was a surprise, therefore to read a report in the *Journal of the American Medical Association* on glucosamine and chondroitin for the treatment of osteoarthritis, which was a systematic, quality assessment and meta-analysis. I urge you to read this paper.

The report is interesting, both because of the specifics of the paper, and for the general consideration of how one makes decisions based upon a variety of inferential data by meta-analysis. There are ways of reaching conclusions or testing hypotheses other than the double-blind, randomized clinical controlled trial. The latter may be very useful for evaluating a single outcome from a single agent, but they may be less useful in looking at multiple agents against multiple outcome parameters.

Meta-Analysis of Glucosamine and Chondroitin Benefits

The paper concludes that trials of glucosamine and chondroitin preparations for osteoarthritis symptoms demonstrate moderate to large effects. Issues related to the product and its reproducible quality have resulted in more scatter and noise about the midpoint than a typical pharmacology study, in which well-defined single molecule materials are used. The takeaway, however, is that there is something worthwhile in these substances. The researchers examined more than 10 studies from 1994 through 1998, with subjects as few as 17 (Kerzberg et al., 1987) or as many as 329 (Rovati, 1997). All were based on oral administration, except the Rovetta et al. study in 1991, which was based on intramuscular administration. All showed positive outcome from glucosamine and/or glucosamine condition.

We are moving into an era in which we are looking at outcome analyses. We are looking at pattern recognition, cluster analysis, multi-factorial or multi-parameter analysis, and meta-analysis, to help us make better information-based clinical decisions.

New and Early Risk Factors in Functional Assessment of Cardiac Risk

Let’s move this discussion into the area of cardiac risk. Dr. Paul Ridker, a cardiologist at Harvard Medical School, has helped us understand risk factors for cardiac disease in addition to the traditionally recognized factors of cholesterol, smoking, hypertension, diabetes, obesity, and sedentary lifestyles. These additional risk factors relate to performance criteria. When woven together they indicate that the heart is not just a pump. In many ways, it behaves as an endocrine organ, and it responds to inflammatory mediators as a neurogenic organ.

The *New England Journal of Medicine* recently featured a paper titled "Abnormal Myocardial Phosphorus-31 Nuclear Magnetic Resonance Spectroscopy in Women with Chest Pain But Normal Coronary Angiograms." I emphasize the concept of diagnosis. When does one cross the boundary to reach a definable diagnosis? If patients with normal coronary angiograms, but yet they have chest pain, do they have a functional disorder that precedes the onset of the abnormal angiogram? The researchers were trying to answer that question by using a functional assessment tool called phosphorus-31, or 31p NMR. In exercising muscle, this tool measures ATP synthesis and utilization. It determines ATP-to-inorganic phosphate ratios as a measurement of biochemical energetics. It is a functional measurement of

energy metabolism. It relates to a series of events—oxygen perfusion, mitochondrial oxidative phosphorylation, energy transport through the cytochrome systems. It is a biochemical energy assessment tool using the exercising muscle as the model.

Hand-Grip Measurement as Functional Early Warning Tool

The investigators found direct evidence of an abnormal metabolic response to exercise. They used a hand grip as the stressor, which was strongly correlated in women with chest pain, even in the absence of angiographically significant coronary stenosis. This may be a functional, early-warning predictor of later-stage problems. You can catch it early on, as an energy deficit disorder of the cardiac muscle that may have come from many variables that may not be picked up yet by coronary angiogram. This study is very interesting from a functional medicine perspective.

In cases in which there is temporal ischemia, low oxygen delivery, and mitochondrial uncoupling, one moves from oxidative phosphorylation to anaerobic glycolysis by which the cells try to keep their energy production going by an inefficient mechanism. Under this condition, there is increased oxidative stress resulting in increased glutathione turnover, Demand for antioxidants increases in response to the oxidants produced during ischemia—hydroxyl radical, superoxide radical, singlet oxygen and hydrogen peroxide. If a person has low ATP recharge rates that correlate to chest pain, could the individual not also have indicators of oxidative stress?

Oxidative Stress Markers

What is a good marker of oxidative stress? Is it 8-hydroxy-deoxyguanosine in the DNA of lymphocytes, which indicates oxidative damage to DNA? Is it whole-blood glutathione levels in the reduced versus oxidized form? Is it elevated serum lipid peroxides, determined by thiobarbituric acid analysis? Or, could it be other variables like isoprostanes, a series of compounds similar to prostaglandins produced as a consequence of increased oxidant reaction with arachidonic acid to form these cyclic endoperoxide derivatives that indicate oxidative stress?

Another potentially useful marker was recently found and discussed in the journal *Clinical Chemistry* which suggests that the amount of glutathione conjugated to hemoglobin is a clinical marker of oxidative stress. There has been substantial interest in oxidative stress and its potential role in the development of many chronic diseases, including not only atherosclerosis and other cardiovascular diseases, but also diabetes, cancer, accelerated aging, and brain dysfunction. (We will discuss that a bit later in this month's *FMU*).

Oxidative Stress and Diabetes

The German chemist Helmut Sies was the first to define oxidative stress as an imbalance between antioxidant and oxidant-generating systems. An increase in oxidative stress has a profound effect on lipoproteins producing a variety of oxidant products, on transcription, due to the effect of ROS on cell signal transduction. Oxidative stress can arise through various mechanisms associated with excess oxygen radical production, such as on oxidation of glucose and glycated proteins and the glycation of antioxidant enzymes. Even in healthy people, high blood sugar is found to be associated with increased fatty acids and hyperinsulinemia, triggering oxidative stress. It is a functional measure well before a

pathophysiological measure.

