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Start with a Smile
After years of commenting on the subject of randomized, placebo-controlled clinical trials, Dr. Bland opens this issue by introducing listeners to a piece published in the *British Medical Journal* titled "Parachute Use to Prevent Death and Major Trauma Related to Gravitational Challenge: Systematic Review of Randomised Controlled Trials." He quotes, from the authors' conclusions, "As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials. Advocates of evidence based medicine have criticized the adoption of interventions evaluated by using only observational data. We think that everyone might benefit if the most radical protagonists of evidence based medicine organized and participated in a double blind, randomised, placebo controlled, crossover trial of the parachute." REF #1

Blockbuster Drugs in the Era of Personalized Medicine
Developing and delivering drugs that fit the individual patient's biology and pathophysiology is one of the biggest challenges facing biotechnology and pharmaceutical companies in the 21st century. The focus is changing from blockbuster medicine to personalized medicine. The news service Reuters recently published an analysis of the future of cholesterol drugs in the wake of a tough regulatory climate, including discussion on the fierce debate over the effectiveness of some newer drugs and the effect these issues will have on physicians, patients, and investors. REF #2-3

A Follow-Up on Xenohormesis
Dr. Bland profiled the work of Dr. David Sinclair in the December 2007 issue of *Functional Medicine Update* and now reports on a recent article published in *Cell*. In this article, titled "Xenohormesis: Sensing the Chemical Cues of Other Species," Dr. Sinclair and co-author Dr. Howitz propose that heterotrophs (animals and fungi) are able to sense chemical cues synthesized by plants and other autotrophs in response to stress, and that these cues provide advance warning about deteriorating environmental conditions, allowing the heterotrophs to prepare for adversity while conditions are still favorable. REF #4

The Search for Biomarkers
While the rise in non-alcoholic fatty liver disease (NAFLD) parallels the increase in obesity and diabetes, a research group at the University of Florida has noted that a significant increase in dietary fructose consumption (primarily in the form of soft drinks) has also occurred. This group hypothesized that increased fructose consumption contributes to the development of NAFLD; they conducted a study that was reported in a recent issue of the *Journal of Hepatology*. The results of the study showed that patients with NAFLD consumed nearly 2- to 3-fold higher amounts of fructose than did the controls. From this observation, the authors suggest that the pathogenic mechanism

underlying the development of NAFLD may be associated with excessive dietary fructose consumption.
REF #5

Epigenetics and Cancer
Historically, transformation events in cancer have been defined as those that initiate a mutational change (initiation events, which contribute to the early stages of neoplastic transition) or those that promote the transformative processes (progression events). Cancer can be caused by alterations in oncogenes, tumor-suppressor genes, and microRNA genes. Dr. Carlo M. Croce published a review article in *The New England Journal of Medicine* on the subject of oncogenes and cancer. In the article, he writes "These alterations are usually somatic events, although germ-line mutations can predispose a person to heritable or familial cancer. A single genetic change is rarely sufficient for the development of a malignant tumor. Most evidence points to a multistep process of sequential alterations in several, and often many, oncogenes, tumor-suppressor genes, or microRNA genes in cancer cells." REF #6

In an article published several years ago in *Advanced Cancer Research*, Dr. LF Jaffe argued that reduced DNA methylation, modifications of the histone code, and tissue disorganization are the three main mechanisms of epigenetic cancer initiation. It was Dr. Jaffe's view that because carcinogenic insults injure many cells rather than just cause mutatations in a few, and because such insults convert so many cells to a precancerous state, there is a question of plausibility about mutation and repair of cells. He further argued that hypomethylation would result in DNA excision repair and that a methyl-deficient diet is carcinogenic. REF #7

From Dr. Jaffe's work, Dr. Bland moves to a more recent article by Dr. Randy Jirtle and his colleagues at Duke University. This group has also been studying DNA hypomethylation in mice and published an article that specifically addressed maternal nutrient supplementation as a counteragent to bisphenol A-induced DNA hypomethylation in early development. This team (as reported in the Proceedings of the National Academy of Sciences) presented compelling evidence that early developmental exposure to BPA can change offspring phenotype by causing a stable alteration in the epigenome, an effect that can be counteracted by maternal dietary supplements. REF #8

Clinician/Researcer of the Month

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Dr. Michael Fenech received his PhD in genetic toxicology from Flinders University of South Australia and has more than 20 years experience in the field of nutrition and genetic toxicology. He is renowned internationally for developing the cytokenesis block micronuclei (CBMN) assay, which is a quick and reliable technique for detecting abnormalities in chromosomes that is now the a standard technique used by the US Food and Drug Administration and major pharmaceutical companies in determining the safety of pharmaceuticals, food ingredients, and radiation-emitting devices.

In 2001, at the 17th International Congress of Nutrition in Vienna, Austria, Dr. Fenech proposed the novel concept that dietary recommendations should be based on genomic stability because damage to DNA is a fundamental cause of developmental and degenerative disease. His current research focus includes investigating which nutrients are required for genome health maintenance, as well as how genetic background influences nutritional requirements for preventing deterioration of the genome.

Dr. Bland and Dr. Fenech discuss many of Dr. Fenech's publications, including a specific study published in the Journal of Nutrition on folic acid deficiency and riboflavin deficiency as important determinants of genomic stability, cell death, cell proliferation, and homocysteine concentration in human lymphocyte cultures. They also discuss at length the concept of the Genomic Health Clinic, a vision for a paradigm shift in disease prevention strategy based on the diagnosis and nutritional treatment of genome/epigenome damage on an individual basis. REF #9-12

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