

November 2010 Issue | Moshe Szyf, MSc, PhD Department of Pharmacology and Therapeutics

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Welcome to *Functional Medicine Update* for November 2010. "Function." What does it mean? That's a very interesting question. It's one that we have been talking around, through, up and down, and examining and microscopically dissecting for the better part of 30 years. In this issue, you are going to be exposed to a real fundamental understanding of what we mean by function. This may be a paradigm-shifting experience. In fact, I would say strap on your intellectual seatbelt. I would even go so far as to suggest that if you are listening to FMU for the first time, you need to find a quiet place to do it. Distraction really would be a disadvantage in fully absorbing what our clinician/researcher of the month has to say and how he says it. Without further ado, let's move right to one of the most extraordinary interviews that I have had the privilege of having in my 28 years of doing *Functional Medicine Update*.

INTERVIEW TRANSCRIPT

Clinician/Researcher of the Month
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Those of you who have been following *Functional Medicine Update* for many years are probably very used to me saying this each issue, and that is what an exciting opportunity we have to hear from the voice of someone who is creating a discipline that is changing the whole paradigm of medicine and health care. We're not to be disappointed this issue because I've been very, very privileged to be able to get Dr. Moshe Szyf to tell us about his work. I've been following it now probably since about 2006. I think it is some of the most pioneering and impactful and paradigm-shifting work that I've had the privilege of reading in that period of time. As I look at it, probably in retrospect, for the last couple of decades.

Let me tell you a little bit about Dr. Szyf. He has a fascinating background. He got his original degree at Hebrew University in Jerusalem. He went on and did a post doc in biochemistry, and then went on to do a post doc at Harvard Medical School in genetics. For the past three decades he has been focusing on understanding how DNA methylation plays roles in genetic transcription and gene expression patterns, and ultimately phenotypic outcome of cells and function of organisms. As you know, we have been spending a reasonable amount of time over the last couple of years trying to get our intellectual arms around this concept of epigenetics, and Dr. Szyf is certainly one of the pioneers in this field.

Looking at how that work emerged and evolved in his lab, he has developed various ways of looking at DNA methyl transferases and how they regulate gene expression patterns, and how that ultimately translates into understanding factors within the environment that might modulate or influence DNA methylation and demethylation in these epigenetic marks that alter the programming of genes and how they express their function. He has published widely. He is I think what I would call a translational researcher. He has been everything from a microscope to a telescope, looking all the way down, using gene arrays, to examine how genes are expressed and epigenetic marks, and looking all the way up, at whole-organism phenotypes through behavioral studies in animals and trying to determine how this all fits together.

Dr. Szyf is at McGill University. He is in the Department of Pharmacology there. Most of us are very aware of the history of McGill Medical School and McGill University. This was the birthing place of the term "stress" in physiology-by Hans Selye. I think "stress" is now the most cited English word in medicine (a single word being appropriated from physics). If Dr. Selye was alive today, I think he would be celebrating Dr. Szyf's work, saying, "I can't believe how this has evolved since my early observational years with adrenalectomy of rats and how far we've come in understanding some of the more detailed mechanisms of how these factors in the environment translate into function."

With that long-winded introduction, Dr. Szyf welcome to Functional Medicine Update. I just can't tell you how much we appreciate you being with us today. Let me start with the first question. From a biochemical/genetics background, what led you into this whole field of epigenetics?

DNA Methylation Patterns Can Tell the Story of a Life

MS: I started my career with epigenetics, and actually the first experiment I did was to look for mutants of E. coli that don't have the enzyme that methylates DNA. I've been doing this for 30-something years. When we started, we looked at phages that infect bacteria, and there was one phage we looked at-it was called Phi X 174-and it has one methyl group and we tried to understand its role. I was fascinated by DNA methylation because philosophically it is a very interesting creature. On the one hand it is part of the chemistry of the DNA. So if you, for example, take a mummy that died 5000 years ago and take its DNA and sequence it you get the ancestral information. You can also sequence the methylation pattern. You get information of DNA methylation, which we now know tells the whole story about the life of that individual. So we have, in between the very fixed DNA structure that is copied by very strict rules, something that is, on the one hand, dynamic, and on the other hand very stable. So it was very clear from the early days that this was something really fascinating, something very different from what we knew about in genetics, and that's why I was attracted to it.

JB: My first contact with your work was, as I mentioned, back in about 2006 when I happened onto an article that you had been a principal author on, on targeting DNA methylation in cancer and how these regulatory mechanisms might play a role.¹ Let's walk down your history. For me, that's where it starts.

DNA Methylation and Cancer Research

MS: Right. After maybe 10 years of working on DNA methylation, it seemed to me to be a great mechanism to explain what happens in cancer. Cancer is characterized by numerous changes in gene expression. Essentially a cell changes a program from one state to the other state. In thinking about what can do that, DNA methylation was a perfect candidate. Our first studies looked at the regulation of the enzyme that methylates DNA and if it changes with cancer. The first discovery was that the enzyme that

methylates DNA goes up when the cells replicate faster. The second discovery was that all of the known cancer pathways turn on this enzyme. Third came a question: so what if it turns on this enzyme? How does it transform a cell? We discovered that what happens in cancer is it turns it on at the wrong time of the cell cycle. So if it is normal for this enzyme to methylate DNA as it is dividing, it is not normal for it to methylate DNA when it is not dividing, because when it does that it adds methyl groups that should not be there.

Then we noticed that in the bottom of the methyl transferase gene there is a regulatory region that was conserved in evolution. When you have that region, the methyl transferase works perfectly well with the cell cycle and cannot change the fate of cells, but when you remove it and put it in a cell, it transforms the cells. It changes the methylation organization of the cell. That led us to the question: what kind of proteins regulate that? We're still working on how this is connected to the cancer pathway.

S-Adenosylmethionine, Methylation, and Cancer

JB: Let me take that, if I could, to an area that I know a lot of our listeners who are clinicians have been following, and that's the interface between methylation and the tetrahydrofolate cycle and the universal intercellular methylating agent, S-adenosylmethionine. There have been interesting reports recently that I'm sure you have seen on things like adenomatous polyps and folate supplementation and does that prevent or does that increase the relative risk to malignancy? What have you-if anything-seen as it relates to the interface of the folate cycle with these things that we are talking about in cancer replication?

