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Small is Beautiful
How small? How beautiful? In this issue, Dr. Bland continues his ongoing discussion of hormesis, which refers to small things having large effects (in some cases, unexpectedly large effects) on the outcome of a system.

Oral Health: Studies Show Links to Chronic Disease
The role of oral infection, especially periodontal infection, in chronic diseases has gained evidentiary strength as research accumulates. Data from multidisciplinary studies lend support to the possibility of causal associations for diabetes, stroke, and cardiovascular disease. Dr. Bland discusses a recent study funded by the National Cancer Institute and published in *The Lancet*. The study aimed to assess the suggestion that tooth loss and periodontal disease might increase the risk of developing various cancers. The analysis was done in a prospective health study (the Health Professionals Follow-Up Study), which was initiated in 1986 when US male health professionals aged 40-75 years responded to questionnaires posted by the Department of Nutrition, Harvard University. In the main analyses, 48,375 men with median follow-up of 17.7 years were eligible after excluding participants diagnosed with cancer before 1986 and those with missing data on periodontal disease. The findings of this assessment indicate periodontal disease was associated with a small, but significant, increase in overall cancer risk, which persisted in never-smokers. The increased risks noted for haematological, kidney, and pancreatic cancers need confirmation, but suggest that periodontal disease might be a marker of a susceptible immune system or might directly affect cancer risk. REF #1

Dr. Bland also discusses a 2007 study published in the *International Journal of Clinical Practice*. This study aimed to investigate the relationship between gingival health status, inflammation, and atherosclerosis in renal transplant recipients. Eighty-three patients were enrolled in this study, which was undertaken because cardiovascular disease is the leading cause of mortality in patients with chronic kidney disease and specifically in renal transplant recipients. The authors of this study found that in renal transplant recipients, gingival inflammation seems to be associated with carotid intima-media thickness (CIMT) in the absence of specific inflammation. They concluded that gingivitis may, in part, play a role in the development of systemic atherosclerosis without causing any aggravation in systemic inflammatory response. REF #2

New Articles Highlight Nutritional Hormesis
Dr. Bland profiles a 2008 article titled "Brain Foods: The Effects of Nutrients on Brain Function." The focus of this article is the influence of specific dietary factors on cognitive processes and emotions. According to the author, Dr. Fernando Gomez-Pinilla, "Understanding the molecular basis of the effects of food on cognition will help us to determine how best to manipulate diet in order to increase the resistance of neurons to insults and promote mental fitness." REF #3

In a 2007 editorial in *Mutation Research*, the challenges of undertaking nutrigenomic studies is addressed, including addressing the complexity of single nucleotide polymorphisms (SNPs), which were once assumed to be the main source of human variability. An increasing evidence base suggests the importance of more subtle gene regulatory mechanisms, including copy number variants. The variant forms of genes often result in disruptions to bacterial homeostasis mechanisms or to signal transduction of the intestinal epithelial cell of the host, and thereby to altered intestinal barrier function, and/or adaptive immune responses. The authors of this editorial state that the field of nutrigenomics raises ethical, legal, and social issues, and will be of genuine benefit to human health only if developed in linkage with adequately trained health professionals. REF #4

Understanding the subtleties of plant stress responses and the interplay between plant development and environmental adversity is key to crop improvement and to predicting changes in species distribution and biodiversity. This topic, discussed frequently by Dr. Bland in his ongoing discussions of hormesis, is addressed in a May 2008 article in *Science* magazine. REF #5

Recent Articles by Dr. Bland and Colleagues

Dr. Bland discusses two recently published articles he co-authored with colleagues. The first, titled "Clinical Safety and Efficacy of NG440: A Novel Combination of Rho Iso-alpha Acids from Hops, Rosemary, and Oleanolic acid for Inflammatory Conditions," was published in the *Canadian Journal of Physiology and Pharmacology*. This report examines the clinical safety of NG440, a phytochemical-based anti-inflammatory formula consisting of a combination of rho iso-alpha acids from hops, rosemary, and oleanolic acid. Results from a multicenter trial indicate that NG440 reduced pain scores in patients with joint discomfort, as measured by VAS (visual analog scale) methodology. As demonstrated in an ex vivo clinical study, these effects on pain relief may be due to reduced inflammatory cytokine production. Human trial data suggest that NG440 does not negatively impact cardiovascular and gastrointestinal markers normally affected by selective COX-2 enzyme inhibitors, including platelet function, blood pressure, blood cell count, or fecal calprotectin, a measure of gastrointestinal injury. NG440 may serve as a safe and efficacious alternative in some areas where specific COX-2 inhibitors have been traditionally used. REF #6

