

## FUNCTIONAL MEDICINE UPDATE

JUNE 2007

ISSN 1092-1761

Vol. 27, No. 6

### **Happy Birthday, Functional Medicine Update: June 1982 – June 2007**

Dr. Bland and long-time recording technician and friend, Jay Johnson, open this milestone issue with brief personal thoughts about the last 25 years and the next.

### **Blockbuster Drugs: Are We Coming to the End of an Era?**

A drug with \$1 billion or more in annual global sales is considered a blockbuster. Blockbusters have become increasingly important for the pharmaceutical industry. In 2000, 17 drugs brought in more than \$1 billion in global sales, while 94 drugs met this threshold in 2005. Trends are suggesting that the blockbuster model may not be sustainable. If the blockbuster declines in importance, the clinical experience may change in fundamental ways. In the blockbuster era, the nature of physician prescribing was sometimes formulaic. In the new era, physicians might have to conduct genetic or biochemical analysis to determine which medication is appropriate. REF #1

### **Chronic Cardiovascular Disease is an International Problem**

Despite reductions in overall cardiovascular death rates in the United States due to major medical advances in prevention and treatment in the final decades of the 20<sup>th</sup> century, the overall incidence of acute myocardial infarction (MI) has not declined and has actually increased among women. Cardiovascular disease is also the major cause of death in developed countries outside of the US, and it is becoming increasingly prevalent in developing countries. As the ability to increase survival after an acute cardiovascular event improves, greater numbers of men and women will live with chronic, clinically manifest cardiovascular disease. Public health infrastructures and healthcare systems must be developed to facilitate global implementation of optimal therapies for cardiovascular disease and reversing the increasing prevalence of obesity, physical inactivity, and their associated complications. REF #2

A study published in the *Journal of the American Medical Association* examined one-year cardiovascular event rates in outpatients with atherothrombosis using the Reduction of Atherothrombosis for Continued Health (REACH) registry, an international prospective cohort of 68,236 patients with either atherosclerotic arterial disease or at least 3 risk factors for atherothrombosis. In this large, contemporary, international study, outpatients experienced relatively high annual CV event rates. Multiple disease locations increased the 1-year risk of CV events. REF #3

### **Use of Statin Drugs and Decreased Libido**

There is evidence in the literature that sexual disorders may occur during therapy with HMG-CoA-reductase inhibitors (statins), widely used for the treatment of hypercholesterolemia. Testosterone in males is produced mainly in the Leydig cells, where cholesterol is the main substrate. Statins may interfere with the synthesis of testosterone in a number of ways. One research group suggests that by genetic

polymorphism, 17-ketosteroid-oxidoreductase may be more vulnerable to interference.  
REF #4

### **Cholesterol Biochemistry Review: Cerebrosterol**

Cerebrosterol is a 24S-hydroxycholesterol that is abundant in the brain. The most important mechanism by which cholesterol is eliminated from the mammalian brain involves a hydroxylation into cerebrosterol followed by diffusion of this steroid over the blood-brain barrier. Recent studies on this new pathway for elimination of cholesterol from the brain have given new insights into the mechanisms by which cholesterol homeostasis is maintained in this organ. These studies have resulted in new diagnostic and prognostic tools in connection with neurological and neurodegenerative diseases.

REF #5

### **Dietary Phytosterols and Cholesterol Dynamics**

Dietary cholesterol intake is variable, but is often less than 300 mg/day; current recommendations suggest less than 200 mg/day. Approximately 25% of the plasma cholesterol is due to absorbed dietary cholesterol, while 75% is accounted for by endogenously synthesized cholesterol. However, dietary cholesterol appears to be quite important because it is inversely correlated with endogenous cholesterol synthesis, which suggests it plays a role in regulation of cholesterol synthesis.

There may be substantial individual differences in susceptibility to dietary sterols. Since the principal route for cholesterol elimination is excretion in the stool, the efficiency of cholesterol absorption is a critical determinant of cholesterol catabolism. Unabsorbed dietary and biliary cholesterol are the largest terminal components of what is often termed reverse cholesterol transport.