MS: We were most interested in S-adenosylmethionine, which is kind of the bottom end of this folate cycle. S-adenosylmethionine is the donor of the methylation reaction. What we found was that many of the metastatic genes get demethylated in cancer-lose methyl groups in cancer-and if we treat the same cancer cells with S-adenosylmethionine, we can methylate those genes, silence them, and block cancer metastasis, both in human cancer cell cultures in vitro and when you transplant into mice in vivo.

One important connection is it seems that deficiency of S-adenosylmethionine (SAM) could enhance cancer metastasis. There is a body of literature that connects S-adenosylmethionine and cancer in rodents, especially in the liver. When rodents are fed a diet that is deficient in the methyl donors, and therefore reduced SAM, they will develop liver cancer at a much higher frequency. And vice versa. You can protect animals from cancer by providing them with S-adenosylmethionine. So this is the positive side of S-adenosylmethionine. We also discovered that S-adenosylmethionine actually blocks the process of DNA demethylation, the opposite of DNA methylation, where enzymes remove methyl groups. So we think there is a big hope for S-adenosylmethionine intervention in preventing cancer metastasis.

Another example where S-adenosylmethionine might be important is in diseases like lupus, where again there is a global loss of DNA methylation and perhaps in those situations there is a need for upregulating the methyl donor facility in the cells. You know, there is a good connection between S-adenosylhomocysteine, which is the opposite of the unmethylated form of S-adenosylmethionine, and cognitive decline in Alzheimer's disease.

There are multiple examples of health problems that are a consequence of lack of S-adenosylmethionine.

That is a downstream consequence of lack of either folic acid or vitamin B12. However, there is the opposite side, which is increased methylation can also cause cellular transformation. There was a fear that folate supplementation might do the opposite, which is increase the risk for cancer. I'm not sure about

how strong this data is. My inclination is that actually high levels of SAM would be, overall, protective from cancer and cancer metastasis.

The big question is: Are these accidents that happen because you have too much SAM or too little SAM and then some stuff happens and some genes get methylated and some genes get demethylated, or the body responds to the signals that come from low SAM or high SAM by resetting programs? I kind of tend to believe in the latter in that both during development and later in life we have mechanisms that sense how much SAM we have and reset, essentially, the entire program of the cell, including the way DNA is methylated, to respond to this environmental challenge. We don't know yet how much folate is sending a signal that is protective from cancer, and at what point that signal will be kind of facilitating the development of cancer.

JB: That was beautifully stated. Very nice summary. It reminds me, as you are speaking, that years ago on Functional Medicine Update we had the privilege of interviewing Dr. David Heber from UCLA, in the medical school there, and he was talking about work that they had done looking, as you say, at liver cancer in folate-deprived animals and the increasing relative risk of carcinogenesis as a consequence of exposure to chemicals.² One of the things that I'm abstracting from your discussion is that there may be multiple variables that together orchestrate this expression alteration that we see as cancer. It's not just a single hit or a single agent.

Thinking Of Cancer as an Adaptive Program

MS: Oh no, I think it's an entire program. And I think we still don't understand what this program is telling us, because I think if we understood why the program is turned on, we would have better ways of dealing with it and preventing it or treating it. I think there are really two concepts in the way cancer develops. One is the Darwinian concept, which is that bad things happen by accident and then if a cell gets a mutation that makes it replicate faster it would be selected and then eventually another mutation happens and you get more selection and then another mutation. This is to look at cancer as a sequence of random events that somehow are selected because of the growth advantage of a cancer cell. And there is the other perspective that I tend to subscribe to more now, looking at the kind of changes that happen in cancer (that really cancer is a program). It's a program that is part of the adaptive programs that our genomes have, and it finds itself in the wrong context and then it becomes a disease. I think there is a very strong connection between these programs and the methyl or mono-carbon cycle in the cell. These send a signal to the cells, reset your program this way or that way, and that program can lead, in certain contexts, to cancer.

JB: That really brings to mind an enigma that I've had in my thought process ever since developmental biology in undergraduate school: What about stem cells? How do they get deprogrammed and reprogrammed into ultimately becoming differentiated cells? Obviously methylation programming plays a big role in that. It strikes me that these are some things that we are really just at the frontier of trying to understand, thanks to your work and others.

By the way, for our listeners, on the bibliography that we'll be supplying along with this, which will list Dr. Szyf's articles, there are a couple of other papers that I think fall into the light of this DNA methylation/cancer. One is titled "DNA Demethylation and Cancer: Therapeutic Implications" that was in Cancer Letters, and another that is a very nice review paper that you put together in the Annual Reviews of Pharmacology and Toxicology in 2009 on "Epigenetics, DNA Methylation, and Chromatin-Modifying

Drugs."3,4 It really, I think, is a pretty forward-looking review of where this field might go, therapeutically.

Let me move to autoimmune disease, because you've also touched upon that and you have a wonderful article in *Clinical Reviews of Allergy and Immunology* that I think is one of those landmark, "aha" articles titled "Epigenetic Therapeutics in Autoimmune Disease."⁵ Can you give us a little bit more thinking about how this epigenetic methylation model fits into the autoimmune constellation of disorders?

Methylation and Autoimmune Disease

MS: There is evidence that the methylation machinery is effective in autoimmune disease. One of those is, for example, lupus, where the evidence is strong. We know that demethylating drugs can induce lupus.

For example, people treated with either 5-Azacytidine or other drugs that are known to be hypomethylating drugs, are at high risk of developing lupus. If you look at the DNA of T cells from lupus, it is hypomethylated--it has globally less methylation--so it is a dramatic change in methylation levels. It seems that they have a defect in their methylation machinery, which results in activating genes that are the pathway of T cell activation that are normally shut down and only activated in response to specific antigens. In this case they are hyperactivated in a very promiscuous way, resulting in an attack of the immune system on the body itself.

The question, of course, is why does this happen? Why do T cells lose their methylation level and become these kinds of cells? Is this some sort of an adaptive response that probably has some sort of physiological role in the proper context and now is out of context? Again, I think there is a program out there. To decipher this program one has to look at not one or five genes to change, but entire circuitries of genes to change, and ask the question, why do they change? Another interesting thing is that in lupus there is a high level of an alpha protein called MED2 that we found is responsible, in part, for demethylation, suggesting that resetting the regulation of demethylating enzymes results in a whole resetting of the pattern of how the DNA is methylated.

I think we can ask the question at many levels, what's the relevance of that? There are ways to deal with lack of methylation. The big question is can we supplement the missing methylation by pharmacological or dietary tools? I think it is worth it. Can we inhibit the demethylating enzymes and remethylate the DNA to make those T cells normal again? And I think we can ask the question at a different level: What is the physiological purpose of this kind of response of T cells? Why does it happen? What does it tell us? And what kind of environment were these cells exposed to that they responded in this way and how can we prevent that? DNA methylation allows us to ask these questions at many levels, from the therapeutics to the diagnostics to the prevention.

