September 2007 Issue | Jeffrey M. Smith Author

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Welcome to *Functional Medicine Update* for September 2007. This is going to be an interesting and unique issue of *Functional MedicineUpdate*. We are going to focus on a topic that at first blush you might not think is that clinically relevant, but hopefully, by the end of this issue, we'll demonstrate how interesting it is to look at some aspects of chronic disease through the genetic expression lens.

What I really want us to do throughout the course of this particular issue of *Functional Medicine Update* is to open our minds to the possibility that many of the conditions we see in patients who present with chronic symptoms and disease are the late-stage manifestations of altered gene expression patterns. These altered patterns modify metabolic function and ultimately become expressed as the phenotype of a particular illness or disease.

I know this upstream-type of perspective is different from what we are often taught about disease (through its diagnostic specification). I think the confluence of altered metabolic function across wide ranges of cell types ultimately gives rise to the expression of what we call disease. I would like to provide a few examples of how this perspective can be of some value in evaluating patients early on and how it relates to where they are heading with the nature of the expression patterns that ultimately express health and/or disease.

Processing Information through Sensing Mechanisms
The information we are getting from the world at large that is picked up by our sensing mechanisms is vast. It can come as electromagnetic information. It can come as chemical information. It can come as information that we probably don't even know yet exactly how to quantify-information that has some type of an intuitive "knowingness" that you can't quantify in terms of a frequency or a wavelength, but you know that it is real.

We hear more and more people talking about synchronicity and that there are no such things as coincidences. Events that appear to be random can occur so frequently that it is beyond random to understand how certain observations are made that are synchronous in nature. These constructs can give us pause. Maybe we are picking up information from all sorts of compartments and we are translating it into physiological, neurochemical, immunochemical, electrochemical activity in our body that ultimately gives rise to messages that are signaling to our genes how to express their response to changes in the environment. This is the molecular action (or a physiological or cell biological connection) between the mind and the body-the construct of a gene expression/gene environment relationship with our outside world and how we perceive it.

We certainly know a lot about tactile sensations and how they get translated into neurological function--those that we can see with our eyes or hear with our ears. The movement of air across our

tympanic membranes and the set-up of sensory perception that trigger certain changes of membrane potential that we call an action potential give rise to a neurological function that ultimately can regulate chemical functions through the release (in our hypothalamus-pituitary-adrenal axis) of a variety of different messenger molecules. These molecules ultimately control action at a distance in our body by regulating gene expression and cell biological function away from the source where we actually received that information (our eardrum). These are interesting parts of what we learn through our experience in life and through the study of anatomy and physiology, but when we translate it down into the cell level, it takes us to a different lens in evaluating, the functional changes in organisms over time.

An Observation of Olfaction and Gene Expression

While reading a recent issue of *Science* magazine, I was struck by how much we are learning concerning the very complex relationship we share with our outside environment.[1] An article was published that was looking at the lowly fruit fly (*Drosophila*n *melanogaster*). I thought this was a very interesting example of how, in an animal, information from the world can influence its gene expression.

The authors of this article describe how the lifespan of the fruit fly can be influenced by the ability of the insect to smell a food that it likes-not even taste the food, but smell the food. The fruit fly likes yeast. In this case, smelling the aroma of yeast without actually having the ability to eat it influences (through olfaction) the expression of genes in such a way as to modulate what are called longevity genes (the genes that are associated with extending lifespan of the animal). It is a very interesting observation: something that didn't even touch the nerve as a direct molecular interaction (this is a odorant), caused some kind of a receptor interaction and sent a signal at a distance through the olfaction system to regulate gene expression across the body of the animal to upregulate longevity genes (the so-called SIRT-like that are silent inducers of signal transduction).

There is a lot yet to be learned about how we regulate our function in response to changing environments, even odorants. Are there certain fragrances or odors that the human picks up, beyond pheromones, that modulate gene expression? What about aromatherapy? What about the way some people feel good when they smell certain fragrances? How does that influence not only the sensory media perception, but maybe other things that relate to stress response and gene expression related longevity and stress management genes? So it is a very interesting conceptual framework that I want to build into our discussion that we'll take from this esoteric level and bring it down into a more clinically applied level.

To hang just for a moment longer on this level of esotericism so I can get the right framework built to look at the clinical implications, I'd like to talk about the translation of information by these systems to our genes to influence a process we call genetic expression. The book of life is coded in our genes, of which there are (in humans) 30,000 plus, that are not all expressed simultaneously. They aren't all being read simultaneously; if they were we would be a mess. They are read selectively, but not one gene at a time; they are read in families that are controlled by orchestrating components, and its these components that ultimately control the expression of the functional genes. So, we get these very interesting ways that genes are organized and expressed. Some of the sites where the components that are involved with the organization of how genes are expressed are found turn out to be within what used to be called the "junk DNA" of our genome.

Regulatory Sequences Control the Expression of Genes

What an interesting term, right? Because we didn't know what this did we thought it was a relic from time

gone by with no real importance in terms of coding for our characteristics, so people called it junk DNA. But now we find that within that region of the genome, which in humans is one of the most significant parts of the genome, resides the regulatory sequences that control the expression of these genes. We get genetic expression differentially in different tissue types under different environmental conditions; it is not just randomly expressed.

The Trilogy of 'Omics

That gives rise to what we call the proteomic message, or the production of proteins that are unique to that cell in response to that stimulus. This then translates itself into different metabolic functions, and that changes what is called the metabolomes. I have traditionally referred to this as the "trilogy of 'omics"-the three 'omics: the genomics, the proteomics, and the metabolomics. This trilogy regulates our phenotype and how that cell, tissue, organ, organ system, or whole organism responds, looks, acts, and feels.

Metabolomics is the third of the three 'omics and it is what we often study on wall charts and memorize for tests in our biochemistry class. It has to do with the Krebs cycle and enzymes. It has to do with glycolysis and aminolysis and all the various catabolic and anabolic pathways in intermediary metabolism. And obviously, metabolomics is tied together with the proteins that are available as enzymes and structural proteins to manifest the control of the metabolic activity. Those enzymes are regulated upstream of the actual gene. So, here we go again, the trilogy of 'omics: genetic expression leads to active proteins, which get post-translationally modified, which then control metabolism, and ultimately, from that, resides the tens of thousands of various molecular species that are part of the metabolome.

New Analytical Technologies

Individuals are now starting to evaluate, using complex analytical profiling, all three of those aspects of our phenotype of our cell: the genetic expression components, using gene array technologies; the proteomics conceptualization, using proteomic chip technologies; and lastly, the metabolome. Integrating these together in an information system requires huge data management mining to try to understand the complex way that these components interact to give rise to the function of what we call the phenotype of the cell.

There is an interesting paper that appeared in *American Genomics/Proteomics Technology*authored by Dr. Chris Beecher titled "Metabolomics: A New 'Omics' Technology."[2] It is about how these intermediary metabolites from wall charts that we studied in school but have forgotten can be measured using different types of analytical technologies and biological fluids. These would be things like GC/MS or LC/MS technologies. The data can be pumped through a complex data set analysis system that is the nearest-neighbor-type of analysis, or artificial intelligence system. This can give rise to understanding these patterns and relating the metabolic patterns (which are not linear, but are complex systems) back to that of the proteomic and the genomic expression pattern. You can ultimately start understanding at a much deeper level how a particular cell (or tissue, or organ, or organ system) is responding to its environment. This is part of the systems biology approach towards medicine that is an underpinning to functional medicine.

