March 2010 Issue | Ego Seeman, MD Austin Hospital and Northern Health

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Welcome to *Functional Medicine Update* for March 2010. This month we are going to address a topic that I believe many of us in functional medicine might consider to be outside of our normal discussion. We often think of function at the whole-organism level to be kinetic function: the movement of substances, the movement of molecules, the movement of tissues, one against the other, like fascia. We think about movement as stretching muscles. We think about movement as nerve impulses and electrolyte transitions and things of that nature. That becomes our stereotype of the word"function"-this kinetic concept of things in movement, things in transit, things in change, dynamic movement against gradients, membrane transport, and things of this nature.

We normally don't think of function as it relates to structural issues that appear to be static, or rigid, or fixed. We say,"Those are just kind of like the architecture upon which function (the process of change) occurs." I think you know what I am speaking to now. I'm speaking about the skeleton. We have often viewed the skeleton as this grid-this template-upon which hangs the functional aspects of the body (the various organ systems that do the work to respond to environmental stimuli). In the world of science, the view of the skeleton and how it will impact medicine is dramatically changing.

In this issue of *Functional Medicine Update* we are absolutely fortunate to have one of the world's experts in skeletal dynamics and bone physiology as our clinician/researcher of the month, Professor Ego Seeman from Melbourne University in Australia. You are going to hear from him directly about the extraordinary work that he and his colleagues have been doing in redefining some of the aspects of skeletal dynamics and the whole nature of the remodeling of the skeleton. Although we think of the skeleton as a fixed mineral matrix, we are going to learn in greater detail how this matrix is really under change all the time. It is another functional part of the organism, responding to environmental stimuli just as all other organs do, and it is in communication (through intercellular signaling processes) with other distant sites in our anatomy and physiology.

Differentiating Skeletal Dynamics from Bone Marrow
This is a very new emerging view of the skeleton. I want to differentiate this discussion of skeletal dynamics from that of bone marrow. I think most all of us are familiar with the effect of bone marrow on the nature of our immune system--the origin of our red blood cells, playing a very active, dynamic, functional role in determining how critical nutrients like oxygen are transported, and how our body's immune system works, and the site of various stem cells that have pluripotentiality. I don't want to diminish our understanding of the functional nature of a component of bone, which is the marrow, but

now we are going to be talking (in this particular issue) more about the structural component of bone-the cortical bone, the trabecular bone that relates to strength and the ability to stand upright against the force of gravity, and relates to being able to maintain structure that controls function over time. It's that component that has often been thought of as being kind of rigid and fixed and not very dynamic. I think you'll be changing your opinion of that concept (if you had it coming into this discussion) as you hear Dr. Seeman's thoughts.

We are starting to recognize that this organism that we each live in (our body) is very interesting in its ability to respond to environmental stimuli and to modify its function accordingly. Those responses are very individualized. This has been a theme that underscores the tenets of functional medicine: uniqueness, biochemical individuality, homeodynamics, the concept of things in transition and flux, and the concept of web-like interaction. There is this communication across barriers that lead to things working together as systems.

You might once again ask the question: How do people ultimately develop their individual response to the environment, knowing that this uniqueness does exist in each individual? It is-again-a result of two factors that we have described so many times in functional medicine: the patient's history, and the concerns, symptoms, and signs that have brought them into the office. These factors reflect an oral history of things locked in place from the genome (the inheritance factors--Mendelian--that they derived from the combination of the sperm and egg chromosomes), and it is also related to what's happened from the moment of conception in the marks that are placed on those genome markers, which are called the epigenetic marks. We have spoken at some length over the last two years in *Functional Medicine Update*, and had some of the world's experts telling us, about the emerging understanding of epigenomics and epigenetics, and the subordinate field that is emerging from that called nutritional epigenetics.

What are these epigenetic marks? They are chemical modifications of certain regions within the chromatin, within the nucleosome, that modifies how our genomic message is read. As we have talked about at some length, it doesn't mean that the genes in and of themselves have changed their composition-it is not like a mutation-but rather it is an imprinting of the genes with a specific...I call it a"paper clip" or"sticky note" that says either,"Don't read this message," or (in the case of a sticky note),"Read here, because this is a part of our book of life that should be read (this chapter or this story)." This imprinting process is very important in developmental biology because it allows an egg, which, once fertilized, has a single set of chromosomes to differentiate upon cellular replication into different tissue types. As you get these replications in embryogenesis, there is an imprinting of the genes that occurs as a consequence of regional differences in where that cell resides within the point of implantation, and all sorts of factors that probably influence the spatial nature of its own environment that causes imprinting to occur. That then results in differentiation of those cells into different cell types from the same chromosomal message. So the same genome gives rise to multiple cell types through this process of epigenetic imprinting and what we call developmental biology.

The really remarkable discovery over the last decade or so is not that there are these alterations in the epigenetic message through methylation, or acetylation, or phosphorylation, or ubiquitination of various components of the nucleosome, but rather that some of these marks are labile. They can be put on, apparently, and taken off over the course of living as it relates to different environmental responses. I think this is where the story gets a lot more interesting related to what we call modifiable factors that

relate to health and disease over the course of living. There are these marks that seem to be very fixed once put on (so a liver cell stays a liver cell, and a heart cell stays a heart cell), but then there are those marks at different regions of the genome that are more exchangeable and can be put on and taken off as it relates to different environmental situations in which that cell or tissue finds itself. These are the ones that then can lead to locked-in functional changes in the organism over the course of living. This appears to be most commonly apparent in the fetal stage and maybe in infancy, but there are now suggestions that these changes may occur throughout one's life because of experiences they are exposed to in their environment. These could be nutritional experiences, toxic experiences, traumatic stress experiences, or drugs and other chemical agents. There may be many different early life environmental factors that change the epigenome and then have an impact over time (not maybe in the immediacy, but over the time of life of the individual) on health outcomes.