The authors of the paper in *Clinical Chemistry* stated that there is a very high level of glutathione conjugated hemoglobin in the blood of diabetic subjects with increased oxidative stress. This seemed to be a marker of insulin-related, dysglycemic, insulin-resistant-related oxidation. Therefore, we could put this on the list of clinical markers of oxidation, or free radical oxidative stress clinical markers. Those clinical markers include LDL oxidation; F2 alpha isoprostanes, arachidonic acid derivatives that resemble prostaglandins; the lipid peroxides, the blood peroxides malonaldehyde byproducts basically; protein glycation products as seen in using things like glycohemoglobin or glycosylated albumin or fructosamine. All are measurements of glycation; things like 8-OHDG (8-hydroxy-deoxyguanosine) which measures damage of DNA in white cells. Now we add to that list glutathionyl hemoglobin as a benchmark for oxidative stress.

Chronic Fatigue Syndrome

We know that oxidative stress also occurs in chronic conditions. In that connection, many researchers have studied chronic fatigue syndrome and its companion problem, fibromyalgia. Dr. Martin Pall, our Clinician of the Month in March of 1999, is at the Department of Chemistry and Biophysics and Program in Basic Medical Sciences, Washington State University. He recently published a paper following up on the association of oxidative stress markers and chronic fatigue syndrome/fibromyalgia. The title of this paper is "Elevated, Sustained Peroxynitrite Levels as the Cause of Chronic Fatigue Syndrome." This medical hypothesis is based on some very interesting data and publications.

Dr. Pall points out that upregulation of the immune system induces macrophage production of nitric oxide. When there is an oxidative stress environment producing more superoxide, the combination of nitric oxide with superoxide produces a secondary chemical called peroxynitrite. Peroxynitrite is a powerful and caustic chemical that damages DNA and starts creating a cascade of events that deplete the ATP or energy reserves by upregulation of an enzyme called PARS (poly-ADP-ribosyl synthase) or PARP (poly-ADP-ribosyl polymerase). This enzyme, when activated, depletes cells of ATP and produces the energy deficit in that tissue. It is all precipitated by a feed-forward lock-in of the immune system that is associated with nitric oxide, oxidative stress, and the formation of superoxide. It is like a dog chasing its tail, according to Dr. Pall.

The Etiology of Chronic Fatigue Syndrome

The etiology of chronic fatigue syndrome/fibromyalgia, therefore, although still obscure and contentious, may relate to events that upregulate the immune system to produce more proinflammatory cytokines like IL-1, TNF alpha, and interferon gamma. These substances induce nitric oxide production from macrophages, which in turn react with superoxide radical to generate the potent oxidant peroxynitrite. Amplification and positive feedback mechanisms perpetuate this environment, leading to a continued depletion of energy and cellular damage.

This may explain why a single event, such as a case of flu that never goes away, can years later have the memory effect we call fibromyalgia or chronic fatigue. It seems to be a total-load effect. It is related to all sorts of variables that may work together to upregulate the immunological system and produce this cascade of events associated with oxidative stress and nitric oxide production of peroxynitrite.

A Therapeutic Program

Lowering the load of antigenic and immunologically active substances to cool off the immune system is step 1. Improving the cellular membrane and mitochondrial membrane production, and cooling off the proinflammatory eicosanoids with essential fatty acids of the omega-3 and omega-6 GLA is step 2. Step 3 would be to balance redox-active substances—coenzyme Q10, N-acetylcysteine, glutathione, vitamin E, and lipoic acid. We have found this course of action useful in our clinical studies with chronic fatigue syndrome. The next step would be to improve hepatic detoxification to lower the load of substances that upregulate Kupffer cell production of these inflammatory cytokines. That would be dietary modulation of hepatic detoxification and gastrointestinal mucosal detoxification. The last step would be to improve the gastrointestinal ecology—reducing the toxic load of endotoxins and improving mucosal barrier function of the gut. That means gut restoration, the 4R Program™ of remove, replace, reinoculate, and repair.

That kind of complex intervention strategy gives the practitioner a variety of approaches that can work together to lower the precipitating factors that keep this feed-forward cycle of inflammation and immunological upregulation in place. It makes it possible to break this vicious cycle in the chronic fatigue patient.

ATP and Cancer Therapy

This cascade of events even seems to be related to AIDS and energy loss in cancer patients. A recent article in the *Journal of the National Cancer Institute* was titled "Is ATP (Adenosine 5’-Triphosphate), like STP®, a Performance-Enhancing Additive for the Tanks of Cancer Patients?" It turns out this low-energy fatigue also relates to the same mechanism of PARP activation and ATP depletion. Therefore, if you can keep the mitochondria functioning and keep ATP up and running, by reducing these inflammatory-mediated oxidative stress reactions, you can keep the process of function at a much higher level.

Even from the pathological perspective, something interesting can be said about mechanisms that tie disease states together in a single explanation for intervention—from the functional, chronic state, all the way through the pathophysiological state.

In discussing risk factors to pathological disorders that start as early-warning changes in function, we began with a discussion of cardiac disease. Then, we moved to chronic fatigue and cancer. I would like to return to a consideration of the other risk factors that Dr. Ridker discusses that relate to functional changes associated with vascular diseases and other chronic diseases of aging. One of those is immunological changes associated with the inflammatory cascade and its relationship to what Dr. Rudolph Virchow, the German physiologist and medical doctor, wrote years ago was the origin of atherosclerosis. He said it was an inflammatory condition, not a cholesterol condition.

