June 2006 Issue | Herbert L. Needleman, MD School of Medicine

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Welcome to *Functional Medicine Update* for June 2006. When your patients sit before you, do you ever wonder how much of their conditions are related to their genes and their family history, as compared to the influence of the environment to which their genes have been exposed? That question is a fairly important one because, obviously, we believe that we cannot change genes, but we can change the environment.

Genes vs. Environment: The Debate Continues

You might think that a patient's condition is solely the consequence of his or her family history, and there is virtually nothing you can do, other than try to manage symptoms. Whereas, if the condition is principally the result of environmental exposures, you can hopefully help your patient to modify the environment to both prevent and treat the condition. The old model we used to use, in which there is a clean separation between genes and environment, has started to lose some of its distinguishing points of differentiation. The field of epigenetic, or post-translational medicine is starting to show us that Lysenko wasn't totally wrong. The debate between Darwin (natural selection) and Lysenko (adaptation), which won Darwin the battle and lost Lysenko his reputation, is being resurrected into a new perspective, because it is now recognized that our environment can modify the way our genes are expressed.

Though we may not change the genes in and of themselves, we may change the way our book of life, locked into our genome, is read. This post-translational effect-through methylation, phosphorylation, glycation, and oxidation of proteins, can lock different physiological function into the cell that can modify function even without modifying the genes. Even in the case of methylation gene patterns, this translational effect can even post-genomically modify what is passed on to the offspring.

I've just said something fairly revolutionary, haven't I, because it flies in the face of everything we have learned about the traditional concept of genetics. We inherit these dominant and recessive characteristics from our mothers and fathers, and they can get passed down as "hard-wired" *tabulae rasae*, from which we ultimately derive our phenotype. The environment in which the egg was nurtured during fetal development ultimately can alter, post-genomically, the way that the book of life can be expressed, closing certain chapters and opening others to being read into the phenotype, and this can be transmitted to the next generation. This indicates that the smoothing of genetic natural selection over millennia does still occur, but there is a much more rapid response potential for changing characteristics in populations through post-genomic-epigenetic or post-translational-modifications.

This might explain why, as I recall hearing many years ago, Lucille Hurley at the University of California at Davis, in the Department of Nutrition, found offspring from animals given a marginal zinc-sufficient

diet (meaning zinc was really lower than what would be optimal for proper development of the fetus) during pregnancy were immune-compromised. It took three generations of subsequent nutrition with higher levels of zinc to get back the original immunological function of the of-zero generation, which means that the characteristic of poor immune function was passed down post-translationally, or epigenetically as a consequence of a mother, three generations before, having been pregnant with a low zinc status. This sounds very much like the Pottenger studies on cats that were done many years ago, showing that suboptimal nutrition of cats led to the first asthmatic cats, which could be passed down to subsequent generations. Again, ironically, it took three generations of proper nourishment, as observed by Dr. Pottenger, before the cats arrived back to the original immune competency of the first-generation parents (that is, the health level before being on the suboptimal diet).

This is raising some very interesting questions. For example: Is a patient affected more by his or her genes or by the environment? These influences are really closely interrelated, though, and we are enough steps down the road in the postindustrial civilization to have had all sorts of post-translational epigenetic influence on gene expression in the absence of actually changing our genes.

People say that we are really Paleolithic humans. Our genes have not changed since Paleolithic times. The actual homology, or the structure of the nucleotide chains, the polynucleotide chains, has not changed; what has changed is the methylation patterns and the histone acetylation patterns that coat the genes and render them available for being read into the phenotype. These are modified much more quickly than is the mutational natural selection processes, smoothing our characteristics over millennia. Darwin talked about that. We are not really Paleolithic humans. The underlying code in our book of life may be that of a Paleolith, but the way it is expressed into the function of the organism is modified in temporal ways by our environmental exposures: changing stress patterns, changing exposures to toxic chemicals, and changing nutritional status.

That opens up many interesting questions about the emergence of various chronic, age-related, degenerative diseases. One might say that the only reason we're seeing increasing chronic disease is because we are getting older and you have to get something as you get older, don't you? But if we start looking at the penetration and prevalence of certain chronic conditions, like asthma, atopy, eczema, and systemic lupus erythematosus in menstruating women, these conditions are increasing in absolute frequency in younger age populations, demonstrating that somehow, without our genes changing, the response we have to our environment is creating a different outcome. We do not have to wait for the process of natural selection and Mendelian genetics to change underlying structural gene patterns in order to see those effects.

This month, we are going to be talking with one of the most remarkable people I have had the fortune of learning from for over 30 years, Dr. Herbert Needleman, at the University of Pittsburgh School of Medicine, who is going to talk to us about his pioneering work in the development of behavioral toxicology. We will look at functional medicine from a functional neurological perspective and ask: What are the things, epigenetically, that modify function in such a way as to create diagnoses that seem to be increasing in frequency, for which we can find no known neuropathology that leads to diagnoses like language processing problems, delinquency, attention deficit disorder, and hyperactivity disorders? Where do these things come from if they are not necessarily a consequence of changing our genes? This is a very profound concept that relates more to a functional medicine perspective than that of a histopathology-based perspective, into which most of us were intellectually born.

With that in mind, you'll notice that I am speaking to a theme that has been a recurrent one in *Functional Medicine Update* for some time-the nutrigenomics/proteomics/metabolomics concept of how our environment and factors that wash over our genes ultimately influence their expression into functional changes within cells, tissues, organs, or in systems and, eventually, the whole organism.

I've been very interested in watching the emergence of the concept of nutrigenomics over the past two or three years because we are starting to see more and more research demonstrating how nutrients serve as signaling substances for modulation of genomic expression, proteomic activity and, ultimately, controlling metabolism through metabolomics. As Dr. John Milner and his colleagues have recently pointed out in an excellent review article that appeared in the *Journal of the American Dietetic Association*, we now recognize that the human genome is estimated to encode over 30,000 genes, and to be responsible for generating more than 100,000 functionally distinct proteins.[1]

One wonders how it is that 30,000 genes can make 100,000 proteins if it is a one-gene/one-protein concept that we learned in our molecular biology classes in the 1970's. Now, we recognize that genes can be expressed in different ways, depending upon such things as which specific exons, the modular sections of a genes, are included in the final transcript and, ultimately, how these are seen as distinctive families of genes that are turned on and off under different environmental circumstances. In many cases, then, it is not just one gene at a time; it is a family of genes. We learned this very beautifully recently from the extraordinary interview we had on nutrigenomics with Ruth DeBusk in the May issue of FMU. Dr. DeBusk helped us considerably in our understanding of this complex topic.