There is a group that has been very actively involved in this work: the department of pharmacology and therapeutics at McGill University (Moshe Szyf and his colleagues). They have been publishing some fantastic papers looking at this whole concept of genomic imprinting and its effect on health outcomes. One of the interesting papers that they authored recently had to do with the influence that long-term pharmaceutical drug exposure might have on epigenetic imprinting and altering the set point for physiology as a consequence of altering imprinting.[1] This has to do with people who become drug tolerant, or people whose physiology seems to change after they have been on a medication for some time (even after they take the medication away, their physiology seems to have changed). According to Szyf and his group, this may, in part, be related to the fact that these medications could alter genomic imprinting (epigenetic effects), which then locks in a different gene expression pattern and changes or alters the web of physiology. It is a very interesting concept about long-term effects of drug use (I'm talking about pharmaceutical, but it could also be recreational drug use as well) that alter physiology over the long term.

There are many environmental factors that can create these changes in the epigenome as well. We heard from Dr. Michael Skinner in *Functional Medicine Update* in 2008. He talked about his research in animal models at Washington State University indicating that environmental exposures to various biocides led to genomic imprinting that was then actually hereditable and passed down through generations, increasing the risk to a whole range of diseases in the offspring that was not necessarily tied into their genes per se, but tied into their epigenome as it related to modification by these biocides.

In a more recent paper, Dr. Szyf writes about the early-life environment and the epigenome and the fact that there are now several lines of evidence pointing to the early origin of adult onset disease that might go all the way back to infancy.[2] The key question has always been: What are the mechanisms that mediate the effects of the early environment on our health? Another important question is: What is the impact of the environment during adulthood and how reversible are the effects of early life later in life? In other words, once imprinted, is it like you can't do anything about it and you are just kind of stuck from then on with regard to whatever happened to you in infancy and you didn't even have a choice, or are there ways that you can reverse and kind of take off some of these messages and put other epigenomic messages on in place?

The genome, as we know, is programmed by the epigenome, which is comprised of chromatin, and we have talked a lot about that. A covalent modification, then, of DNA by methylation and also by non-coding RNAs modulates epigenomics and ultimately gene expression. All of these are, in fact, responsive

to environmental pressures or environmental factors. The epigenome is sculpted during gestation, and it results in the diversity of gene expression programs and distinct cell types. The data that has been accumulating over the past year or so suggests that epigenetic programming of gene expression profiles is sensitive to the early-life environment, and that both the chemical and social environment early in life could affect the manner by which the genome is programmed by the epigenome. With this concept, I think the environment is broad in its scope of impact, both social effects as well as chemical and biological effects. This could be things like infection, drugs, and chemical exposures, as well as traumatic stress disorders, deprivation, a feeling of no love, attribution, or depression. All of these various things can have influence (apparently, based on the animal models that have been studied to date) on the imprinting of the genome into the epigenome, and how that then influences over time the expression of genes in terms of the phenotype. You might call it the"phenome" of the organism.

Szyf has proposed that epigenetic alterations early in life can have a life-long lasting impact on gene expression, and thus on the phenotype, including susceptibility to many diseases. He discusses data from animal models as well as recent human studies that support the hypothesis that early-life social adversity leaves its marks on our epigenome and affects stress responsiveness, health, and mental health later in life. The interesting part of this that is emerging is that these factors appear to be somewhat reversible-that these are more labile epigenetic marks that seem to not only be put on but can be taken off or modified with different exposures.

I think one of the ways we will see functional medicine applied in the future, as kind of a general and broad concept, is to learn how we therapeutically modulate epigenetic marks that have been put on under times of environmental pressure, and then restore expression patterns back to that which is consistent with a systems biology approach to health. Why would the body shift itself into a pattern of expression of disease? Maybe it doesn't shift itself into a pattern of disease, but rather it shifts itself into a pattern that is consistent with response to that environmental pressure, and it is adapted (or let's call it even"selected") for that kind of response that is advantageous for the organism in the short term. The problem is once stuck in that physiology, when the pressure is removed, that new physiology-that new steady state function-is now a state function that leads to less optimal overall function, and we call that"dis"-ease, or a chronic dysfunction, that ultimately becomes an ICD-9 arterial atherosclerosis, or autoimmune arthritis, or type 2 diabetes, or inflammatory bowel disease, or dementia. In other words, the sequence of events that traveled downstream over time played out, once stuck in this physiology, into a disease that later can be patho-mnemonically identified.

I think the work that is going on at McGill is very interesting both theoretically and also practically, because you can imagine over time that using, say, buccal cells from the mouth, one might be able to analyze epigenetic imprinting fairly readily to look at these labile sites, to put a person on a therapeutic intervention program, and to re-measure their imprinting patterns and see, in fact, whether they are being normalized relative to these genes that are associated with stress response, or insulin response, or oxidative stress, or bioenergetics. I think this is a whole new way of functional diagnosis at the cellular and molecular level that is tied into this epigenomic mechanism. We are going to be talking about that in much more detail, but I wanted to just get you to once again see, as we go into a discussion of bone remodeling, that some of these things get stuck early on in life, and then we have to restore function by altering the epigenetic marks.

This model I have just described was further advanced in a very remarkable paper that appeared in

the *American Journal of Clinical Nutrition*. I think this is one of those papers that has an"a-ha" associated with it because it really opens up our thinking about potential new routes for remediation of problems that have been historic, and I'm not talking about obesity. Obesity, as a word, almost inspires a Rorschach-like response (a visceral response), because it seems so pandemic and it seems like we can't do anything about it. It's coming on almost like a plague or an infection. In fact, those of you who have seen the maps produced by the National Institutes of Health each year that look at the prevalence of obesity state by state in the United States may recognize that when you go back and look at these annual maps that are produced, where the red colored regions of the country represent the rising tide of more than 30{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of the population of a state having obesity, the spreading of that color red over the last 15 years looks almost exactly like that of an infection (like an epidemic). You can actually model it using the same mathematics that you would model an epidemic. Some people even say,"Well, that indicates that obesity is an infectious problem. That there must be an infectious organism associated with obesity because it looks too much like an epidemic-the slow, rising tide of an epidemic." Whether it is caused by an infectious organism or not I guess is not as important for what I am going to be talking about: the nature of its spectrum of concern in the country. Does the rising prevalence of obesity cause the rising prevalence of things like type2 diabetes, and does it increase the relative frequency of a form of cardiovascular disease that is associated with hyperinsulinemia and insulin resistance? Does that ultimately result in kind of a new public health challenge that basically, in the future, will bankrupt the healthcare system?