We are starting to see nutritional proteomics develop. Animals are given specific diets, the proteins that emerge as a result of genetic expression are analyzed, and then the metabolites are analyzed. This process allows you to start getting an understanding of how various nutrients can influence the regulation of metabolic function through this trilogy of "omics" (the genomic expression, proteomics, and ultimately

metabolomics). I am now quoting from a recent paper, "Nutritional Proteomics: Methods and Concepts for Research in Nutritional Science," which appeared in *Annals of Nutritional Metabolism* in 2007.[3]

This is still in its early stages of development. The point I am trying to get you to understand is that we are starting to see tools emerge that will allow us to explore many of questions that have been around for at least 30 or 40 years about how things in our environment influence our genes and our phenotype, and modulate our health and/or disease patterns. This will no longer just be open for speculation; we'll be able to actually start exploring this.

With all of that as a background, let's now take this discussion from the esoteric to the clinically applied. Let's use a couple of examples that we might be more familiar with.

Let's look at hypertension, which I think is a very big problem in our culture. The major form is called essential hypertension, or idiopathic hypertension, meaning it has no known specific etiological agent that it is causing it. It is influenced by a complex shift in our metabolic function that gives rise to changes in vascular endothelial compliance, leading less to vasorelaxation and more vasoconstrictive responses, which then elevates our blood pressure.

We have learned from the fundamentals of basic nutrition that cations in the diet play a role in the pathogenesis of hypertension. Certainly we have hormonal systems in the body that are there to regulate cations, such as the monovalent sodium and potassium, as well as the divalent magnesium and calcium, which all play roles in the regulation of pressure and vascular endothelial function.

In a recent review that appeared in the *New England Journal of Medicine* titled "Sodium and Potassium and the Pathogenesis of Hypertension," it was pointed out that high blood pressure/hypertension affects approximately 25 percent of the adult population worldwide, and its prevalence is expected to increase by 60 percent by 2025, when a total of 1.56 billion may be affected.[4] It is a major risk factor for cardiovascular disease and it is responsible for the most deaths worldwide. Primary hypertension, also known (as I said) as essential or idiopathic hypertension, accounts for about 95 percent of all cases of hypertension, and therefore it is really a functional somatic syndrome (to come back to our discussion we had in September of 2007 in *Functional Medicine Update* where I was defining, from the article that appeared in *The Lancet*, what a functional somatic syndrome is).

It is a condition that is psychosomatic, right? It ties the brain and the body together, and that is essential idiopathic hypertension. It has no single, organ-specific cause, but rather it is a complex, physiological dysfunction that we might say has its root origin in the alteration of the translation of messages from the environment through the HPA axis and through the gut, ultimately into-what? Altered gene expression, altered proteomics, and altered metabolomics at various tissue levels that produces what we see clinically as elevated blood pressure.

I think you can get my reasoning here that the blood pressure doesn't elevate just because it doesn't have another thing to do. It does so because it is influenced by these altered cellular functions that occur from a change in gene expression with a changing environment.

That leads us to the question of the dietary environment and hypertension. What about dietary sodium and hypertension? As you probably know, primary hypertension and age-related increases in blood pressure

are virtually absent in populations in which individual consumption of sodium chloride (salt) is less than 50 mmol per day. These are the people who don't use salt in food processing and they don't salt their foods. In fact, in the historical record, people who lived inland from the oceans-one of the major risks they had was sodium deprivation back in the early days of human history because salt was not prevalent or common. Individuals could get into a sodium deficiency situation and it was a very significant problem. That is why salt was so highly valued as a trading commodity in early civilization. We clearly know that's not the case today with the prevalence and plentiful nature of salt, which ends up being a food additive in our processed foods, in which now we start to see tremendous increase in the sodium intake (approximately 9.9 grams [170 mmol] of sodium chloride is excreted per day in people in the 32 countries that were recently studied).

So we are starting to see much higher levels of sodium intake. Mean systolic blood pressure is about 5 mm Hg higher and diastolic pressure about 3 mm Hg higher when sodium intake was increased by 50 mmol per day. So we know there is this connection, and it is even a stronger connection between sodium and blood pressure in individuals who have a genetic propensity towards what is called salt sensitivity. These are individuals who have marked elevation of blood pressure with even modest increases in sodium intake.

So we have a combination of high sodium diets and low potassium diets (potassium is the other problem because potassium is higher in vegetable foods). We have cut down vegetable foods and increased salted processed foods, so the ratio of sodium to potassium in our diet now is extraordinarily high. We have almost completely reversed the ratio of sodium-to-potassium that was found in our indigenous diets, which were low sodium/high potassium-now they are high sodium/low potassium-and that then influences the renin-angiotensin system and how it influences through the adrenal hormones the retention of salt and retention of fluid, which then ultimately causes an increase in blood pressure and altered endothelial nitric oxide output, lowered vasodilation, and increased risk to high blood pressure.

So, this interesting story is starting to emerge that connects together food to gene response to cell signaling and ultimately to hormonal messages, which regulate stress response. A high-salt diet might be considered, by this definition, kind of a stress factor because it encourages a response at the renin-angiotensin-aldosterone system, that then looks like a stress response and is associated with vascular dynamic changes and increased blood pressure.

With all of that in mind, you might ask what you should do to lower relative risk. One thing, of course, is to lower processed food intake (salty snacks). That seems like a very easy first step. Another step is to increase vegetable products, particularly fruits and vegetables in their whole form because they are relatively rich in potassium. Fruits are higher in sugars and vegetables are not, so generally we are talking about increasing vegetables. Vegetable juicing is very high in potassium. Through vegetable products, you can get a much higher level of potassium and a much lower level of sodium (as long as you avoid the salted, canned variety of vegetables).

So that is one part of the story. Another part of the story is magnesium. We recognize that magnesium is another important vasorelaxing divalent cation. Magnesium is found in green leafy vegetables. Magnesium is associated with the chlorophyll molecule, and chlorophyll gives rise to the color green in plants, so green plants are generally high in magnesium. So the potassium and magnesium components, along with a lowered sodium intake have a salutary effect upon blood pressure. Again, I want to

emphasize there are genetic uniquenesses to this sensitivity, and there are some people that are extraordinarily sodium sensitive for whom the modification of their sodium/potassium ratio in their diet has a dramatic effect on altering their blood pressure.

What about substances in the natural plant food world that may have agents that regulate blood pressure? Are there things that would either increase or decrease blood pressure that are found in the plant world? I think the most interesting example of this, and one that we all learn in school but sometimes forget, is the most studied botanical medicine and flavorant that has historically been discussed in the world's literature, going way back to the Yellow Emperor's handbook; I'm talking about licorice. As you probably recognize, this is a very, very interesting story-the whole licorice-blood pressure connection.