The *Lancet* recently published a paper titled "Salivary Endothelin Concentrations in the Assessment of Chronic Heart Failure." This assessment of another salivary marker shows the increased interest in saliva as biological fluid for prognosis and possibly is a diagnostic medium for evaluation. In this paper, investigators showed that salivary endothelin concentrations were elevated in patients with chronic heart failure and indicate the progression of disease severity.

Analysis of Salivary Endothelin Concentrations

Plasma concentrations of vasoconstrictor peptide endothelin-1 are raised two- to threefold in patients with chronic heart failure. These concentrations correlate with hemodynamic alterations and functional impairments of the heart well before the onset of severe pathology and are an independent marker of outcome from other variables that have been studied. Plasma endothelin-1 concentrations are lowered by drug treatment for chronic heart failure that is known to reduce mortality. It appears to be a good prospective marker. We are seeing that salivary levels—assessing the endocrine and immune interrelationship to heart function—is a good assessment tool. Endothelin salivary analysis can be an indicator of heart function

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INTERVIEW TRANSCRIPT

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Introducing Dr. Robert Sapolsky

JB: This month as our Clinician of the Month, we are fortunate to have Dr. Robert Sapolsky, who is at Stanford University and is the author of the best-selling book, *Why Zebras Don't Get Ulcers.* He also wrote *The Trouble with Testosterone.* Dr. Sapolsky has been called a Renaissance Man. The accolades heaped upon him in the literature are all justified. He spoke at our International Symposium on Functional Medicine in Tucson in 1999 and was evaluated very highly as a presenter at our Applied Functional Medicine in Clinical Practice training program in Gig Harbor. The clinicians in the program found his presentation riveting when he discussed precepts of neurology and what's happening in the area of Parkinson's and Alzheimer's disease.

I have asked Dr. Sapolsky to help us understand how the intellectual fabric of the field of medicine is changing and where it may lead us as we move into the 21st century. Dr. Sapolsky, it's a great treat and privilege to have you as part of our *FMU* this month.

RS: Thank you. Obviously, you've been talking to my mother.

Stanford University Work

JB: Tell us about your present position at Stanford and the kinds of things you are doing. Stanford University's distributive education systems allow people to range across different disciplines. What are you up to there?

RS: I am technically a professor in the biological sciences at the university, in neurology at the medical school. I think I'm what's called an adjunct in their human biology program, which is a nice program that Stanford has, trying to look at biology and disease in the context of the person in whom it's happening. It therefore includes all sorts of social and societal factors, as well. I'm also a research associate at the National Museums of Kenya in their Primate Center. Some of what I do is field endocrinology on wild primates each year. It reflects the range of things I've been thinking about, which

is broadly in three areas.

The first one is how a neuron dies as a result of aging, as a result of neurological insults—acute insults like stroke or seizure, and prolonged insults like Alzheimer's disease. Thus, my lab asks, what are some of the common features of the cell biology of neuronal vulnerability? The second area I've been thinking about for a long time is the role of stress in potentially accelerating such neuron loss (basically bad news all around), and the possibility of designing gene therapy strategies to save a neuron during one of these neurological crises. The third area is the one that I concentrate more on in my East African research. Despite all the bad news about stress and its adverse effects on health, most of us have not collapsed into puddles of stress-related diseases. Most of us cope. The persistent mystery is why some individuals cope so much better than others. What I try to understand with these wild baboons I've been going back to year after year for 20 years now, is what do social rank, social behavior, and personality have to do with which baboons get the stress-related diseases and which don't?

The Importance of Variability

JB: That creates a pretty broad playing field for our discussion. One might summarize or distill down those areas of interest into questions of how the environment and the experiences it provides ultimately influence, through various propio receptor systems and neurological sensory systems, cell biological function. It moves to different levels of organization, from the macrocyclic down ultimately to the biochemical. How do you combine your observations in East Africa with your studies at the cell level?

RS: I do it with mixed success at various points. On a certain level, the baboon work in the field is meant to counteract a common attitude in lab science. You study something or other in the lab and you're hoping for some nice effect as a result of the manipulation you've done. The bane of every lab scientist's existence is to have a lot of variability in the endpoint, a large standard error. The result is not clear; it's not significant. You've got to do the experiment over again. You're not going to get your grant. You're not going to get your tenure. Variability is a bad thing.

Fieldwork is entirely built around the fact that variability is not only inevitable, it's a great thing. What that means is amid a general picture of the adverse effects of aging, of stress of that sort, there's no subset of individuals who are doing spectacularly. Lab science has finally formalized this in one area—gerontology. We now have this whole sub-field of successful aging, what used to be the irritating source of variability—oh, no—10 to 15 percent of subjects don't have renal filtration rates that get worse with age, don't have blood pressure rising with age, etc. Instead, they're doing just fine. They're even doing better. Instead of that being an irritant, it's now viewed as the most interesting thing to focus on. What are these successful agers doing right? Where can the rest of us sign up? So, The fieldwork has left me with a taste for idiosyncratic individual differences, even in inbred lab mice and rats.

Limitations of RCTs

JB: Many doctors who took their basic sciences in medical school learned about the double-blind, placebo controlled, randomized clinical control trial, as if it's the only way of addressing a hypothesis. We're often confronted with this in a society where a lot of our actions are not single actions against single endpoints. How do we use Randomized Clinical Trials to answer these questions that might be very valuable? Do you see any limitations in the RCT to address, or the way that the double-blind, placebo-

controlled trial has been conceived, in answering complicated questions of outliers that may be at the ends of the gaussian curve?