Phytosterols are structurally similar to cholesterol, but have slight modifications of the aliphatic side chain. Phytosterols are thought to act primarily in the gut lumen. As cholesterol analogs, they compete for cholesterol in absorptive micelles. Phytosterols are inactive as supplied in pure form and must be solubilized or emulsified to achieve biological activity. Natural dietary phytosterols, which may be bioactive in their natural food matrices, may be potentially more important than supplements. More work is needed to establish evidence that eating phytosterol-rich foods improves LDL cholesterol. REF #6

### **Caloric Restriction: Benefits and Challenges**

Caloric restriction (both daily and intermittent) improves numerous health indicators in both animal and human subjects, including those associated with cardiovascular disease, type 2 diabetes, and cancer. Despite evidence of beneficial effects, continuous caloric restriction diets generally result in poor adherence in human subjects.

Alternate day calorie restriction (ADCR) is a dietary regimen in which subjects eat ad libitum every other day while consuming less than 20% of their normal calorie intake on the intervening days. A study was recently published in *Free Radical Biology & Medicine* that was designed to determine if overweight asthma patients would adhere to

an ACDR regimen, and to establish the effects of the diet on symptoms, pulmonary function and markers of oxidative stress, and inflammation. Ten subjects participated in this study over an 8-week period. Compliance with the ACDR diet was high, symptoms and pulmonary function improved, and oxidative stress and inflammation declined in response to the dietary intervention. The findings demonstrated rapid and sustained beneficial effects of ACDR on the underlying disease process in subjects with asthma, suggesting a novel approach for therapeutic intervention in this disorder. REF #7

In a recent article published in the *Journal of the American Medical Association*, Dr. Luigi Fontana and Dr. Samuel Klein published the results of an analysis that was undertaken with the objective of evaluating the physiological and clinical implications of calorie restriction with adequate nutrient intake. Evidence was acquired through a search of PubMed (1966-December 2006) using terms encompassing various aspects of calorie restriction, dietary restriction, aging, longevity, life span, adiposity, and obesity, in addition to reviews of select journals and reviewed reports. The authors concluded that calorie restriction in adult men and women causes beneficial metabolic, hormonal, and functional changes, but the precise amount of calorie intake or body fat mass associated with optimal health and maximum longevity in humans is not known. REF #8

There is evidence that the silent information regulator 2 (SIR2) gene, which encodes nicotinamide adenine dinucleotide (NAD)-dependent deacetylase, regulates lifespan and mediates calorie restriction (CR) in lower species such as *Saccharomyces cerevisiae* and *Caenorhabditis elegans*. The role of mammalian SIR2 homologs in regulating physiological changes triggered by calorie restriction may indicate a connection to diseases of aging. There have been recent advances on small molecules that activate the enzymatic activity of SIR2 as potential CR mimetics. The SIR2 family represents an evolutionarily conserved lifespan regulator. Modulating the activity of SIR2 might provide effective CR mimetics to combat diseases of aging. REF #9

#### **A Recent Article by Jeffrey Bland**

An article titled, "Type 2 Diabetes and Heart Disease: All Roads Lead Through Altered Insulin Signaling," by Dr. Bland appears in the May 2007 edition of the *Townsend Letter for Doctors and Patients*. There is accumulating evidence that phosphoinositol-3-kinase (PI3k) inhibitors may represent a new class of therapeutic agents that are important for the prevention of many chronic diseases including type 2 diabetes, rheumatoid disease, asthma, atherosclerosis, hypertension, and stroke. Dr. Bland's research group has been involved in evaluating specific phytochemicals that historically have been part of the diet in populations that have a lower incidence of type 2 diabetes and cardiovascular disease for ability to serve as selective kinase response modulators (SKRM). Nutritive substances shown to inhibit the kinase-mediated processes may be beneficial for insulin resistance and inflammation. Several phytochemicals have been shown to have uniquely high specificity and activity as inhibitors of the kinases that are involved in altered insulin signaling and intramyocellular lipid deposition. REF #10