Glycerrhiza glabra, or licorice, has a very long history of being known as an agent that will modulate stress and will have an impact upon blood pressure and arousal. Licorice contains probably a thousand different phytochemicals, some of which have extraordinarily different effects from one another. We shouldn't jump to a conclusion to say just licorice in and of itself. Some people call licorice by different forms, like the deglycerinized licorice. We know the glycerrhizen within the licorice plant has some blood pressure-regulating effect, so some people talk about DGLA or DGL (deglycerinized licorice) as having a different effect, obviously, on blood pressure than the full licorice plant. I want to make sure that we recognize different phytochemicals can have different effects on this trilogy of 'omics (this translation through genetic expression into proteomics and ultimately into metabolomics and how that influences, differentially, specific cell types).

Let's go back and examine licorice as an agent that modifies HPA axis function (hypothalamus-pituitary-adrenal function) and ultimately can have an effect on blood pressure. I'll take you back to the *Journal of Clinical Endocrinologyand Metabolism* in 1978-an article that was principally authored by MT Epstein from the Princess Margaret Hospital in Christchurch, New Zealand that talked about licorice raising urinary cortisol in humans.[5] This was an interesting paper in which the authors discussed individuals who elected to consume 100 to 200 grams of whole licorice candy (these were 13 normal volunteers and they consumed this for 1 to 4 weeks) and had an assessment of their HPA axis function made before, during, and one-week after a cessation of licorice ingestion. Urinary cortisol excretion was found to be more than doubled in 10 of the 13 subjects when they were taking the licorice, and some excretion rates were found similar to those that had Cushing's syndrome, which is, I think, a very interesting observation. Urine cortisol excretion remained significantly elevated above controls for at least one week after licorice was withdrawn, and despite these increases, urinary steroid metabolites were not affected (those are metabolites of cortisol). Plasma cortisol and HCTH levels were unchanged, and there was a normal diurnal variation of plasma cortisol. The direct intraadrenal infusion of the active mineralocorticoid component of licorice, which is this glycyrrhetinic acid, in two sheep who had autotransplanted adrenal glands failed to stimulate cortisol secretion acutely. It was concluded from these early studies (this is, again, I want to emphasize, back in 1978) that changes in cortisol excretion are not a result of adrenocortical stimulation, but more likely a represented change in the renal handling of cortisol, according to this article in 1978 in the *Journal of Clinical Endocrinology andMetabolism*.

Later, in a very nice review paper that appeared in 1994 in *Endocrinology and Metabolism Clinics in North America*, Brian Walker and Christopher Edwards talk about licorice-induced hypertension and syndromes of apparent mineralocorticoid excess.[6] It looks like these people have hyperaldosteronism who have this licorice impact upon their blood pressure.

The reason I'm going through this is this specific example illustrates how agents in our world can influence-in a genetically unique way-a messaging system that translates the activity of specific molecules (in this case, licorice-the glycyrrhetinic acid) into a modification of gene expression, to a proteomic modification, and ultimately a metabolomic modification at a cell-specific level that regulates, in this case the hormones that control sodium-potassium balance, and ultimately electrolyte regulation and blood pressure. So this is a specific example of a more general theme as to how our diet and our lifestyle and things that we are exposed to can be transduced or translated into functional changes in the individual.

The good news about that is if you can identify these agents that are inducing a stress response (meaning something that is causing an adverse response) by modulating or taking away that stimulus, you can have, then, an anti-stress outcome (meaning it gives you the potential for therapy). Without relying on drugs to try to neutralize that effect, what we are doing is taking away the precipitating agent that changes the function of the individual. So it is a different strategic approach; this is the functional medicine model.

Looking, again, at licorice specifically in this article that was in *Endocrinology and Metabolism Clinics*, the authors point out that the use of licorice and its hydrolytic product, glycyrrhetinic acid, dates back to at least 1000 BC, where stores of the root were found in tombs of ancient Egyptian pharaohs, and its therapeutic activity was known for a wide variety of elements and was extolled in the writings of the Greeks, the Romans, and the Chinese. Licorice was rediscovered in Europe in the 15th century and became an established treatment for dyspepsia, and so now we recognize that as a confectionary agent (as a flavoring agent), it finds itself within a variety of different foods.

A Case of Licorice Sensitivity

We actually had an interesting case history a little while ago-I think it was 2 years ago-in the Functional Medicine Research Center. An individual (an older-age gentleman) was slated to have surgery for a hernia, but his surgeon was not going to perform surgery until his serum potassium and sodium ratios normalized. He was told he was a surgical risk in the absence of getting those normalized because of potential adrenal-related difficulties. He was very worried, his hernia was getting worse, and he did a consult with us. One of the questions we asked him was, "Are you consuming licorice?" And he said, "Well how do you know that? How do you know that that is my favorite before-bed snack? I take licorice every evening because it is kind of just a nice thing that makes me feel good and I sleep better?" So we encouraged him to discontinue the use of his licorice for awhile. His serum potassium ratios normalized. He went ahead and had a very successful surgery, and the outcome of this particular story was that he was one of those licorice-sensitive individuals; it had an adverse effect on his electrolytes and also had an effect on his blood pressure.

When licorice is administered therapeutically it results in the chemical features of primary aldosteronism. Clinical manifestations include those of sodium retention, so you get elevated sodium with peripheral edema, breathlessness, and hypertension potentially resulting, and hypokalemia, a low potassium polyurea due to the nephrogenic effects that seem to mimic that of diabetes or proximal myopathy. Biochemical markers for the excessive activation of the minerocorticoid receptors in the distal nephron associated with excessive licorice intake include hypokalemic alkalosis and suppression of plasma renin activity.

It is very interesting to see how this effect of licorice-induced minerocorticoid what-appears-to-be excess

may be very individualized in its response, possibly showing genetic uniqueness, this concept of biochemical individuality that Roger Williams talked about. There seems to be a paradox of renal minerocorticoid receptor specificity associated with this particular observation. The classic model of corticosteroid action in the kidney, aldosterone is known to bind a minerocorticoid (or type I receptors) which have a restricted distribution in the distal nephron. In contrast, cortisol binds to glucocorticoid (or type II receptors) which have a ubiquitous distribution and more variable effects on tubular function. It is central to the model that there is little cross reactivity between the glucocorticoid and the minerocorticoid receptors. So your cortisol and your aldosterone receptors seem, by a traditional thought process, that they don't interconnect or have cross-talk, so cortisol does not activate minerocorticoid receptors. However, one would predict that the specificity of minerocorticoid receptors for aldosterone would be dictated by this binding efficiency of its enzyme, but with regard to the case of licorice, it appears as if there is some cross-talk between the cortisol levels and the aldosterone receptors, so you get this kind of interesting paradox between individuals that have connection through genetic modulation of an enzyme which is 11β-hydroxysteroid dehydrogenase, and polymorphisms of that enzyme apparently make individuals more sensitive to licorice-related hypertension and hypokalemia.

Again, what we are seeing here through this case example is a very interesting case of uniqueness, likely related to altered genetic expression affecting proteomics, which then downstream regulates metabolomics, and, in this case, can induce, then, altered monovalent cation distribution and blood pressure. I hope that you take away a couple of things from this discussion. Number one is the connection between licorice and blood pressure and licorice and the sodium-potassium balance; secondly, the uniqueness of how that affects individuals; and third, the kind of general example/case that comes out of this specific example about how agents in our environment (even small molecules like glycyrrhetinic acid) can influence cellular function. You can actually induce this not just in humans but in animals as well. *Glycyrrhiza glabra*, or licorice, when administered to animals at high levels, is demonstrated to have influence on the adrenal-kidney-pituitary axis.[7] We see a generalized effect of these bioactive molecules.