RS: There's exactly that problem that you point out, which is picking up the outliers. The outliers are potentially the most interesting thing you see. I think the other limitation is that the "gold standard" approach precludes many types of studies, such as those in which you're never going to be able to do that type of manipulation because you're pulling out correlative data. You can't do a double-blind control on an entire society, for example, in trying to figure out why there's a socioeconomic gradient to health.

It's ironic that we have this personal realm where I'm constantly butting my head against this, concerning my two small kids. There's something absolutely crazy-making for a scientist to have to make sense of the entire literature out there through the 10-second sound bytes on the evening news. "Three minutes a day of Mozart and you triple the SAT scores and double the myelinization in your child's brain"—that kind of stuff. As a scientist, you sit there and say these are studies that don't fit any of our basic rules as to how you control for them, and then you realize you can't do those sorts of studies with kids. No parent is going to consent to that. You can't do those sorts of studies with normative pregnancies. You can't do those studies with societal levels of health and psychology issues that are critical. I think you point out the absolute limitations. It's a wonderful experimental, testing approach for one very limited realm of clinical medicine.

New Types of Testing

JB: Other than double-blind, placebo-controlled trial, what strategies are available to help address questions and aid in evaluating new technologies and approaches?

RS: One is the anthropological approach, one version of which is the case report or the single society or single cultural report, which has a lot of limitations. The other, in circumstances in which you can't do an experimental manipulation, is to get a huge number of examples and see if there are predictive rules that cut across different social groups, settings, and societies. In the zoological version, where you can't do an experiment with culture, you look for rules that cut across different species. You can't do an experiment with evolution, but if you see similarities across 20 different species or 11 different cultures, certain patterns allow you a certain predictiveness. After a while, that winds up being science.

Research on Stress and the Aging Brain

JB: Can we use what you've learned in your research on stress and brain aging as an example of how one looks at various information and filters it down into hypotheses that can be tested?

RS: Some of my baboon work might be even a better example. One theme I've had over the years is that if you're going to be a baboon in the Serengeti, if you've got a choice in the matter, you don't want to be a low-ranking baboon. One thing you find is that subordinate animals have elevated blood pressure and basal levels of corticosteroids. They have less optimal immune function and the insulin-like growth factors needed for wound repair. In short, they have an array of problems we now recognize as increasing the likelihood of their developing various stress-related diseases.

In a general way, this makes perfect sense. If you're a subordinate animal, you have a disproportionate

burden of physical stressors. You have a lot of psychological stressors. You're working harder for your food. You don't have as much control or predictability over resources. So, seemingly, we've just learned something about rank and physiology. This sort of thing makes it very difficult to actually do a manipulative experiment out in the wild, but you begin to see, nonetheless, that having a certain rank means a very different thing in a different sort of primate society.

Cross-Cultural Studies in Primates and Humans

In primatology these days, a term we use, which is not anthropomorphic at all, is that different primate groups have different cultures. This is an absolutely seriously accepted term these days. In the realm of baboons, you find that in some troops, it's a lot more misery-making to be a low-ranking animal than in other troops. There's more displaced aggression. There's less control of resources. Food is more limited. You may have fewer outlets for your frustration. Fewer animals are willing to groom you—that sort of thing. One thing I've seen across a number of different baboon troops is that it's not just your rank that's important, but it's the sort of society in which that rank is occurring. That's the sort of correlative evidence that would be very tough to test out in the wild in a manipulative study, where you now generate a different sort of primate society. It's not only difficult to do, but it is also generally quite frowned upon. In a wild setting, you shouldn't go about removing individuals, removing food, and that sort of thing. Instead, you look at the variability that comes across and you begin to see something interesting.

In much the same way, a fascinating thing to me in terms of the gradient between socioeconomic status and health in humans is what was initially a story very much about healthcare access. There are major deficits if you are poor in a Westernized capitalist country. It's got to have something to do with healthcare access because you can't afford to go to the doctor as readily. If you do the cross-cultural approach, suddenly you see the gradient is virtually as strong in socialist countries, in countries with universal healthcare access. If you look at 30 different societies with very different economic systems showing the same pattern, you've just learned some important stuff. It probably has nothing to do with healthcare access.

Changing Perception of Locus of Control

JB: You have spoken at length about the locus of control and how that translates into a sense of perceived stress. Do you think it is possible to modify an individual's perception of locus of control? Could one employ that as a tool to alter neurochemicals associated with long-term functional changes?

RS: Absolutely. There are two levels of answers to that question. First is on the level of the individual organism. Locus of control is a major modifier of physiology. In classic experiments, you take two lab rats, and they both get electric shocks of the same intensity, same duration, same everything. Their bodies are being challenged to exactly equivalent extents, but one of them has its psychological environment manipulated so that it has a sense of control. It can press a lever that it believes decreases the likelihood of a shock. Or perhaps that rat has predictive information. A warning light goes on 10 seconds before each shock, creating a manipulated psychological setting in which that physical stressor occurs. Studies show you can cause a tenfold difference in the likelihood of an ulcer, the likelihood of hypertension, and things of that sort. This internal locus of control stuff, the psychological filters with which an external trauma occurs, can have an enormous impact on some health outcomes.

The second level is more societal. It shows that an internal locus of control is not always a good thing. There is a really interesting exception, a personality profile called John Henryism, which is very predictive of cardiovascular disease and hypertension.

John Henryism and Hypertension

John Henryism, basically, is an extreme version of an inner locus of control. These are individuals who, on personality profiles, endorse statements like: "When the going gets tough, I just work harder." "There's no problem you can't solve just by applying yourself." "If some fellow disagrees with me, I will just talk to him and we should be able to see eye to eye after a while." This sounds terrific, doesn't it? This is a very internal locus of control. Just by effort, you can overcome the problems thrown at you.

