

by Roger Clemens & Peter Pressman

Doubts About Vitamin B Fortification

The food industry has a rich history of improving public health through nutrient fortification and enrichment. However, doubts exist about the benefits of fortification with B vitamins.

Epidemiological data from the National Health and Nutrition Examination Surveys suggest that reduced plasma folic acid and vitamin B-6 and hyperhomocysteinemia are associated with an increased risk of cardiovascular disease (Selhub et al., 1995). Additional epidemiological data support

mask pernicious anemia. These doses may resolve hematologic parameters, yet neurological manifestations that are sometimes mistaken for multiple sclerosis, such as paresthesias, weakness, clumsiness, and an unsteady gait, may progress.

Recent evidence from a 3.5-year clinical trial among 3,749 Norwegian patients (Bonna, 2005) suggests that the administration of prophylactic doses of these B vitamins may *not* reduce the risk of cardiovascular events. Subjects were assigned to daily doses of

the study was statistically underpowered, it questions the certainty of this kind of supplementation to reduce risk of cardiovascular and peripheral vascular disease, and begs the question as to the suggested role of folic acid as a protectant against certain cancers.

Epidemiological studies suggest that elevated tHcy, a direct neurotoxin, may be associated with cognitive impairment and dementia. In a 4-year study among 937 dementia-free Italians over age 65, Ravaglia et al. (2005) found that elevated plasma tHcy and low serum folate were independent predictors of the development of dementia and Alzheimer's disease. Tucker et al. (2005) reported similar results in a 3-year study assessing the cognitive function of 321 elderly men. What remains uncertain, of course, is whether the relationship of elevated plasma tHcy and decreased serum folate to cognitive decline is causal or reflects some independent and overarching metabolic perturbation.

The intervention of folic acid fortification to reduce the risk of neural tube defects, while benefiting one population, may in fact, exacerbate "hidden" health issues. These kinds of epidemiological studies must be translated to clinical trials to fully evaluate the homocysteine hypothesis, and to adequately assess the potential impact that nutritional intervention with folic acid and vitamin

B-6 may have in the general population in reducing the risk of cardiovascular events and declining cognitive function. Intervention policies cannot rest on epidemiological data alone. **FT**



Roger Clemens, Dr.P.H., Contributing Editor - Professor, Molecular Pharmacology & Toxicology, USC School of Pharmacy, Los Angeles, Calif. • clemens@usc.edu



Peter Pressman, M.D., Contributing Editor - Attending Staff, Internal Medicine, Cedars-Sinai Medical Center, Los Angeles, Calif. • ppressman@grbb.xohost.com

Clinical trials [are needed] to adequately assess the potential impact [of] nutritional intervention....

the earlier observations with respect to elevated total plasma homocysteine (tHcy) level and increased risk of a cardiovascular event (Homocysteine Studies Collaboration, 2002). However, questions on possible mechanisms, the issue of causality, and the very definition of clinically significant homocysteinemia remain unresolved.

Despite these questions, virtually every primary care physician in the U.S. insists on folic acid and vitamin B complex supplementation for any patient in whom atherosclerotic or coronary disease is suspected. The typical dosing and combination is 2.2 mg of folic acid, 25 mg of vitamin B-6, and 1 mg of vitamin B-12 per day, even though folic acid in doses >0.1 mg/day may

either 0.8 mg of folic acid, 40 mg of vitamin B-6, both, or a placebo during hospitalization following an acute myocardial infarction.

The primary endpoint of this study was a composite of fatal and nonfatal myocardial infarction and stroke. While the subjects on the folic acid arms experienced a 28% mean reduction in tHcy, the primary endpoint was recorded in 18% of the placebo group and those assigned to either folic acid or vitamin B-6 alone. Subjects receiving both B vitamins experienced a 20% increase in relative risk of the endpoints and a 30% increase in cancer.

These data suggest that none of the study groups benefited from supplementation with folic acid and vitamin B-6. While

REFERENCES

- Bonna, K.H. 2005. NORVIT: Randomized trial of homocysteine-lowering with B-vitamins for secondary prevention of cardiovascular disease after acute myocardial infarction. Presented at European Society of Cardiology Congress, Stockholm, Sweden, Sept. 5.
- Homocysteine Studies Collaboration. 2002. Homocysteine and risk of ischemic heart disease and stroke: A meta-analysis. *J. Am. Med. Assn.* 288: 2015-2022.
- Ravaglia, G., Forti, P., Maioli, F., Martelli, M., Servadei, L., Brunetti, N., Porcellini, E., and Licastro, F. 2005. Homocysteine and folate as risk factors for dementia and Alzheimer disease. *Am. J. Clin. Nutr.* 82: 636-643.
- Selhub, J., Jacques, P.F., Bostom, A.G., D'Agostino, R.B., Wilson, P.W.F., Belanger, A.J., O'Leary, D.H., Wolf, P.A., Schaefer, E.J., and Rosenberg, I.H. 1995. Association between plasma homocysteine concentrations and extracranial carotid-artery stenosis. *New Eng. J. Med.* 332: 286-291.
- Tucker, K.L., Qiao, N., Scott, T., Rosenberg, I., and Spiro, A. III. 2005. High homocysteine and low B vitamins predict cognitive decline in aging men: The Veterans Affairs Normative Aging Study. *Am. J. Clin. Nutr.* 82: 627-635.

Avian Flu: Chicken Little, Owl Wise

Avian influenza has triggered an international alarm regarding its possible transformation into a deadly human killer.

The genetic phylogeny of avian influenza, caused by the type A influenza virus, H5N1, indicates that the genesis of all influenza viruses occurs among birds, such as ducks and other waterfowl. The majority of these viruses are highly species-specific and remain among their species of origin. On rare occasions, a virus may cross the species barrier and develop the capability of invading and

which is harbored in their intestinal tract and shed in their feces. Susceptible birds are infected through inhalation of the viral particles in nasal and respiratory secretions, and through contact with the feces of infected birds (Cardona, 2005). Similarly, the high density of human contact with birds and feces enables aspiration of the virus by handlers.

Before examining the human health implications of the H5N1 strain of avian influenza, it is important to note that influenza affects 20% of the United States population annually and typi-

effectiveness of antiviral medications such as oseltamivir (Roche Laboratories, Inc.'s *Tamiflu* oral tablet) and zanamivir (Glaxo Wellcome, Inc.'s *Relenza* inhaler) is uncertain.

Michael Osterholm, Associate Director of the National Center for Food Protection and Defense, recently commented that our capacity to produce vaccine is limited based on 1950s egg-based technology (Osterholm, 2005). For example, to make 300 million doses of influenza vaccine for global immunization programs, more than 350 million chicken eggs

ing, and environments that may be contaminated with excreta from wild birds.

Vaccinating domestic poultry to prevent clinical symptoms of a variety of influenza infections is not practical. Current vaccines are not cross-protective for the 15 virus subtypes that can infect poultry. Perhaps future biotechnology will produce effective vaccines to be incorporated into the feed of domestic poultry and thus reduce the risk of avian influenza.