Understanding the relationship among genes, gene products, and dietary habits is fundamental to identifying those who will ultimately benefit most from being placed at risk by specific intervention strategies. Unraveling the multitude of nutrigenomic, proteomic, and metabolomic patterns that arise from ingestion of foods or the exposure to substances in the environment that modulate these processes of genomic expression will not be a simple task, but is likely to provide insights into a tailored approach to health, diet, and environment that will, be matched to an individual's needs. This is what Roger Williams talked about in the late 1940's as genetotrophic disease and biochemical individuality. It is what Dr. Linus Pauling talked about as molecular medicine and, later, orthomolecular medicine.

We are starting to witness this very interesting emergence of a concept that is theoretic at first, but becomes more clinically applicable as we start to evaluate these single-nucleotide polymorphisms and families of genes that are expressed as differing variants. An example is the methylenetetrahydrofolate reductase polymorphism associated with folic acid metabolism, which is one of the more well-recognized examples of polymorphisms that are influenced by nutritional status, or nutritional status and function that is influenced by polymorphisms, depending on how you want to look at it.

When we take this theme and map it against the patient sitting there before you, who expresses these complex symptomatologies, you may think that you have just been intellectually stimulated by listening to *Functional Medicine Update*, but now you are really confused because you don't know exactly what to do with all this information. Let me go back to basics, because actually you do know quite a bit about what to do with this information, if we simplify it into one or two steps. The questions that bear on that individual patient are: What are the environmental factors unique to his or her life? What does he or she do? What is he or she exposed to? And how does the patient respond to those exposures in such a way that it demonstrates a phenotype of dysfunction?" Now, why do I suggest dysfunction? Because it is

highly unlikely that this patient came to see you because he or she feels good and wants to find out why. It is more likely that the patient is seeing you because he or she wants to find out what is wrong. The patient has some level of dysfunction, which means the alignment between genes and environment is somehow not optimal.

We go first to diet. Diet is a shared, common human experience. Everybody has eaten at some time. The bioactive components of our diet influence the whole array of genomic expression-proteomics, kinomics, metabolomics, lipomics-and can ultimately create different phenomics (the outcome in the phenotype of the individual). We eat bulk ingredients. Over the course of living, we may eat 20 or more tons of food, which are potential bioactive-molecules, many of which differ from those from which we are made. Our body has a very complex process for separating out friends from foes in our diet and hopefully delivering neutral information from which our energy-processing systems can be powered up, as well as our cell-signaling systems, ultimately leading to homeostasis, or control.

When the patient is sitting with you in the exam room with a rash, headache, sore throat, sore joints, chronic irritable bowel syndrome, upper respiratory problem, or a chronic obstructive pulmonary disorder, you need to ask what is going on unique to that individual that gives rise to these complex symptomatologies. You need to address how the environment may be seen by the receptor systems in this patient's body; for example, as "foe," as an alarm agent which, in another patient (in fact, in the majority of people) might be seen as a "friend." We talk about diet because it presents a bulk series of ingredients, or substances, for which our receptor systems have evolved over millennia of living, to give rise to signaling messages. This is a whole different way of looking at eating, isn't it? In the past, we thought eating was for hedonic gratification, gustatory satisfaction, and satiety, and for preventing scurvy, beriberi, pellagra, xeropthalmia, rickets, kwashiorkor, marasmus; for preventing anemias; and for keeping our blood albumin levels adequate-all those kind of traditional clinical nutrition relationships between diet and function. But now we see that, within our foods, are literally thousands of differing phytochemicals and other substances that influence cellular signaling processes and ultimately, the genomic/proteomic/metabolic triad. Over historical periods of time, we may have removed things from the diet that had evolved to set up signals to our genes and control function.

Why am I saying that? Let's look at the Mediterranean diet. How does that diet differ from a diet of fast food? Obviously, one of the differences involves the amount of fat, sugar, and processed white starch. There is also the absence of the substances that were taken out to make those things white, which are all the things found in a colorful, Mediterranean diet. If we look at the scientific evidence of interventions using the Mediterranean Diet, what do we find?

There is a wonderful review that appeared just recently in *Nutrition Reviews*.[2] The Mediterranean diet has been associated with greater longevity and quality of life in many epidemiological studies. The application of this evidence-based medicine to the area of public health nutrition involves, by necessity, the development of clinical trials in order to understand how this epidemiological association is related mechanistically to the reduction in risk or incidence of disease. The authors of this paper reviewed, in a meta-analysis, experimental studies on the Mediterranean diet and disease prevention. They examined a total of 43 articles corresponding to 35 different experimental studies. The results of these studies were analyzed for the effects of the Mediterranean diet on lipoproteins, endothelial resistance, diabetes, antioxidative capacity, cardiovascular disease risk, arthritis, cancer, body composition, and even psychological function. Through this meta-analysis, the Mediterranean diet was found to have favorable

effects on lipoproteins, endothelial vasodilatation, diabetes and antioxidative capacity, improved insulin resistance, reduced metabolic syndrome, and increased antioxidant capacity. Myocardial and cardiovascular mortality was reduced, and cancer incidence in people with previous myocardial infarction and obese people was also lower.

Is this just because we modified the levels of protein, carbohydrate, and fat in the Mediterranean diet? The alteration of the bulk macronutrients may play some role, but it's much more than that. The results of the Mediterranean diet in health outcomes is related to the complex array of colored, secondary metabolites in plants called phytochemicals, that modulate function in very unique ways not found in a phytochemical-poor diet. It is a consequence of taking a lot of things out and adding some things back that gives rise to the dietary association with a changed environment on an epigenetic modification of function of the individual.

When that patient sitting there in front of you is suffering with a chronic illness (sinusitis, rhinitis, headaches, eczema, or chronic irritable bowel syndrome), you suspect that, something related to the way their environment is being picked up by their receptor sites is translated into dysfunction of alarm (immunological imbalance). Therefore, you should be reviewing what in their bulk exposures, first, might be triggering factors. Then you go to the secondary factors. Then you go to the tertiary factors. But start with the big variables first. And diet is a big variable because, as I said, most of us eat three meals a day, and those bulk molecules have a relationship with modifying our function. In looking at the Mediterranean diet studies, the results disclose mechanisms of how the Mediterranean diet is involved with disease prevention, particularly in secondary prevention of cardiovascular disease. We see that these genomic/metabolomic/proteomic effects as a result of modifying dietary signaling molecules, have a significant influence on function, well before the onset of pathology.

