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Epigenetics and Dietary Factors: Colorectal Cancer
Observational studies lend support to the impact of environmental factors, especially diet, on colorectal cancer (CRC) carcinogenesis. Advances have been made in understanding the biology of CRC carcinogenesis, in particular, epigenetic modifications such as DNA methylation. Compared with other human cancers, promoter gene methylation occurs most commonly within the gastrointestinal tract. Emerging data suggest the direct influence of certain micronutrients, such as folic acid and selenium, on DNA methylation. A review of these dietary factors was published in 2008 in the journal *Epigenetics*. REF #1

The Role of Maternal Nutrition on Disease Susceptibility Later in Life
Major epigenetic programming events take place during gametogenesis and fetal development and are thought to have long-lasting consequences on adult health. Post-translational modifications of histones are the subject of intensive investigations with the aim of decoding how they regulate, alone or in combination, chromatin structure, genomic stability, and gene expression. REF #2

In a review paper published in the *New England Journal of Medicine* in 2008, a group of international researchers state that many lines of evidence, including epidemiologic data and data from extensive clinical and experimental studies, indicate that early life events play a powerful role in influencing later susceptibility to certain chronic diseases. They contend that both the genome and the epigenome interactively influence the mature phenotype and determine sensitivity to later environmental factors and the subsequent risk of disease. In this review, the authors synthesize evidence from several disciplines to support the contention that environmental factors acting during development should be accorded greater weight in models of disease causation. REF #3

Epigenetic Modulation and Metabolic Syndrome
The relevance of epigenetics to the metabolic syndrome and how it may affect cancer is beginning to capture the interest of the scientific community. Dr. Bland discusses a review published in the *American Journal of Clinical Nutrition* in 2007 that focuses on data supporting the hypothesis that diet-induced changes in epigenetic programming during fetal and postnatal development may precipitate the metabolic syndrome. REF #4

B-Vitamins and Disease Causality
Genetic information has already contributed greatly to the understanding of B-vitamin metabolism and the heterogeneity of responses to intake. It has the potential to provide further nutritional insights and to assist in the elucidation of causal mechanisms. Dr. Bland cites an article published in the *Proceedings of the Nutrition Society* in his discussion of research pertaining to epigenetics and disease development. REF #5

New Article by Dr. Bland
Dr. Bland discusses a recent editorial he wrote for *Alternative Therapies in Health and Medicine* titled "The Future of Nutritional Pharmacology." In this article, Dr. Bland takes the reader through the lineage of the field of nutrient pharmacology and addresses the question: As the basic science of nutrigenomics unfolds in the 21st century, how will it be applied to improve health outcomes? REF #6

Follow-Up on Hormesis: Dietary and Environmental
As a follow-up to his interview with Dr. Edward Calabrese in the October 2008 issue of FMU, Dr. Bland discusses new articles related to the concept of hormetic dietary phytochemicals. Researchers from the National Institute on Aging have published an article in *Neuromolecular Medicine* that discusses emerging findings suggesting that several dietary phytochemicals benefit the nervous system and, when consumed regularly, may reduce the risk of disorders such as Alzheimer's and Parkinson's diseases. In this article, the authors describe the hormesis hypothesis of phytochemical actions with a focus on the Nrf2/ARE signaling pathway as a prototypical example of a neuroprotective mechanism of action of specific dietary phytochemicals. REF #7

The Mediterranean diet is rich in phytochemicals and there is now some consensus about recommending it for the prevention of coronary heart disease (CHD) and cancer. A new article by Dr. Michelle de Lorgeril and Dr. Patricia Salen titled "The Mediterranean Diet: Rationale and Evidence for its Benefit" has recently been published. This article focuses on how the many micro- and macronutrients characteristic of the Mediterranean diet interact in a synergistic way to induce states of resistance to chronic diseases. REF #8

In the September 17, 2008 issue of the *Journal of the American Medical Association*, Lang, et al published the results of a study using data from the National Health and Nutrition Examination Survey 2003-2004 on the association of urinary bisphenol A (BPA) concentration with medical disorders and laboratory abnormalities in adults. In an editorial response, authors Frederick vom Saal, PhD, and John Peterson Myers, PhD, call for follow-up longitudinal studies to be made a high priority based on the findings of Lang and colleagues suggesting that BPA is linked to some of the most significant and economically burdensome human diseases. The authors urge US regulatory agencies to declare BPA a "toxic chemical" requiring aggressive action to limit human and environmental exposures. REF #9-10

Dr. Bland concludes this discussion by referring to two additional and recent studies on the Mediterranean diet, one showing reduced prevalence of clustered cardiovascular risk factors, and the other addressing the association between dietary patterns and indices of bone mass in a sample of Mediterranean women. REF #12-13

Clinician/Researcher of the Month

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Dr. Michael Skinner is a reproductive biologist whose laboratory has been based at Washington State University (WSU) in Pullman, WA since 1996, when Dr. Skinner was recruited by Washington State University to form and direct the Center for Reproductive Biology, a joint center with WSU and the University of Idaho (UI). In 2002, Dr. Skinner also established the Center for Integrated Biotechnology. The WSU and UI Center for Reproductive Biology is the largest university-based reproductive biology research center in the world. It currently has program areas including testis biology, fish reproduction, reproductive toxicology, and plant reproduction. The WSU Center for Integrated Biotechnology research program project areas provide an interdisciplinary integration of research in the biotechnology area.