It sounds like a wonderful thing. Why is it associated with an adverse health outcome? Because John Henryism is a marker of hypertension in working-class African Americans. You can't solve some societal problems just by working harder. You can't solve racism, for example, by just sitting down with a guy, realizing we're all the same, and finding common bonds. John Henrys are people dealing with uncontrollable external sources of stress with a coping style that assumes they can control the uncontrollable. This personality style is highly predictive of hypertension in working-class African Americans, and it's not predictive of hypertension in middle-class blacks or working-class whites. I think in that case, you see, insofar as psychological baggage can be highly protective, once again, in certain societal settings, it works a lot better than in other cases.

Stress-Induced Dwarfism

JB: You give an example in your book, *Why Zebras Don't Get Ulcers*. In relation to the impact of stress on physiological function, it is the example of J.T. Barrie and stress-induced dwarfism. Could you briefly describe that? It might help people think of this across a wide range of the spectrum of effects.

RS: That's a fabulous story I cannot resist. This disorder—stress dwarfism, psychogenic dwarfism, psychosocial dwarfism—this is a very rare "zebra" disorder. Kids can be so psychologically stressed they stop growing. Its characteristic is that it doesn't involve disease, malnutrition, or parasites. The mechanisms underlying it on the neuroendocrine level are reasonably well understood. It is absolutely rare.

I love to cite the single most bizarre, unnerving example of stress dwarfism I've ever heard of. Years ago, when I was reading a lot about growth hormone, I noticed that a lot of these textbook chapters inexplicably had these weird references to Peter Pan. They would have some quote from Peter Pan or some snide comment about Tinker Bell. I had seen this for years and had no idea what was going on, until one day I finally saw the explanation. This was a textbook chapter talking about psychological regulation of growth hormone release, stress dwarfism, and it gave the following case history.

Peter Pan

An 8-year-old boy was growing up in Victorian England in the 1870's. One day, he saw his beloved 12-year-old brother killed in front of him in a horrible accident. Trauma destroys the whole family. There are no other siblings. The father was never on the scene. This was the mother's favorite child who had

died, and in this Victorian swoon, she takes to her room with the shades drawn for the next decade or so. The kid is growing up in horrible emotional isolation. Terrible scenes occur. For example, he's bringing a tray of food for the mother in the bedroom and she says: "Oh, David, David, is that you? (David the dead son.) David, have you come back to me? Oh, it's only you." This 8-year-old grew up being "only you."

Apparently, the only thing the mother ever spoke to him about was this crazy idea she had grabbed onto that if David had to have died, at least he died when he was perfect. He was still a little boy. He's not of these boys who grows up and doesn't need his mother anymore. He'll always need his mother because he was this perfect little boy. He didn't grow up.

The Case of J.N. Barrie

This kid hears this with a vengeance. It is a wealthy family. There is no evidence of malnutrition or disease. The kid stopped growing at this point. He lived to be 60; his height was 4'10" as an adult. He never reached puberty, which was confirmed on autopsy. He had an unconsummated marriage. It is a bizarre example of stress dwarfism. The chapter concludes by informing us this was J.N. Barrie, the author of *Peter Pan*. If you read about this man's adulthood, he was incredibly disturbed man. He had endless sadomasochistic relations with little boys that he had to keep buying his way out of to keep out of the newspapers. He produced books and plays about boys who die and come back as ghosts and marry their mothers and all sorts of stuff like that. It is an example of this psychosocial disease and this man's very unsuccessful life-long attempts to deal with it. It is an absolutely bizarre story.

Growth Hormone Therapy and Aging

JB: That is a fascinating example of the mind/body connection. Tell us your opinion about growth hormone. In your endocrinology reviews and research, you've seen the tendency now with aging humans to use growth hormone support or replacement therapy. It's been a back-and-forth risk/benefit discussion within the literature. Do you have any thoughts about growth hormone replacement in adults who are just trying to prevent some of the signs of aging—improving muscle strength, skin tone, and vitality?

RS: It's not my area of endocrinology, but my basic gut reflex is to be skeptical and cautious, in part, because of the tendency of clinicians to overpathologize normative aging. On the other hand, I'm in my early 40's, so I'm only beginning to overpathologize my normative biology a little bit myself. Nonetheless, the results are pretty impressive in those studies in terms of the good outcomes—energy, muscle mass, and sense of well being. Probably the safest course is excessive moderation in this regard. Be very cautious about potential side effects.

The Androgel Story

I'm much more concerned about the media attention and excitement about androgel, which is about to come out on the market. This is going to be the user-friendly replacement of injectible androgens for testosterone therapy. It will be an absorbable gel that's rubbed on the skin. There is absolute hysteria in the media about this. There were cover stories on it in *Time*magazine, the *New York Times Sunday Magazine*, and it is featured on every single TV station. The story is that it will not only be fabulous for pathology—cases of marked testicular suppression (related to HIV, for example), but it will also be a panacea for normative age-related declines in testosterone levels in males.