There have been many studies published in the literature involving diet intervention trials in which the concept of controlling for phytochemicals in the diet was not considered as a variable. This means we may have a huge amount of inappropriate conclusions about a diet-health connection because we did not control for a very important variable-the presence or absence of certain phytochemicals in the diet. Maybe what we assumed were results of changing the carbohydrate, fat, and protein ratios, were also modified by taking out or adding specific phytochemicals, based

This is a very important issue because we often discount these factors as playing important roles in any kind of physiological outcome. But, as we have learned much more about nutrigenomics, we recognize the important role the various phytochemicals play. For instance, let's look at the effect of different types of millet versus a control of corn starch on oxidative stress and glycemic status in a controlled animal study involving alloxan-induced diabetic rats. This study compared corn starch versus a complex starch mixture that has lots of phytochemicals. What was the outcome? I'm speaking now to a very interesting paper that appeared in *Nutrition Research*, in which the authors showed that by not changing the protein, carbohydrate, or fat level in the animal diet, but just changing the presence of different phytochemicals, they had a tremendous change in oxidative stress and diabetes-related risks in the animals.[3] I conclude that this is because these phytochemicals were participating in signaling processes that modulated insulin sensitivity, mitochondrial oxidative phosphorylation, and the influence it has on a whole array of metabolomic influences that can result in dyslipidemias, dysglycemia, and oxidative stress. It is not just the starch carbohydrate; it's not just the protein; it's not just the fat. It is the presence of these other factors, some of which are not even considered essential nutrients.

Let's use another example. What about soy? Soy has been in the news heavily recently. The pendulum seems to swing back and forth very quickly with the changing in public opinion about nutrition and health. One moment, we hear fiber is very important and valuable; the next moment, we hear that fiber is bad, and then fiber comes back on the radar screen as being good. We have seen the same thing with carbohydrate: High-carbohydrate diets with Pritikin and Ornish were considered good, then they became poison, and now they are coming back into favor once again. There is a difference between the unrefined high-complex carbohydrate diet and the high-glycemic-index diet of refined sugar and white starch. These trends tend to swing back and forth as well, and we have to be very cautious not to jump on bandwagons or we will be whip-sawed around with the changing of opinion. There is some truth that we need to keep in mind related to the trajectory of clinical and experimental research in these various areas.

Such is certainly the case with soy. Right now, the pendulum seems to be swinging back to soy being an unfavorable component of the diet. This flies in the face of literally thousands of epidemiological, animal and human intervention studies, as well as clinical-controlled trials that have shown the benefit of soy or its components in a whole array of physiological, functional outcomes. Beneficial soy components include whole soy in the diet, with its lignans, fibers, isoflavones and proteins, and essential fatty acids. Looking at soy isoflavone-enriched diets and markers of lipid and glucose metabolism in postmenopausal women, do we find any favorable association in Caucasian women by including soy foods on a regular basis as it relates to their serum lipids and glucose? This issue has been examined in many studies, but one that I thought was quite interesting was recently published in the *American Journal of Clinical Nutrition*. The authors show that the isoflavones found in soy, like genistein and daidzein, are substances that modulate function in a favorable way.[4] In fact, they found that isoflavone supplementation could increase HDL cholesterol in a specific estrogen-receptor-polymorphic subgroup. Therefore, there may be women with certain types of gene patterns who have a much more enhanced benefit from a soy-based diet than others.

We too often tend to regress our conclusions to the mean. We say that the "average" person would respond in the following way. Maybe what we should be doing is recognizing that the person sitting in our office for consultation responds in her own unique way, and the diet is to be modulated to her needs. In fact, with soy isoflavones and lignans it has been found that the lignans are converted by certain enteric bacteria into a secondary metabolite called equol. Equol is a hormone modulator and a very important chemopreventive substance for estrogen-modulated dysfunction. Only about 50 percent of women convert their lignans into substantial amounts of equol as a consequence of the GI metabolism from their enteric bacteria. You might want to have more women convert these soy constituents into equol because that's a favorable outcome, and it is associated with a reduced risk to breast, endometrial, and ovarian cancer. The way you might do that is to modify the GI enteric environment by changing the bacterial flora

I am introducing another complicating factor. Not only is it just the diet that the person eats and his or her unique response to it, it is also the secondary metabolism of some of these phytochemicals by these living organisms-two-and-a-half to three pounds of these several hundred species of living organisms in our gut. This makes our gut a bioreactor, resulting in the production of secondary metabolites that our body sometimes may see as toxins, and other times may find as favorable immune-activating or -stimulating substances, or cell-physiological normalizing substances.

This introduces another variable. Now, you may want to try a modified diet with your patient, doing it in

a step-wise fashion, getting away from a diet of white to a diet with more diversity of information in the form of phytochemical-rich foods. We need to recognize that maybe some of the benefits of these are occurring as a consequence of secondary metabolism by gut bacteria, so we have to be very cautious and conscious of gut physiology and think of the gut as a bioreactor.

This is a very important thing when doing what we call the 4R Program, which is the gastrointestinal restoration program-Remove, Replace, Reinoculate, and Repair. The third "R," which is Reinoculate, is to add back to the GI milieu the friendly bacteria, bifido bacteria and certain strains of acidophilus, with prebiotics, the selective foods like arabinogalactans and beta-glucans that are fermented by the friendly bacteria into secondary metabolites that would serve as gut fuels and, as appropriate, selective substrates upon which the friendly bacteria can grow. I'm introducing some complexity in this discussion because this nutrigenomic concept goes beyond just the specific substances you add; it is also how they get processed and the biochemical result of that processing. This also relates to things like food allergy and food hypersensitivity because it may turn out that the patient is not allergic to the food you have given him, in and of itself, but rather to a secondary metabolic compound that is formed from the food. On a skin test, you may not see a positive, but in terms of the biotransformation of that substance through the gut reactor system, it produces a reactive substance that the gut-associated-lymphoid-tissue, the immune system of the gut, picks up as a foreigner. You will notice that we are trying to layer on different levels of understanding and sophistication as to how the nutritional environment can influence function unique to individuals and their specific genes and metabolism.