With that in mind, what is another thing that can influence endothelial function, vasorelaxtion, and blood pressure? Of course, that is insulin. We know that high levels of insulin have an impact on endothelial nitric oxide output, on endothelial dynamics, and on the regulation of blood pressure. Certainly this is one of the hallmarks of hyperinsulinemia and insulin resistance syndrome: marginally elevated blood pressure and increased levels of plasminogen activator inhibitor 1 and how this influences, ultimately, electrolytes with increased sodium/lower potassium and what appears to be an adrenal stress, so to speak, relative to insulin resistance and metabolic syndrome. And so you might ask the question, "What about medications that are used to manage dysinsulinism, or type 2 diabetes associated with insulin resistance? Like the PPAR (or peroxisome proliferated activator receptor gamma agonist drugs) such as rosiglitazone or piaglitazone?"

A Controversial Article about Rosaglitazone Use in Individuals with Type 2 Diabetes or Insulin Resistance/Hyperinsulinemia

There was a recent paper published in the *New EnglandJournal of Medicine*-quite a controversial paper, I might add-that was a meta-analysis, authored principally by Steven Nissen and Kathy Wolski, that talked about the effect of rosaglitazone on the risk of myocardial infarction.[8] This was a meta-analysis study in which it was said that there was an increased incidence of cardiac risk to sudden cardiac events as a consequence of the taking of the rosaglitazone PPAR-γ agonist medication that is used for people who

have type 2 diabetes and even those who might have insulin resistance/hyperinsulinemia.

The article goes on to point out that one potential contributing factor may be the adverse effect that this drug has on serum lipids. It is now recognized that these PPAR-γ agonists, such a rosglitazone, have very complex biological actions and effects, not just single actions, resulting from the activation or suppression of dozens of genes (so a single molecule has an effect upon multiple genes). This is not just a class effect, because it is interesting that piaglitazone appears to have a more favorable effect on lipids, particularly triglycerides, than does rosaglitazone. The use of blood glucose measurements as a surrogate endpoint for the diagnosis and treatment with these drugs is probably not warranted because glucose is not a very sensitive measure for really what is going on at the cell physiological level relative to these PPAR-γ agonist drugs. We probably should be looking at things like LDLs and HDLs and even the apolipoproteins, like apolipoprotein B and apolipoprotein A, which are related to atherogenic lipoproteins, and the apolipoprotein A-1, related to HDL assembly. So, I suggest the apolipoprotein B-to-apolipoprotein A-1 ratio to be less than 0.6 to 1, and that above 7.7 to 1 (which is often seen in the insulin resistant patient) there is much significant increase in atherogenic risk and sudden coronary event risk.

What has been said is that single molecule rosaglitazone may have multiple effects on genes, which influences different patients in different ways. It may regulate glucose only to alter (in an adverse way) serum lipids and endothelial dynamics and induce other kind of secondary adverse side effects.

GlaxoSmithKline has characterized the article as premature and flawed as a meta-analysis study and have come back and said that there is data that actually refutes this contention.[9] But even if refuted, it still does raise some very interesting points, I believe, about the pleotrophic effects of many of these medications and how they don't just influence one gene but may influence multiple genes that have downstream effects on proteomics and metabolomics that can vary from individual to individual.

You might say, "What is a safer clinical way to regulate insulin, and to modulate endothelial dynamics, and to not produce dysfunctional effect upon lipids that might induce, then, dyslipidemia and relative risk to coronary events?" And, of course, we come back again to what is tried and proven, historically, from both epidemiological and intervention literature and that is things like the dietary approaches to stopping hypertension diet (or the DASH diet). Numerous papers have been published indicating the powerful benefit of the DASH diet (a more vegetable-based diet).

The Mediterranean diet is a modification of the DASH diet and has been shown to have improved indices of insulin sensitivity, vascular endothelial effects, and altered lowered blood pressure and improved lipid profiles. There are many papers that have been published in this area, including one recently in the *Journal of the American College of Nutrition* in 2007 showing the salutary effects of the Mediterranean diet in modulating these factors that associate themselves with proper control of blood pressure.[10]

When you are talking about nutrient sensing and metabolic decisions, nutrients are sensing agents. They are signaling molecules and they influence these complex arrays of signals that translate into functions so our genes are waiting for these triggers-things that regulate these families of intercellular signal transduction enzymes called kinases, which are part of the proteomic profile or the proteome. These kinases pick up these nutrient signaling information molecules that are found in a whole diet-these rich array of phytochemicals that we eat in a colored, complex, minimally processed diet. It translates that into

functional changes at the cellular level to alter our proteome and our metabolome.

There is a marvelous article that describes nutrient sensing and metabolic decisions that appeared in *Comparative Biochemistry and Physiology*.[11] It really shows us once again how molecular mechanisms of insulin resistance are associated with altered signal transduction that comes from "alarm" molecules that are being received by receptor sites on cells that translate themselves into altered function that we see as stress response: altered minerocorticoids, altered adrenosteroids, and ultimately altered insulin signaling as well.

Many articles have been published recently on the molecular mechanisms of insulin resistance and how it contributes to inflammation. If we were to put all this together, what is the takeaway? The takeaway is without changing genes, but changing the information that comes to genes from the outside world through taste, touch, smell, feel, and maybe even extrasensory types of information, it alters our genomic expression, alters our proteome, and alters our metabolome in such a way as to alter our function. And the major events we have to change these at the clinical level are not the drugs that we prescribe to patients, but the things that the patients do everyday: the dietary information, the exercise patterns, the stress management patterns, the things that are in our environment that are foreign chemicals that may contribute to alarm signaling. These are the things that form the basis of altered genetic profiling in the individual that give rise ultimately to the risk of chronic disease.

With that in mind, we are then going to move to a very interesting part of that, which is the agricultural system and our food supply system and the sanctity of these messages that come from our food that ultimately trigger these either alarm or anti-stress responses.

INTERVIEW TRANSCRIPT

Clinician/Researcher of the Month
Jeffrey M. Smith
Author,
Genetic Roulette: The Documented Health Risks of Genetically Engineered Foods
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I'm very fortunate to have the opportunity to talk with you about a very uniquely different format than we've ever had in the 25 (going on 26) years of Functional Medicine Update. There is no better time, nor better person, to change our format slightly than Jeff Smith, who is going to be our discussant person on this edition of Functional Medicine Update.

Jeff Smith doesn't fulfill our normal kind of criteria for a clinician or a researcher, but yet he represents everything that we are about in Functional Medicine Update and have been about for 25 plus years. He is an advocate who is bringing to the world an understanding at a deeper level of the impact of genetically modified foods and genetically engineered foods. I think this is a very extraordinary topic that you might say (at some level, as a clinician), "How does it relate to the health of my patients?" I think after this discussion that we are going to have with Mr. Smith you'll much better understand this.