JB: In your review article-your article titled "Epigenetic Therapeutics and Autoimmune Disease"-you also introduce a concept that I hadn't thought much about, which is quite interesting, and that's the counter-current communication (or cross-talk) between histone acetyl transferases and histone deacetylases, the acetylation of the genome as contrasted to the methylation if you think of the methylation as "stop" function and the acetylation as "read here" function. And then that ties into things like, "Does this have any relationship to phytochemicals like resveratrol that influence independent histone deacetylases?"

MS: Absolutely.

JB: And so is there a SIRT1 longevity relationship here of cells? I'm sure you're thinking about all these things, but it sounds fascinating that there is a circuit, possibly, of epigenetic programming and with methylation tied to acetylation that is a very important switching point.

The Relationship between Histone Acetylation and DNA Methylation

MS: Right. As you recall, we published several papers showing that if you change histone acetylation you also change DNA methylation, so these things cross. And that has significance both for the impact that wine can have on humans, as well as drugs. A good example is valproic acid. It's a drug that has been used in the past (for decades) as an anti-epileptic drug. Nobody thought that it was an epigenetic drug, but now it is quite clear that it is a histone deacetylase inhibitor. But again, nobody thought that it changes DNA methylation, and now there is very strong evidence that it changes DNA methylation.

So now you can ask two questions: What is the toxicology of valproic acid that is associated with changing DNA methylation? We never thought about it. As well as: What are the pharmacological therapeutic utilities of valproic acid in certain cases where we actually want to change DNA methylation? Can we use it? For example, can we use it in cancer? Or can we use it in certain psychiatric situations where actually demethylation could be useful? These questions are being asked now.

I think the other implication is that almost every chemical that we are exposed to has to be tested, as far as its impact on the epigenome and the connections. The fact that one chemical changes histone deacetylation doesn't mean that it only changes histone deacetylation; it also can change DNA methylation, and therefore histone methylation, etc. etc.

Epigenetics and Pharmacology

JB: You've authored at least two papers that I've read that really were kind of mind-bending in this area for me. One is titled "The Dynamic Epigenome and Its Implications in Toxicology," and then the more recent one is "Epigenetic Side-Effects of Common Pharmaceuticals: A Potential New Field in Medicine and Pharmacology."^{6,7}

I think very few people that I've ever spoken to have conceptually thought about what would happen with long-term use of specific drugs that modulate epigenomic methylation patterns. Maybe you can speak to your thought here because I think it is pretty powerful.

MS: I think the classical tests that we give drugs are very short and intense. Essentially we test whether they work in animals, and whether they cause genetic mutations and if they don't we are very happy. The thing about epigenetics is epigenetics is a memory for the genome to an exposure. It can hit you many years down the line. So you are treating with a drug that gives you whatever effect you think it is acting on-blood pressure, or GABA receptors, or something like that-assuming that that is what you want to do, and then you inject it into rats, and you figure out the toxic BLD50, and you are happy because you are well below that and it doesn't change blood pressure and other things, and off you go. The drug is approved. But at the same time, it modulates one of the enzymes that controls the epigenome, and there are dozens and dozens of those enzymes.

The scary part is that they are all connected, so if you change one you will change the others. And if you change DNA methylation, you essentially change the memory of the genome; you change the way the genome is programmed. And the impact might not be immediate, but it might be down the line. The other scary part is that we thought in the past that DNA methylation is only of interest to cells that divide,

because there was a dogma that you cannot lose DNA methylation because it is such a strong chemical signal unless the cells divide without an enzyme that methylates DNA. And since most of our body doesn't divide, we're not worried about effects like this. That was the general concept. But now we realize that neurons that don't divide-and as you know, we did quite some work on behavior-are highly affected by methylation and demethylation. So you give somebody a drug that is supposed to be lowering his blood pressure or acting on acne in his skin, and they demethylate genes in the brain (or hypermethylate genes in the brain), and the consequence of that will be felt long after.

What if it changes the methylation pattern of germ lines or germ cells? And then these effects will go to the next generation and to the third generation? Essentially we are starting to reexamine a lot of those safe things that we did-how safe they really were.

JB: There are so many fantastic things that you are bringing up. My mind...every neuron is firing because it's just raising all sorts of interesting questions. Let me, if I can, focus on revisiting the autoimmune story as a model. There has been a long anecdotal history suggesting that certain dietary approaches can improve autoimmune disease. These are diets that are generally low in animal products, richer in vegetables, and lower in processed foods and sugar and so forth. But there has never been really a mechanism to explain why this might be.

I know I'm over-extrapolating here, but in listening to you, it sounds like it would be at least possible that these very phytochemical-rich diets that have been associated with lowered autoimmune disease could have influence on-because of the role that we know that some of these phytochemicals have (we've talked about resveratrol, but there are many of them)-these methylating enzymes and on the acetylation enzymes, that maybe you are really modulating some of these things in immune cell lines that you are describing with these diets in a much more profound way than we previously understood. Is that at all possible?

MS: It is possible and it is testable. I mean, that's the beauty of DNA methylation; you can actually measure it. You can measure it at a global level. You can measure it at a gene-specific level. You can measure it at a whole-genome level. You can measure it at the resolution of every CG in the genome. I think what I'm really saying is that we have to examine these things scientifically, both the positive and the negative things that we are doing. Positive biases, as we know, epidemiologically have a positive effect. It is worthwhile examining what impact they had on the epigenome and vice versa. They are all testable hypotheses and they could be easily modeled. The immune system is actually one of the best ones to test because it is relatively accessible. You're not talking about deep brain structures; you are talking about the cycling, itself, that you can access. What is needed is a controlled experiment where you can actually follow the epigenetic states of different kinds of T cells, for example, before and after the intervention and compare it to a control group.

JB: A clinician listening to your extraordinary story might distill this down to when they are sitting with a patient in the exam room and say, "Gee, does that mean that I should-because these are methylation defects in these autoimmune patients-see homocysteine plasma elevations in these patients as an indication of their methylation defect?" I think what I'm hearing is we shouldn't jump to the conclusion that this necessarily always would be translated as something that we see as elevated blood homocysteine.