We learned about this in the Functional Medicine Research Center, in a clinical trial that we have recently published. This appeared in the journal *Nutrition*. [5] The title of this paper is "Effect of a low glycemic index diet with soy protein and phytosterols on CVD risk factors in postmenopausal women." This was work was overseen by Dr. Daniel Lukaczer and Dr. Robert Lerman. It's a very interesting study because it recruited a group of postmenopausal women who were not diabetic, had no cardiovascular disease, were modestly overweight (meaning elevated body mass indices), had some evidence of dyslipidemia and insulin resistance (as measured by elevated-fasting-triglycerides-to-HDL ratios). These women were randomized into two study groups: both groups were isocaloric and got the same exercise program, which was a regular walking program. They also spent the same amount of time with a professional nutritionist/dietitian, who counseled them on their dietary programs. The two programs they were randomized to were: (1) the American Heart Association (AHA) Program, which is a standard of identity for nutritional intervention studies for reducing cardiovascular disease markers; (2) a low-glycemic index diet with a soy protein based phytosterol beverage.

Therefore, there were two groups with the same calories with the main differences the glycemic index of the programs and the phytochemical and micronutrient compositions. For those who still believe in The Zone, as if there is some magic number of protein, carbohydrate, and fat that will lead to optimal physiological function, it appears, from the results of this study, that these may be secondary to the signaling molecules that are present within a diet. Why am I saying that? Because after 12 weeks, the differences between these two groups were absolutely remarkable, with many variables showing statistically significant differences at the $P < 0.001$ to 0.005, meaning highly significant differences. Triglycerides are an example. The fasting triglyceride levels in the low-glycemic index diet group went down 57{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} over baseline versus only 12{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} over baseline in the American Heart Association diet group. The HDL levels remained constant in the AHA

diet group, but were elevated in the low-glycemic index diet group, meaning the triglyceride-to-HDL ratio (a surrogate marker for metabolic syndrome) was extraordinarily improved and, as a result, the ratio of triglyceride-to-HDL went down by almost one-and-a-half points in the low-glycemic index diet group versus the American Heart Association diet group. In fact, in reviewing the literature, there seems to be no pharmacological product that one could prescribe that would produce the same benefits as seen in the low-glycemic index with phytosterol and soy beverage group that were achieved in these women. You could not use a combination of metformin with statins and ACE inhibitors to produce the same favorable outcome across all these parameters.

When it is said that it is all about the ratio of protein, carbohydrate, and fat, and it is all about the number of calories alone, that is very short-sighted. There are many other signaling molecules present in a complex diet that give rise to modified function that we should be paying attention to when we are doing biochemically tailored, or individualized diet planning.

Let's move to another microingredient found in our diet that is being seen as a very important modulator of function, one that we have spoken to in previous issues of FMU. I want to bring you up to date with some more recent information on vitamin D3. There are significant barriers for optimizing vitamin D3 intake, particularly for older-age individuals. Available data on metabolic utilization of vitamin D3 indicates a total daily equivalent of about 4000 IU, or twice the current tolerable upper level in certain individuals necessary to maintain health.[6] In young individuals, most of this comes from the skin. However, cutaneous vitamin D3 synthesis declines with age, creating a need for increasing oral intake to maintain optimal serum 25-hydroxyvitamin D, and that is what we should be measuring in patients to evaluate sufficiency. Now, the levels we are trying to shoot for are 50 nanograms per mL, or greater. Estimates of the population distribution of serum 25-hydroxy D3 levels coupled with available dose-response data indicate that it would require input of an additional 2600 IUs per day of oral vitamin D3. That is about 65 micrograms to give an equivalency to ensure that ninety-seven-and-a-half percent of older women have 25-hydroxy D3 values at or above desirable levels. This has been recently published in the *Journal of Nutrition*. [7] In this article, the author (Robert Heaney) states that the age-related decline in cutaneous input, taken together with the low published upper limit, creates a substantial barrier to the deployment of public health strategies to optimize vitamin D status.

When we establish the clinical level for vitamin D3 for a patient, we should be looking clinically at two important variables. One is the calcium-phosphorus ratio in the blood (to make sure it's not elevated), and the second is the level of 25-hydroxy D3 in the blood. If you do not see an elevated 25-hydroxy D3, and you do not see an elevated serum calcium-phosphorus ratio, then, in fact, that patient is not toxic with vitamin D. There is very high concern for vitamin D toxicity because of hypercalcemia, but we should be measuring these parameters and then titrate to the patients need using the serum calcium-phosphorus ratio and the 25-hydroxy D3 serum level to determine the sufficiency of the person and comparing it with their clinical symptomatologies. Again, the kind of things that I have often had reported to me (seen in patient's that have come through our Functional Medicine Center) are those who have eczema or psoriasis, or hair loss of unknown origin, looking like autoimmune alopecia areata, thyroiditis, or arthritis-like symptoms. When placed on a vitamin D supplement to raise their 25-hydroxy D3 into the proper level, they have clinical remediation of many of these symptomatologies. It is quite a remarkable part of our biochemically tailored nutrition story that is starting to emerge.

We recognize that even the human mammary epithelial cells express a CYP 27B1 with vitamin D

metabolism, which is being investigated as a surrogate marker for risk to breast cancer.[8] 25-hydroxyvitamin D3, as determined by Dr. Colleen Hayes at the University of Wisconsin, is also utilized a substrate by the macrophage to produce 1,25 dihydroxy D3, which attenuates the inflammatory process activated through interferon gamma released by T-helper cells. In the immune system, and in the neuroimmune system-the glia-vitamin D plays a very important role through its 25-hydroxy metabolite in controlling immunological activation and inflammation.

Vitamin D has been recently found, at least in the animal model, to help prevent colonic cancer, and there is relevance for human colon malignancy. I'm now quoting from a paper that appeared in the *Journal of Nutrition*, in which results show that colonic vitamin D synthesis is not only under stringent control by nutritional calcium, but also of folate, which suggests that there is epigenetic control of vitamin D hydroxylases, which then may regulate the immunological potential in the gut mucosa and in the colon.[9]

There is a complex interrelationship between methylation, through folate chemistry, vitamin D hydroxylation, and ultimately, the regulation of immune function. This takes us to the role that is emerging for vitamin D and autoimmune diseases, and implications for the practice from multiple sclerosis literature. I'm now back to an article in the *Journal of the American Dietetic Association* that reviews studies that link vitamin D with several autoimmune diseases, not only multiple sclerosis, but also SLE and maybe even rheumatoid arthritis. [10] Animal studies are suggesting a strong connection, and the limited human data are showing possible benefit from vitamin D supplementation as well.