With regard to avian flu, we cannot function as alarmist and ignorant Chicken Littles. The scientific community, health care professionals, public health officials, and food industry leadership must be Owl Wises who engage historical perspective, current evidence, and measured reasoning and action. **FT**

We cannot function as alarmist and ignorant Chicken Littles.

The scientific community ... and food industry leadership must be Owl Wises.

infecting humans. Fortunately, most of the influenza viruses are similar and are considered to be weakly pathogenic to birds and to humans.

Avian flu has killed more than 150 million birds in Southeast Asia since 2003. In addition, Indonesia, Viet Nam, Thailand, and Cambodia have 61 confirmed human deaths from 118 cases of avian influenza A (H5N1) as of this writing. The apparent widespread nature of this avian virus and the human mortality figures suggest that there may be a direct risk of infection as the virus passes from poultry to humans.

Waterfowl and migratory birds act as natural reservoirs of the avian influenza virus,

usually more than 200,000 people are hospitalized each year due to flu symptoms. Globally, more than 1 million succumb annually due to influenza, and about 30,000–50,000 deaths occur in the U.S. because of influenza virus infections. To put this into perspective, hunger affects more than 843 million people in developing and transition countries, and approximately 16,000 children die each day from hunger and malnutrition.

In 2003, 70–80 million people in the U.S. received the flu vaccine. Historical data indicate that flu vaccine is generally only 40–60% effective in preventing flu. The risk of human-to-human transmission of the bug *du jour* is questionable, and the

would be required and more than 6 months of production time would be needed after the initial isolation of the implicated viral strain. He said that new cell culture-based vaccines should be developed that include antigens present in all subtypes of influenza virus. This approach will reduce production time and increase production yield. There should also be an international approach to public funding that will pay for excess production capacity required during a pandemic.

Good management practices can prevent and control avian flu from affecting domestic poultry. These practices include cleaning and disinfecting surfaces, equipment, cloth-



Roger Clemens, Dr. P.H., Contributing Editor - Director, Analytical Research, Professor, Molecular Pharmacology & Toxicology, USC School of Pharmacy, Los Angeles, Calif. • clemens@usc.edu



Peter Pressman, M.D., Contributing Editor - Attending Staff, Internal Medicine, Cedars-Sinai Medical Center, Los Angeles, Calif. • ppressman@grbb.xohost.com

REFERENCES

Cardona, C.J. 2005. Avian influenza. www.vetmed.ucdavis.edu/vetext/inf-po_avianinfluenzafs.html.

Osterholm, M. 2005. Preparing for the next pandemic. *New Eng. J. Med.* 352: 1839-1842.

by Roger Clemens & Peter Pressman

Is C-Reactive Protein a Valid Biomarker?

C-reactive protein, an indicator of acute inflammation, is the subject of considerable controversy as an important biomarker of cardiovascular health.

It is important to recognize that CRP levels are not specific to any area of inflammation and that there are many conditions that may cause inflammation and stimulate elevation of circulating CRP several times that above normal. There are also numerous non-inflammatory processes

and even obesity are associated with elevated CRP levels. Factors associated with cardiovascular risk, such as smoking, aging, and body mass index are also associated with elevated CRP.

There are also factors that may interfere with the significance of CRP assessment. These include diet, stress, exercise, some medications, and pregnancy. Healthy physical activity and emotional stress can also lead to increased CRP levels.

endothelial injury and subsequent production of inflammatory substances contributed to the issuance of these guidelines. Yet, these markers cannot and should not be accepted as stand-alone indicators of risk. In this case, CRP is not a golden marker for inflammation, even though the Multiple Risk Factor Intervention Trial (Kuller et al., 1996) and Physicians' Health Study (Ridker et al., 1997) reported a higher increase of cardiac mortality and incidence

biomarker do not necessarily establish the existence of an inflammatory process. In fact, a minimal response of an indicator, such as CRP, may only reflect normal fluctuations in non-inflammatory processes, and possibly other chronic conditions or lifestyle, including aging (Kushner, 2001). **FT**

C-reactive protein, an indicator of acute inflammation, is the subject of considerable controversy as an important biomarker of cardiovascular health.

that cause local release and systemic exposure to inflammatory mediators, such as CRP.

CRP is produced by the liver and vascular endothelial cells, such those that line the arterial walls of major blood vessels of the heart and other vital organs. This protein is produced whenever an inflammatory process is initiated in the body and under normal physiological conditions, such as everyday stress, pregnancy, and aging.

Many clinical conditions contribute to the elevation of CRP. The classic work by Gabay and Kushner (1999) has enhanced our understanding of the role of CRP in acute inflammatory processes. For example, heart attack, unstable angina (recurring chest pain), rheumatic fever, rheumatoid arthritis, cancer, post-operative infection and healing, general trauma, hypertension, diabetes,

In 2003, the American Heart Association and the Centers for Disease Control and Prevention issued guidelines for measuring inflammatory markers such as CRP in assessing the risk of cardiovascular disease (<http://circ.ahajournals.org/cgi/content/full/107/3/499>). These guidelines stem from the vital need to identify better biomarkers that assess clinical risk that are based on many factors, including epidemiological studies and utilization of other markers to predict health outcomes. Plasma cholesterol concentration, lipoprotein profile, and homocysteine levels are a few of the other markers currently incorporated into the toolbox for assessment of the risk of coronary artery disease.

The emerging understanding of the atherosclerotic process and the development of atherosclerotic plaque that leads to

of myocardial infarction among men in the highest quartile of CRP.

It is interesting to note that scripted cholesterol-reducing medications, such as the statins, and over-the-counter anti-inflammatory/anti-platelet aggregation medications, such as aspirin, a COX-1 inhibitor, are considered the first line of treatment or prophylactic agents for individuals with hypercholesterolemia. These medications can inhibit or reduce the inflammatory process and thus reduce blood levels of CRP. In many cases, however, cardiac disease risk factors are reduced with appropriate weight reduction and dietary management, as indicated in guidelines from the National Cholesterol Education Program (<http://hlnhlbi.nih.gov/ncep.htm>).