It is a totally erroneous interpretation of the literature. The literature is absolutely clear that on average, there is not a big decline in testosterone levels in normative aging—roughly, a 50 percent decline from age 20 to age 60 or so. Most important, reinstating testosterone levels up to that 100 percent level will have no effect on levels of aggression, sexuality, libido, sexual performance, or muscle metabolism. Testosterone is what endocrinologists call a "permissive hormone," which is to say, you need the stuff for normative physiology and behavior, but with anywhere from roughly 10 percent of normal levels up to about 200 percent, you're going to get the same effects. It has a step function. Below the 10 percent level you get pathology, and testosterone replacement is going to be real helpful. Take tons of anabolic steroids and raise your testosterone levels above 200 percent and there are probably going to be some psychological effects there. But stay within the normative range of 95 percent of healthy males, and manipulating testosterone isn't really going to do much of anything. I suspect we are about to enter a realm of some astonishing placebo effects.

The Future of Neurodegenerative Disease Treatment

JB: What is your vision of the future in regard to neurodegenerative diseases that a few years ago may have been considered intractable, incurable, and perhaps a natural part of the aging process? I know you have done some work into neurologic aging-related phenomena in Parkinson's or Alzheimer's. Where is this research taking us?

RS: There is some very encouraging news within the realm of incremental preventive medicine. It may not do much good in terms of what you can do once a neurological disaster occurs, but we're seeing exciting trends in terms of prevention of Alzheimer's disease. For example, postmenopausal estrogen replacement appears to decrease the risk of Alzheimer's disease markedly, as does taking relatively small amounts of nonsteroidal antiinflammatory compounds when you are in your 50s. There are some pretty impressive protective effects in the range of a 50 to 70 percent decrease in the likelihood of late-onset Alzheimer's. This is absolutely extraordinary in terms of the good news.

There is even some good news in the realm of what-can-be-done-once-all-hell-breaks-loose, Parkinson's has occurred, the stroke has occurred, the grand mal seizure. There is some exciting progress with neurotrophic factors, compounds that can stimulate elaboration of neuronal processes. There's also progress with neuronal transplants and some hints that gene therapy may be useful in saving neurons after an insult.

Neurogenesis in the Adult Brain

There's a recent revolution of understanding that the adult brain, even the aged brain, still undergoes neurogenesis. This is overturning 100 years of dogma that you've got all the neurons you're ever going to have by age 3. All of these are areas of tremendous optimism in terms of being able to prevent the neuron loss in the aftermath of a neurological disaster. We may be able to replace the neurons by stimulating neurogenesis or neuronal transplants, and getting the remaining neurons to make more complex interconnections. There is tremendous optimism in the field at this point.

Inflammation and Brain Aging

JB: In the list of therapeutic approaches to prevention, you mentioned nonsteroidal anti-inflammatories,

NSAIDs. This research suggests be an inflammatory component of Alzheimer's and other neurodegenerative diseases may interrelate stress with inflammation and microglial function. Is a theme emerging that suggests chronic mediators of stress are related to inflammation, which has a relationship to brain aging?

RS: At this point, it's not completely clear, mainly because inflammatory pathways and inflammatory cytokines are so complicated. For the most part, the stress hormones, in particular, the corticosteroids, have a well-earned reputation for being anti-inflammatory. Within the nervous system, there is far less of a precedent for such anti-inflammatory effects and some evidence for pro-inflammatory effects. So in that regard, the jury is still out regarding just how much ongoing stress can contribute to chronic inflammation within the nervous system in response to ongoing neuron death.

It is clear, though, that inflammation has moved to center stage in neurodegeneration in a way people simply didn't use to pay attention to. You look at the old Alzheimer's literature of 20 or 30 years ago, and the neuropathology is absolutely screaming inflammation. Most individuals ignored it because it was viewed as a nonspecific marker and a nonspecific consequence of the neuron loss. It's clear now from the NSAID studies and from the more experimental manipulative ones, as well, that inflammation is not only quite early on in the process, but it plays a major role in secondary damage. Lose a neuron and get uncontrolled inflammation in that neighborhood, and that's really not going to be a good thing for the neighboring neurons. Inflammation has assumed center stage for understanding Alzheimer's and some of the other chronic degenerative diseases as well.

Dr. Stanley Prusiner and Prion Research

JB: Do you believe Dr. Stanley Prusiner's work has been involved in with prions and the discovery that these proteoid molecules may influence certain functions within the nervous system will open a new chapter in this text, or do you think it is an outlier discovery that has a unique isolated implication?

RS: I personally think it's astounding stuff. I've been watching his work since I was a grad student at the conference where he first presented his heretical notion of the protein-only transmissible agent. People walked out of there saying this guy just destroyed his career, and this is madness. It's been amazing to see it culminating in the Nobel Committee's making a pretty risky decision to choose somebody involved with what is still a controversial subject. What remains uncertain is the extent of the impact of prion diseases on life. It has moved from an obscure disease in New Guinea to explaining some terrifying stuff with Creutzfeld-Jacob and atypical variance going on in the United Kingdom. Whether that is going to be pandemic in the U.S., nobody is clear on at all.

A few of the mechanisms Prusiner has posed also remain unclear. There are still reasons to be a little bit skeptical about the protein-only notion, and Prusiner and others are now looking for factor X, for modulatory factors that could well still be a traditional virus-containing nucleic acid. What has been totally revolutionary on Prusiner's part is getting people to think about the structure of proteins and, most of all, multiple confirmations of proteins, with the exact same amino acid sequence, and these multiple confirmations having real different consequences for disease. Get the wrong confirmation and proteins start aggregating, and you've got a plaque disease. What was once a real backwater of physical chemistry is now central to understanding a variety of neurodegenerative and vascular diseases. He's been an utter lone voice and pioneer in that regard. It's really important stuff.