MS: No, not at all, because there are so many ways to change the methylation pattern. Homocysteine is

probably one way; I'm not sure it's the strongest way. It could be all of the things you've mentioned—drugs the person has taken—and you would not see homocysteine differences. It will be a response of the machinery of the DNA methylation and epigenome machinery to whatever signal that exposure is given, and it might not be seen in homocysteine levels. However, you can examine epigenetic levels. That's doable and that should be done.

JB: One of your many papers—and I know I'm just hitting spots along your very remarkable and productive scientific life here—was in the *Journal of Medical Primatology* and had to do with organ and gestational effects of maternal nutrient restriction on global methylation.⁸ I think this is work done in baboons. Can you tell us a little bit about what happens when you restrict nutrients on the methylation patterns that were seen in primates?

Effects of Nutrient Restriction on Methylation Patterns

MS: There are dramatic global changes in DNA methylation. Obviously there are dramatic changes in health and that is manifested later when these animals become adults; we know that. But we didn't know what the possible mechanisms are. One mechanism is an overall change in the way the DNA is methylated, suggesting kind of an overall response of what we call the methylome (the entirety of the DNA methylation signals around the genome in critical tissues).

The question is, why is it happening? You can have a mechanical explanation: that when you deprive animals of amino acids you also deprive them of donors of the methyl group that goes into S-adenosylmethionine, eventually inhibiting the methylating enzymes and stimulating the demethylating enzymes. That's one way of explaining it. The other explanation is that what we are seeing in these animals is essentially an adaptive response—that life under nutrient deprivation is a different life than life under nutrient excess. What the mother is doing by the nutrient deprivation is sending a signal to the developing fetus. "You're going to have a tough life, and therefore you need to reprogram your genome to deal with that." If you are under nutritional deprivation, any piece of food you eat has to be stored as fat because you never know when the next meal is coming, therefore you have to push all the enzymes (the genes encoding these enzymes) to deal with metabolism towards fat storage and towards insulin resistance. Whereas if you are in a world where there are high nutrients, you need a different genome. You need a genome that takes every piece of food and just turns it into energy and doesn't store it as fat.

There are two ways to look at it. Is this DNA methylation change an accident that happened because of a mechanical defect in the enzyme because they were not supplied with whatever they needed to work? Or, is it a signal that the environment of the mother, through the amount of food, is sending to the developing embryo on how to program the genome? I believe in the latter, as you can guess from what I have told you before. I think that all these things, from autoimmune disease to type 2 diabetes, to depression and stress, are all adaptive responses, many of which are programmed early in life by signals that come from the environment. These signals could be nutrients. They could be the maternal stress. They could be the social environment early in life. All of these signal to the developing genome what kind of world you are going to live in. They can result in disease when there is a disconnect between the program and the real world that the animal or the human is finding themselves later. This monkey was nutrient-deprived as an embryo, and then he is provided a rich cafeteria diet in the American way of raising primates. There is a total misfit between the programming early in life and what happens now, and that monkey will become obese and will develop type 2 diabetes. However, if he was in the jungle, probably that genome was perfectly adapted to the kind of world he had to live in, where there is no food.

JB: I think we need to take-the listeners-an intellectual deep breath, here, to re-oxygenate the brain. What you've just said is unbelievably profound as it pertains to the etiology of chronic age-related diseases, of morbidity patterns, of the birthing of pharmacology, of how medicine is constructed. The spreading effect is both sociologically and technically and medically profound.

This is why we have called this "functional medicine," because at some level what you are really describing to me is how things function. Not the predetermined kind of hard-wired sense that we were born with the set of genes that were rigid and would play out their orchestration regardless of what we did, but rather this a more plastic model of the environment/genome interaction that creates a functional outcome. It's a very different model than many of us learned in medical school that we are talking about, it seems to me.

MS: I think so. I think we are undergoing this transformation from the genetic determinism to a much more dynamic way of looking at things. It might change the way we do medicine, and we understand medicine, and even the kinds of drugs we're giving our patients. I think the main problem that our genomes have, if you think about it, is that our genomes are very, very static machines. DNA is replicated by very strict Watson and Crick rules. It's not very adaptive. And I think what the methylome does-the methylation pattern-is it confers upon that fixed genome the dynamic that it needs to deal with the kind of world we are living in. The world is changing, and the genome is not changing fast enough to deal with it, and so you have this interface.

JB: Yes, the way that I've actually described this when I've been asked by docs, "Can I put this into a sound bite or elevator speech?" is I say that the genome, as we have thought about it-the code, the linear string of nucleotides-is like the course tuning knob (natural selection mutation followed by natural selection course tuning). But we need a fine tuning knob to tune into the frequencies of the moment to get the right station that we want to play, and that's the epigenome.

MS: Absolutely. Very good.

The Role of the Social Environment on the Epigenome

JB: Let me just close with two very important last parts of what could be almost a continued (almost ad infinitum) discussion. You related to the work that you've done, which I think is also extraordinarily pioneering, about the role the social environment has on the epigenome. A couple of articles that you have authored are titled, "The Social Environment and the Epigenome" in *Environmental and Molecular Mutagenesis* in 2008, and then a very interesting review paper that I really like that you authored with Mike Meaney on "Environmental Programming of Stress Responses through DNA Methylation."^{9,10} This is where I got to thinking about Selye and McGill and your work and "Life at the Interface between a Dynamic Environment and a Fixed Genome." Just the title alone is enough to bring goosebumps to the reader. Could you tell us a little bit about how that translates to things like maternal care of the epigenome and phenotypic differences in behavior? People almost would say, "I don't believe it. You can't tell me that there are signals coming from behavioral aspects of the environment that are kind of marking the genes. It just doesn't seem reasonable."¹¹

MS: Right. The thing is we needed to find a mechanism that can link things. Actually doctors knew and psychologists knew for a long time that the early environment and the early maternal environment (or family environment early in life) has a profound impact on the health of the individual later in life. One of

the strongest determinants of health is, for example, socioeconomic status early in life. And also what epidemiologists have noticed for decades is that if, for example, people shift from adversity early in life to life of privilege later in life, it doesn't have as much of an impact as being privileged early in life. So early in life privilege and lack of social stress and social adversity has a profound impact on health, and the question is why?

We did a series of rodent studies, and then we looked at humans and monkeys as well, to look at a connection between what happens early in life and perhaps DNA methylation mediating it. The way we think about it is like this: The maternal environment results in activating pathways in the brain that respond to that. For example, serotonin responds to so-called reward pathways. And that pathway activates a series of sequence events in critical cells, like in the hippocampus, that eventually result in epigenetic programming of a set of genes (now we know it is not just one gene but the entire circuitry of genes is methylated differently in response to the maternal care).