To really give Mr. Smith an introduction I want to just quickly quote from a forward by Frances Moore Lappe, who has been-for the better part of 3-plus decades-one of my heroes in the field of nutrition. This is a forward to Jeff Smith's first book Seeds of Deception: Exposing Industry and Government Lies about the Safety of Genetically Engineered Foods. Ms. Lappe says that Jeff Smith's book really talks about more than just nutrition. It talks about the whole nature of information, about the whole nature of truth and discovery and full disclosure. It talks about the freedom of information and access of citizens to enough information to make informed choices, which doesn't seem to have been the case as it relates to this extraordinary topic of genetically engineered foods.

Her comments really are voiced by so many others who have read this book and been deeply affected by it, including one of my good friends, Jim Turner, who is the author of The Chemical Feast and the Nader report on the Food and Drug Administration many years ago and is a well-respected lawyer in the area of food advocacy. Most recently, Jeff Smith has authored an updated and more definitive book that was just published and it is absolutely fantastic; it is called Genetic Roulette: The Documented Health Risk of Genetically Engineered Foods. It is that book that I would put on everyone's mandatory reading list. If you are not a person that has read this book then you are really not up to date with what has been going on in this extraordinarily important area of applying molecular biology and genetic engineering to the food supply.

So with that as an introduction, we are talking to Jeff in England, no less. He is on a tour and having the opportunity to speak to Parliament and at academic centers around Europe concerning this extraordinary topic. Yesterday he was discussing this with members of Parliament in Australia, and of course he has an extraordinary advocacy here in North America as well, through his advocacy expressed in Seeds of Deception and now with Genetic Roulette.

Jeff, it is really a treat and a pleasure to have you as part of our history in Functional Medicine Update. Let me, if I can, just start first by introducing you to our audience and secondly asking if we can start with a definition. Could you define for us what genetically engineered foods are as contrasted to our traditional foods?

Definition of Genetically Engineered Foods

JS: Well, thank you. With genetically engineered foods you take single genes or combinations of genes, typically you make changes in the structure of them, and then you artificially force them into the DNA (the genome) of other organisms. So it is not natural, but it is rather a method of selecting certain traits, pulling it out of context, and transferring it into species that would never naturally contain those genes. The process itself also causes massive collateral damage in the DNA, causing mutations and changed gene expressions, etc.

JB: When we look at genetically engineered foods, I think there has been a long-standing misunderstanding, even with those who are fairly well informed. I recall a conversation I had not too many years ago with a very esteemed vice president of a large food company, and his particular point of view was that we have been tampering with genes of plants in the formation of foods for centuries (or, actually, at least for decades) through selective breeding programs, so why is this any different than genetically modified foods? Maybe you could help differentiate for us what the difference is between the traditional methods of selective breeding and that of genetic engineering?

JS: Well, when you want to genetically engineer a crop, typically you take genes and you add an artificial "on" switch (a promoter). You add an antibiotic-resistant marker gene to verify that the transformation has occurred. You make millions of copies and put it into a gene gun and blast it into millions of cells in the hope that some of your genes make it into the DNA of some of those cells. Then you douse the remaining cells with antibiotics, killing almost all of them. Those that survive indicate that the antibiotic-resistant marker gene is inserted correctly into the DNA and is functioning. Then you clone the resulting cell (using tissue culture) into full plant, and this is a lot of things, but it is not sex. It is not natural selection. It is nothing that has ever been done before in history. Genes are not like Legos®; you can't just snap them into place and have them function independently, producing exactly what you want.

The process can cause hundreds or thousands of mutations and changes that can, in turn, change protein expression and the expression of the plant compounds, of which there may be thousands in a particular plant. They have measured changes. For example, in the DNA they found 2{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} to 4{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} difference (due to mutation) just from the results of cloning the cell into a full plant. They also found massive changes in DNA in gene expression when a single gene was inserted into a human cell-up to 5{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of the functioning genes changed their levels of expression when a single gene was input. So we are talking about global changes, and yet engineering was based on a reductionist model of individual genes functioning independently.

JB: That was a brilliant description and differentiation. You know, it is interesting, because when you talk to proponents or members within the genetic engineering community, they will tell you things like they have protected against some of these risks that Mr. Smith is talking about because we (they) have put (as you say) the candimycin marker gene in there to tell us what is going on. And we (they) make sure that the plant can do its normal functions and it looks like the plant, tastes like it, and produces the same protein, carbohydrate, and fat, so a lot of this is theory of concern and in actual fact it doesn't happen. How do you respond to those kinds of debate questions?

Little Testing is Done Following Transgene Insertion

JS: I think your example is great. It looks like, it tastes like, and we have three or four data points, so it must be the same. You know, they don't even check to see if the transgene ends up the way they intended it to be. In fact, there were studies in Paris that found that they sequenced the transgene (the gene that was inserted into these crops) and in all five cases, what they found was different than what the company had registered. And so either it changed during insertion or was unstable and was changing over time. Likewise, the protein that is being produced from the transgene might be different, and they don't necessarily check that either. For example, they'll check five amino acid sequences and they will assume that the rest of the six hundred are the same. They will also assume that the transgene will produce the right protein even though the transgene can be interpreted differently. In one transgene, 30{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} was lopped off altogether, and the resulting protein was a combination of the inserted gene and part DNA. And they don't actually test the food itself on animals, in many cases. What they do is they create a surrogate protein from bacteria and then test that with a single dose on a rodent to see if there has been any death occurring within 7 to 14 days and that is their animal-feeding study. So they don't test in ways that would even evaluate these unpredicted changes in the crops themselves. They create artificial circumstances to force the conclusion that these foods are safe.

JB: Well I think you used in your book Genetic Roulette, and also in Seeds of Deception, a remarkably powerful example that illustrates what you are talking about and that is the amazing work of Dr. Pusztai that maybe you could tell us a little bit about? I think that really dramatically illustrates what you are describing.

Concerns in Europe about Genetically Modified Foods

JS: Well he is a very pro-GM scientist, the leading leptin scientist in the world, working at one of the top nutritional research laboratories in the world in the UK. He received a grant from the UK government to create the ideal testing protocol to evaluate the safety of genetically engineered crops that was to be used EU-wide. And he created a genetically modified potato engineered to produce an insecticide (a leptin), and the insecticide turned out to be harmless to animals (he had studied it for six and a half years and characterized it quite well). But the potato that was engineered to produce the insecticide caused damage to virtually every system in the rats that were fed the potato. They had potentially precancerous cell growth in the digestive tract; smaller brains, livers, and testicles; partial atrophy of the liver; and damaged immune systems, among other things.

He was alarmed because he realized it was the inherent process of creating the genetically engineered potato that was responsible for the damage. He went public with his concerns, was fired from his job after 35 years, and silenced with threats of a lawsuit. His 20-member research team was disbanded, and he was maligned by the institute he had worked for and by the established pro-GM UK scientists, among others. When he eventually was able to speak because of an act of Parliament, he got his data back and it is now published in The Lancet and it remains the most in-depth animal-feeding study yet produced on genetically engineered crops.12 , 13

What it shows is that if that same potato which proved to be so damaging had been subjected to the same superficial studies that got the GM crops on the market (soy, corn, cotton, and canola, for example), those potatoes would have also gotten onto the market. In addition, the other products were made from the same process of genetic engineering that he used to create the potatoes, so they might be creating these types of damage in human beings over the long term, but we don't know since the studies have not been done.