We are starting to recognize the development of an epigenetically-based medicine that is taking us beyond the genes-environment separation into this continuum, and we are going to hear about this from a different perspective-environmental-behavioral toxicology, and how small, toxic molecules in the environment can regulate function, from our Clinician/Researcher of the month, Dr. Herbert Needleman.

INTERVIEW TRANSCRIPT

Clinician/Researcher of the Month
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JB: It's time for our Clinician/Researcher of the Month. This month's guest has been a seminal figure in my education and intellectual development over the last 30 or more years-Dr. Herbert Needleman, who is at the School of Medicine, University of Pittsburgh at the Western Psychiatric Institute and Clinic. Dr. Needleman is a medical doctor, and board-certified in both psychiatry and pediatrics, which gives him a very interesting perspective of the field in which he has been such a pioneer-behavioral toxicology. His contribution was first made evident by publication of a series of studies, on which he was principal author, in the early 1970's. These studies looked at the effect of low-level lead exposure on cognition performance and intelligence in children. In the past 30-plus years, he has expanded this model to look at the effect of lead on cognitive performance in delinquents, as well as in post-menopausal, aging women

and many other individuals. He has focused specifically on lead, but his work has general implications to the whole developing field of behavioral toxicology and the sometimes very vigorous debates about the effect of the environment on behavior. Dr. Needleman, we welcome you to Functional Medicine Update and thank you so much for being with us.

HN: Happy to be here.

JB: I'd like to go back to 1971 or thereabouts. Please tell us the fascinating story about how you got into this field and about the time you were at Harvard, when you made some extraordinary observations.

Early Work with Lead Poisoning

HN: Well, I was a practicing pediatrician and I made house calls. In my training at the Children's Hospital of Philadelphia, I treated my first case of lead poisoning-a very sick little Hispanic girl-and I just followed the recipe. She got better, and I felt very exalted. I told the mother what I had been trained to say, and that is, if the little girl was re-exposed, she was essentially doomed. I told her she had to move out of that house. She asked me: Where will I move to? She said that any house she could afford would be no different from the house she now lived in. And that shocked me and smartened me up.

I realized that lead poisoning and the approach to it wasn't simply making a diagnosis and giving a drug. It had to do with how children lived. I was sensitized to the fact that there probably was more lead poisoning around than was being recognized. At Children's in Philadelphia, the year I was a resident, we admitted 12 cases, which was much more than any other hospital in the city. But the year I was the chief resident and insisted on certain standards for drawing blood lead, we doubled the rate just by making the residents do a blood test on any kid who had a behavior change, anemia, or a stomach ache. That showed me that there was much more lead out there doing its damage, and that stayed with me when I went into psychiatry.

I began to wonder about the children in north Philadelphia where I trained at Temple. How many of these kids were, in fact, behavior disordered or were doing badly in school because they were lead poisoned? My office was across the street from a public school and I'd watch these kids go to school. I wanted to go in to the first grade classroom, measure their lead burden, and then do IQ tests, but lead in the blood has a short-term half-life-28 days. So, if a child was exposed at two- or three-years of age, the blood lead might well be normal by the time they are six or seven and in the first grade. I began to think about what I could do to look back in the child's history.

Now, lead goes to the bone and most of the lead in our bodies is in our bones and it stays there a much longer time, but you can't do bone biopsies. It occurred to me that there was a spontaneous, painless bone biopsy, if you were there to catch it, and that's the deciduous tooth. I collected a lot of deciduous teeth from children in the Philadelphia school system. I went back to the records at Children's Hospital and found children who had been discharged as lead poisoned and was able to get teeth from five of them. We showed that tooth lead levels in inner-city kids was 5 or 10 times what it was in suburban kids, and that 20 percent of the ostensibly undamaged, unexposed inner-city kids had blood leads higher than lead-poisoned kids.

Measuring Lead Levels in Teeth

The rate of severe exposure was extremely high: one child out of five had evidence of severe lead

exposure. The next thing was to see if that exposure had any impact on their brain function. At that time I had gotten an invitation to Harvard and the Boston Children's Hospital where I had the good fortune to have an office across the hall from a superb epidemiologist, Al Leviton. With his guidance, I designed a study in which we collected about 2500 deciduous teeth from about 2000 children in the Sommerville and Chelsea school systems, measured their tooth lead levels, and brought the children in the highest tenth percentile and the lowest tenth percentile of lead levels in for a clinic visit-none of whom had ever been recognized as having a problem with lead. We found that in that group of children who had high lead in their teeth had a significantly lower IQ score and poorer performance on a number of attentional measures. We followed them and, when they were 18 years old, they were doing worse than they were when we first examined them. The news was that lead exposure effects are permanent and they are expressed in life success measures, like how far you go in school. There was much higher failure to graduate, lower IQ measurements, and a decreased ability to attend to stimuli in the high-lead group. The message was that lead exposure has long-term serious consequences for child success.

JB: I originally read your article in The New England Journal of Medicine in 1974.

HN: The first tooth study was in 1974. The lead and IQ study was in the Journal in '79.

JB:. You had a cute way of measuring attention. Didn't you use the game, Simon, or something like that to evaluate the children?

Measuring Attention Span

HN: It was very simple. I actually stole it from a very prominent psychologist at the NIH who used it to study schizophrenia and whose name escapes me at the moment. A child has a telegraph key, and they're instructed to hold the key down, and when they hear a musical note, take their finger off as quickly as they can. That's hooked up to electronic clocks and we measure the response latency. Then we tell them that when we say "Ready," that means the note is coming, so get ready. By varying the time between the "Ready" signal, Ready...beep and Ready...six seconds...beep, and measuring the reaction time, we see how long they can maintain their cognitive set, which is one of the functions that describes attention. We showed very clearly that children with higher lead in their teeth had longer response latencies than children with low lead, and that was duplicated in England by Bill Ewell, in South Africa, and a couple other places.

JB: From our perspective in the field of Functional Medicine, we would probably call that functional neurology. It's really a functional stress test, a neurological stress test, in some ways.

HL: Yes, it is. It's so simple, but it's so informative.

JB: I want to compliment you. Your ability to publish your work and keep it out in front of us so that we can understand what's going on has been superlative. Just tracing through your record of over 100 publications, it gives us a wonderful record of the whole development of this concept. It seemed to me early on that there was an attempt to trivialize some of the observations you had made because they were only seen in children of low socioeconomic background who are deprived in some way, who are perhaps eating the lead in the paint on their cribs or in their homes. The sound byte was to downplay it. Was that your experience?