It doesn't sound as magical once you understand that. When there is maternal care, the animal responds with high serotonin. The high serotonin acts on receptors that trigger, on what we call signaling pathways, a series of phosphorylations that eventually activate transcription factors that can read addresses in the genome and take to the genome a load of chromatin- and methylation-modifying enzymes and program the genome accordingly.

Does it make sense? We think it makes sense, because this is the way the mother programs the child to the kind of world they need to live in. If it is a stressful world, and the mother, through her behavior, sends the signal to the offspring by lack of maternal care, there is going to be lack of firing of serotonin and that will give a signal that life is bad: "There are a lot of bad guys around and you better be stressed and anxious because otherwise you'll be shot." On the other hand, if the mother sends a signal that life is privileged, serotonin goes up, that turns on the right enzymes, that programs the genome to say, "Life is good. There is no reason to be overstressed."

Again, I believe this is an adaptive response. This is a beautiful way nature allows our fixed genomes to function in the world. I also tend to believe that this signal is not limited to the brain, but the entire body is reset to respond to it. Recently we have been doing studies where we are looking at blood cells-for example, T cells-in response to social adversity early in life and seeing the DNA methylation differences in adults that we can associate with early social adversity. Why would T cells respond? Because I think the immune system and the brain are highly interactive, and perhaps in evolution it was a package deal. If it was a bad world, there were also a lot of microbes around that you needed to take care of. So stress and the immune system always went hand in hand, and the social information and the immune information are together packaging the young child to deal with the world.

JB: I'm amazed, actually. Even if I look at the title of your program there at McGill, I think that the title alone is so epic in this shifting paradigm: The Program for the Study of Behavior, Genes, and Environment. It maybe would have sounded almost like an oxymoron 10 years ago. Your work is just to be applauded. Could you just briefly tell us about that extraordinary experiment you did where you separated the grooming mothers? I think the results are just fascinating.

Animal Studies Document the Effects of the Early-Life Environment on Stress Response Later in Life
MS: The things you can do with rodents you obviously can't do with humans. We are limited with our

human studies although they are the most interesting. We can't really randomize children to be with a good mother or a bad mother, but we can randomize animals. Michael Meaney, who worked on this system for a decade, noticed that there is a nice correlation between the amount of maternal licking and grooming, which is the way a rodent mother takes care of her pups, and stress responses later in life. The big question was, why?

We offer this epigenetic mechanism. We can show that the pups that were licked more also had a very different epigenetic program than the pups that were licked less, and you could see that difference in adult pups and adult offspring. So now the big question was, was it genetic or was it epigenetic? Because you can argue that maybe the pups that were licked more also had better genes and that's why their mother licked them more, because they had those better genes and that's why they are doing better in stress response than the others. Or was it the maternal licking that actually did that--it was not her genes, but it was her behavior that programmed the offspring to have a different stress response?

The way to do that is what we call cross-fostering. You divide the pups of one mother to two different kinds of mothers. Now, the pups that come from the same mother are split to two different mothers. One is a high-licking and grooming mother, and the other one is a low-licking and grooming mother. Now there is no genetic transfer of information between the caring mother and the child; the only information of this transfer is the behavior. What it seems is that the behaviors of the mothers serve as a vector of inheritance. This inheritance doesn't go through the germ line, it goes through the behavior of the mother. We were doing similar experiments with Rhesus monkeys, where you can separate monkeys (some are reared by mothers and some are not), and show exactly the same thing: that it is not the genes that they inherited, but it is the behavior that they are exposed to early in life that actually defines how the genes are programmed, and how they will behave as adults, and how they will sire their own offspring. So you can have, really, a transmission of a phenotype without having germ line transmitting it.

JB: I'm sure you've been asked this question more times than you ever wanted to answer, but I'm obligated to ask it. We are a world-historically, it's not just right now-of war. We have all sorts of things that produce what we call (in this country, at least) post-traumatic stress syndrome and post-traumatic stress disorder (PTSD). What I am sure you have been approached by all sorts people with--returning veterans and all the implications of war around the world--what is the message? This must be a complicated question for you to have to deal with.

Philosophical Questions and Social Policy Implications

MS: I think the message is that war has an impact well beyond the point at which the war has ended. Populations of children that were raised under the stress of war will become different kinds of adults. That is how, probably, an aggressive behavior is perpetuated from one generation to the other. That is a negative side effect, but the cross-fostering experiment suggests that you can easily erase it by changing the environment early in life.

JB: The implication of that is so profound, but it is also quite optimistic. It gives us some thought of how to reconstruct society--re-engineer it--in light of what appears to be maybe just very fundamental mechanistic science can extrapolate up, like this microscope/telescope argument I was talking about before, to become a profound motivator for a positive change in society.

MS: It has important solid policy implications. Because you can extrapolate from what you are seeing in your experimental paradigms, or small samples, a mechanism that makes sense, and you can test it by a

policy intervention. I was asked once, by a group that was working for peace in Afghanistan, what is the best intervention you can have? And I said, have women teach the kids at a very young age and break the cycle of aggression. Because if you pass aggression to the young children, it is going to be very hard to change them when they become adults. If you ask yourself, "Where should I spend the billions of dollars? Should I spend them on UN troops or should I spend them on supporting early life education?" Perhaps boosting early life education in some of these areas could have a profound impact, if we take the rat and the monkey animals as a good example.

JB: In the bibliography we're going to supply some of Dr. Szyf's more recent articles, like the one that you had, I think, in *Biochim Biophys Acta* recently on the early life environment and the epigenome.¹² And then one that I really liked was in *Trends in Molecular Medicine*, this review you had on "Epigenetic Mechanisms of Perinatal Programming of the HPA Function"-the hypothalamic/pituitary/adrenal function.¹³ This is, I would say (and I hope I'm not being disrespectful; I'm trying to be complimentary), like Hans Selye revisited at a much more profound level of genomic expression modulation. And then lastly I'll just ask you (and we'll close on this one), the article that you authored in *Nature Neuroscience*, "Epigenetic Regulation of the Glucocorticoid Receptor in Human Brain Associates with Childhood Abuse."¹⁴ That was, to me, another really profound implication. Could you describe that study?

MS: In this study essentially we wanted to translate what we saw in the rats to humans. It's impossible, obviously, to translate it perfectly well. The question we asked is, can we see in brains of adults the methylation patterns that we would associate with early life child abuse? In the rats we saw differences in the way the glucocorticoid receptor was programmed based on maternal care, and in humans we asked if we can see whether early life abuse ended up in a different methylation pattern in the brain when these victims died.