A careful evaluation of the epidemiological data indicates that small changes in a single



Roger Clemens, Dr.P.H., Contributing Editor - Director, Analytical Research, Professor, Molecular Pharmacology & Toxicology, USC School of Pharmacy, Los Angeles, Calif. • clemens@usc.edu



Peter Pressman, M.D., Contributing Editor - Attending Staff, Internal Medicine, Cedars-Sinai Medical Center, Los Angeles, Calif. • ppressman@grbb.xohost.com

REFERENCES

- Gabay, C. and Kushner, I. 1999. Acute phase proteins and other systemic responses to inflammation. *New Eng. J. Med.* 340: 448-454.
- Kuller, L.H., Tracy, R.P., Shaten, J., and Meilahn, E.N. 1996. Relation of C-reactive protein and coronary heart disease in the MRFIT nested case-control study. *Multiple Risk Factor Intervention Trial.* *Am. J. Epidemiol.* 144: 537-547.
- Kushner I. 2001. C-reactive protein elevation can be caused by conditions other than inflammation and may reflect biologic aging. *Cleveland Clin. J. Med.* 68: 535-537.
- Ridker, P.M., Cushman, M., Stampfer, M.J., Tracy, R.P., and Hennekens, C.H. 1997. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *New Eng. J. Med.* 336: 973-979.

by Roger Clemens & Peter Pressman

Chocolate and Affairs of the Heart

It has been 220 years since Thomas Jefferson penned the following words to John Adams: "The superiority of chocolate, both for health and nourishment, will soon give it the same preference over tea and coffee in America which it has in Spain." These prophetic words seem to resurface repeatedly in the consciousness of consumers and the food industry—and in the world of medical nutrition.

Montezuma is said to have presented Cortez in 1519 with *chocolatl*, a warm liquid extract from cocoa beans. The Spaniards found this "food from the gods" bitter (high in potassium), and mixed it with cane sugar as a sweetener. The resulting concoction quickly became tremendously popular and was spiked with vanilla and cinnamon once it reached Europe.

Preliminary findings from the consumption of flavonol-rich dark chocolate...

may mean that cocoa is good for heart health and nourishment...

Finally, in 1876, milk was added, and chocolate production took off at an unprecedented rate.

In a recent survey, 52% of adults in the United States proclaimed chocolate their favorite flavor (Arabe, 2005). At this point, it is accepted that 65% of Americans prefer milk chocolate, which of course requires whole milk and cocoa butter. American consumers represent about one-third of the chocolate market, which seems ironic in light of the health risks associated with easy excesses of nonessential calories in dessert foods such as chocolate. These risks, reflected in the "metabolic syndrome" and in cardiovascular

disease, are associated with annual health care costs in excess of \$300 billion.

Lest we panic about chocolate, there is some emerging good news: Epidemiological studies in Finland, the Netherlands, and the U.S. and clinical evidence suggest that dietary flavonols (epicatechin and catechin) and oligomeric procyanidins from tea, wine, and cocoa may promote cardiovascular health and reduce the risk of mortality from ischemic heart disease (Murphy et al., 2003).

Several short-term clinical studies among a limited number of healthy adults 25–50 years of age and those with essential hypertension but otherwise healthy indicated that the consumption of dark chocolate (88–500 mg of flavonols) improved insulin sensitivity and decreased blood pressure

following the dietary intervention period (Grassi et al., 2005a, b; Engler et al., 2004). These studies suggest that the flavonol components in dark chocolate improve endothelial function, a nitric oxide-dependent vasorelaxation. The importance of these findings resides in the fact that this function is impaired in type 2 diabetes and is a significant contributor to cardiovascular disease.

The clinical relevance of these preliminary findings from the consumption of flavonol-rich dark chocolate—namely, a decrease in systolic blood pressure, improved vascular relation, and enhanced insulin sensitivity—may mean that

cocoa is good for heart health and nourishment, as penned by Jefferson.

It is important to remember that the flavonol content of much of the chocolate on the store shelves today is quite variable. Thus, the potential health benefits may not be realized from the routine consumption of cocoa-containing products. Modifications of cocoa technology and bean processing will be necessary to retain most of the flavonols while maintaining the desirable sensory characteristics of chocolate.

Chocolate has a rich history associated with its medicinal value. Cardinal Richelieu, Prime Minister of France, drank chocolate to treat his spleen, and women drank it to regain their strength during particularly exhausting days. It is incumbent on us to remember that while chocolate and cocoa impart pleasure, they are rich in fat and calories. These kinds of products can be part of a prudent diet, but their intake should

be limited. Meanwhile, additional large-scale clinical trials that either confirm or refute these actions of dark chocolate or other flavonol-containing foods are essential.

It may be that medical evidence, nutritional science, and food technology will soon validate Jefferson's insightful words. **FT**



Roger Clemens, Dr.P.H., Contributing Editor - Director, Analytical Research, Professor, Molecular Pharmacology & Toxicology, USC School of Pharmacy, Los Angeles, Calif. • clemens@usc.edu



Peter Pressman, M.D., Contributing Editor - Attending Staff, Internal Medicine, Cedars-Sinai Medical Center, Los Angeles, Calif. • ppressman@grbb.xohost.com

REFERENCES

- Arabe, K.C. 2005. A chocolate fix. *Ind. Mkt. Trends*, Feb. 14. http://news.thomasnet.com/IMT/archives/2005/02/a_chocolate_fix.html.
- Engler, M.B., Engler, M.M., Chen, C.Y., Malloy, M.J., Browne, A., Chiu, E.Y., Kwak, H.-K., Milbury, P., Paul, S.M., Blumberg, J., and Mietus-Snyder, M.L. Flavonoid-rich dark chocolate improves endothelial function and increases plasma epicatechin concentrations in healthy adults. *J. Am. Coll. Nutr.* 23: 197-204.
- Grassi, D., Lippi, C., Necozione, S., Desideri, G., and Ferri, C. 2005a. Short-term administration of dark chocolate is followed by a significant increase in insulin sensitivity and a decrease in blood pressure in healthy persons. *Am. J. Clin. Nutr.* 81: 611-614.
- Grassi, D., Necozione, S., Lippi, C., Croce, G., Valeri, L., Pasqualetti, P., Desideri, G., Blumberg, J.B., and Ferri, C. 2005b. Cocoa reduces blood pressure and insulin resistance and improves endothelium-dependent vasodilation in hypertensives. *Hypertension* 46: 398-405.
- Murphy, K.J., Chronopoulos, A.K., Singh, I., Francis, M.A., Moriarty, H., Pike, M.J., Turner, A.H., Mann, N.J., and Sinclair, A.J. 2003. Dietary flavonols and procyanidin oligomers from cocoa (*Theobroma cacao*) inhibit platelet function. *Am. J. Clin. Nutr.* 77: 1466-1473.

ADDITIONAL READING

- Keen, C.L., Holt, R.R., Oteiza, P.I., Fraga, C.G., and Schmitz, H.H. 2005. Cocoa antioxidants and cardiovascular health. *Am. J. Clin. Nutr.* 81(Suppl.): 298S-303S.
- Steinberg, F.M., Bearden, M.M., and Keen, C.L. 2003. Cocoa and chocolate flavonoids: Implications for cardiovascular health. *J. Am. Dietet. Assn.* 103: 215-223.

Fighting Obesity: Surgery or Lifestyle Modification?

An increasingly popular response to morbid obesity affecting both adults and adolescents lies with bariatric surgery—gastric-restrictive and intestinal-bypass procedures. With the widespread public awareness of bariatric surgery, there has been a near explosion in the number of practitioners in the community who perform these operations. Similarly, the number of major academic centers with bariatric surgery programs has dramatically increased in the past several years.