Let's start looking at that model-the kind of epidemic proportions of obesity. Does obesity cause those problems or is there something that is causing the metabolic disturbance that then results in a concurrent increase in alteration of energy economy that we call obesity, and diabetes, and certain forms of cancer like breast, prostate, ovarian, and gastrointestinal cancer? And does it also relate to things like cognitive dysfunction and Alzheimer's disease? Are these all covariables that interrelate with some central force of distorted functional physiology at the systemic level that then plays itself out as all of these things in concert? So it is not that obesity necessarily causes these, it's that they are all cofactors that respond to the phenotypes as a result of the central features that are creating this problem. And could the central features that are creating this problem be related to things that are associated with epigenetic imprinting? Or associated with distortion of the metabolic web in such a way as to shift all the physiologies in these tissues, such as the adipocyte cells that associate themselves with fat and energy storage, or the hepatocytes, or the beta cells in the pancreas, or the myocytes, or the osteoblasts, or the neurons, or the cardiocytes? Are all of these cell types influenced by some kind of a distortion of the physiological process of the web of interaction by central features in the genes of those cell types? I didn't talk about endothelial cells (those certainly would be at the head of my list as a cell type that could be influenced as well). All of these cells then have their physiology shifted to a different phenotype as a consequence of these genomic modulations as associated with an environmental pressure. Do these get imprinted and locked into a different state-a steady state-of chronic illness?

I hope you can understand the model here. I think it is a very different model, conceptually, than the model of a disease that comes out of eating too much cholesterol in your diet. Or a disease that comes out of just having genes for arthritis. We are really talking about a much more complex interaction of environment with genetic pluripotentiality to express an altered or distorted phenotype that then later expresses itself as a disease and may be locked in to that pattern through epigenomic modulation.

Let's go back to this very interesting paper that appeared in the *American Journal of Clinical Nutrition*.

The title of this paper is"Differential Epigenomic and Transcriptomic Responses in Subcutaneous Adipose Tissue between Low and High Responders to Caloric Restriction."[3]Big title. A lot of words. What the heck does it mean? I think this paper really has some"below the water line" significance. The question the authors are asking is this: Does epigenetic modulation that is unique to an individual influence the transcription of their genes in such a way that it modulates or modifies adipose tissue physiology and creates, in a person, a higher risk to obesity that is less responsive to caloric restriction (meaning normal food intake modulation)? These are people who are, say, resistant individuals. These people-even on very extreme caloric restriction-have difficulty losing weight and don't keep the weight off. Is there any relationship between these people considered to be low responders to caloric restriction and differential epigenomic and ultimately transcriptomic responses in their adipose tissue?

Some of you may leap to the conclusion immediately that what I'm talking about here is this: These people, therefore, must be genetically inclined to be obese. That's not really what I'm saying. What I am saying is there may be genetic uniqueness within the series of genes that control metabolism for which epigenetic marks placed on those genes (in certain family relationships of genes) create, then, a physiological distortion that makes these people more susceptible to obesity and resistant to caloric restriction. Simultaneously, those genes may be associated (when altered in their expression) with insulin resistance, and with inflammation, and with a state of physiology that is a state of alarm. Basically, what I am saying is those individuals who have resistant obesity are individuals who may be in kind of a physiological push-back to environmental factors that have created an alarm response in which the adaptation of the body is to store and to maintain an energy storage so that the whole physiology shifts into this insulin resistance/inflammatory"mount the guard and do battle" type of status.

What did they find in this very interesting study? This was an intervention study done in individuals who had biopsy work done by taking their subcutaneous adipose tissue and measuring it using PCR (polymerase chain reaction)--kind of gene amplification--looking at various genes and then examining the epigenetic imprinting using bisulfite reactions to actually measure the methylation patterns in the genes. They looked at DNA methylation and gene expression as two variables in the subcutaneous fat. When they did this they found that there was a very dramatic difference between the low responders and the high responders to caloric restriction. High responders were people who, if you put them on a modest calorie restriction, lost weight and improved their body mass index. The low responders were individuals who, on a similar calorie restriction, would not lose weight; they would be resistant to that, and it would appear as if thermodynamics were not working on their side. What the study authors found is the low responders had a different methylation pattern and a different transcriptomic (or different expression pattern of their genes) than the high responders.

Which Genes Are Epigenetically Altered?
If you are mapping the epigenome between the two groups, can you define the genes that appear to be different in the way they have been epigenetically marked? The answer is yes, you can. It appears as if the genes that are likely altered between the low and the high responders are those genes involved in metabolic pathways related to things like angiogenesis, and things like insulin sensitivity, mitochondrial oxidative phosphorylation, and insulin secretion. The genes, once they were kind of personalized to their function, clustered around these characteristics that associate themselves with (in an altered state of function or expression) the diseases that are common today, like diabetes, and neuronal apoptosis/dementia, and inflammatory conditions, and cell replicative conditions that we ultimately associate with cancer.

Why do certain people have a different epigenetic response to their environment compared to others? I think that's a very interesting question. The question cannot yet be fully answered, but it may be that the response they are having to their environment in part relates to the slight differences in the environment that we don't yet understand. The environment is a very complex situation, just as the genome is. We are exposed to many, many things, a number of which we still have very little understanding. Not only things like chemicals and radiation within the known short wavelength/ high frequency part of the electromotive spectrum, but we also are exposed to long wavelength energy, like radio waves and microwaves. We have psychosocial interactions that alter our function that you can't even measure in EMF, really. There are different kinds of functional frequencies that modify our neuroendocrine immune function in such a way as to create different states of outcome. I would say that it would be very hard for us, in a controlled experiment, to really understand exactly what environmental circumstances influence what genomic imprinting and create what epigenetic changes. But I think we can say from the study (at least we can conjecture) that there is evidence that epigenetic changes do, in fact, account for part of the differences in outcome in things like obesity and resistance to dieting or proper calorie control, and inflammation and insulin resistance, and things of that nature.