#### **The Effects of Soy Consumption on Metabolic Syndrome**

Little evidence exists regarding the effects of soy on metabolic syndrome in humans. A study was recently published in the *American Journal of Clinical Nutrition* that aimed to determine the effects of soy consumption on components of the metabolic syndrome, plasma lipids, lipoproteins, insulin resistance, and glycemic control in postmenopausal women with the metabolic syndrome. This was a randomized crossover trial in which 42 postmenopausal women were randomly assigned to consume a control diet (Dietary Approaches to Stop Hypertension, DASH), a soy-protein diet, or a soy-nut diet for 8 weeks. Red meat in the DASH period was replaced by soy-protein in the soy-protein period and by soy-nut in the soy-nut period. The results showed that short-term soy-nut consumption improved glycemic control and lipid profiles in postmenopausal women with the metabolic syndrome. REF #11

### **Obstructive Sleep Apnea and Metabolic Syndrome**

Some studies have suggested that obstructive sleep apnea (OSA) is associated with metabolic syndrome. Increased understanding on the independent associations between OSA, metabolic syndrome, insulin resistance, and microalbuminuria status is important in order to develop appropriate therapeutic strategies to reduce the high cardiometabolic risks in patients with OSA. In one hospital-based cohort, OSA was found to be independently associated with metabolic syndrome, but not insulin resistance state. The observed independent association was largely driven by fasting glucose and triglyceride levels. The authors of this study concluded that pharmacological interventions for patients with OSA should include strategies to lower serum triglyceride and glucose, in addition to lifestyle intervention and CPAP therapy. Another group of researchers has suggested that activation of nuclear factor kappa B by stress hypoxia and/or by increased adipokines and free fatty acids released by excess adipose tissue is the final common inflammatory pathway linking obesity, OSA, and metabolic syndrome both individually and, in many cases, synergistically. A group of investigators from the University of Hong Kong investigated the relationship between OSA and metabolic syndrome with a prospective, cross-sectional, community-based study of Chinese adults. The results of this study indicated that subjects with OSA had a five-fold risk of having metabolic syndrome. REF #12-14

### **Celiac Disease in Patients with Severe Liver Disease**

Celiac disease may occur in patients with severe liver disease and in those who have undergone liver transplantation. These were the findings of a group of investigators in Finland who studied patients with severe liver failure and liver transplant patients. In the cases of severe liver disease, hepatic dysfunction reversed in all cases when a gluten-free diet was adopted. The research group recommends that the possible presence of celiac disease should be investigated in patients with severe liver disease. Dietary treatment may prevent progression to hepatic failure, even in cases in which liver transplantation is considered. REF #15

### **Clinician/Researcher of the Month**

**Jeffrey Blumberg, PhD, FACN, CNS**  
**Director, Antioxidants Research Laboratory**  
**Jean Mayer USDA Human Nutrition Research Center on Aging**  
**Professor, Friedman School of Nutrition Science and Policy**  
**Tufts University**  
**711 Washington Street**  
**Boston, MA 02111**

Dr. Jeffrey Blumberg is a Senior Scientist and Director of the Antioxidants Research Laboratory at the Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University. His research efforts are focused on the biochemical basis for the role of antioxidant nutrients and their dietary requirements in health promotion and disease prevention during the aging process via their modulation of oxidative stress status. Dr. Blumberg is also a Professor in the Friedman School of Nutrition Science and Policy at Tufts University where he teaches graduate students, trains post-doctoral fellows, and participates in activities relevant to the incorporation of sound nutrition science into public health policy. Dr. Blumberg has published over 180 scientific articles and currently serves on several editorial boards. REF #16-17