Structure/Function Relationships of Linus Pauling

JB: That overview reminds me of Dr. Linus Pauling's work on structure/function over the years, and his assertion that if we would understand these structure/function relationships in molecules, we would understand a lot abou the disease. It's ironic that Gajdusek, as one of Pauling's students, had the concept that these disorders were related to a slow-reacting virus, when really we now start seeing it's perhaps protein confirmations that relate to some of these interesting neurological disorders. It seems as though Pauling has come 360 degrees in this whole process.

RS: It is not the first time it would have happened with him. A very basic truism of biology is how structure equals function.

The Need for New Types of Research

JB: How do these various disciplines relate to the future of medicine? Are you optimistic or pessimistic?

RS: I'm optimistic in terms of the basic reductive science that's going to tell us about the underpinnings of a spectacular number of diseases with amazing insight. I feel pessimism in that this is, in a lot of ways, going to be mopping up the wave of diseases that have been being eliminated over the last century or so, the ones that have single explanations. I feel pessimism in terms of there not being enough researchers employing the non-reductive approach necessary to making sense of diseases that are multi-factorial, highly individualistic, highly dependent on social setting context.

This research would demand a retreat from one of the backbones of Western science for centuries now, which is believing that reductionism is the answer to everything. The current version of that thinking is the belief that sequencing the human genome will be the answer. The notion is that if you want to study something complex, you have to understand its constituent parts. When you look at the really complex, multifactorial diseases that get us heart disease, diabetes, neurodegenerative disorders—as opposed to yellow fever, dengue fever, or anthrax—you see they are not going to be resolvable at the level of their constituent parts. Instead, they have emergent features that are going to demand a very different type of science, for which neither scientists nor clinicians get particularly good training. I am pessimistic in that regard. We've got to do some different education in that realm.

Conclusion

JB: I appreciate your thoughtful comments on every level. It's given us guidance and some motivation to keep vigilant in how we're learning, keep our minds open, and be prepared for seeing the universe perhaps in slightly different ways to help remediate some of the age-related disorders. Thank you very much, Dr. Sapolsky.

Measuring C-Reactive Protein to Predict Cardiac Disease Risk

Dr. Sapolsky talked about inflammation, which we discussed on side I of this month's *FMU*. The *New England Journal of Medicine* March 12, 2000 issue contained an article titled "C-Reactive Protein and Other Markers of Inflammation in the Prediction of Cardiovascular Disease in Women." Once again, it confirms what we have been saying for several years in *FMU*. Measuring C-reactive protein improves

cardiac prognostic screening specificity beyond measuring only lipids. It identifies women at risk for cardiovascular events. Co-authors of this paper, from Dr. Paul Ridker's laboratory, include Charles Hennekens and others from Harvard Medical School, Center for Cardiovascular Disease Prevention Unit.

Medicine has not traditionally looked for inflammatory markers as risk factors for vascular disease. Those markers are beginning to be accepted, but there is still not protocol that allows reimbursement for this assessment. This fact raises questions about who or what drives medical progress. Is it technology and improved understanding of ways to help patients, or is it the ICD9 code book and the possibility of third-party reimbursement. I will side-step this question of the politics and economics of medicine, but it is also interesting in the context of type II diabetes.

You may recall the paper that appeared in *Diabetes Care* in November of 1999 titled, "Impaired Glucose Tolerance: Why Is It Not a Disease?" The author asked why there is not diagnostic code for impaired glucose tolerance, since one can treat a patient when there is a diagnostic code. Until you have a diagnostic code, the condition doesn't exist, although people continue to die of premature coronary mortality as a consequence of impaired glucose tolerance.

Folic Acid and B6 Used for Subclinical Atherosclerosis as Tested by Functional Means

We are familiar with the connection of folate/B6/B12 connection to heart disease. This is the homocysteine connection to subclinical atherosclerosis. Dr. Kilmer McCully more than 30 years ago pointed out the connection between hyperhomocysteinemia and coronary atherosclerotic and vascular diseases. Other diseases now discovered to have a homocysteine connection include Down syndrome, bone loss, arthritis, and perhaps even cancer and dementia. The *Lancet* contained a report on the homocysteine-lowering effect of folic acid plus B6 in healthy siblings of patients with premature atherosclerotic disease. The authors found it was associated with a decreased occurrence of abnormal exercise electrocardiography tests, which is consistent with decreased risk of coronary events, based on functional assessment with the electrocardiography test.

This paper connects a number of topics we have been describing. We now have a functional test to evaluate possible later-stage pathology risk. It uses a metabolic indicator called hyperhomocysteinemia that can be ameliorated by nutritional intervention at the level of need based of the individual, not the group mean as is the mythical Recommended Dietary Allowance level. This research incorporates Roger Williams's concepts of biochemical individuality and Dr. Linus Pauling's concepts of molecular medicine. Kilmer McCully helped us understand this contributor to premature, modifiable disease risk.

Serum folate is also correlated with the severity of atrophy of the neocortex in Alzheimer's disease. The Nun Study was conducted with elderly Catholic sisters who lived in a single convent, ate from the same kitchen, and were highly comparable for a wide range of environment and lifestyle factors. The only significantly different factor was their genes; all other variables were kept constant. The sisters comprised a nearly ideal laboratory for assessment.

Researchers found a strong association between low serum folate and atrophy of the cerebral cortex in genetically susceptible nuns. This result moves beyond the association of homocysteine associated with atherosclerosis and cerebral vascular disease. It moves into a temporal sequence related to Alzheimer's dementia and the effects revealed as early-stage dementia. This fairly powerful suggestion again indicates

that fundamental mechanisms of understanding lead to broad potential outcomes.