In monozygotic twins, there are often very different discordance between the body weights. If obesity was strictly a genetically controlled characteristic with a single allele-type locus, we would see a very strong concordance of obesity between twins. There is a relationship, but there is discordance. Although they had the same genome, the imprinting of their genes over the course of living between two identical twins was altered. The outcome was they had different patterns of weight and different body mass indices, and (I would offer at least as a hypothesis) different disease risks and different mediators that would be floating around in their bloodstream and in their tissues that would modulate function in different ways.

This model of epigenomic imprinting and its influence on the trajectory of physiology over time and how it ultimately expresses itself in the phenotype is a very important part of our understanding of how to treat (in the broadest sense of the word"treat") a patient. There may be certain loci of the genome that, when imprinted, are very difficult to change and require very aggressive intervention to result in lasting change and low recidivism. And then there may be other regions of the epigenome that are more labile and more easily changed by more mild intervention.

Often the theme with drug therapy is if the patient doesn't get a response in a couple of days or a week, somehow the therapy didn't work. People are used to that"quick fix" mentality. But to really alter the epigenome in such a way as to recreate a functional state of less disturbance might take much more aggressive intervention, and for a much longer time. I think, therefore, our patients need to have patience. They need to be cognizant of the fact that to alter basic cellular biochemistry and genomic imprinting it may not just take a week, it may take months. And it may take a very aggressive therapy, not just a mild therapy, to reset some of these processes.

By the way, some of these imprinting processes may require augmented doses of specific nutrients in order to overcome blocks, or to wipe out one physiology to be replaced by another. Knowing that many of these epigenetic marks are, in part, dependent upon nutrient status may be one of the extraordinary thresholds for understanding why certain high-dose nutrient pharmacology is beneficial in the short term to restore certain types of physiological functioning.

I think that we are starting to see a new concept evolve here that gives rise to a different way of looking at

origin of disease and how it can be modified--how to ask the right questions in the clinic, what kind of therapeutic agents are required to modify the function over the long term, and what kind of tests might we need to develop in order to really understand how we are shifting this epigenomic imprinting. I think this paper on the differential epigenetic and transcriptomic responses in subcutaneous adipose tissue is like the tip of the iceberg. I think we are going to be seeing many more of these papers and this kind of research being published over the years to come. This kind of work helps us to understand what genes might be the most labile, what types of things differentiate responders from non-responders, and what type of potential therapeutic agents might be necessary for a new pattern of imprinting that creates positive functional outcome

With that in mind, and to get ready for the discussion with Dr. Ego Seeman about bone and recognizing that it also is a tissue in dynamic interrelationship and has its own epigenetic origin and imprinting, let's talk a little bit about vitamin D.\ Vitamin D, as we know, is a bone-related nutrient (we all learned that early in school). We now recognize, with more recent work, that vitamin D is a seco-steroid hormone, as we talked about with Dr. Trevor Marshall recently in *Functional Medicine Update*, and has remarkable pleiotropic effects on many different factors of genome expression as a member of the nuclear orphan receptor family of modulators. It is a central factor in many of the processes that I am describing, pertaining to how genes get expressed into function.

Vitamin D signaling plays a very important role in immune-mediated disorders. There is a wonderful paper that appeared in *Molecular Aspects of Medicine* in 2008 that is about the hormonal form of vitamin D, 1,25-dihydroxy cholecalciferol, and its influence on the vitamin D receptor to form this kind of heterodimer with things like T3 from thyroid hormone or the dimerization with vitamin A to induce certain gene expression patterns.[4] The evidence seems to indicate that the physiology of vitamin D and its relationship with the vitamin D receptor is such that it plays roles in modulating stress response genes and genes that are related in the immune system to inflammation and inflammatory sensitivity.

It may be as a consequence of these factors, which are many in their mechanistic origin, that we are seeing so many clinical impacts of vitamin D when properly modulated or properly normalized in a person by looking at their 25-hydroxyvitamin D level as a biomarker. We are starting to see so many different influences: type 1 diabetes, rheumatoid arthritis, neuromuscular disorders and MS, and aspects that are related obviously to immune function and infection, and even chronic pain syndrome. There was a recent report of women who are on aromatase inhibitor drugs and have chronic myalgia and arthralgias that had remediation of their pain syndromes when supplemented with high-dose vitamin D.[5,6] I think that we are starting to recognize this from a mechanistic level as an example of how a modulator of genomic expression, in this case the seco-hormone 1,25-dihydroxyvitamin D3, can play such a significant role in modulating so many functions in the organism. So it is not just like one drug for one outcome. It's like one biological agent to modulate a variety of gene expression patterns that control all sorts of functions in different cell types in unique ways.

That would then raise the question: If it is so profound in its influence, would there be the possibility of too much of a good thing? That is, in part, what Dr. Marshall was talking about in his interview. There is a very nice article titled"The Yin and Yang of Vitamin D Receptor Signaling and Neoplastic Progression: Operational Networks and Tissue-Specific Growth Control."[7] This appeared in *Biochemical Pharmacology* in 2010. In this very well-written article, the authors write about the substantive evidence

that implicates vitamin D receptor, along with 1,25-dihydroxyvitamin D3, in modulation of tumor growth. Both human and animal studies indicate that the tissue specificity is very high, and epidemiological studies have shown both inverse (meaning high vitamin D lowered cancer incidence) and also direct relationships (meaning high vitamin D and increased risk to cancer) between serum 25-hydroxyvitamin D levels and certain solid cancers.

Vitamin D receptor, as we learned is very pleiomorphic; it controls many, many different genes. It has to do with carcinogen-induced tumorogenesis in tissue-specific model systems. It has to do with all sorts of things related to cell cycling and cell replication. The question is: Is there a place where too much vitamin D-in other words, too high a level of 1,25-dihydroxyvitamin D3-might, in fact, influence adversely some of the cell signaling properties that are associated with vitamin D? The conclusion that I can derive from this article is: We should be aware of that. Everything has a level at which it gets to be too much, including air and water, and that we ought to be in that safe range with the appropriate dosing so that we are somewhere in the 30-50 nanogram per milliliter level for 25-hydroxyvitamin D, but not assume that if a little is good, a whole lot more will be better. We ought to once again be mindful of the very subtle controls and metabolism that these bioactive molecules-these regulators-that regulate at what I call metabolic acupuncture points in this web of interacting physiology play very important roles.