JB: It is really very, very fascinating, isn't it, how things of this importance, which are discovered by very diligent people, can be held in check and the information not made available to the broader public. I guess we have to really commend what happened in Europe as a consequence of the fall out of this because it seems like it was the catalyst for putting in place regulations about genetically engineered foods that we don't see in the United States. Why didn't we see a translation of this from one continent to another?

Many Americans Unaware of Presence of Genetically Modified Foods

JS: Well, when Pusztai was able to speak on February 16, 1999, it touched off a major headline war about GMOs. One commentator said it divided the society into two warring blocks on the GM issue, and within six to eight weeks, Unilever, Britain's largest food manufacturer, publicly committed to remove GM ingredients from their European brands. Within a week, virtually every other major food manufacturer followed suit. However, in the United States, Project Censure describes that (our Pusztai issue) as one of the most underreported events of the year. And so we don't really have an open press right now reporting the risks, instead we have press that read like a biotech brochure. This has been the case for many years.

If you ask the average American, "Have you ever eaten a GM food in your life?" Sixty percent say no, 15{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} say I don't know, and those that don't want to eat GM don't know how (they have labeling over here in Europe but not over there in the United States). And so the structure of the way that they have been improved and sort of slipped into our diet without notice has been responsible for the fact that Europe has rejected it and the unknowing US consumers have not.

JB: So now that leads us (obviously) to the inevitable discussion about the business opportunity and how that has been a motivation for kind of circumventing (maybe) the normal process of consumer education and discussion and kind of general political support for the concept. Tell us a little bit about the Roundup Ready seed movement because it seems like it plays a pretty interesting role in this whole discussion here in the states.

Roundup Ready Seed Movement

JS: About 80{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of genetically engineered crops are designed to withstand death by a particular herbicide. So the company markets their (for example) Roundup Ready seeds or soy to withstand sprays of Roundup herbicide. And what it does over time is it increases the use of that herbicide in the city and in the fields. By 2004, for example, Round-up Ready soy fields received an estimated 86{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} more herbicide than the natural soy fields, and it allowed Monsanto to maintain a de facto domination of the glyphosate market (that's the active ingredient in their Roundup even though the patent was expired in 2000). Now if you look at the potential impacts of Roundup, because there have only been about two dozen peer-reviewed, published, animal-feeding studies on the health aspects of GM, and only one published, peer-reviewed, human-feeding study, we have to take our information from several sources to get a big picture.

Immune-System Reactions to GM Soy Reported

Soon after GM soy was introduced to the UK, soy allergies skyrocketed by 50{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36}. We know that in an analysis of the composition of GM soy by Monsanto (information that had been left out of their study and found later) that among cooked soy, the trypsin inhibitor (which is a know allergen) was seven times higher than compared to one variety of non-GM soy. We know that in another study, eight individuals showed a skin-prick reaction to GM soy, but only seven of them to non-GM soy, showing that one person had a unique allergic or immune-system reaction to the GM variety.

When they then did a profile of the proteins within the soy, they found a unique allergenic protein in the GM soy, one that was able to bind with IgE antibodies. We also know that the Roundup Ready protein that was intended to be created within the Roundup Ready soy has two sections of amino acid sequence that are identical to known allergens, which (according to the WHO) either should have stopped approval or forced further tests. And finally, we know that the high levels of Roundup residue might also be associated with food sensitivity or allergic-type reactions. In addition, there is a mouse study that showed the production in the pancreas of digestive enzymes was dramatically reduced in the mice that were fed the GM soy.14 Any reduction in (for example) protein enzymes could allow the protein to last longer in the system, causing it to be more likely to achieve an allergic reaction, so it potentially could increase allergic reactions not just to soy proteins, but to other proteins. When the GM soy was fed to mice and rabbits they showed changes in DNA expression and enzyme expression and metabolic activity in all the

major organs that were tested.15 Also, mice that were fed GM soy had problems in the development of their young sperm cells and the embryos showed altered gene expression as well. And in the Russian National Academy of Sciences they fed rats genetically engineered soy and about over 50 percent of the offspring died within three weeks compared to about 10 percent of the offspring whose mothers were fed non-GM. The size of the offspring from the GM-fed mothers was also radically smaller, and they were not able to reproduce in subsequent studies. And they also fed soy to males and they found that the testicle structure was also considerably different among the GM-fed group. So we have a lot of information from the very few studies that have been done indicating that this thing is not just an accident waiting to happen, but might already be creating a health catastrophe in the United States if 89 percent of the soy acreage in the US is GM.16,17,18

JB: Well that was about as eloquent and complete an answer to that question as we could ever expect. Thank you very much. You know, for those who are going to read the book (Genetic Roulette-your book) which I think (as I mentioned) is mandatory reading, they might ask, "It seems so self-evident-the way that you describe it. Are your assertions documented and supported?" And if you look at the endnotes in your book (I haven't counted up specifically how many references you have cited to support your points), but certainly it is in the thousand range. I think anyone who would like to know if you are speaking from what has been published in the authentic literature the answer is a definitive yes.

JS: There are over a thousand endnotes and it is a combination of published literature and reports from the field. As I mention at the beginning of the book, if we had thousands of appropriately done studies, we wouldn't need to look at medical reports or correlational relationships.

Worldwide Consequences of Bt-Toxin Use Reported

For example, Bt-toxin. Here's an example where they took a toxin and they put it into food supply, so it was produced, for example, in every cell of corn (which means in every bite of corn) on the assumption that the toxin had a history of safe use because it is used in organic agriculture, that the protein was truly destroyed during digestion, and that there were no receptor cells in humans or mammals so it would pass right through even if it weren't destroyed during digestion. So they didn't have a whole hoard of scientific studies and data points to say that this toxin in our food supply would be safe. It was based on assumptions as so much of the GM approvals are. However, even among the small number of data points that were there, they had overlooked the fact that about five hundred individuals complained of allergic-type reactions when they got sprayed with the natural version of this Bt -toxin that was used for Gypsy moth infestation in the Pacific northwest.19,20

Now, they take that gene and they make the Bt-toxin at three- to five-thousand times more concentrated than the natural spray version, and farmers in India who are harvesting GM cotton (or loading it onto trucks, or working in ginning factories) are complaining of the same allergic-type reactions that the five hundred people complained about in the Pacific northwest. Then they let sheep graze in the Bt cotton plants after harvest, and within five to seven days twenty-five percent of the herds died (about 10,000 sheep in total). About two dozen farmers in the United States complained that certain Bt-toxin corn caused their pigs or cows to become sterile. There is a German farmer and others in the Philippines that claim that the Bt corn caused death among their animals (their livestock). And in the Philippines, also, people living next to the Bt corn field developed skin, respiratory, intestinal reactions, and fever during the time that the corn was pollinating.21

The following year, the same seeds were planted in four other villages and during the time of pollination when they were breathing in the pollen, they had more reactions among people living nearby. Now these are all medical reports or farming reports that are documented, yes, but not necessarily in peer-reviewed journals. For the studies that got Bt crops approved, they are typically not peer-reviewed by the companies; they are submitted only to the regulatory bodies and labeled "Confidential Business Information." However, a lawsuit forced Monsanto's Bt corn study for their Mon 863 into the public domain a couple of years ago. It turns out that they had an enormous amount of problems with the rats that were fed the GM corn, and some scientists recently re-evaluated the raw data based on the study and found clear signs of toxicity in the liver in kidneys that was not reported or acknowledged by Monsanto or the regulators that approved the product. So even among the company's own studies, which I describe in great detail in part three of Genetic Roulette-how they meticulously design their studies to avoid finding problems (using the wrong samples, the wrong control group, the wrong statistics, under-reporting the details)-even with all that, they found signs of toxicity.