The second article is co-authored with Dr. Deanna Minich and is titled "Dietary Management of the Metabolic Syndrome Beyond Macronutrients." This article appears in the August 2008 issue of *Nutrition Reviews*. In the literature, there has been continued debate over the definition of metabolic syndrome and whether it is clinically relevant. Regardless of the terminology or the precise definition, metabolic syndrome provides an intersection of markers that leads to a spectrum of chronic diseases. Some of these factors have been shown to be responsive to dietary treatment, such as low-glycemic foods, Mediterranean-style diets, and plant-based eating. In turn, these dietary approaches contain more than the relative ratio of macronutrients. The phytochemicals that reside in foods inherent in these food patterns may be important for insulin-signaling pathways.

From the aspect of prevention, chronic consumption of phytochemicals, whether through a whole-food diet rich in fruits and vegetables or from specific extracts, may provide consistent healthy insulin-signaling patterns to ensure protection against metabolic syndrome (although stronger scientific support for this premise is needed). REF #7

Clinician/Researcher of the Month

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Dr. Edward Calabrese is a board-certified toxicologist who is professor of toxicology and Chair of the Environmental Health Sciences Program at the University of Massachusetts, School of Public Health, Amherst. Dr. Calabrese has researched extensively in the area of host factors affecting susceptibility to pollutants, and is the author of more than 600 papers in scholarly journals, as well as more than 40 books, monographs, and conference proceedings. He has been a member of the US National Academy of Sciences and NATO Countries Safe Drinking Water committees, and on the Board of Scientific Counselors for the Agency for Toxic Substances and Disease Registry (ATSDR). Dr. Calabrese also serves as Chairman of the Biological Effects of Low Level Exposures (BELLE) and as Director of the Northeast Regional Environmental Public Health Center at the University of Massachusetts.

Dr. Bland and Dr. Calabrese discuss the concept of hormesis, a subject on which Dr, Calabrese is a recognized expert. Dr. Calabrese recently published a comprehensive review in *Environmental Toxicology and Chemistry* titled "Hormesis: Why it is Important to Toxicology and Toxicologists." The article indicates that the hormetic dose response is the most fundamental dose response, significantly outcompeting other leading dose-response models in large-scale, head-to-head evaluations. Because the hormetic biphasic dose response represents a general pattern of biological responsiveness, it is expected that it will become progressively more significant within toxicological evaluation and risk assessment practices as well as have numerous biomedical applications. REF #8-10

References

1. Michaud DS, Liu Y, Meyer M, Giovannucci E, Joshipura K. Periodontal disease, tooth loss, and cancer risk in male health professionals: a prospective cohort study. *Lancet Oncol*.2008;9(6):550-558.
2. Genctoy G, Ozbek M, Avcu N, Kahraman S, Kirkpantur A, et al. Gingival health status in renal transplant recipients: relationship between systemic inflammation and atherosclerosis. *Int J Clin Pract*. 2007;61(4):577-582.
3. Gomez-Pinilla F. Brain foods: the effects of nutrients on brain function. *Nat Rev Neurosci*. 2008;9(7):568-578.
4. Ferguson LR, Shelling AN, Lauren D, Heyes JA, McNabb WC. Nutrigenomics and gut health. *Mutat Res*. 2007;622(1-2):1-6.

5. Voesenek LACJ, Pierik R. Plant Stress Profiles. *Science*. 2008;320:880-881.
6. Minich DM, Bland JS, Katke J, Darland G, Hall A, et al. Clinical safety and efficacy of NG440: a novel combination of fho iso-alpha acids from hops, rosemary, and oleanolic acid for inflammatory conditions. 2007. *Can J Physiol Pharmacol*. 2007;85:872-883.
7. Minich DM, Bland JS. Dietary management of the metabolic syndrome beyond macronutrients. *Nutr Rev*. 2008;66(8):429-444.
8. Calabrese EJ. Hormesis: why it is important to toxicology and toxicologists.*Environ Toxicol Chem*. 2008;27(7):1451-1474.
9. Calabrese EJ. Hormetic dose-response relationships in immunology: occurrence, quantitative features of the dose response, mechanistic foundations, and clinical implications. *Crit Rev Toxicol*. 2005;35(2-3):89-295.
10. Ames BN, Elson-Schwab I, Silver EA. High-dose vitamin therapy stimulates variant enzymes with decreased coenzyme binding affinity (increased K(m)): relevance to genetic disease and polymorphisms. *Am J Clin Nutr*. 2002;75(4):616-658.