With that, let's move to Dr. Ego Seeman, and really try to take this concept of structural integrity and functional integrity into a better understanding of bone and bone physiology.

INTERVIEW TRANSCRIPT

Researcher of the Month
Ego Seeman, MD
Austin Hospital and Northern Health
University of Melbourne
Victoria
Australia
www.unimelb.edu.au

Here we are once again at that section of Functional Medicine Update that I know you, like I, look forward to with such great anticipation. You're not going to be disappointed this issue. We have the fortune of being telephonically linked with a person I consider to be the world's leader in the area of bone mineral metabolism, bone integrity, and bone strength, and that is Professor Ego Seeman, who is at the University of Melbourne, Department of Endocrinology. I think his name (and reputation) precedes him. You probably don't need me to say a lot about him other than the fact that he has won extraordinary recognition for his over 270 publications and 22 book chapters in the area of bone mineral metabolism. He has recently been awarded the IOF Medal of Achievement, awarded every two years by the International Osteoporosis Foundation.

I think one of the things that strikes me about his work is it is both novel and integrates so much prescient information into an understandable package. This is very difficult to do as a primary researcher-to look at the body of the world's work and to take your perspective and integrate it and come up with something fresh and novel that really moves a field forward. Dr. Seeman has done that.

Dr. Seeman, it is really a privilege to have you as a guest on Functional Medicine Update. Maybe we can just start talking a little bit about the difference between bone integrity, bone mineral metabolism, and bone quality. I know that you have done extraordinary amounts of work looking at this kind of differential effect of osteolysis/osteogenesis, and then how that ultimately translates into the clinical sine qua non, which is bone quality.

ES: Thank you. Thanks for saying those nice things. Only my mother would believe all of that sort of stuff you said, really. I guess that I do not distinguish the words"bone quality" or"bone density." In fact, I think the word"bone quality" is actually quite a dangerous word, itself. From a historical point of view, the place that we have come to now is a product of many things, but the main one being, how could we measure those qualities (with an"s") of bone that determine its strength? Or, in other words, its ability to resist breaking? Its ability, on the one hand, to tolerate loads and be stiff, so that it doesn't bend too much, or it is sufficiently flexible so that when I'm running or doing a jump from a ladder down onto the ground, when the impact of my body weight is such that the energy that is conferred by my body weight to the bone is actually absorbed by the bone, where the bone functions a bit like a spring, so that it can bend a little, just to absorb the energy (and the energy is absorbed by the change in length of the bone) without it actually snapping?

These are seemingly contradictory properties of bone. On the one hand it needs to be stiff, but not too stiff. On the other hand, it needs to be flexible, but not too flexible and bend too much, as it were. Bone is unique. It is amazing in that it can do these two seemingly contradictory things. And it does that by having different material composition. So on the one hand, it's a rope, it's a string, it's like one of these big helices of big ropes that you see boats tied to at the end of a pier. But that's not the only thing. These ropes can extend a little, compress a little, shorten a little, lengthen a little. Yet to confer the stiffness of the bone, the rope is then impregnated with crystals of calcium hydroxyapatite. Nature chose calcium hydroxyapatite for certain reasons. It could have taken particles of iron, or glass, or stones, but no, it took calcium hydroxyapatite. And it put just enough of this mineral into the rope to give it those special material properties that make it stiff yet still flexible. That's one level. That's the material construction, or the material structure of the bone.

That material then is taken and threaded by God, if you will, through the eye of a needle. And then that needle is used to sew a material-a structure, a three-dimensional structure like a house, or a bridge, or a support for a light in a street-into this three-dimensional architecture that also has this property of strength. So when we talk about the"quality" of bone, I prefer to use the term that was actually first coined, I think, by Michael Parfitt, who is really one of my great heroes in the bone field, and that is bone"qualities"-the different material composition (the rope and the mineral), and then the three-dimensional structure of bone that confers its strength.

Do you want me to go on?

JB: No, I think that's a very good way to set the tone. You've got many wonderful publications, one of which really struck me was back in...I think it was 2006...in the New England Journal of Medicine on bone quality and the structural basis of bone strength.8 You talked a little in that article about the heterogeneity in the pathogenesis of bone fragility because I think most people think about bone fragility being associated with increased bone resorption, but yet when you showed that diagram in the article it was quite fascinating because the heterogeneity between bone formation in the osteoblasts and

osteoclastic resorption didn't directly correlate with fractures. So it seems like there is something else going on. Could you tell us a little bit about that?

"Flying" Through Bone

ES: Okay. When bone is built...bone is built by a machine. It is built by what I like to refer to as a"cellular machinery." Although people think of bone as like some hard"stuff," I think it's a wrong way to think about bone. Bone is a very complex structure that is made of these crystals, and if you could get a tiny space machine...You remember that movie? I can't remember the name of it, where the guys got shrunk down and they were then injected into a vein... Fantastic Voyage, I think it was called...20 years ago, probably. Anyway, if you could get a tiny airplane, you could fly into the bone. You could fly into one of the canals, just like the many freeways in the Los Angeles downtown area. And you could fly around these corridors and canals of bone that contain vessels and nerves and then they branch off to the left and the right, and so this maze or myriad of canals that form the canals inside cortical bone. It's called compact bone, but it's not really compact at all; it's just compact when you look at it from an airplane down. It really has all of these canals. These canals are made of surfaces. They have a surface, and on the surfaces, this is where the action is. The cells of bone that line those surfaces can become activated, so that when there is a tiny crack within the matrix of the bone itself and there is damage, that crack actually tears the nervous system of bone, which consists of osteocytes with their dendrites (with their tentacles). It is like the nervous system in the brain. These dendrites, once they are torn, they kill, they knock off the little osteocyte cells that undergo death by apoptosis. This is a very fashionable way to die. Anyway, so necrosis is out, apoptosis is in in the 21 st century, and these cells die. When they die, they send signals, and we don't quite know what those signals are yet. They send signals to the lining cells that form the walls of these many canals.

