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Dr. Bland begins this issue with the interview.

Clinician/Researcher of the Month

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Dr. Moshe Szyf is currently a Professor of Pharmacology at McGill University. He completed his graduate education and earned his PhD at Hebrew University in Jersalem, followed by post-doctoral work in genetics at Harvard University. For the last three decades, Dr. Szyf's research has focused on understanding the basic principles of DNA methylation machinery. In 1994, following a decade of studies of the DNA methyltransferase gene and its regulation, Szyf proposed that DNA methyltransferase is a prime anticancer target. The Szyf lab has developed antisense and direct inhibitors of DNA methyltransferase and has demonstrated their efficacy as anticancer agents in preclinical models. They have also demonstrated that DNA methylation is a reversible biological signal. This has paved the way to realizing that DNA methylation could be modified after birth and be responsive to external environmental signals (the concept of epigenetics).

Dr. Bland has been following Dr. Szyf's publications for a number of years and has long-anticipated this opportunity to discuss his research. He makes note of the fact that McGill University was also the location of Dr. Hans Selye's laboratory, where Dr. Selye conducted groundbreaking research on stress and human physiology. In describing his early work and what drew him to the field epigenetics, Dr. Szyf describes DNA methylation as telling the whole story about the life of an individual: "Something that is, on the one hand, dynamic, and on the other hand very stable."

Dr. Bland and Dr. Szyf begin their discussion with his research on cancer. In a 2006 article titled "Targeting DNA Methylation in Cancer," Dr. Szyf writes: "The normal pattern of distribution of DNA methylation is altered in cancer. A number of genes are regionally hypermethylated but many parts of the genome are hypomethylated. Hypermethylation of tumor suppressor genes is involved in silencing strategic genes. DNA hypermethylation has received much attention and a number of clinical trials are

underway with different inhibitors of DNA methylating enzymes. It is now becoming clear however that hypomethylation also plays a role in cancer by activating genes required for invasion and metastasis." In another article he writes: "Understanding the relative roles of hypomethylation and hypermethylation in cancer has clear implications on the therapeutic use of agents targeting the DNA methylation machinery."

From cancer, Dr. Bland and Dr. Szfy move to a discussion of the epigenetic model and autoimmune disease. Dr. Szyf specifically discusses the global DNA hypomethylation seen in lupus. This leads to a conversation about therapeutics and a paper titled "Epigenetic Side-Effects of Common Pharmaceuticals: A Potential New Field in Medicine and Pharmacology," which was authored by Dr. Szyf and his colleague, Dr. Antonei Csoka, and was published in *Medical Hypotheses* in 2009. In this article Dr. Szyf writes: "It is becoming increasingly apparent that chemicals can cause changes in gene expression that persist long after exposure has ceased. Here we present the hypothesis that commonly-used pharmaceutical drugs can cause such persistent epigenetic changes." He goes on to discuss examples of both direct and indirect mechanisms that may alter epigenetic homeostasis. He continues: "Any epigenetic side-effect caused by a drug may persist after the drug is discontinued…If this hypothesis is correct the consequences for modern medicine are profound, since it would imply that our current understanding of pharmacology is an oversimplification. We propose that epigenetic side-effects of pharmaceuticals may be involved in the etiology of heart disease, cancer, neurological and cognitive disorders, obesity, diabetes, infertility, and sexual dysfunction."

Dr. Szfy and his research group have done many studies on DNA methylation and epigenetic effects in animals, some of which have been concerned with maternal nutrition and stress during fetal development and also during early life. They specifically discuss a series of studies Dr. Szyf has worked on with his colleague, Dr. Michael Meaney, and the articles that have been published as a result, such as "The Social Environment and the Epigenome," "Environmental Programming of Stress Responses through DNA Methylation: Life at the Interface between a Dynamic Environment and a Fixed Genome," and "Maternal Care, the Epigenome and Phenotypic Differences in Behavior."

Because of his hypothesis that early life social adversity leaves a mark on the epigenome and can affect stress response, health, and mental health later in life, Dr. Bland and Dr. Szyf include such topics as war and childhood abuse in their discussion. Dr. Szyf offers his opinion on how a cycle of aggression may be broken, perhaps with more emphasis on and investment in early childhood education programs. He describes an extraordinary study he did involving postmortem examination of human brain tissue from individuals who had and had not experienced childhood abuse (as well as controls). Distinct DNA methylation differences in the glucocorticoid receptor genes were noted, and in addition, he tells Dr. Bland, "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."
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Interview Commentary

Dr. Bland considers his conversation with Dr. Moshe Szyf to be a landmark event in the history of his *Functional Medicine Update* interviews. He states, "This is absolutely one of those paradigm-shifting moments in the history of biomedicine, science, and the sociological and cultural aspects of it." He wraps up the issue by revisiting some of the points mentioned during the interview and commenting on them more thoroughly. He again reviews some of Dr. Szyf's publications, which are extensive and varied. He also attempts to connect some of Dr. Szyf's research with that of other researchers interviewed for Functional Medicine Update on the topic of epigenetics, including Dr. Randy Jirtle and Dr. Michael Skinner. He closes by describing Dr. Szyf's interview as "a profoundly moving, paradigm-shifting, bias-altering experience."

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