We readily, even enthusiastically, acknowledge that with careful patient selection and fine operation performed in a first-rate center, some morbidly obese patients with significant medical co-morbidities may lose hundreds of pounds and recover an otherwise lost life.

Brittle diabetes may be brought under control; hypertension may virtually disappear; and an ever-present wheelchair may be disregarded. But all too often, unhappy overweight and obese patients may choose to undergo bariatric surgeries either prematurely or seemingly in the absence of meaningful efforts at prescriptive social and behavioral weight-loss programs.

Bariatric surgery is arguably in its infancy, and, with a variety of operations and the plethora of settings, outcomes and morbidity have simply not yet been fully studied. It is not unreasonable to suggest that informed consent

itself for these procedures is a dubious proposition.

In clinical practice, a disproportionately large number of bariatric patients appear to suffer from chronic and severe dumping syndrome, other sequelae of malabsorption and malnutrition, acid reflux, blood pressure and body temperature instability, and loss of the usual sensations of taste, cravings, and satiety.

Despite the change in body habitus and improvement in global medical condition, it is not uncommon for physicians and health care providers, including nutritionists,

Bariatric surgery is arguably in its infancy . . . and outcomes and morbidity have simply not yet been fully studied.

to hear patients express regrets as often as satisfaction in the wake of bariatric surgery. Erratic and incomplete reporting may well be clouding perceptions of the basic safety and wisdom of obesity surgery.

This observation is particularly disturbing in light of multiple studies, especially in the pediatric population, that demonstrate the efficacy of family-based programs of dietary intervention, exercise, and other evidence-based behavioral modification strategies. At a recent Academy for Eating Disorders meeting, Marsha Marcus of the University of Pittsburgh reviewed multiple studies in obese children that have shown sustained weight reduction a decade after treatment: 30% of subjects were no longer obese.

We know that intensive counseling by health care professionals is effective in increasing the level of physical activity in previously sedentary individuals' physical activity alone. We also know, from the Physicians' Health Study and the Harvard Nurses' Health Study, that physically active obese individuals have a lower incidence of many chronic diseases than unfit obese counterparts and that physical activity independent of obesity lowers the risk of both diabetes and coronary events. These observations are certainly in line with what is known about

the physiology of exercise and promotion of endothelium-dependent vasodilation, reversal of insulin resistance, and increase in lipoprotein lipase activity.

In the realm of food and nutrition, we know that caloric reduction, i.e., dieting in conjunction with properly adjusted and meaningful aerobic exercise, generally leads to weight loss. Why is it that we as a nation are in such nutritional trouble when our fund of knowledge and our level of technology have never been greater? It seems to us that it is time to revisit questions about the adequacy of our collective professional efforts to help the morbidly obese eat better, live better, and lose weight more safely.

Have we done studies that compare socioculturally

appropriate environment-focused interventions with individual behavioral approaches to control obesity? Have we looked at innovative public health/education approaches to collaboration with mass media, the insurance industry, social support networks, religious groups, and "big business"? Have we fully explored and exploited opportunities to deliver smaller, healthier portion sizes in cafeterias and vending machines? We are pleased to see that current trends indicate that food portions are declining while offering a variety of healthful choices, school

cafeterias are modifying their menus, and vending machines are providing alternative food choices for a healthy lifestyle.

If we are to stem the tide of what may well be an excess of serious surgeries often associated with unacceptable morbidity, let us re-examine our commitment to developing and studying nutritional intervention for this complex and difficult public health problem. **FT**



Roger Clemens, Dr.P.H., Contributing Editor • Director, Analytical Research, Professor, Molecular Pharmacology & Toxicology, USC School of Pharmacy, Los Angeles, Calif. • clemens@usc.edu



Peter Pressman, M.D., Contributing Editor • Attending Staff, Internal Medicine, Cedars-Sinai Medical Center, Los Angeles, Calif. • ppressman@grbb.xohost.com

by Roger Clemens, Dr.P.H., and Peter Pressman, M.D.

Food Craving: A Signal of the Heart, Head, or Heritage?

Food craving, defined as an intense desire to eat a specific foodstuff, is a common occurrence across all cultures and societies. These yearnings, and those associated with non-foodstuffs such as pagophagia (the practice of consuming ice) and geophagia (literally, earth-eating), are not linked to any obvious nutrient insufficiency. In some individuals, food cravings and dietary restriction may be related; however, these observations are inconsistent with the majority of published studies.

A number of mechanisms have been advanced to explain

able social experience. Using chocolate consumption as an example, it follows that there may be constituents in chocolate that influence satiation or alter our acceptance of the treat, including psychoactive or mood-altering endogenous compounds such as phenylethylamine, tyramine, serotonin, tryptophan, and magnesium. It is important to note, however, that many other foods, including dairy products, also contain these compounds at higher concentrations. Yet, these foods tend to have somewhat lesser emotional appeal than chocolate.

Chocolate craving, especially

mood, and the menstrual cycle is complex.

Some investigators have proposed that carbohydrate craving (with resulting consumption) attenuates depression. This theory results from some observations that diet can modulate the serotonergic system in the brain, which is linked to mood. Research shows that administration of naloxone, an opiate antagonist, appears to reduce food intake and provides additional evidence for a nutrition–neurological interaction. This effect appears to inhibit mainly the consumption of sweet, high-fat foods such as chocolate.

Studies of cannabinoids and antagonism of cannabinoid receptors have shed more light on the complex neurochemistry of selective appetite. In addition, research on satiety or appetite-control mechanisms residing in the gastrointestinal tract has led to the identification of an entire spectrum of gut neuropeptides with elaborate central nervous system feedback.

After acknowledging the complexity of the influences on appetite and the mechanisms of “normal” appetite and craving, it is important to review what we know about pathology. For example, pagophagia is frequently observed in children, pregnant

women, and young adults. This behavior can both signal and lead to severe iron deficiency anemia. Geophagia, such as eating termite hills in Africa, is a practice in many cultures. This eating disorder can result in a host of bacterial and parasitic infections as well as various poisonings and life-threatening toxicities.

Several mechanisms have been proposed to assist our understanding of food cravings and pica, the desire to consume nonfood items. Nutrient deficiencies may result from these abnormal behaviors; however, the scientific literature does not support a causal relationship with food cravings or pica. “Cravings” undoubtedly represent a true bio-psycho-social paradigm in which sociocultural factors, stressful environments, and hormonal fluctuation participate in a complex drama performed on a neurological stage. The result has varied and as yet incompletely understood implications for nutrition and health. **FT**

Several mechanisms have been proposed to assist our understanding of food cravings. . . .

the physiological and pathological changes in behavior that lead to food cravings and a loss of control over eating. The latter, of course, is a major concern with obesity and a number of eating disorders.

Researchers have employed functional magnetic resonance imaging (fMRI) to explore the neural basis of cravings. The imaging data suggest that components of the amygdala, anterior cingulate, orbital frontal cortex, insula, hippocampus, caudate, and dorsolateral prefrontal cortex are activated during periods of pining for food. It appears that there may be a network of neural regions that is involved with the emotion, memory, and chemosensory stimuli of food craving.