The Fabric of Reality

Dr. David Deutsch, in his book *The Fabric of Reality*, explained that as medicine evolved to become a true science, it would be able to predict from first principles, the outcomes of therapies before they are even tried. We are moving in that direction by seeing unified approaches toward the amelioration of function based on genomic uniqueness that then can modify the course of pathophysiology.

Prospects for New Treatments in Parkinson's Disease

The same is true with conditions like Parkinson's disease, to which Dr. Sapolsky referred. A recent article in *Nature* describes the roles and prospects for restorative and neuroprotective treatments in Parkinson's disease. The language in this article is familiar to *FMU* listeners. We are on the cusp of where this change is occurring. The authors explain that the progressive nature of Parkinson's and the slow and protracted neuronal degeneration in the substantia nigra present opportunities for therapeutic intervention aimed at blocking or slowing down the degenerative process. This is the neuroprotective therapy approach.

> "Recent neuroimaging and autopsy data indicate that there is a preclinical period of 4-5 years before symptoms appear, and that the rate of cell loss and decline of dopaminergic function in the striatum is likely to be in the order of 10{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} per year, with the disease progressing relatively more rapidly during the early phases than in the more advanced stages of the disease. Both PET and SPECT imaging seem to be able to detect a decline in striatal dopamine function before clinical symptoms appear."

This is the functional period of decline before pathophysiology that we have been describing. The authors go on to say:

> "The neurodegenerative process in PD is likely to involve a cascade of inter-related events—oxidative stress, mitochondrial dysfunction, excitotoxicity with excess formation of NO and O2, and inflammatory changes, leading to both apoptotic and necrotic cell death."

This information leads us to recognize that neuroprotection against Parkinson's disease may in part relate to things like antioxidants that help to prevent oxidative damage and apoptotic death of cells, or the neurotrophic Dr. Sapolsky discussed.

> "The largest known neuroprotective clinical trial conducted to date, the DATATOP study, involved two putative antioxidative agents, vitamin E and deprenyl (selegiline). Vitamin E had no significant effect at the doses used, but deprenyl slowed the early progression of symptoms and delayed the emergence of disability by an average of nine months. However, being an MAO-B inhibitor, this drug has symptomatic effects of its own, which has confounded interpretation of the results. Interestingly, animal studies have suggested that the neuroprotective effect is not

> dependent on MAO-B inhibition *per se*, but rather on an antiapoptotic effect of the metabolite demethyl-deprenyl, possibly acting on protein transcription."

People are looking at different kinds of antioxidants—lipoic acid, NAC, glutathione precursors and how they interrelate, as well as nitric oxide modulators. Similarly, with excitotoxicity, they are finding ways to reduce the NMDA excitation pathway or the glutamate excitation pathway. Then, as Dr. Sapolsky explained, there are neurotrophic and anti-apoptotic factors. There is reason for optimism about neurochemical research and neurobiology. We are moving into new ways of preventing, starting at the functional decline level, not just at the stage where you have lost 70 or 80 percent of the dopaminergic neurons. At his later stage, one may have remediation of symptoms for a short period of time, but never get back to full function.

Dr. Sapolsky also pointed out the correlation between elevated levels of amyloid b -peptide in the brain and cognitive decline. These twisted proteins, or amyloid ropes, are associated as aggregates with the damage seen in Alzheimer's disease. Levels of amyloid b -protein 40 and 42 are elevated early in dementias and levels of both peptides were strongly correlated with cognitive decline, In the frontal cortex, amyloid b -peptide was elevated before the onset of serious symptoms. Authors of this recent paper explain these results support an important role for amyloid b -peptide in mediating initial pathogenic events in Alzheimer's dementia. They suggest that treatment strategies targeting the formation, accumulation, or cytotoxic effects of amyloid b -peptide should be pursued.

Once again this provides a functional measure well before the onset of pathology. Medical research appears to be moving toward early precursor markers for functional declines and pathophysiological changes that occur at the cellular level well before the onset of gross pathology.

Environmental Effects on Neurologic Development

Dr. Sapolsky described the role of environmental enrichment as a neuroprotective agent. In volume 1 of the new journal, *Clinical Practice of Alternative Medicine*, edited by Dr. Derrick Lonsdale, an original paper was published titled, "The Developmental Profile: A Quantitative Measure of Neurologic Development in Brain-Injured and Normal Children." The authors, from the Institutes for the Achievement of Human Potential in Philadelphia, described the use of assessment protocol developed at the Institutes to evaluate neurological performance in children. Environmental enrichment programs using improved exercise performance, musculoskeletal patterning, dietary intervention, and intellectual enrichment, they indicated, enabled these children to regain tremendous neurological function. Dendritic branching and cognitive and physical function improved dramatically.

The brains of some of these children, who appeared to be seriously or perhaps irreversibly injured, according to traditional though that the brain can't repair, do repair, and they function at high levels. In fact, years later, these children might may seem to be above normal, or gifted. This optimistic report moves away from the deterministic view that once the brain is injured, it can't repair.

We should probably also view the gut as a part of the nervous system. The enteric nervous system of the gut contains as many neurons as the spinal cord, and many chemical messengers that regulate feeding by the brain have similar functions in the gut. This gut/brain connection to intestinal motility, intestinal

permeability, autointoxication, and enterotoxinemia is related to the cell signaling message to the microglia, the brain's immune system, and apoptotic cell death and neurological injury. The environment, both external and internal, plays a significant role in the enteric bacterial environment. This emerging view indicates exciting new opportunities for both prevention and treatment.

Thanks for being with us. We'll talk again in August.

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