Dr. Skinner's laboratory has had a long-standing research program to study gonadal development and function on a molecular level. More recently, the ability of environmental factors to act on gonadal development has been shown to cause epigenetic transgenerational disease. Dr. Skinner and his colleagues have found that environmental toxicants (i.e. endocrine disruptors) have the ability to modify local cell-cell interactions in the testis and ovary. Further study of this phenomena and its impact on disease etiology is in progress.

Dr. Bland and Dr. Skinner discuss his background, including details of a 2005 article published in *Science* magazine. They discuss supportive evidence for epigenetics as a mode of action, including the research of Dr. Randy Jirtle at Duke University and Dr. Marcus Pembrey in England. Dr. Skinner provides a brief history of the field of epigenetics, which actually dates back to research begun in the 1940s. They also look toward the future, and discuss Dr. Skinner's thoughts on future directions for epigenetics research. REF #13-18

References

1. Arasaradnam RP, Commane DM, Bradburn D, Mathers JC. A review of dietary factors and its influence on DNA methylation in colorectal carcinogenesis. *Epigenetics*. 2008;3(4):193-198.
2. Delage B, Dashwood RH. Dietary manipulation of histone structure and function. *Annu Rev Nutr*. 2008;28:347-366.
3. Gluckman, PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. *N Engl J Med*. 2008;359(1):61-73.
4. Ross SA, Milner JA. Epigenetic modulation and cancer: effect of metabolic syndrome? *Am J Clin Nutr*. 2007;86(3):s872-877.
5. Haggarty P, B-vitamins, genotypes and disease causality. *Proc Nutr Soc*. 2007;66(4):539-547.

6. Bland J. The future of nutritional pharmacology. *Altern Ther Health Med*. 2008:14(5):12-14.
7. Son TG, Camandola S, Mattson MP. Hormetic dietary phytochemicals. *Neuromolecular Med*. 2008 Jun 10. [Epub ahead of print]
8. De Lorgeril M, Salen P. The Mediterranean diet: rationale and evidence for its benefit. *Curr Atheroscler Rep*. 2008;10(6):518-522.
9. Lang IA, Galloway TS, Scarlett A, Henley WE, Depledge M, et al. Association of urinary bisphenol A concentration with medical disorders and laboratory abnormalities in adults. *JAMA*. 2008;300(11):1303-1310.
10. Vom Saal FS, Myers JP. Bisphenol A and risk of metabolic disorders. *JAMA*. 2008;300(11):1353-1355.
11. Sanchez-Tainta A, Estruch R, Bullo M, Corella D, Gomez-Gracia E, et al. Adherence to a Mediterranean-type diet and reduced prevalence of clustered cardiovascular risk factors in a cohort of 3,204 high-risk patients. *Eur J Cardiovasc Prev Rehabil*. 2008;15(5):589-593.
12. Kontogianni MD, Melistas L, Yannakoulia M, Malagaris I, Panagiotakos DB, Yiannakouris N. Association between dietary patterns and indices of bone mass in a sample of Mediterranean women. *Nutrition*. 2008 Oct 10. [Epub ahead of print]
13. Anway MD, Cupp AS, Uzumcu M, Skinner MK. Epigenetic transgenerational actions of endocrine disruptors and male fertility. *Science*. 2006;308(5727):1466-1469.
14. Fraga MF, Ballestar E, Paz MF, Ropero S, Setien F, et al. Epigenetic differences arise during the lifetime of monozygotic twins. *Proc Natl Acad Sci USA*. July;102(30):10604-10609.
15. Kaati G, Bygren LO, Pembrey M, Sjöström M. Transgenerational response to nutrition, early life circumstances and longevity. *Eur J Hum Genet*. 2007;25(7):784-790.
16. Lee DH, Lee IK, Porta M, Steffes M, Jacobs DR Jr. Relationship between serum concentrations of persistent organic pollutants and the prevalence of metabolic syndrome among non-diabetic adults: results from the National Health and Nutrition Examination Survey 1999-2002. *Diabetologia*. 2007;50(9):1841-1851.
17. Crews D, Gore AC, Hsu TS, Dangleben NL, Spinetta M, et al. Transgenerational epigenetic imprints on mate preference. *Proc Natl Acad Sci USA*. 2007;104(14):5942-5946.
18. Olshansky SJ, Passaro DJ, Hershow RC, Layden J, Carnes BA, et al. A potential decline in life expectancy in the United States in the 21st century. *N Engl J Med*. 2005;352(11):1138-1145.