Eating is generally a pleasur-

among women, may result from a sense of deprivation, in reaction to stress, perimenstrual hormonal fluctuation, and modulation of neuropeptide concentrations. Regardless of the factor or factors that initiate chocolate cravings in women, the apparent physiological explanations are inconsistently expressed in a diversity of cultures, especially among those that consume large amounts of chocolate. Spanish women, for example, eat relatively large quantities of chocolate and exhibit limited chocolate craving. This is in contrast to many American women, who consume a similar level of chocolate per capita yet present a stronger chocolate craving. Clearly, the relationship between food preferences,



Author: Roger Clemens, Dr.P.H.,
Director, Analytical Research,
Professor, Molecular Pharmacology &
Toxicology, USC School of Pharmacy,
Los Angeles, Calif. • clemens@usc.edu



Author: Peter Pressman, M.D.,
Attending Staff, Internal Medicine,
Cedars-Sinai Medical Center, Los
Angeles, Calif.
• ppressman@grbb.xohost.com

SUGGESTED READING

Pelchat, M.L., Johnson, A., Chan, R., Valdez, J., and Ragland, J.D. 2004. Images of desire: Food craving activation during fMRI. *NeuroImage* 23: 1486-1493.

Rogers, P.J. and Smit, H.J. 2000. Food craving and food “addiction”: A critical review of the evidence from a biopsychosocial perspective. *Pharm. Biochem. Behav.* 66: 3-14.



ROGER CLEMENS, Dr.P.H.
 Director, Analytical Research
 Professor, Molecular Pharmacology & Toxicology
 USC School of Pharmacy, Los Angeles, Calif.
 clemens@usc.edu



SHELLEY GOLDBERG, R.D.
 Associate Director, Nutrition Communications
 International Food Information Council
 Washington, DC 20036
 goldberg@ific.org



TAZIMA DAVIS
 Program Coordinator
 Nutrition and Food Science Communications,
 International Food Information Council
 Washington, DC 20036
 davis@ific.org

MyPyramid Adds New Dimension to Food Guidance

The revision—and revitalization—of the 1993 Food Guide Pyramid adds new dimensions to the discussion of conveying food guidance to consumers, especially with the addition of the physical activity component to the new symbol.

The new MyPyramid food guidance system, released on April 19, 2005, is an interactive nutrition education tool intended to help consumers apply personalized dietary guidance to achieve a healthful lifestyle. While the *2005 Dietary Guidelines for Americans*, released this January, represents a comprehensive review of nutrition science and health and can serve as a blueprint for product development, MyPyramid may shift attention toward innovative package design to encourage consumers to implement the revised guidance on food choices and physical activity.

MyPyramid features vertical bands of color—one for each food group. These bands are wider toward the base of the pyramid to encourage consumers to choose nutrient-dense foods more often. The bands become narrower toward the top, indicating moderate intake of less nutrient-dense (high-calorie) foods. The latest addition to the symbol, the figure ascending a staircase, reminds consumers to include physical activity as part of a healthful lifestyle. MyPyramid uses a practical approach to harmonize dietary guidance messages with the *2005 Dietary Guidelines* by incorporating the concepts of personalization, gradual improvement, physical activity, variety, moderation, and proportionality (aka balance).

The government projected the need to move away from a one-size-fits-all model to use a more customized approach. Eric Hentges, Executive Director of the U.S. Dept. of Agriculture’s Center of Nutrition Policy and Promotion, explained that the newly developed interactive tools allow consumers to personalize MyPyramid based on their age, sex, and level of physical activity. Research by the Dietary Guidelines Alliance found that consumers respond favorably to consumer-tested messages consistent with those in MyPyramid. Some effective consumer-tested messages include encouraging consumers to be flexible in balancing food

choices with physical activity over several days, to be sensible in enjoying foods without overdoing it, and to be adventurous in choosing a wide variety of foods.

For food scientists, the release of MyPyramid means helping consumers to seek better food-based solutions in an effort to reduce obesity and the risk of chronic disease. The revised recommendations may seem daunting to some consumers, and therefore creative product reformulation and packaging development may help.

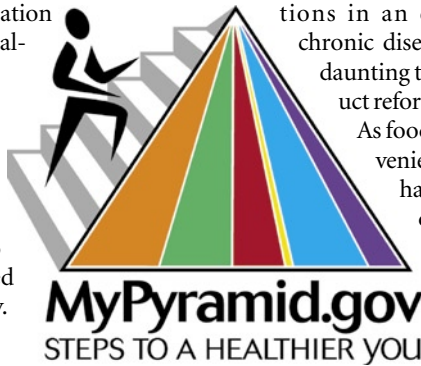
As food purveyors in an increasingly demanding, convenience-oriented food environment, food scientists have a unique and challenging opportunity to develop even more healthful foods that deliver taste, value, and convenience.

As consumers implement changes in diet and physical activity, they may seek additional foods that support a healthful lifestyle. To help consumers use MyPyramid in implementing new dietary guidance, it will be important show them where these foods fit.

MyPyramid is an innovative tool to help consumers take steps toward improving their personal health. Food producers can also take steps to become partners in encouraging consumers to use MyPyramid. Many companies have already announced that they will participate in efforts to educate the public by including MyPyramid graphics and Dietary Guidelines recommendations in revised package designs. Furthermore, collaborative efforts, through public and private partnerships, can minimize resistance, enhance acceptance, and

encourage implementation of the dietary guidance.

The Hot Topics session entitled “The Opportunities and Limitations of Food Science and Technology in Implementing Nutrition Recommendations through Food-Based Solutions” at the IFT Annual Meeting + FOOD EXPO® in New Orleans in July is designed to continue this important dialogue and to help build a bridge between food science and nutrition. Other related symposia include “*2005 Dietary Guidelines for Americans: The Science*” and “*2005 Dietary Guidelines for Americans: What Consumers and Food Product Developers Tell Us.*” They will be worth attending. ●



For food scientists, the release of MyPyramid means helping consumers to seek better food-based solutions in an effort to reduce obesity and the risk of chronic disease.



ROGER CLEMENS, Dr.P.H.
 Director, Analytical Research
 Professor, Molecular Pharmacology & Toxicology
 USC School of Pharmacy, Los Angeles, Calif.
 clemens@usc.edu



PETER PRESSMAN, M.D.
 Internal Medicine
 Geller, Rudnick, Bush & Bamberger
 Beverly Hills, Calif.
 ppressman@grbb.xohost.com

Detox Diets Provide Empty Promises

The theory that our bodies are full of dangerous environmental toxins that can be purged has now gained widespread acceptance and international promotion. Hundreds of detoxification diets are available in the United States, Canada, Europe, and Australia from pharmacies and health food stores, the Internet, and women's magazines.