We had three groups of brains: we had victims who died from suicide who were abused as children (this was quite a large group); and then victims who died by suicide who were not abused as children (so we could actually test whether it was suicide that caused the methylation changes or whether it was the child abuse that did that); and, of course, the control group of people who died accidentally and were not abused as children. We saw some distinct DNA methylation differences in glucocorticoid receptor genes. Since then, we expanded this to other parts of the genome and there are profound differences all over the genome that we can associate with early childhood abuse, suggesting that what you do to children early in life is actually memorized in the brain, and can affect their behavior years and years later in life.

Why does this happen? I still believe it's an adaptive response. Child abuse is a signal. The child is getting a signal--"This is really a bad world"--and he or she programs the brain to deal with this kind of world. And if that child is found in a civilized world, there is a tremendous disconnect between the programming and the kind of world that person is living in. I think the major implication of it is that whatever we do counts, and is memorized, and nothing is really transient. There are mechanisms that kind of print those things in our genome and program our genome to respond to those signals.

JB: Well, in close, I know that you have received tremendous accolades for your work and acknowledgement of both the high science that you've done and the implications of the science, but I just want to add my note to probably the hundreds that you've gotten. Hopefully the people who will listen to this interview let it kind of work over their nervous systems and start to see many things that come out of

what you said, one of which is the power that basic research can have in ultimately creating a different sense of our reality. It moves us beyond what we thought were facts to a whole other landscape of what may be the real facts, at least facts as we know them at a different time. That, then, translates and maps itself ultimately into the social milieu, and produces-hopefully-a stickiness for us to reevaluate how we've actually looked at dysfunctions at many levels, from histopathology to social pathology, and those things that we might have thought were determined indelibly and could not be modified which now give, through your work, a much more optimistic potential for plasticity and modification. And lastly, the implication that structure and function are intimately interrelated and that structure is constantly changing-morphing-and being altered through its interaction with its environment. This is a duality, and that extraordinary dance-that orchestration-is what plays out in peoples' lives that ultimately gives rise both to their own health and disease patterns, and might be even transmissible without changing their genes, but rather the epigenome into that of their offspring. Very profound concepts here. As just one of probably thousands of people admiring your work, I want to thank you for the diligence that you put into it and the way that you describe it.

MS: Thank you so much.

JB: It has really been a privilege.

Highlights from Dr. Szyf's Interview and Connections to Other Researchers

I'm sure your impression of Dr. Szyf is the same as mine. Once you've heard this story from him, you are never the same. This is absolutely one of those paradigm-shifting moments in the history of biomedicine, science, and the sociological and cultural aspects of it. We've been building up to this point for the better part of a couple of years now on Functional Medicine Update, with the remarkable opportunities we've had to speak with the people who are defining this domain, creating this space, and moving the ball forward, so to speak, in our understanding of the mechanisms of disease, and where dysfunction arises, and this whole context of gene/environment interaction. We've had Randy Jirtle speak to us twice, now, about his pioneering work in epigenetics.

We've had Michael Skinner speak to us. We've had the extraordinary discussion about hormesis and how low levels of effects at the right metabolic and epigenetic pressure points can create more profound influences on function than we would have predicted (this nonlinear dose response relationship that we've talked about). We've had presentations that relate to environmental aspects of signals that influence, then, gene expression, like the gut biome discussions we've had with the group from Louvain University in Belgium, Dr. Cani and Dr. Delzenne. We've looked at the effects that the oral cavity has through gut microbial activity in the peridontium, and how that can send signals to modulate expression patterns in the immune system that are associated with diseases such as cardiovascular disease. The list goes on; I won't do an exhaustive review. But just to remind you of this landscape that we've been describing that really paints a different picture to the origin of disease than that which most of us learned in our organ-system-specific, histopathology-oriented educational background. This is the time of tremendous change. This is the time where the dominant view as to how illness emerges is starting to really take this more plastic view that was so eloquently described by Dr. Moshe Szyf in his interview.

I'd like to follow up with a few of the points that he made just to make sure that we didn't lose some of the substance, because there was so much density, wasn't there, in his discussion? It was like, "Oh my word, I'm going to just capture that idea for a moment. I've got to let this settle in." Each one of those was

almost iconic as we went through the discussion with him.

Let's backtrack and review. We started off with Dr. Szyf talking about targeting DNA methylation and how it relates to malignancy, and the fact that there is alteration in cancer cells in their methylation patterns, both hypomethylation and hypermethylation, and that relates to the dysregulation of genes and their dedifferentiation and embryonic transition into this replicative state. He then went on to say that this might explain why, in animal studies where you prohibit the exposure to proper methylating nutrients (folate, B12, B6) and expose them to low levels of carcinogens, that their relative incidence of carcinogenesis and cancer goes up dramatically over the animals that are properly nourished with regard to these folate nutrients. In fact, he even went on to talk about studies that have been done about its relationship to low folate sufficiency (low one-carbon pathway of sufficiency) and relative production of cancer, and even drugs that induce demethylation and how that can encourage cancer.

Dr. Szyf then also led us to recognize that the methylation patterns don't work in isolation, they crosstalk with other genomic regulators of expression such as acetylation. And acetylation takes us into a different family of enzymes (these are the histone deacetylases that remove acetyl groups from the genome and the histone acetyl transferases that put acetyl groups on the genome). So we have the methylating and demethylating enzymes, and we have the acetylating and deacetylating enzymes, and those interrelate in terms of their crosstalk, one with the other, so if you modulate histone acetylation/deacetylation, you also influence methylation because you may open up the genome to a place where methyl groups can then be delivered or removed. The SIRT1 gene (the so-called longevity genes) are associated with NAD-dependent histone deacetylase activity, and we know there are a variety of phytochemicals that activate these acetylation/deacetylation activities, like resveratrol that has gotten a tremendous amount of attention, and EGCG (epigallocatechin gallate). We recognize that curcumin plays roles in these pathways, so there are a variety of phytochemicals (plant-derived materials) that modulate, in a very subtle way, these epigenomic patterns and can then lead to the expression of different chapters in our book of life, so to speak, like those relates to the SIRT genes, which are signaling information genes related to insulin signaling, and inflammation, and cellular cycle regulation, meaning they have roles in prevention and management of things like diabetes, heart disease, inflammatory disorders like arthritis, and dementia, and cancer. These are very fundamental mechanisms that cut across many different disease families.