Dr. Bland invites Dr. Blumberg to comment on a meta-analysis recently published in the *Journal of the American Medical Association* that has received much attention for linking the use of antioxidant supplements with an increased risk of mortality. Dr. Blumberg provides a well-informed and insightful breakdown of the study, pointing out fundamental flaws in both the study design and conclusions of the investigators. Dr. Bland and Dr. Blumberg go on to discuss many aspects of antioxidant use and research, including studies that have demonstrated benefit. REF #18

## **References**

1. Cutler DM. The demise of the blockbuster? *N Engl J Med.* 2007;356(13):1292-1293.
2. McDermott MM. The international pandemic of chronic cardiovascular disease. *JAMA.* 2007;297(11):1253-1255.
3. Steg PG, Bhatt DL, Wilson PW, D'Agostino R, Ohman EM, et al. One-year cardiovascular event rates in outpatients with atherothrombosis. *JAMA.* 2007;297(11):1197-1206.
4. De Graaf L, Brouwers AHPM, Diemont WL. Is decreased libido associated with the use of HMG-CoA-reductase inhibitors? *Br J Clin Pharmacol.* 2004;58(3):326-328.
5. Bjorkhem I. Rediscovery of cerebrosterol. *Lipids.* 2007;42:5-14.
6. Ostlund Jr. RE. Phytosterols, cholesterol absorption and healthy diets. *Lipids.* 2007;42:41-45.
7. Johnson JB, Summer W, Cutler RG, Martin B, Hyun DH, et al. Alternate day calorie restriction improves clinical findings and reduces markers of oxidative stress and inflammation in overweight adults with moderate asthma. *Free Radic Biol Med.* 2007;42(5):665-674.

8. Fontana L, Klein S. Aging, adiposity, and calorie restriction. *JAMA*. 2007;297(9):986-994.
9. Chen D, Guarente L. SIR2: a potential target for calorie restriction mimetics. *Trends in Molecular Medicine*. 2007;13(2):64-71.
10. Bland J. Type 2 diabetes and heart disease: all roads lead through altered insulin signaling. *Townsend Letter*. May 2007:72-74.
11. Azadbakht L, Kimiagar M, Mehrabi Y, Esmailzadeh A, Padyab M, et al. Soy inclusion in the diet improves features of the metabolic syndrome: a randomized crossover study in postmenopausal women. *Am J Clin Nutr*. 2007;85:735-741.
12. Gruber A, Horwood F, Sithole J, Ali NJ, Idris I. Obstructive sleep apnoea is independently associated with the metabolic syndrome but not insulin resistance state. *Cardiovasc Diabetol*. 2006;5:22.
13. Alam I, Lewis K, Stephens JW, Baxter JN. Obesity, metabolic syndrome and sleep apnoea: all pro-inflammatory states. *Obes Rev*. 2007;8(2):119-127.
14. Lam JCM, Lam B, Lam C, Fong D, Wang JKL, et al. Obstructive sleep apnea and the metabolic syndrome in community-based Chinese adults in Hon Kong. *Respir Med*. 2006;100(6):980-987.
15. Kaukinen K, Halme L, Collin P, Farkkila M, Maki M, et al. Celiac disease in patients with severe liver disease: gluten-free diet may reverse hepatic failure. *Gastroenterology*. 2002;122:881-888.
16. Meydani SN, Meydani M, Blumberg JB, Leka LS, Siber G, et al. Vitamin E supplementation and in vivo immune response in healthy elderly subjects. A randomized controlled trial. *JAMA*. 1997;277(17):1380-1386.
17. Lawenda BD, Smith DE, Xu L, Niemierko A, Silverstein JR, et al. Do the dietary supplements epigallocatechin gallate or vitamin E cause a radiomodifying response on tumors in vivo? A pilot study with murine breast carcinoma. *J Soc Integr Oncol*. 2007;5(1):11-17.
18. Bjelakovic G, Nikolova D, Gluud L, Simonetti RG, Gluud C. Mortality in randomized trials of antioxidant supplements for primary and secondary prevention. *JAMA*. 2007;297(8):842-857.