Cell cleansing, immunity rejuvenation, skin revitalization, body flushing, colon decontaminating, and liver purging are among the myriad of descriptors applied to these detox diets. They are advocated by those who contend that indulgence in the traditional food supply and exposure to environmental pollutants and naturally occurring toxins and their by-products contribute to lack of well-being, weight gain, acute disease, and chronic health problems.

Detox approaches generally focus on but restrict fruit and vegetable intake, prohibit animal protein consumption, and promote the intake of extracts and unorthodox recipes. These approaches are contrary to scientific consensus and medical evidence and are not consistent with the principle that diets should reflect balance, moderation, and variety. The scientific basis for these kinds of stringent diets is lacking, and adherence to these regimens may mask clinical presentations or delay diagnosis of a health-compromising illness.

Despite the absence of sufficient scientific merit and medical evidence on the safety and efficacy of these programs, detox dieting has been a recurrent theme in many traditional health systems in various cultures for thousands of years. There are thousands of testimonials that describe experiences of less bloating (actually the result of eating less food), clearer skin (improved hydration), decreased headaches (reduced alcohol and caffeine), and reduced bad breath (potential "sweet" ketosis).

It is not surprising that individuals following a detox diet report feeling better and more energetic—these results reflect a negative energy balance rather than elimination of toxins. A heightened drive state and even a sense of euphoria often accompany the initial stages of this sort of regimen. However, the suggestion that elimination of noxious agents is enhanced because of this regimen is categorically unsubstantiated and runs counter to our understanding about human physiology and biochemistry.

Healthy adults appear to happily survive, and may well feel better, as a result of any approach to reduction of caloric intake and simplification of what may have been a "poor diet." This observation must not lead us to conclude that there is a causal linkage between a "detox" routine and health.

Like other fad diets, the rather grim limitations of detox regimens do not appear to support compliance in most individuals we have seen clinically, which is probably for the best. What amounts to protracted starvation and nutrient insufficiency may ironically slow metabolic rates and breakdown of fat stores, and while an antioxidant-rich diet is probably a desirable goal, the negative impact of protein and calorie deprivation and other possible sequelae likely far outweigh whatever beneficial effects may accrue.

During our interviews on this topic with CNN and CBS, we have emphasized that healthy adults, even overweight adults, have been endowed with extraordinary systems for elimination of waste and regulation of body chemistry. Our lungs, kidneys, liver, gastrointestinal tract, and immune system are effective in removing or neutralizing toxic substances within hours of consumption.

Are these detox diets dangerous? Certainly, says the medical community, there may be significant health risks associated with these kinds of regimens. They should not be followed by people who are undergoing growth and development, such as children and adolescents, pregnant or breastfeeding women, older adults who may have impaired renal or hepatic function, those with heart disease or diabetes, those with irritable or functional bowel disorders, those who are struggling with chronic illness, who may suffer from protein calorie malnutrition, anemia, or malabsorption (such as gastric-bypass or eating-disorder patients), those who may be on "blood thinners"—all may be subject to significant adverse reactions or interactions on the typical detox vegetable/fruit and water regimen.

The bottom line is that a more healthful lifestyle includes eating a variety of foods from the basic food groups while staying within energy needs, increasing daily intake of fruits and vegetables, whole grains, and nonfat or low-fat milk and milk products, and participating in physical activity every day, as outlined in the 2005 *Dietary Guidelines for Americans*. ●

Detox approaches . . .
 are contrary to scientific
 consensus and
 medical evidence. . . .



ROGER CLEMENS, Dr.P.H.
 Director, Analytical Research
 Professor, Molecular Pharmacology & Toxicology
 USC School of Pharmacy, Los Angeles, Calif.
 clemens@usc.edu



PETER PRESSMAN, M.D.
 Internal Medicine
 Geller, Rudnick, Bush & Bamberger
 Beverly Hills, Calif.
 ppressman@grbb.xohost.com

Hyperhydration—Can Too Much Fluid Hurt?

Bottled water is a big competitive business, with retail sales reaching nearly \$9 billion in 2004. It has emerged as the No. 2 beverage in the United States, behind soft drinks. Consumers and athletes pay a premium for splashes and fortified and flavored waters in their quest to remain hydrated as part of the apparent health and wellness movement.

The Food and Drug Administration regulates the quality of bottled water, and the Environmental Protection Agency regulates the quality of tap water from municipal sources.

With regard to nutrition—and in the context of the enormous advertising and consumer push for “pure” water at the desk, in the gym, or on the track—symptoms of hyperhydration (too much water) and hyponatremia (not enough sodium) are on the rise. The potential health risks of drinking too much fluid with insufficient sodium before and during exercise are being reassessed by leading exercise physiologists, the American College of Sports Medicine, the National Athletic Trainers Association, team physicians, and sports nutritionists.

In a 2004 report, “Dietary Reference Intakes: Water, Potassium, Sodium, Chloride, and Sulfate,” the Institute of Medicine’s Food and Nutrition Board warned that physically active people should avoid drinking too much water, which in extreme may result in hyponatremia, a condition which occurs when the blood sodium level falls below normal (<135 meq/L). It is a clinically important concern among some of our “healthiest” consumers.

The FNB report (www.nap.edu/openbook/0309091691/html/) suggests that high levels of dietary sodium may contribute to or exacerbate several clinically important conditions, such as hypertension and diabetes. At the same time, it is important to realize that disturbances in total body sodium content affect extracellular volume, and that perturbations in total body water affect serum sodium concentration. Thus, the significance of maintaining the balance of water and electrolytes, especially sodium, in plasma and the body’s tissues cannot be understated, particularly when advising those involved in extensive physical activity.

A pathological model for this condition of hypervolemic (expanded blood volume) hyponatremia is manifest in some

endurance athletes, military personnel, hikers, and weekend exercisers with congestive heart failure. These individuals may have an increased total body sodium content and total body water content due essentially to decreased kidney blood flow (renal perfusion). These same individuals may also become hyponatremic because of the “functional” underfilling of their arterial circulation, which stimulates vasopressin secretion from the hypothalamus; this stimulates thirst and a powerful urge to drink, which in turn leads to water retention and reduced urine volume induced by antidiuretic

hormone secreted by the pituitary gland. These events override the negative feedback effect of the body’s osmoreceptors that normally act to decrease vasopressin secretion in response to hyponatremia.

The risk of hyponatremia is significant in healthy endurance and weekend athletes involved in low-intensity exercise who may overhydrate in response to a belief that tremendous water intake is generally protective. This situation seems especially salient among those with slower pace (>4 hr) in running events such as marathons and triathlons. Symptoms of severe, acute hypervolemic hyponatremia typically

encompass central nervous system parameters, including but not limited to lethargy, confusion, agitation, and even seizures. As these symptoms may mimic frank dehydration, some athletes mistakenly conclude that plain bottled or tap water may be the most desirable approach to rehydration. Nothing could be further from the truth—too much fluid can hurt!