Environmental Health and Conflict with Vested Interests

HN: Oh, yes. If you're going to do environmental health, you're going to get into conflict with vested interests. When I first described the tooth analysis, that got me a trip to the Netherlands to an international meeting. EPA paid my way, and there was a huge audience, most of whom were people working for the fuel companies. Any time somebody got up and said they thought that lead is dangerous, a whole crew of people would attack them. A very well-prepared group of people would challenge them. That same thing happened to me. I presented my tooth data, and I realized that this was not just a scientific meeting: this was a war. Thereafter, any time I published something, the lead additive industry and the lead paint industry would challenge my statements of association between lead and brain damage by saying, as you said, it's really confounded by poverty, by race, and by other issues, which we controlled for in our analyses as carefully as we could.

JB: As I remember, in your Boston study in The New England Journal of Medicine, there wasn't a connection between socioeconomic status and level of lead in the dentin of the deciduous teeth. Is that correct?

Umbilical Cord Blood Lead Levels

HN: After we did the lead in deciduous teeth study, in which we did put socioeconomic status in the model, we did a study of lead beginning at birth, looking at umbilical cord blood leads, and following children until they were ten years of age. The strongest lead effect in that group was in the children of the middle class, and that was because of an unusual distribution. We went back and looked at that, and the children who had the highest lead levels lived in Beacon Hill and they were children of professors at Harvard, etc. They were middle class children and had the biggest effect, so that emphatically challenged the issue of social class as a confounder.

JB: I would credit you and your group's work with the impetus for this. Eventually, the mounting pressure was to remove lead from gasoline, assuming that that was going to solve this problem. What politics and communication was going on related to your papers in that period around removing lead from gas?

Removing Lead from Gas

HN:. When we published that paper in '79, that was a critical time, because William Ruckelshaus, at the administrative EPA, was making a decision about banning lead in gasoline. Up until that time, they had a regulation that every gas station had to have one lead-free pump, but the next step was to-in step-wise fashion-take lead out of gasoline. And he was considering that at the time that we published that paper and it was very influential in his decision. And then, a real battle occurred over getting lead taken out of gasoline. The industry spent an enormous amount of money trying to convince people that this was a frivolous thing. I remember them saying repeatedly that nobody ever got sick from lead in the air, and that if you take it out of gasoline, nothing will happen. Well, what happened was, when lead was taken out of gasoline, beginning in the late 70's, the blood lead levels in this country went from a mean of 15 to where they are now, below 2. Millions of children and adults have been spared nasty lead exposure because of that one step.

JB: There was also some pressure brought to bear from the lead acid battery industry, as well, because they had some vested interest in the whole lead issue.

HN: Oh, yes.

JB: How did that manifest for you as a scientist? You were just trying to dig into the truth and find an answer about why some kids may have less performance than they're capable of.

HN: They challenged me and a couple of psychologists who were consultants to the lead industry accused me of scientific misconduct. They came to my office and I allowed them access to my data files and they submitted to the NIH a charge that I had manipulated the data, which effectively took three years out of my work life defending myself. At the end of that, there was no evidence of misconduct. The NIH ran the regressions, and the university ran the regressions based on my data and got exactly the same result. It did serve to muddy the waters for a considerable period of time.

JB: For those of us who have never had the prominence of making the discovery you have, how does one handle this level of inquiry? It sounds like it's almost one of those guilty-until-proven-innocent type situations. You get into a confounder in which the front end of negative press may never be buttressed by the truth that comes out later that you were exonerated.

HN: Yes, that's true. The answer is, you fight as much as you can, I guess. It was a very difficult time. We didn't get a lot of work done because I was too busy writing responses to inquiries, but in the long run, it worked out.

JB: Did it adversely affect your ability to get funding for your research?

HN: No, I have had almost continuous support from the federal government since the 1970's.

JB: Well, that's very encouraging. Let's move from there to the question of international issues of lead. We often think very provincially about our own domestic problems, but it appears to be a global problem. What about the developing countries? I'm familiar with a little bit of work in Latin America.

Global Issues with Lead

HN: In Africa, there are still enormous amounts of lead in gasoline. What happened was when the Ethyl Corporation was barred from distributing it in this country, they exported it to some countries in Europe and to Africa. Africa has enormous amounts of lead in gasoline, in the air, and in the children. I don't have the numbers at my fingertips-but the blood leads are very high. And that's true in some South American countries. Venezuela makes a lot of gasoline. They export lead-free gasoline, but the gasoline for home consumption has lead in it.

JB: In 1998, you authored a paper published in the American Journal of Public Health, titled "Childhood Lead Poisoning: The Promise and Abandonment of Primary Prevention." It's a very powerful discussion of how things get twisted in the process. Can you tell us a little bit about that?

Testing for Blood Lead Levels in Young Children

HN: Yes, I can. I had been the chairman of the advisory committee to the Centers for Disease Control in the 70's, and then was a member of the committee, and then a consultant. I think it was in 1991, we recommended that every child in this country have a blood lead test at one and two years of age. Blood lead tests now cost somewhere between six and ten dollars, and that would have been a very powerful public health maneuver. In 1993, the CDC began to retreat from that. In '94, when the election put the Congress in the hands of the Republicans, there was a great move to cut back on public health policy, and

CDC knuckled under to that. I wrote a piece which described the forces that led to this retreat from universal screening, which I still think is an enormous bargain and would be an incredibly powerful pay off for our country. Instead of universal screening, they developed a very complex system for deciding where you should do blood lead tests in children. As soon as you do that, the people who need it the most fall through the screen. I wrote that and made a lot of enemies and a few friends out of it.

JB: In the 1990s, I recall going to a meeting and having a kind of off-the-meeting-floor discussion with some people in the field in which they said that one of the problems of doing serial blood analysis, or looking in screening, is that it will pick up a lot of children that possibly have excess blood lead. Then, the question is, do we have enough money in the public health service to afford to give them therapy, so maybe not asking is the right approach. Did you hear anything like that?