JB: So that leads us into an interesting question. Michael Pollan, in his recent book Omnivore's Dilemma, talks about this concept that often when farmers are feeding corn to their animals that are genetically engineered and the animals have a choice of the genetically engineered corn versus the non-genetically engineered,they will preferentially choose the non-genetically engineered, suggesting (at least from anecdote) that animals know the difference. Is there any history of that that you have seen in the way that animals respond to these foods?

JS: Absolutely. There are reports from all over North America that show cows, pigs, geese, elk, deer, raccoons, mice, and rats all avoided GM feed when given a choice. In fact, the CEO of Calgene, that put out the first approved, genetically engineered food crop (the Flavr-Savr tomato) said that even if you were Chef Boyardee, these rats were not going to eat their GM tomatoes. They force fed the rats the tomatoes and several developed stomach lesions and seven of twenty died within two weeks. We know now from documents made public from a lawsuit that the FDA was willing to let that go on the market as is. Calgene voluntarily used a different line of their transformed tomato to introduce to the market.22

But it shows you that the FDA was ready to turn a blind eye to some pretty serious results. Now the FDA has no required consultation (it is all voluntary), so that was the only study in which raw feeding-study data was ever submitted to the FDA (that was basically summary conclusions and very, very superficial and flimsy reports that are voluntarily submitted). If the FDA asks for further studies and further questions, they are typically ignored.

This voluntary consultation process came about because the 1992 policy of the FDA claimed that the agency was not aware of any information showing that foods created from these new methods differed in any meaningful or uniform way. On the basis of that sentence, they said that if Monsanto wants to introduce a GM crop to the market, they can determine whether it is safe and don't even have to tell the FDA. That sentence turns out to be a deception. Documents made public from a lawsuit show that the overwhelming consensus among the FDA's own scientists was that GM crops were inherently unsafe and could create hard-to-detect, unpredicted toxins, allergens, new diseases, and nutritional problems and had, in fact, urged their superiors to require the long-term safety studies that they chose not to require.

JB: What do we do? That is the question. You have already told us that in terms of labeling there is no mandatory requirement in the United States for labeling foods that were produced by genetic engineering.

In your extraordinary website and institute (the Institute for Responsible Technology) you talk a little bit about what we should do and where we are going. Maybe you can help us to kind of define a strategy.

JS: Well, I think that among all the health and environmental problems in the world that we face, ending the current generation of GM crops is one of the easiest things we can do. I emphasize the words "current generation" because I'm not against the possibility that someday in the future we can safely and reliably and predictably manipulate the DNA for the benefit of human health and the environment, but the current generation is a primitive technology based on obsolete science and faulty assumptions. So how do we stop that?

Grassroots Consumer Action Could Halt Use of GM Crops in US

I think what we talked about earlier-the result in the European situation-when a certain number of consumers reach the tipping point of pushback against GM, who are unwilling and very unhappy about the fact that the diet was being converted to GM, when that tipping point was reached, the food industry reacted for the sake of protecting market share. And that kept GM crops out of Europe in spite of a very pro-GM European commission and a pro-GM European food safety authority. So we need to create the tipping point of enough consumers in the United States to say no to GM.

Now remember, the food industry gains nothing from these GM crops, in about 80{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} are herbicide tolerant and about 20{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36}produce their own pesticide. They do not have consumer benefits, so the food industry gains nothing from using GM, and if they saw a drop in market share of just a few percentage points and they perceived a trend that might grow over time, it is very easy to see how the stampede away from GM could be repeated in the United States as it was in Europe.

I am predicting that with as little as 5{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of the US consumers avoiding GM ingredients very consciously, that 15 million people could drive the decisions for the entire food industry. So where can we get 15 million people? Well, certainly health-conscious shoppers are low-hanging fruit since there are already 28 million people who buy organic food on a regular basis, but they rarely avoid GM ingredients in their non-organic purchases. I'm working with some CEOs of major food companies in the natural food industry, and what we are doing is we are cleaning out any remaining GM ingredients from the entire natural food sector, setting up GMO information centers in all the health food stores, non-GMO shopping guides, and later on, in-store, on-shelf labeling of any products that have held out and not participated in the clean-up.

We are also working with communities around the country, showing a video that I created with others called Hidden Dangers in Kids' Meals, alerting parents and schools to the fact that children are most at risk to the health dangers of GM foods and we are establishing GM-free campaigns around the country. Likewise, we hope to approach religious leaders to explain to them the dangers. They, themselves, may believe that "GMO" means "God Move Over" and are unwilling to participate in this experiment and might choose to distribute the non-GMO shopping guide. And the fourth demographic that are really important is the health practitioners-the doctors, the nurses, the dietitians, those who evaluate science and make recommendations to their patients and clients. If the word got out to the food industry that more and more doctors are now prescribing diets to be free of GMO, then GMO will be over in the United States very quickly. And I do know many doctors who tell their patients to avoid eating GMO foods. That is

why this interview is so important.

What we hope to do at ResponsibleTechnology.org is to post patient education materials that doctors can download. In the meantime, they can always use Genetic Roulette in their waiting rooms. It is designed for a quick, five-minute flip-through in the way that is has executive summaries on one side and detailed text on the other side of each two-page spread.

We have one doctor, an allergist, who said he used to do soy allergy tests all the time but now that soy is genetically engineered he tells his patients just don't eat it unless it says organic. He buys in bulk this audio CD we created called, You're Eating What? Stop Eating Genetically Engineered Foods and Please Copy this for your Friends. So he buys them for a dollar or so off our website and sells them to his patients for a dollar and has distributed over a thousand to his patients. So we have ways that we are working with the medical community so that we create this buzz that healthy eating means no GMOs, so then quickly we can reach the tipping point and the food companies will end this dangerous experiment, even if our government is unwilling to act.

JB: Well, Jeff, that is an incredible advocacy. I think it was very important for our listeners to hear that you are not a Luddite by nature. You are not a person who is just anti-technology, regardless. I think your point is that if we knew enough about what we were doing that would be a very different story than doing an experiment that is early on in our understanding of the gene and how it is translated into protein and function and that that uncertainty is really the cause for great concern. I share that concern.