Hyperhydration, which contributes to hyponatremia, is an emerging concern among trainers and health care professionals and a condition that can be prevented. Adequate consumption of properly formulated and clinically tested electrolyte-containing beverages as part of a fluid-replacement regime during exercise and endurance events can prevent or reduce the risk of hyponatremia and related sequelae, while maintaining fluid balance and important physiological functions. ●

ADDITIONAL READING

- Grandjean, A.C. and Campbell, S.M. 2004. “Hydration: Fluids for Life.” ILSI North America, Washington, D.C. www.ilsa.org/publications/pubslst.cfm?publicationid=556.
 Flinn, S.D. and Sherer, R.J. 2000. Seizure after exercise in the heat. Recognizing life-threatening hyponatremia. *Physician Sportsmed.* 28(9). www.physsportsmed.com/issues/2000/09_00/flinn.htm.

The potential health risks of drinking too much fluid with insufficient sodium before and during exercise are being reassessed. . . .



Tazima Davis
Program Coordinator
Nutrition and Food Science Communications,
International Food Information Council
Washington, DC 20036
davis@ific.org



WENDY REINHARDT, R.D.
Associate Director, Health Nutrition
International Food Information Council
Washington, DC 20036
reinhardt@ific.org

The Dietary Guidelines: Where Food Science and Nutrition Converge

The 2005 *Dietary Guidelines for Americans* asks consumers to look at food from a different perspective—from the vantage point of health promotion and weight management. The revised Dietary Guidelines, released on January 12, 2005, and available at www.health.gov/dietaryguidelines, include a shift in focus from nutrient adequacy to weight management and reducing the risk of chronic disease.

This shift is consistent with the many articles and reports documenting the increasing rates of chronic disease and overweight among Americans and the need to address these trends.

According to consumer attitudinal research by the International Food Information Council (IFIC) Foundation, many consumers state that they strive to live a healthful lifestyle but have trouble translating theory into practice. Despite their desire to achieve a healthful diet, many consumers feel over-stressed and over-scheduled. They value convenience, accessibility, and taste and often choose foods based on these criteria. Consumers state that they need “real-life” solutions that assist them in making a healthful lifestyle “easy” and “doable.”

The new Dietary Guidelines set forth specific, science-based recommendations designed to help the public reach target nutrient levels and promote health. They clearly emphasize making choices that promote intake of nutrients vital to health through increased consumption of vegetables, fruit, low-fat dairy products, and whole grains. They also highlight reduced intakes of saturated and *trans* fats, added sugars, salt, and calories. With an emphasis on calories and weight management, they encourage selection of nutrient-dense foods as a means to meet nutrient intake goals while also maintaining caloric balance.

As information about public health and nutrition science evolves, so might the direction of food product development. Critical to this discussion is the clinical relevance of the foods we develop and their impact on health. Like consumers, food scientists are asked to balance many competing priorities—both

in the reformulation of existing products and in the development of new products. As food scientists, we are charged with meeting revised product specifications, yet we must also reconcile product functionality to preserve consumer acceptance. Still, the opportunity exists to present consumers with viable food science solutions that help them meet dietary recommendations while offering taste and convenience.

Developing such products can be challenging, especially with growing expectations for technologies to solve current conundrums, such as sodium and *trans* fat reduction. Sodium helps keep foods safe and enhances the flavor of the products in which it is used; however, dietary recommendations encourage reducing sodium intake to support cardiovascular health. With regard to *trans* fat reduction, regulatory discussions and consumer demands are driving industry toward zero levels. Efforts thus far reveal no easy answers as food scientists seek alternatives that preserve taste and functionality, do not increase saturated or total fat, and are available in volumes to meet production demands.

Where do food science and dietary recommendations converge? Those currently leading the way in the marketplace are setting new product profile targets in line with the Dietary Guidelines. Many companies already offer “healthy” product lines and “better-for-you” varieties of traditional products. Some companies are also using portion-control packaging, in combination with product development, to assist consumers with convenience and calorie reduction. As food scientists, it may help to ask the right questions and direct the discussion to develop quantifiable targets, define related objectives, and determine measures of success. Furthermore, initiating and maintaining an open dialogue between food scientists and nutrition scientists is essential in assuring that consumers have access to products that help them meet the Dietary Guidelines. Now and in the future, food scientists, alongside nutrition professionals, can take full advantage of this unique opportunity to develop “real-life” food science solutions to support and promote health. ●

An open dialogue between food scientists and nutrition scientists is essential in assuring that consumers have access to products that help them meet the Dietary Guidelines.

JAMES W. ANDERSON, M.D.
Clinical Professor, Metabolic Research
University of Kentucky, Lexington
janders@pop.uky.edu

M. KATHRYN PATTERSON
Graduate Research Associate
University of Kentucky, Lexington
mpatter1@uky.edu

Soy Protein and Women's Health

In the age of medicinal drugs and quick fixes for every health condition, safe, efficacious, natural alternatives to hormone replacement therapy (HRT) such as dietary interventions are often overlooked. Women's health is one area where small dietary changes may be an adjunct to prevention and treatment of various problems. The inclusion of soy foods in the diet may constitute an example of an alternative or complementary approach to promote women's health.

• **Coronary Heart Disease.** Pre-menopausal women have a lower risk of CHD than men of the same age. However, following menopause, a woman's risk is comparable to a man's risk. One of the factors contributing to this delay in CHD in women relates to the production of estrogen, an endogenous cardioprotectant.

Observational studies and clinical evidence support the use of soy in preventing heart disease in all persons, specifically post-menopausal women. Setchell (2001) suggested that soy isoflavones resemble selective estrogen receptor modulators (SERMs) in adults and thus appear to protect women from CHD through mechanisms similar to that of estrogen. In addition, soy protein may reflect its impact on several types of lipoproteins, improvement in vascular health and reactivity, protection from oxidative damage, reduction of inflammation, and lowering of blood pressure; yet safety and efficacy of soy protein as a cardioprotectant remain to be sufficiently demonstrated in large, at-risk populations (Park et al., 2005).

• **Menopause.** Support for the use of soy foods to treat menopause symptoms has also been found. It is especially attractive for women who cannot or will not use HRT. Since the safety of HRT is questionable, especially for women who have a history of breast cancer, dietary soy may provide an alternative. The phytoestrogens found in soy have been shown to have estrogenic effects, which may act to substitute for the declining estrogen levels in women after menopause (Albertazzi and Purdie, 2002). However, earlier clinical data seem to support the inclusion of two to three servings of soy foods per day with naturally occurring isoflavones rather than using soy isoflavone supplements (Mackey and Eden, 1998).

• **Breast Cancer.** One of the most provocative areas of soy research lies in the realm of neoplastic disease. Interest is spurred by findings that populations with high consumption of soy foods seem to have lower rates of breast, uterine, and colon cancers than societies with low soy food intakes. Despite many limitations in the epidemiologic and animal data, there remains intriguing support for the hypothesis that food components, particularly soy food and

vegetable intake, are associated with a reduced risk of breast cancer (Greenwald, 2004). Genistein and other soy isoflavones are hypothesized to account for most of the cancer-protection properties of soy foods by inhibiting estrogen receptor-sensitive cell growth. Although the evidence for soy consumption in cancer reduction is inconclusive and divided, some research is suggestive of various chemoprotective properties of soy.