And then cells are recruited-the osteoclast and osteoblast cells are recruited. And the osteoclast cells start to dig down to find where the damage is. They target the damage, and nature has this way of repairing damage. The osteoclast cell, which is like going to the dentist, comes in, removes bone, removes the crack in the bone, then there is what is called a reversal phase (nothing much happens), then the osteoblast cells come in and they fill the cavity like a dentist, just filling the hole up with new bone, which undergoes primary and then secondary mineralization. In other words, crystals of calcium hydroxyapatite are deposited. These crystals then enlarge, and you reform the hole-you refill and reconstruct that hole that has been formed and fill it up.

The problem is that after about 25 to 30 years of age, this cellular machinery that removes old bone and puts new bone back becomes sick. Something happens to it. Either the holes that are dug are too big, or not enough bone is put back in the bigger hole, or both of them. And that's where the heterogeneity comes in. Some people dig bigger holes; other people don't. Some people put less bone back; other people don't. And you have a different pathogenetic mechanism from person to person that finally translates into fracture. We think,"Oh, everybody's got fractures. It must be the same cause." But it is not. And it varies from person to person. And we're still not very good at identifying the specific abnormalities-the cellular abnormalities-responsible for making fragile bones in one person as opposed to another. And once we get better at doing that, and once we get better at identifying whether some people have a decayed cortical bone full of holes, or a trabecular honeycomb architecture that has been decayed and destroyed, we can better target treatment in accordance with the specific pathogenesis in that individual. And I hope that once we do that, we'll be much better at preventing fractures than we are, because we're not bad at it, but we're not really great at it. And we're not really good at preventing those bad fractures, like hip fractures

and what's called nonvertebral fracture (all of the long bone fracture-forearm fractures, pelvic fractures, upper humorous fractures, ankle fractures); we're not that good at preventing those right now.

JB: For me, as a non-expert in the field, that raises a very interesting question. This is truly a blank slate question. It sounds to me, as you so eloquently describe this architecture of bone-I felt like I was on the Invisible Voyage, with you, there, that was really fun, actually, as we went into the trabeculi of the bone-I'm wondering...these cells that line these surfaces-this sounds almost like a model that comes out of vascular biology with endothelial cells lining the vessels, one-cell-thick...

ES: Exactly.

JB: Is this partly analogous to an endothelial dysfunction of bone?

ES: There are analogies. I agree that we could look at bone as a vascular structure. This is very complicated and I don't understand it. I'm a clinician. I'm not a basic biologist. Forgive my ignorance, here.

The process of bone remodeling is like the clotting cascade, but much more complex. It's not just two cells. It's not just a sort of two step with osteoblasts and osteoclasts. And it's not even a three step, with osteoblasts forming bone, osteoclasts resorbing bone, and then the other cells I talked about (the osteocytes that are buried in the bone) forming the nervous or the sensor system. These three cells are the three big ones, but then there are lots of other cells in the marrow and within the blood stream. The T cells, for example (the immune cells), that participate in the cascade, which renders damage when damage occurs. There is a cascade of cellular events that lead to the production of osteoclasts (osteoclastogenesis) and osteoblasts (osteoblastogenesis). And those cascades involve lots of cells, including vascular cells.

And so the coming together of vascular cells to the lining cells of the bone...these come together to form what is called a bone remodeling compartment. And there is communication between the vessel, which delivers precursors of both osteoblast and osteoclast cells to this remodeling compartment, which then targets the damage. It is very hard to discuss this without a blackboard and some slides, but I hope you sort of get this picture. But it is a very complex cascade of local cytokines, local cell differentiation, coming to remodel the bone to keep it new.

But again, as we age, that remodeling machinery that is so vital and healthy and can repair bone in youth, starts to become abnormal as we age, and particularly in women. With bone remodeling, with the loss of female hormone, and with the loss of female hormone in men as well, incidentally (because testosterone is converted to estrogen in men and estrogen is important in both sexes), with this advancing age and the rapid decrease of female hormone (estrogen) after menopause in women, and the slower decrease of testosterone and estrogen in men, we have abnormalities in the intensity of remodeling-not just the balance in remodeling with either increased resorption and/or decreased formation in that resorbed or excavated cavity.

New Drug Therapies Are Being Developed

JB: Now you've raised all sorts of interesting questions for me. Let's take this, if we can, one step at a time. First of all, cell signaling and activation through different altered gene expression profiles that are related to unhealthy bone. I know that Amgen is working on approval in the States of a drug that is a monoclonal antibody for receptor of NFkappaB ligand that is part of the signaling transduction pathway

that you are describing. Do you have any sense as to whether this going to be a major breakthrough?

ES: Yes, I think it is. I think it's a great breakthrough. I'm a co-author on one or two of these papers, and I work and consult with Amgen, as I do with other companies, and they are a very exciting company. They are very innovative.

When we start to understand the physiology and the pathways of bone, which I think has been one of the major contributions of genetic research (to identify novel pathways), the textbooks, as you and I knew them when we were kids, are being completely rewritten. It's no longer that bone is bone, or the brain is the brain, or the liver is the liver. We now recognize that bone is regulated by brain, and that bone, itself, regulates insulin secretion, for example. And so, everything is being smashed to pieces, and it's fantastic. You can either embrace this new information or be fearful of it and say,"Oh my God, I'll never know anything." Well of course we'll never know anything. It's infinite in its complexity.

Coming back to RANK ligand, genetic research has recognized that this RANK ligand pathway, that a protein that is present on osteoblast precursors is like a key, and it fits into a keyhole on precursors on osteoclasts that switches these keyholes on, and these osteoclasts differentiate to become Pacmen, and they start eating up the bone. So here's a drug-the antibody to RANK ligand-that in its essence, stops the key from going into the keyhole, and stops the synthesis of the osteoclasts, which is a very novel way of stopping bone resorption. Because the other way that we have is the family of the bisphosphonates, which kill osteoclasts once they are formed. Mind you it's not the only way they work. They work in many, many different ways. But that is one of the main ways that the osteoclasts, that the bisphophonates...you take the bisphosphonate tablet, then it goes into the bone (it's absorbed onto the bone). The osteoclast comes, resorbs some of the bone, eats it, then it takes in the bisphosphonate that essentially knocks it off. So we have different mechanisms of action. As we learn newer and newer pathways of the cellular biology, if you will, of bone resorption and bone formation, this gives us doors into finding drugs. And another one drug that is being developed is the anti-sclerostin antibody. Do you want me to go on about that?

