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Ongoing Research on the Epigenome

Dr. Bland has been following the research of Dr. Moshe Szyf and his colleagues at McGill University for some time. He begins this issue with a discussion of articles by this group, including one published in 2009 titled "The Early Life Environment and the Epigenome." In this article, key questions are explored: What are the mechanisms that mediate the effects of the early environment on our health? What is the impact of the environment during adulthood? How reversible are the effects of early life later in life? REF #1-2

Dr. Bland moves on to discuss an article titled "Differential Epigenomic and Transcriptomic Responses in Subcutaneous Adipose Tissue Between Low and High Responders to Caloric Restriction" that appeared in the *American Journal of Clinical Nutrition* in 2009. The objective of this study, which was carried out by a group of Canadian researchers, was to determine whether epigenetics and gene expression changes may play a role in weight-loss responsiveness. Overweight/obese postmenopausal women were recruited for a standard 6-month caloric restriction intervention. Abdominal subcutaneous adipose tissue biopsy samples were collected before and after intervention, and the epigenomic and transcriptomic profiles of the high and low responders to dieting, on the basis of changes in percentage body fat, were compared using microarray analysis. Significant DNA methylation differences at 35 loci were found between the high and low responders before dieting, with 3 regions showing differential methylation after intervention. This and other data from the study show that both DNA methylation and gene expression are responsive to caloric restriction and provide new insights about the molecular pathways involved in body weight loss. REF #3

Vitamin D Signaling in Immune-Mediated Disorders

The active form of vitamin D is a central player in calcium and bone metabolism. More recently, important immunomodulatory effects have been attributed to this hormone. Dr. Bland discusses a 2008 review, in which the authors aimed to summarize the data on the role of vitamin D in the pathogenesis of immune-mediated disorders, with special focus on type 1 diabetes, and on the therapeutic opportunities for vitamin D in the prevention and treatment of this autoimmune disease in mouse models and humans. REF #4

As a part of this discussion, Dr. Bland mentions a recent study involving women (breast cancer survivors) on aromatase inhibitor therapy and experiencing musculoskeletal problems (joint pain and stiffness, bone and muscle pain, and muscle weakness. The primary purpose of this pilot exploratory study was to determine whether serum levels of 25-hydroxyvitamin D concentration were below normal in these women, and if musculoskeletal symptoms were related to these low vitamin D levels. This study

documented a significant relationship between vitamin D levels and muscle pain in this group of women on aromatase inhibitor therapy. REF #5-6

When Can You Have Too Much of a Good Thing?
Dr. Bland finishes his discussion of vitamin D by talking about what he feels is an important 2010 article, "The Yin and Yang of Vitamin D Receptor (VDR) Signaling in Neoplastic Progression: Operational Networks and Tissue-Specific Growth Control." Evidence implicates vitamin D receptor (VDR) or its natural ligand in modulation of tumor growth, but both human and animal studies indicate tissue-specificity of effect. Epidemiological studies show both inverse and direct relationships between serum 25(OH)D levels and common solid cancers. The commentary in the article highlights some differences of VDR growth control relevant to colonic, esophageal, prostate, pancreatic, and other cancers. REF #7

Clinician/Researcher of the Month

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Ego Seeman is Professor of Medicine and Endocrinologist at the Austin Hospital, University of Melbourne. He is past president of the Australian and New Zealand Bone Mineral Society, and a board member of the International Osteoporosis Foundation (IOF), the International Bone Mineral Society, and Osteoporosis Australia. Professor Seeman is the author of some 270 publications and 22 book chapters. He has contributed to studies of the definition, epidemiology, pathogenesis, and treatment of osteoporosis in women and men, as well as studies of corticosteroid-related disease, genetics, skeletal growth, and structural diversity in determining bone strength. In 2002, Professor Seeman was awarded the American Society of Bone Mineral Research Fred C. Bartter Award for his work. In 2009, Professor Seeman was awarded the prestigious IOF Medal of Achievement. The award honors individual researchers who have significantly advanced the field of osteoporosis through their original and outstanding scientific contributions.

Dr. Bland and Professor Seeman discuss his research, starting with Professor Seeman's 2006 article published in *The New England Journal of Medicine*, "Bone Quality—The Material and Structural Basis of Bone Strength and Fragility." They also discuss current concerns about the use of bisphosphonates. Professor Seeman mentions important research by several of his colleagues, including Dr. Roger Zebaze, Dr. Pierre Delmas (now deceased), and Dr. Gerard Karsenty.

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