Variability of Toxic Blood Lead Levels

HN: Yes, I've heard that at frequent intervals. When I started in the field of lead toxicology, we thought that 60 micrograms (mcg) per deciliter (dL), 60 millionths of a gram per milliliter, was the threshold for toxicity. Because of developing data over time, it went down to 25 to 20, and now it's at 10, and there's very good evidence that there are health effects below 10 micrograms (mcg) per deciliter (dL). There seems to be no threshold for lead effects. Because of that, the CDC and the NIH sponsored a study about the efficacy of treatment of children who had no symptoms, but who had elevated blood leads. These were children who had blood leads over 25 and under 45. They found that using the current drug Succimer, dropped the blood lead levels, but the control group, over a slightly longer period of time, came down to the same level, and there was no difference in the IQ of the control group versus the treated group. There's no efficacy in using a pharmacologic treatment in children whose blood leads are below 45. It seems quite clear. What does that mean? Well it means that the only response to that is primary prevention, which means getting lead out of the environment and that's a very expensive task, but the monetized payoff for that is much higher than the expenses.

There was a CDC study done a few years ago, I think in 2002, which looked at the payoff to a one-year cohort of children in the United States, the 4 million children born in, I think, 1998, whose blood lead (if we hadn't taken lead out of gasoline), would have been 15, and instead it was 2. And the payoff for that one-year cohort was between 100 and 300 billion dollars.

There's an enormous profit to be made from doing good. Now that the major source of lead for children has been found to be lead in old housing paint, we need to develop a unified strategy to attack the worst houses first, get the lead out, sequester it in safe places, and move on to the next group of houses which are not in as bad repair. That poison will stay there for as long as that house is up, and the only answer is removing it. Now, in removing it, you create jobs where they are most badly needed. So the money spent on de-leading a house would have many multiples. It would put people back to work. Our worst problems in the inner-city right now are lead paint, no jobs, and bad housing. The multiplier for doing the right thing is enormous.

JB: Some of your publications have also extended this into cognitive function of older women (language processing in adults), and adjudicated delinquents, suggesting, as you indicated, that this has a trajectory that doesn't stop in infancy or childhood. Can you tell us a little bit about what happens-you've alluded to it-as you grow older and you have a higher body burden of lead?

Lead Body Burden in Postmenopausal Women

HN: I think the effect of lead exposure on the aging is a very important issue. Susan Muldoon, who was a graduate student here at Pitt a few years ago,(we have a study of healthy aging in women in the area) looked at postmenopausal women, and compared the cognitive ability of those whose blood lead was over 8 to those who were under 4. There was a significant difference. I think what that means is that when people get older, their bones demineralize, and that huge store of lead in the bone has to go someplace. Some of it gets into the brain. Susan's paper quite nicely showed that. Now, there's another issue. I've often wondered about whether lead has any association with dementia. This lead recirculates. Some of it gets back into the brain, and how much of the disordered thinking of aging is due to that?

Fetal Exposure to Lead

A very clever neuroscientist at the University of Rhode Island, Nasser Zawia, gave minute amounts of lead to one-day-old mice, and their APP (amyloid precursor protein which is associated with Alzheimer's), went up, and then came down to normal. At 21 months, which is old age for a mouse, he looked at their APP and it was up again. This may be one of the examples of fetal exposure and disease late in life, which is one of the hottest new subjects in neuroscientific research. We are pursuing the question, as to whether there is some association between early exposure to lead and later dementia. You asked me about another issue?

JB: It was about language processing and the adjudicated delinquent problem.

Association of Bone Lead Levels with Delinquency and Arrest Rates

HN: I did a study of children in the Pittsburgh school system who were not considered lead poisoned and who were not considered delinquent. I measured their bone lead levels with a relatively new device, actually fluorescence, and then measured the association between bone lead and scores on the child behavior check list, which is a well validated inventory of behaviors. We showed, after controlling for other factors, such as race and socioeconomic status, that bone lead levels were associated with increased aggression, increased delinquency, and poor attentional function. We published that in the Journal of the American Medical Association, I think in 1992.

The next step was to see if it had anything to do with arrest rates. With the cooperation of the court here in Pittsburgh (the Allegheny County Juvenile Court), we looked at 195 male youths who were adjudicated as delinquent (arrested and adjudicated) and we compared their bone leads to controls from the same high schools that were not delinquent. The bone lead levels in the delinquents were 7 times what they were in the controls. By doing a statistical procedure called logistic regression, we measured the strength of the association between lead and delinquency after adjusting for the possible confounding factors. We found that the odds ratio for delinquency, if you had high lead in your bone, was 4. In other words, you were 4 times as likely to be delinquent if you had elevated bone lead levels. If you have the odds ratio, and if you know what the exposure was when they were children, you can make an estimate of what's called the population attributable risk: how much of the delinquency in the population is attributable to lead exposure? We did that, and for Allegheny County, the population attributable risk was between 11 and 38 percent. We estimate that between 11 and 38 percent of the delinquency in Allegheny County is attributable to lead exposure. That is a lot of children.

JB: I've heard some discussion in which people have said that there is a very good correlation between this lead burden and these behavioral changes, however, it may be a surrogate marker rather than a causal

agent, and there may be other things that are the primary causal agents. Do you have any thoughts about that?

Lead Burden at Birth and Behavioral Changes in Later Life

HN: First of all, we showed in our prenatal study that the blood lead level at birth was associated with IQ and attention later in life, so there is no question about which came first. And the criteria for making a causal inference are priority in time (that the cause comes before the effect), dose-response relationship (the more of the culprit you have, the more the response you have), non-spuriousness (that is, you've adjusted for the other factors), and that it makes biologic sense. And lead subscribes to all of those criteria.

JB: One of the things that we've seen, obviously, is an increasing public awareness of what has been labeled attention-deficit hyperactivity disorder (ADHD). Do we see a difference in the prevalence of ADHD in lead-exposed environments versus in those that may be less lead exposed, or can you not make those correlations?

Lead Exposure and ADHD

HN: Right now I'm analyzing the data on a study we've done that examined that question. I can't answer it yet, but there are a number of reports that lead is associated with poor attention, as I described earlier with that test of response time and parents' reports that a child will not sit still. So, I think it's a plausible association. We have looked at bone lead levels in, I think it's 190 children with attention deficit disorder (clinically diagnosed), and controls.

JB: We'll stay tuned for that. That sounds like its going to be a very interesting additional part of the story.

HN: Yes.

JB: There's so much, obviously, that we could talk about, but I don't want to take too much of your time. This is just a fascinating development of something that probably, for most people, in the absence of your work, would still be considered a mystery. This is a tremendous addition to our understanding of where certain disease patterns might originate. As you've been in this field for the better part of more than three decades, how important do you feel the environment is in our disease patterns, and the inter-relationship between stuff out there and stuff that goes on inside the human being?