JB: Before you do that, let me just make sure we check in on your very eloquent discussion of RANK ligand monoclonal antibody. I think what that would suggest, obviously, is that there must be something going on in the bone remodeling unit that's related to activation of the inflammatory cascade that is suppressed by RANK ligand antibody. And that that might then also say why when women lose estrogen or men lose estrogen that there is some different expression patterns of various cytokines and NFkappaB that relates to activation or, let's say, taking the foot off of the brake and allowing this inflammatory process to occur. Does that, in part, say something about the mechanism of estrogen as an anti-resorptive agent?

ES: Yes, maybe. This is a little out of my expertise. I'm a little reluctant to start talking about inflammatory cascades and so forth. That's outside my training. But other than to say that there is no question that with estrogen deficiency, various inflammatory local factors or cytokines, interleukins are released, and they are part of this cascade leading to increased bone remodeling and bone resorption leading to the loss of bone. But I don't want to go there.

JB: That's great. That's fine. Does the 1,25-dihydroxycholecalciferol play any role in this process, as we are describing it?

ES: Yes. It may be. There are systemic factors like parathyroid hormone, vitamin D metabolism that may be contributing. I don't think that these are major factors because bone remodeling is time and space dependent. In other words, it is focally specific. You can take one point in bone, which is quiescent (quiet-nothing is happening), another point in bone, where there is resorption, another point where there is a different phase of resorption, another point where there is a different phase of resorption, another point where there is formation. These are locally regulated events, and the precise regulation of these local events is, again, very point-specific. I'm not sure that systemic factors would explain that very well.

Controversy About Bisphosphonates and Necrosis of the Jaw
JB: Okay. Let's go back to your bisphosphonate. There has been-at least from my reading-some concern about the effects on osteoclasts and mandibular necrosis. Is that a real clinical concern or is this just an artifact?

ES: With prolonged bisphosphonate therapy and repeated therapy, particularly in patients with cancer who are given lots of bisphosphonates, often to suppress hypercalcemia of malignancy, after prolonged therapy, there have been case reports of what's called osteonecrosis of the jaw, which generally follows a tooth extraction. Is it real? Yes. Is it related to the bisphosphonates? Probably. Is it common? No. Is it common in the postmenopausal osteoporosis? No. Has it been exaggerated by the dentists? Yes. Is it causing problems for patients and doctors? Yes, it is. It is a real event, but it is very uncommon. It is doing more harm than good with this broad advertisement or discussions that are really disproportionate to the problem. The mechanisms are not understood; they could be effects of bisphosphonate actually on the endothelium in the mouth and altered healing within the socket of the tooth.

SERM Connection to Bone
JB: I think that's very helpful. Let me move onto SERMs because this is another area, obviously. You've had some very interesting tissue seal activity, something like tamoxifen (its effects on ERalpha and ERbeta and its differential effects on breast versus bone). Could you tell us a little bit about the SERM connection, because that seems clinically very interesting?

ES: Yes, it is interesting. The overwhelming problem with the SERMs is that they do not reduce non-vertebral fractures, okay? That's it. There are now 8-year follow-up studies with raloxifene. The studies are very well executed and designed, and there is no evidence that the SERMs reduce non-vertebral fractures.9,10 More recently investigated SERMs confirm this. The great hope was that lasofoxifene and some of the other newer SERMs that have been studied would reduce non-vertebral fractures, but this has not been shown to occur.

Why is that important? It's important because in the community, the majority of fractures are non-vertebral. Our history came from the genius Fuller Albright, who first recognized vertebral fractures in postmenopausal women in 1941, about 70 or so years ago. Since that time (the next 30 years), there was enormous concentration on the pathogenesis of vertebral fractures. So much so that when you say to someone,"Do you have osteoporosis?" The immediate thought is,"Am I at risk for a vertebral fracture?" And that's wrong. That is the 20th century view of osteoporosis and we have to change it. The burden of disease is non-vertebral fractures, and therefore we need drugs that reduce both vertebral and non-vertebral fractures. The SERMs are very interesting drugs, there is no doubt. But they do have these opposite effects: they reduce the risk of breast cancer, they do reduce the risk of vertebral fractures, and that makes them very attractive (and they also have very anti-lipid effects that have go some benefits but

not others). So they are interesting drugs, but I'm not sure that they are the right drugs for this field.

JB: Is the difference between the vertebral and non-vertebral fracture related to the differing trabecular versus cortical bone physiologies?

ES: Yes. That's a very excellent question. The short answer is yes. Eighty percent of the skeleton is cortical; 20{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} is vertebral. Some of the work that I have been doing that has been driven, actually, by one of my students (his name is Roger Zabaze-brilliant young man), has been directly looking at cortical bone and making the point that the loss of bone with aging is mainly cortical, not trabecular.11 A woman halves her skeleton during aging; she loses half of her skeletal volume or skeletal mass. Now only 20{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of the skeleton is trabecular. There is no way that this can all be trabecular bone. Most of the trabecular bone that we have is lost by about the time that we get to 75-80 years of age. And after 65 years of age, most of the loss of bone is cortical, and it is coming from what is called the intra-cortical compartment. This is Roger's work. He has shown that these holes-these cavitations within the cortex itself, which arises from the Haversian canals that I described to you before (all those canals we were flying through)-they are the source, and these holes enlarge, so you end up with a cortex called compact bone that, by 80, looks exactly like a sponge when you look at it in cross section. That's why the orthopedic surgeons are having such a tough time keeping a hip prosthesis in when they replace the hip-keeping it firm-because there is nothing to hold onto anymore. That bone is a sponge. It ain't compact bone any longer.
JB: If we were to start looking at the clinical approach that you have to deal with everyday, given that we are still imperfect in our knowledge and probably will be for some time with the complexity of this field, how do you assemble this information in designing the program for the patient.

ES: That's a very good but a very tough question. I think firstly we need to think about bone as a structure, as a complex three-dimensional structure, and we need to have methods to define the abnormalities in it in specific terms. In other words: the size, the cortical thickness, the area, the number of holes, the number of trabeculi, the thickness of the trabeculi, the bone remodeling, the resorption markers, the formation markers, and whether a patient has a fracture or doesn't have a fracture, and take the clinical and biochemical and structural features and put them together into a matrix where we can define risk.