Recently I was at a very interesting meeting at Harvard University Medical School that was attended by a variety of leaders in the field of basic and clinical science, including the CEOs of a number of the major pharmaceutical companies, and the presidents of a number of the major medical schools, and the CEOs of large insurance healthcare providers. One of the principal speakers on the podium who was talking about what we have learned in the last ten years in basic science said, "What we have learned is that the blockbuster agents of the future are not blockbuster drugs to treat a disease, but blockbuster agents to modulate the mechanisms of disease." He said that we should be treating blockbuster mechanisms, not blockbuster diseases. I thought that was a profoundly functional medicine-esqe statement. It really shows that this concept that we in functional medicine have been talking about for 20-plus years is really starting to have a general sense of traction within the nature of medical education and ultimately medical logic and treatment.

Another of the presenters at this meeting was Dr. Jeffrey Flier. Jeff Flier is the Dean of Harvard Medical School and is revamping the curriculum there and went on to say that they have, at this point, pretty much

done away with the traditional method of teaching medical students the organ-specific type of organ-systems approach, where you studied an organ system, shut the textbook, took a test, and then moved on to the next one, as if they were isolated, one to the other. He went on to say that they have abandoned that approach and they are now integrating their approach in such a way as to talk about systems biology, and cross-functional activity, and shared aspects of mechanism that ultimately give rise to dysfunction that become disease. That was a pretty exciting moment for me to hear the Dean of Harvard Medical School talk about principles that we've been trying to promote and discuss within Functional Medicine Update for 28 years.

Dr. Szyf presented information to us about folate cycle, and methylation dependency, and how S-adenosylmethionine may serve as a very powerful therapeutic agent for the management of metastatic cancer. He described how it both assists in methylation and blocks demethylation, and how that interrelates, then, with regulating gene expression and keeping certain characteristics, like oncogenes, silenced, so you don't get into this dedifferentiated proliferative state for a cell. These were very, very interesting and profound new ways of thinking about cancer and some of the modifiable aspects.

He went on from that to talk about autoimmune disease. I thought that was a very nice and fascinating step over because you might think this is a whole departure from talking about malignancy. But really if you think about it, with autoimmune disease we get clonal increases in various components of the immune system. Various types of T cells are clonally increased and we get an overactive number of cells. You start to have an immune system that has kind of gone into overdrive, so to speak. Is there a shared connection between malignancy and immune hyperactivity that relates to clonal increases in cells of the immune system and their heightened vigilance?

He talked about the fact that in an autoimmune disease (particularly, he was referring to systemic lupus erythematosus), demethylation is a common feature in the genome of the immune cells in patients with SLE. He also talked about drug-induced lupus. Most commonly the family of drugs that do this are demethylating drugs. To me, it was very gratifying for him to say that because it was about ten years ago that I did a seminar series on the autoimmune disease/environment connection, in which I used as an example the fact that an alteration in genomic messaging associated with demethylating drugs was one of the precipitating factors in drug-induced arthritis, and particularly in SLE. I think-again-the body of the understanding of these things is starting to gain visibility. We are starting to get a higher degree of resonance, so to speak, around these ideas.

Dr. Szyf also went on to talk about valproic acid, this anti-epileptic drug which now may have off-label use for things that are related to methylation/demethylation defects, like things pertaining to Alzheimer's dementia, or things pertaining to arthritis, which were not in the initial approval of the drug, but because of the mechanism of action having this effect on epigenetics, this may prove to be a very useful secondary application for certain medications.

I asked him: "Can you diagnose this solely by looking at blood homocysteine?" He responded: "No."

Obviously this question of methyl dynamics within cells is much more than just the homocysteine outcome as it relates to plasma or serum levels, and what we are really looking at is mechanistic effects inside cells, not the "smoke" that falls outside cells that is the homocysteine level. He thought that was not a really sensitive biomarker for derangements at the molecular and cellular level that are related to epigenomic methylation.

Dr. Szyf also made a very nice point in talking about how agents of diet can possibly, in a complex diet, have a very different orchestrated set of signals that influence the epigenome, versus those in a diet that is very simple, has been chemically modified, and may influence altered epigenomic patterns. He also talked about the effects of various drugs and the role that they have on epigenetic modulation. We didn't have time to go into it in great detail, but this article that he authored titled, "Epigenetic Side-Effects of Common Pharmaceuticals: A Potential New Field in Medicine and Pharmacology," is pretty profound. In this article, he talks about how the epigenome that refers to the overall epigenetic state of a cell serves as an interface between the environment and the genome, and it is dynamic and responsive to environmental signals, not only during development, but throughout life.

We used to think these epigenomic modifications were only occurring in embryonic life, but now it is being seen there is some plasticity throughout all of our life. It is becoming increasingly apparent that chemicals can cause changes in gene expression that persist long after exposure has ceased that appears to relate to epigenetic marks that are laid down through chemical exposures. This includes things like bisphenol-A, for instance, and other low-level environmental chemicals that may have hormetic effects on altering cellular signaling, well below what we consider traditional toxicological effects. These are the more subtle orchestrated effects-the fine tuning knobs-that may influence function over long periods of time.

Drugs may alter epigenetic homeostasis also-direct effects of drugs could be influencing chromatin architecture or DNA methylation. Examples include such things as the anti-hypertensive medication Hydralazine, that is known to inhibit DNA methylation. An example of an indirectly acting drug is Isotrienerin, which is a transcription factor activator, and therefore that two-tier mechanism could be involved with both indirect and direct effects that influence drugs' influence on that individual's function well after the person has even stopped taking the drug. They have modulated the epigenome in such a way as to kind of freeze a certain functional structure in place that follows them. These could be epigenetic side effects that have long memory effects, basically, of pharmaceuticals.

Dr. Szyf goes on to say that if this model is looked at seriously, this could lead to a new approach to pharmacology, which would be called pharmacoepigenomics, the impact of which might be equal to or greater than that of pharmacogenetics itself, and that we have to look at these kind of longer term potential implications on modulating peoples' epigenome and what influence that could have on off-target adverse side effects or other things that appear later in life. I think that was a very interesting part of his story-things that, again, we might not immediately think of that come out of this conceptual framework.

Also, he talked about the extraordinary influence that behavior and environment have. These could be environmental chemicals, like I mentioned such things as pesticides, herbicides. Or in the case of bisphenol A, plasticizers that at very low levels that we might think of as normally having benign effects might influence, subtly, the epigenome in such a way as to regulate function downstream and lock a person into a different physiological state of function.