Mercury, Pesticides, and Phthalides

HN: There are so many xenobiotics-chemical substances that are not natural that we haven't had a million years to adapt to. Most of them, at some dose, could produce harm. Lead is the best study, but not the only toxin we should be looking at. There is mercury, and then the many endocrine disruptors. We don't know how smart our children could be, or how healthy our lives could be if we were separated from these unnecessary exposures.

We just need to get careful data to document these things, and it's beginning to come in. Mercury is a real risk factor. The pesticides are an important risk factor. Phthalides, which are in plastics, are endocrine disruptors. I think these are things are just coming into attention. I think it's very informative to look at the history of lead, in that at the end of the 19th century, people believed that children were not at risk for

lead toxicity; it was a disease of workers. Then it was accepted that children could become lead poisoned, but it was thought that (look at the pediatric literature in the 30's)- if the child survives the acute episode and is separated from lead, they're untouched by the disease. Then, in the 1940's, it was shown that lead exposure produces long-term effects, but they were only supposed to occur in children who had obvious symptoms, such as lead encephalopathy. And then it was shown, beginning in the 70's and conclusively now, that lead exposure in the absence of any symptoms, interferes with cognition, attention, and social adjustment. And, it's not just my studies. There are at least 30 studies of lead in children around the world, almost all of which converge on the same thing.

JB: I saw a paper-I think was in 2005-in an environmental health prospectus, which is a collaborative group of investigators from the Cincinnati Children's Hospital and others, including yourself, looking at low-level environmental lead in children's intellectual function in international pool analysis that certainly supports exactly what you are saying.

HN: Bruce Lanphear pulled everybody together and he did a remarkable job. There are seven very good studies, and they all converge on the fact that lead effects exist down to 10, and probably below, and that most of the damage occurs even below 10.

JB: In closing, I'd like to give you an opportunity, in the strength of the wisdom of experience that you've had, to talk to the clinicians who are listening. What message would you like them to take away from three plus decades of very diligent work?

HN: My instruction to clinicians would be, I think every child in your practice should have a blood lead test at one and two years of age. If they don't have an elevated blood lead at two, they're going to be okay, probably. I mean, the risk goes way down. The only effective response to the national problem, or the international problem, of lead exposure is getting at it at the source.

JB: Did you say above 2 micrograms per dL is considered something of concern?

HN: The slope of the regression curve between 0 and 5 is steeper than it is between 5 and 10, so it looks like the lower the blood lead you can get, the better off you are. I don't know if there is any nontoxic level.

JB: On behalf of all of our listeners, and on behalf of myself, personally, over the 30 plus years I've had the pleasure of reading your work and listening to you a couple of times at different conferences, I want to thank you. Sometimes, it's a lonely world when you come up with something new that's not agreed upon by everybody, and it takes a very special person to stay on task, fight those battles, and come out on the other side. You certainly fought a very important battle for the health of millions of children and we want to thank you.

HN: Thank you. I've enjoyed very much talking with you.

JB: Likewise. The best to you.

Final Thoughts
It's probably unfair of me to add anything to the brilliant thoughts and comments of Dr. Needleman, but I

feel obliged to say a couple of things because he is so self-effacing and understated. His work has been unbelievably important for all of us, not only specific to the lead issue, but to raise the question of behavioral toxicology to a higher level of science and inquiry, and at the highest levels of epidemiology, behavioral science, toxicology, immune function, and neurology. This has crossed-disciplines and is truly what we would embody as a functional medicine concept because he's really discussing neurological function as it relates to these low levels, well before neurotoxicity.

The functional medicine concept is trying to define the space in-between optimal physiological function and pathophysiology. In that intervening gap, there is a tremendous range of differing functional abilities of the organism. In the case of the nervous system in children, which is a very sensitive biomarker group for toxicity, we can start demonstrating using these extraordinarily interesting neurological stress tests that Dr. Needleman has employed in his studies. We can look at the functional changes in the neurological system that make our understanding of the impact of the environment on our function much more scientifically understandable and definable than waiting for the endpoint of neuropathology.

Most of the conditions of concern that we were describing-IQ, learning, language processing, behavior, delinquency, and attention disorder-are not pathologies as much as they are functional changes in the organism. And yet, in medicine, we are still in search of the Holy Grail of the diagnosis as if, through it, we will understand its treatment, when the functional changes that precede diagnosis are the places where we can most likely intervene at lower technology, lower expense, and lower risk, with higher outcome in performance. Dr. Needleman's work symbolically identifies the juxtaposition between the pathophysiologically based medicine that most of us learn, the medical taxonomy of learning by memorization, and lists of histopathological identification of specific named diseases.

What people really walk around the world with is compromised function as a consequence of an imbalance between cellular capabilities and environmental exposures. And this gene-environment interaction gives rise to these functional decriments that precede the onset of pathophysiology and demonstrate, in a society, whether it's healthy or sick.

I read articles about ten years ago, discussing that one of the reasons the USSR fell apart as a country was because the workplace environment was so polluted, and such high levels of body burden were placed on young men and women, that absenteeism, work productivity, and illness (particularly respiratory illnesses) became so frequent that their overall productivity was compromised to the point that they could no longer manufacture and produce enough for the large size of the country. As a consequence, they could not even mount an effective military because so many young men had health problems that were not allowing them to pass muster as candidates for the military. These are not pathophysiological effects; they are subtle effects that undermine the patency, or capability, of a society, and are seen as the outliers and yellow canaries of health effects. And then we wait in the wings of medicine, with our remedies, trying to treat those conditions at the endstage, knowing that, at best, we may be marginally successful.

Dr. Needleman expressed it very well when he was talking about what kind of therapy would be used in individuals with excess lead body burden. He pointed out that in studies that had been done with intervention on marginally lead-impaired individuals that intervention with chelating agents did not result in significant improvement. You have to catch it earlier. Prevention, primary prevention, was better than trying to catch it after the fact. This work of Dr. Needleman's is paramount. It is significant. It is like the work that we saw with Kilmer McCully with homocysteine. It is revolutionizing our view of the

interaction between our environment and our function, ultimately giving rise to what we see as a decreased health pattern with increasing healthcare expenditures. It is why we need a functional medicine.

Thanks so much. I look forward to being with you next month.

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