What we do in the 21st century so far is that we are using bone densitometry, which I think is a useful method, but it's not the be all and the end all. For example, most fractures in the community occur in people with bone density above minus 2.5 T-score. In other words, in people who don't have osteoporosis, as we define it using the bone density machine. We've got to take the red pill and get out of the matrix of the BMD machine. Many of these people who are breaking bone who have normal bone density actually have high porosity, or architectural abnormalities. We need to identify those abnormalities and we can then target treatment to those people who have it. We have to learn how to investigate patients more completely than we are currently doing, and then we will be able to target treatment to those, and, of course, avoid treating people who may have osteoporosis by the bone density machine, but that simply may be not osteoporosis at all; they've just got smaller bones that are measured by this silly machine and it looks like their BMD is low, but in fact their bones are just small. You follow what I mean?

JB: Absolutely.

ES: Okay. The machine we are using is okay. It was a good beginning, but it ain't where it's at. We need much better technology. And we are getting there, you know. We are getting this technology. And we are getting better measures of bone remodeling. I think that the future is bright. There are advances. And you can bad mouth all of these drugs like the bisphosphonates and so forth, but you know, they are pretty good drugs. And by and large, for the majority of people, they are pretty safe. We just need to learn how to use them better.

JB: When you do your serological evaluation, is there a panel that you find most useful in pulling out some of these markers or is really there is no discreet biomarker panel that would be better than any others?

ES: This is a little out of my area as well. I'm not an expert. My buddy, Pierre Delmas, was the king of that. You can use a range of bone markers. A bone resorption marker such as NTX, or bone formation marker such as osteocalcin, or better still, P1NP. And we are still on a learning curve with these markers. There are still problems with them. The blood has to be taken properly. It has to be taken fasting, first thing in the morning. It has to be separated quickly. There has to be a lot of meticulous care to get the reproducibility that we need (the within-patient reproducibility that we really need) to say,"Okay, we can use the marker. This guy or this woman is a high bone remodeler. Let's treat her with drug X. This person is a low remodeler. She's not losing much bone. Let's leave her alone right now." We are getting there, and we are better at it, but we've got to be much more meticulous about how we sample than is routinely done in day-to-day clinical practice.

JB: Very good. There is one last thing. By the way, you have hit on so many extraordinary little bits of wisdom and we could follow each one of these, probably, for hours. I want to ask one follow-up on something you were speaking to earlier, which is this throwing out the physiology textbooks, where we have siloed each individual bit of our anatomy and physiology as if they are independent and separate and now we've looked at things more as a systems biology approach to physiology. There is an emergence in the literature that I have seen around bone, specifically, of the gut connection to bone physiology. Now we are seeing things on serotonin and the Wnt signaling pathway and through the lipoprotein receptor 5 polymorphisms. Is this something that looks like it is going to stand up?

ES: Yes, it's fantastic and the guy to talk to-you should ring him-is Gerard Karsenty. He's at Columbia. I think he is one of the great-really a genius-in bone. You should talk to him. I think this is his shtick, you know. You should talk to this guy, not me. This is out of my league.

JB: I don't think there's anything out of your league in this area from the reading of your papers, but you are being very kind.

Links Exist between the Gut and the Brain and Bone Metabolism

ES: It is out of my league. You talk to him. I mean, he's the guy that has done the work, that has put it together, and he's a visionary. He has found the link between this peptide (uncarboxylated Gla or osteocalcin-this particular form of osteocalcin) and that it increases the insulin sensitivity and secretion. He's also found the link between the gut and the brain and bone metabolism. He's the main man! Talk to him.12,13

JB: Obviously you hit on vitamin K indirectly, there, with the uncarboxylated versus carboxylated Gla. There is a lot of interesting nutritional endocrinology, it appears, in this field as well.

ES: That's right, and he's actually done some work in that as well. This is the beauty of biology. As the world is infinite in its galaxies outward, it is also infinite in its galaxies inward. Either we embrace it and say we're never going to know anything-and we don't, we don't know anything-but we're going to see little bits of the magic of life. That's what it is: magic.

JB: Beautifully said. As we close, is there anything, to clinicians, that you would like them to have as a takeaway thought? It's hard to summarize all of your work-270 plus papers and chapters...

ES: To clinicians I would say,"Don't believe anything. Don't believe anything I've said. Don't believe anything you read. Just learn to be skeptical and embrace skepticism." I think it is the pathway to progress. That's the fun of science: not believing your friends, and not believing anything in a conference. That is how critical reading is absolutely crucial to survival of science and medicine as a scientific method. Without that proper design-the proper execution of studies-we know nothing, and we can't believe anything we read. And it doesn't matter where it appears. It doesn't matter the name of the person. It doesn't matter if it is The New England Journal of Medicine. That does not make it right. What makes it right is reading the method section and saying,"Yes, these guys designed the study right, they asked the right question, they answered and executed the study properly, so therefore I can believe what they have said." But if they can't-if they haven't done it right, if there are 50{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} dropouts in the trial, and you do calcium and vitamin D studies but everybody's calcium and vitamin D replete-you can't even test the hypothesis that calcium deficiency or vitamin D deficiency causes the disease much less test whether replacement of calcium or vitamin D has any benefit, because you have a population that wasn't calcium- or vitamin D-deficient in the first place, you can't make any inferences. And that's an example where the calcium and vitamin D field completely breaks down. I've got a paper in press where I go through all of that. I think it is the American Journal of Kidney Diseases. I've gone through that literature pretty carefully. My message is critical reading is the future.

JB: I can see why the International Osteoporosis Foundation president, Professor John Kanis, said about you,"Dr. Ego Seeman is among the most respected thought-leaders in the field of osteoporosis research and is renowned as a scientist, educator, scientific editor, and speaker." I think you fulfilled all of those in this brief discussion. I want to thank you very, very much, Dr. Seeman. It is clearly obvious that medicine is built on the shoulders of people who have this critical thinking, as you have exemplified. Thank you very much for being available all the way down there in Melbourne. We really appreciate your work.

ES: Thanks very much. Thank you for that. Goodbye.

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