It seems like many of the dominant-what we consider "truths"-in molecular biology when I took my first course in 1962 in molecular biology, like the "one gene, one enzyme concept" and the fact that there was all this "junk DNA" that was present in the genome has now been pretty much refuted. It is not just "one gene, one enzyme." Genes can express themselves in different ways and this "junk" is really not junk at all; it is where a lot of the information molecules are for organizing the genetic expression patterns that ultimately control how genes are regulated. It seems like we jump prematurely with the kind of sophomoric view (the "wise fool" view) about what we knew about the gene and started inserting that knowledge prematurely into our food supply and I think that position that you have taken is a very, very scientifically supportable position. It is not a Luddite position or an anti-technology position; it is a rational thinking position.

JS: You know, it is interesting. I agree with you completely, and yet the public relations spin by the biotech industry, which has been so successful around the world, wants people to believe that those of us who are demanding more science are anti-science. But there is also another very dangerous aspect. You mentioned this with respect to Arpad Pusztai, but I've interviewed scientists all over the world who have incredible pressure silencing them, taking away their funding from doing research, denying them access to genetically engineered seeds to do their research. Doctors have had information stolen. Even scientists in government have had documents stolen from their locked file cabinets as is the case with the scientists in HealthCanada who were evaluating Monsanto's genetically engineered bovine growth hormone. They also said, for example, that Monsanto had offered them a bribe of one- to two-million dollars to approve their drug and that also Monsanto go fined 1.5 million dollars by the US Justice Department for bribing up to 140 Indonesian government officials to try and get their patent approved there.23 It is not just an avoidance of science, it is actually a rather sophisticated manipulation with very big goals in mind.

Arthur Anderson Consulting admitted at a 1999 biotech conference that they had consulted with the executives at Monsanto by asking them to describe their ideal future in 15 to 20 years. And the executives described a world in which 100 percent of all commercial feeds were genetically engineered and patented.24 And they went backwards from that goal to create a strategy and tactics to achieve it.

Imagine if they had been successful. Imagine if there hadn't been pushback from Europe. We would be replacing the genomes-the DNA-with self-propagating genetic pollution and reducing the number of seeds around the world, because they obviously would have taken over a larger percentage of the seed supply and reduced the amount of natural seeds made available, causing a much higher level of food insecurity. If they had gone forth with their plans they would be gambling with our entire food supply on this untested, primitive technology. They are not above really risking as much as you can possibly risk.

Self-propagating genetic pollution will outlast, theoretically, the effects of global warming and nuclear waste. We have never had an experience like this before in our history. Going slow, going cautious, going with plenty of consensus and thinking is the only way to proceed with such a technology, and yet we are seeing just the opposite. So I want to applaud you for taking this up as well as all of your incredible work in all the areas that you are working on, Jeff.

JB: Well, thank you so much, and I think (again) the listeners can see the urgency to read Genetic Roulette and really become more knowledgeable and informed and assist their patients in making informed decisions in this area. Once again I want to cite your website because I think it is a very valuable and dense source of information; it is www.responsibletechnology.org.

Jeff, I just want to thank you. I know you have taken time out of your busy schedule there in Europe to share this information with us but be assured it is being listened to by people who are very advocacy-minded and it will have a significant impact in how they counsel and discuss this with their patients.

JS: Thank you and I want to add one thing. We have a geneticroulette.com site. We have 65 health risks of genetically engineered foods documented in Genetic Roulette, so we posted a page for each one of those 65 health risks and then asked the biotech industry and others to give updates, challenges, corrections, etc. in the hope that it can become the world's forum on discussing the health risks. Not only that, but it is actually a gauntlet. We are throwing down a gauntlet to the industry, saying "You must respond to these 65 risks with rigorous scientific data showing that they are not concerns, otherwise there is no justification for allowing these foods to be on the market."

I'm traveling and speaking to parliamentarians and others, and I testified before the EPA and met with senators and congressmen, saying "We want to reframe the issue now. There is overwhelming scientific evidence that these foods are unsafe. We have parsed it out into 65 main risks. Let's give them the checklist. If they can respond to the 65 risks, we have no further questions. If they respond with more assumptions and no data points and sweeping dismissals, then they have no justification to allow the food to be fed to humans or to animals."

JB: Very, very convincing. Once again, thank you and thanks for your tireless efforts and we will keep the fire burning here from the practitioner side.

JS: Great. Thank you, Jeff.

We thank Mr. Jeffrey Smith for that extraordinary discussion and interview. Certainly it was provocative and opened our minds to all sorts of questions and important issues, I'm sure.

Tagging the Rice Transcriptome

I want to follow-up the interview with a recent article that appeared in *Nature Biotechnology*, a very well-respected primary journal in the biotechnology area. This article was titled, "Tagging the Rice Transcriptome."[25] As you probably know, rice is one of the most important food crops in the world, obviously. There is a tremendous amount of work going on to find ways of modifying the genetic structure of rice to give it certain attributes that would be considered commercially more valuable.

This particular article was authored by Dr. Antoni Rafalski. Dr. Rafalski is the DuPont/Pioneer Hi-Bred International Genetic Discovery Group chairperson at Experimental Station in Wilmington, Delaware. In this particular article he is talking about some of the things they are learning by tagging the rice transcriptome with 50 million express sequence tags and looking at a complex collection of the RNA species that are then derived by microarray types of analysis.

I thought it was very fascinating in light of what Jeffrey Smith was just talking about to talk a little bit about Dr. Rafalski's conclusions. He says a unique aspect of this study is cataloging the small RNAs in a crop. Small RNAs have recently emerged as critical regulators of a wide variety of developmental and physiological pathways in plants, including stress responses. Transcripts, particularly these small RNAs, were found for essentially all annotated rice transponsons and retrotransponsons. Their location corresponds to highly methylated regions of the genome, suggesting a very significant genetic complexity in the way that the rice genetic information is expressed.

So now I quote, from the end of this article, which I think you'll find very fascinating in the context of the previous discussion that we had with Mr. Smith. Mr. Rafalski says, "A significant fraction of intergenic space in the rice genome, sometimes thought of as 'junk' is functionally active. From a biotechnological perspective, transgenic modifications that disrupt transcription of any of these intergenic regions may have unintended consequences. Although the genic environment of transgenes is routinely surveyed in the process of governmental approval, better insight into which sequences in the rice genome are transcribed and thus presumably functionally important, will facilitate efforts to avoid transgene insertions within expressed regions."

The point I am really trying to get you to understand is not to convert you into a molecular geneticist or a molecular biologist, but rather to recognize that even from an expert in the field, we are acknowledging that there is lots yet to be learned about how insertion of genetic information can influence the expression patterns in a particular plant and ultimately the function or the phenotype that it has. We are just learning about things such as these rice transponsons and retrotransponsons, transcriptional noise, small RNAs and things that relate to the regulatory regions of genes that used to be called junk DNA (which we now recognize have very important roles in how they are epigenetically modified by methylation to be expressed or not expressed).

I think you can see just from that little language I'm giving you that there is a lot yet to learn and a lot more than we thought, probably, about the complexity of the genome and how it is expressed ultimately into the phenotype. But yet, we moved ahead quite rapidly in the introduction of these genetically

modified foods. So I think what we are recognizing now is that there are still many questions yet to be understood before we can totally jump on this bandwagon with security and safety as it pertains to modifying the genome of our plant foods.

We thank Mr. Smith once again for his eloquent description and historic information, and urge your reading of *Genetic Roulette* . Thanks for being with us. We'll look forward to seeing you in October 2007.

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