• **Diabetes.** Among the leading disease-caused fatalities in the United States, diabetes is ranked fifth, and diabetics are at a greater risk for multiple and concurrent health problems than non-diabetics. Unfortunately for diabetic women, there is a greater frequency of complications than are seen in diabetic men. The risk for cardiovascular disease (CVD), which is already higher among diabetics, is even higher for diabetic women than for men.

Because of these additional complications, it may be important for diabetic women to take advantage of dietary adjustments, such as consuming soy foods, toward reducing some of their health risks. For example, dietary soy may lower postprandial glucose levels, contribute to improved insulin levels and insulin sensitivity, reduce hyperglycemia, and possibly promote reduction in the reliance on medications to control and stabilize blood glucose levels, as well as modulate plasma lipid profile and concomitantly reduce a woman's risk of CVD (Friedman and Brandon, 2001).

There are many popular approaches to the application of alternative and complementary medicine interventions for women's health problems. Increased soy consumption appears to be one avenue for safe and effective augmentation of mainstream medical therapy. Future research in personalized nutrition and expanded investigations in nutrigenomics may reveal additional health benefits of soy consumption. ●

REFERENCES

- Albertazzi, P. and Purdie, D. 2002. The nature and utility of the phytoestrogens: A review of the evidence. *Maturitas* 42(3): 173-185.
- Friedman, M. and Brandon, D.L. 2001. Nutritional and health benefits of soy proteins. *J. Agric. Food Chem.* 49: 1069-1086.
- Greenwald P. 2004. Clinical trials in cancer prevention: Current results and perspectives for the future. *J. Nutr.* 134: 3507S-3512S.
- Mackey, R. and Eden, J. 1998. Phytoestrogens and the menopause. *Climacteric* 1: 302-308.
- Park, D., Huang, T., and Frishman, W.H. 2005. Phytoestrogens as cardioprotective agents. *Cardiol. Rev.* 13: 13-17.
- Setchell, K.D. 2001. Soy isoflavones—Benefits and risks from nature's selective estrogen receptor modulators (SERMs). *J. Am. Coll. Nutr.* 20: 354S-362S.

The inclusion of soy foods in the diet may . . . promote women's health.



ROGER CLEMENS, Dr.P.H.
 Director, Analytical Research
 Professor, Molecular Pharmacology & Toxicology
 USC School of Pharmacy, Los Angeles, Calif.
 clemens@usc.edu



PETER PRESSMAN, M.D.
 Internal Medicine
 Geller, Rudnick, Bush & Bamberger
 Beverly Hills, Calif.
 ppressman@grbb.xohost.com

Probiotics and Lessons Learned from Vitamin C

Limes, oranges, and lemons were probably the first clinically documented functional foods. James Lind noted in 1742 that scurvy—a common malady leading to significant loss of life during lengthy voyages at sea—could be cured and prevented by the administration of these fruits. Unfortunately, it was another 62 years before the British navy adopted the use of “limes” to avoid scurvy.

Modern science suggests that there is more to citrus fruits than their antiscorbutic properties. Similarly, there appears to be more to fermented milk products, especially the cultures used in many fermentation processes, than what Eli Metchnikoff discovered a century ago. A contemporary definition of probiotics indicates that these are living microorganisms, using lactic acid bacteria, that when consumed in sufficient quantities can provide health benefits.

Major challenges confronting the scientific community and regulatory agencies relative to these bacteria are strain identification, mechanisms of action, and establishment of clinically relevant biomarkers of health. Emerging studies addressing these challenges now include proteomics, metabolomics, and genomics as tools to investigate and support effects of body functions relative to novel food ingredients, such as probiotics. The clinical aspects, including possible modulation of the inflammatory components of cardiovascular disease, atopy, digestive disorders, cancer, and diabetes, lie far beyond the traditional expectations of lactose digestibility, microflora modulation, and diarrhea management.

Despite a relative paucity of clinical interest, between 1999 and 2003 nearly 200 randomized and nonrandomized clinical trials with *Lactobacillus* and approximately 40 such studies with *Bifidobacterium* were published.

Based on the emerging scientific interest and clinical evidence, the World Health Organization/Food Agriculture Organization published two guidelines that provide scientific advice in relation to the nutritional and safety assessment of probiotics, and general guidance for the assessment of the pathogenicity, toxicity, allergenicity, and other specific features relevant to their nutritional properties or safety. These guidelines may be found at http://who.int/foodsafety/fs_management/en/probiotic_guidelines.pdf and www.fao.org/es/esn/food/foodandfood_probio_en.stm.

Our own clinical experience affirms the utility of probiotic strains (readily available in the retail setting) among patients presenting routine gastrointestinal disorders such as irritable

bowel syndrome (IBS) and antibiotic-associated diarrhea. In more serious illness such as inflammatory bowel disease (IBD), the introduction of probiotics may contribute significantly to management of the pathology.

The potential implications of probiotics as adjuncts to conventional pharmacologic therapies is tempered by the realization that we must not generalize either the positive or negative effects of one strain with those of other strains. It is also noteworthy that

most of the clinical studies to date involve a limited number of subjects, since the application is generally among populations at risk, such as those with IBD or IBS. The potential role of probiotics as a prophylactic in the general population is uncertain, since the measurable medical outcomes, other than the absence of disease, have not been identified.

Future research will involve at least six key elements: dosage, mode of action, genetic stability, antimicrobial resistance, health claims, and physical stability. There

is a lack of consensus as to whether health benefits are associated with a single strain or a cocktail of organisms, their doses, the time of introduction (infancy vs adulthood), the duration of exposure, and the appropriate physiologic condition under which the strain is introduced. The molecular interactions of probiotics with the normal flora and host mucosal cells are not well defined. The genetic stability may be important for permanent or transient “colonization,” survival, and functionality of the organisms, as well as safety of the probiotic-containing product.

The absence of antimicrobial resistance is an issue stipulated in the WHO guidelines. Yet, our genetic analysis and that of others indicate that many organisms used in commercial products, such as cheeses, yogurts, and kefir, have an innate antimicrobial resistance without any apparent negative health impact on the consumer. The physical stability without refrigeration is critical throughout the food supply chain. And, with the growing interest in health claims, the public health implications need stronger validation.

Research on probiotics sets the tone and standard for research and understanding of other “functional food” ingredients as we attempt to provide food with benefits beyond classical nutrition. Let’s not delay the research process another 62 years, as with vitamin C, or even a century, before embracing the possibility of health and nutritional benefits of probiotics. ●

Let’s not delay [future research] before embracing the possibility of health and nutritional benefits of probiotics. . . .