We transitioned from that into what is considered by many to be the "I don't believe it" part of the story, which is that behavior can modify the epigenome, that experience in life can modify the epigenome, that laughter, fun, joy, bliss versus rage, anger, fear, and isolation can set epigenetic marks that create a whole different way for cells-not just in the immune system itself, but other cells within the body-to express their function. That conceptual idea is so powerful that it almost rivets you in your place. This is when he

starts talking--from a fundamental basic science and then later an animal science, perspective--about the rearing of the rat pups by their mothers, and the translocation effects, and how these effects are transgenerationally transmissible through breeding. He says it may take three or four generations to breed out these characteristics to bring them back to their F0 generation of genomic methylation. These are almost heretical thoughts compared to the way that many of us learned genetics, embryology, behavioral science, and even medicine. It really attacks the functional concept at a very dynamic, kinetic, real world way that puts us all in the center of our own life experience. And it gives the relationship between the provider and the patient a much more...I would call it dynamic environment to engage both in discussion and therapy as it pertains to modulating the patient's environment and reconstructing an epigenome that will send the signals of success rather than the signals of being at war.

When Dr. Szyf was talking through this extraordinary story, he mentioned that from his work, he has a different view about the origin of disease than what has been historically accepted. His view is that rather than these diseases being hard-wired into our genes, that our responses that give rise to disease are adaptive responses to an altered environment, in which the outcome over time, through the epigenetic modulation, becomes a disease. In other words, we don't have diseases wired into our genes, we have physiologic responses to environmental modulation wired into our genes that then creates an outcome that's later called our phenotype of health or disease.

You might think that this is just word-splitting and I'm just playing an intellectual exercise with you, but I believe this is a profoundly significant conceptual difference from the way that we have thought about the origin of disease that leads to a profoundly different way of managing the origin of disease, and ultimately treating disease in and of itself. I'm not talking so much about emergency room or acute care. I'm talking about ambulatory care with chronic age-related diseases, where you have the time to really create different signals that could influence positively the reconstruction of the epigenome and regulate the gene expression away from the signals of alarm to the signals of being at peace. I think these are really dramatic examples of how we would contextualize this form of health care, because it's not like taking an antibiotic from a gram-negative bacterial infection in which you expect to block that cell wall synthesis of the microbe and the next morning that person is going to be over their fever and feeling better. In this case we are reshaping the way that our book of life has been guarded in our vault called the genome, and reshaping how it is going to be expressed, and signaled, and modulated into its pattern that we see as a phenotype (the collection of cells to tissues, to organs, to organ systems, to the whole organism).

Dr. Szyf talked about the fact that, yes, we know about the genome's influence on the immune system, we know about its effect in the central nervous system, but we now recognize that these epigenomic influences are occurring in all cells-not just the rapidly dividing cells, but also in cells that we might have considered to be post-translational, like neuronal cells, where you might have said, "Well they are way over the time where epigenetics will have any influence on them because they're not dividing." Now we see that these marks (these enzymes) are still active in these cells. Even if the genes are not in and of themselves dividing in mitosis, the genes are being regulated in their cellular biochemistry as a consequence of the activity of these enzymes (the methylating/demethylating, acetylating/deacetylating, and so forth-enzymes that are modeling and remodeling the epigenome.

These are really, really profound concepts that marry and dock directly with the whole fundamental patient-centered medicine constructs of functional medicine. They really represent Roger Williams'

biochemical individuality concepts at even a deeper level, because it's not just the genes in and of themselves, but it is how they have been epigenetically marked that might influence the function of that organism. It takes the molecular medicine concept of Linus Pauling and it moves it into an even more robust kinetic environment. The life of a cell becomes this dynamic dance between the pluripotentiality of the genome and its outside environment. And then we take that and we start applying it to conditions like neuropsychiatric conditions, and we think of Dr. Abram Hoffer's extraordinary work in orthomolecular psychiatry, and how nutrients, as members of the B complex vitamin family, can alter certain neuropsychiatric disorders in individuals who may have been suffering from conditional insufficiencies of epigenomic modulation. It's a whole new frontier of explanation at a mechanistic level of what we have observed phenomenologically for some time, but has been dispelled, or dismissed, or said is not true because we don't have a mechanism to rationalize the observation.

We have seen published studies that have dismissed folate in large clinical intervention trials, saying it really has not been proven to be effective. You have to ask the question: "Have we been able to segment and stratify these studies correctly, so that those individuals with the most dynamic responsiveness of their epigenome to that principle, knowing that there are multiple factors that regulate these pathways, that we have selected the right people because maybe what happens if by not segmenting we lose the ones that are most responsive in the noise of those that don't have that unique contribution to their etiology?" It's a different way of looking at the way we design research, at how we evaluate outcomes, and actually how we would even set up studies to look at responders and discriminate from non-responders. Dr. Szyf said, as you heard, that these are all testable hypotheses. Using a different model, we can now start to karyotype the epigenome. We can start looking at these different methyl patterns, and promoter regions in the CpG islands of cells where methylation occurs, and look at how these CpG islands are methylated and demethylated under certain principles, and start to tie together certain genetic characteristics with environmental modulators that then produce outcomes that could lock a person into the physiology of alarm.

And then lastly, of course (and not least in this discussion) was the social science implications, the societal design, the nature of us as real people in a complex world-our political and economic structures and the way that we relate to one another in tribes, so to speak. Or the feeling of isolation, the feeling of no attribution, the feeling of no love and how they translate through these signaling systems into what might be considered altered epigenomic regulation and ultimately physiological response of alarm, which tracks back with inflammation, and heart disease, diabetes, cancer, osteoporosis, and dementia and so forth. What are we doing with our children as we have exposed them to this environment of fast-paced life environments that are associated with violence and with lack of respect? What are all of the messages that we are getting and how are they imprinting epigenomic methylation, demethylation, acetylation, and so forth, the architecture of the epigenome that then regulates how the pluripotentiality of the genes of that individual would be expressed in their life. These are very, very profound concepts and topics that are really at the forefront of this tree that functional medicine set up years ago to try to understand, in the complexity of a systems biology approach to medicine, the ultimate etiology of chronic age-related diseases in a way that you can do something about it at the origin rather than just at the symptom and sign level up in the high order of the tree. Instead of how the leaves get brown, we should be treating the roots and the trunk of the tree.

With that, we thank Dr. Szyf. What a profoundly moving, paradigm-shifting, bias-altering experience we've all just been exposed to thanks to not only his extraordinary work, but the way he described it. I

look forward seeing you in December, next month.

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