by Roger Clemens & Peter Pressman

Comfort and **Mood Foods**

As the holiday season approaches, we anticipate gatherings with friends and family where memories are often shared during the preparation and consumption of comfort foods. Indeed, foods and eating may powerfully awaken memory and its associated mood.

Basic neurophysiology teaches us that olfactory neurons are not myelinated, effectively potentiating perception and processing of these kinds of stimuli. It may be that the unique imbrication of olfactory data with emotion is somehow entirely discrete on some dimensions from visual or auditory processes.

Equally intriguing are observations that women and men demonstrate differences in sensitivity to these stimuli, and that obesity, anorexia, and bulimia nervosa affect these neurological responses. These gender differences in response to and identification of comfort foods may provide emerging opportunities in the functional foods market.

The relationship between food and mood in normal subjects appears to depend on many variables. The time of day, the type and macronutrient composition of food, the amount of food consumed, the age and dietary history of the subject, and beliefs and expectations about the impact of a particular food all may influence cognition. Changes in the macronutrient composition, particularly fat-to-carbohydrate ratio, of breakfast have differential effects on mood and cognitive function. Raising brain serotonin levels by administering tryptophan or supplementing a carbohydrate-rich/protein-poor diet with tryptophan produces changes in mood. Dexfenfluramine, an agent known to promote serotoninergic neuronal activity, also may elevate mood state.

A reduced level of brain serotonin is associated with depression and cognitive dysfunctions and may also underlie some memory deficits frequently associated with premenstrual syndrome. Administration of bovine α-lactalbumin, a protein with a high tryptophan content, during the premenstrual phase may, in part, improve memory performance and some aspects of long-term memory. A tryptophan-rich diet not only raises brain serotonin levels but may also reduce cortisol concentration, an indicator of physical and emotional stress, while improving one's mood. Since α-lactalbumin is the dominant whey protein in breast milk, this protein may, in part, account for an infant's alertness and contribute to the infant's visual tracking development.

Other possible and intriguing sources of nutritional effects on mood involve cholecystokinin (CCK), the most abundant neuropeptide in our cerebral cortex and limbic system. At "drug-level" oral doses of ~50 mg, CCK acts on sites in the brain that appear to modulate anxiety and panic behavior. One provocative approach to the management of anxiety disorders might be the use of food rich in CCK. There are few data on natural sources of CCK or similar potentially bioactive peptides, but screening common foods for this protein may be an effort that the current fascination with functional foods will support.

***The relationship between food and mood** in normal subjects appears to depend on many variables.*

Observations that polyphenol-rich extracts from grape seeds, blueberries, and soy may modulate select neuroproteins and thus function as neuroprotectants in rodent models may have significant clinical implications in the management of cognitive disorders and the sordid use of psychoactive drugs through functional improvements of the nervous system.

Caffeine, one of three major methylxanthines found in our diet (theobromine and theophylline are the other two), is an integral bioactive component in the socially engaging beverage, coffee. These mood-altering compounds are also found in seasonal favorites such as chocolate and tea. These and other innate psychoactive compounds in these widely consumed products improve mental alertness and cognitive performance. Neurologically, they may act to strengthen the brain's central information processing capabilities. Clinically, they may have positive effects on sleep disorders associated with anticonvulsant therapy, and reduce the risk of Parkinson's and Alzheimer's disease in some population segments. For chocolate lovers, it appears that methylxanthines provide psychostimulant effects, arouse emotions, and may even evoke guilt feelings.

The beliefs of history and culture may well be validated and explicated through science. We may well be acquiring another level of appreciation of the prospects and the challenges presented by health claims for various foods. And perhaps we also are presented with a window on the future design and application of foods in health and medicine. **FT**

References for the studies mentioned above are available from the authors.

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by Roger Clemens & Peter Pressman

Heyday in **Grain Land**

Sales of whole-grain food products and dietary fiber have increased significantly since February 2006, when the Food and Drug Administration issued its definition of "whole-grain foods" and a draft guidance for industry on whole-grain label statements

Relative to 2005 data, sales of pasta increased by 26%, white bread products 55%, and fresh bagel goods 30%, according to the Whole Grains Council. In addition, total feed grain (corn, sorghum, barley, oats) use and domestic use experienced moderate increases between 2001 and 2006, while disappearance data indicate a 17% increase in food, alcohol, and industrial use of these grains.

The importance of whole grains in supporting improved health is emphasized in the government's *2005 Dietary Guidelines for Americans* and *Healthy People 2010* reports and supported by public health experts in the United States and Europe and by emerging clinical data.

Epidemiological evidence suggests that healthy lifestyles include whole-grain foods. The inclusion of three servings of whole grains/day may reduce the risk of type 2 diabetes, cardiovascular disease, obesity, and possibly certain types of cancer. While each of these pathologies is associated with multiple risk factors and etiologies, concerted dietary intervention that includes whole grains may be important based on a number of clinical endpoints.

• **Diabetes.** Dietary intervention studies suggest that regular consumption of whole grains and legume foods may be important in post-prandial glycemic control among type 2 diabetics. Large prospective studies since 2000 suggest a significant negative risk of developing type 2 diabetes when three servings of whole grains are consumed daily. An 8-year prospective cohort study of more than 41,000 women indicated that a higher weekly consumption of whole grains, calcium, magnesium, and dietary fiber was associated with a lower risk of type 2 diabetes.

• **Cardiovascular Disease.** Epidemiological and experimental data suggest that consumption of whole grains may be more cardioprotective than other commonly consumed foods, and that this benefit may be independent of dietary fiber. The possible physiological mechanisms to explain these benefits remain speculative. Some of the speculation focuses on a variety of fat- and water-soluble components, such as phenolics, phytosterols, and lignans. Their functions may include reducing insulin resistance in the case of diabetes; modulating vascular and endothelial inflammatory responses in the case of CVD; and assisting in weight management in the case of obesity. Each of these conditions is a risk factor related to CVD.

• **Obesity.** Several studies investigating a possible relationship between whole grain consumption and weight management yielded mixed results. Data from the Nurses' Health Study and Health Professionals Follow-Up Study suggest no differences in body mass index (BMI) between low and high quintiles of whole-grain intake. On the other hand, data from the Framingham Offspring Study and Iowa Women's Health Study indicated a significant trend of BMI reduction among higher whole-grain consumption participants. A smaller, short-term study among overweight or obese diabetics indicated that the inclusion of whole grains can improve insulin sensitivity.

***Regular consumption of whole grains** is part of a healthy lifestyle.*

• **Cancer.** A large, 15-year cohort study among women assessed a possible relationship between whole-grain consumption and incidence of colorectal cancer. The relative risk of colon cancer was significantly reduced among those consuming 4.5 or more servings of whole grains/day but no differences in the incidence of colorectal cancer or rectal cancer among the study groups.

These kinds of results remain controversial, since there is considerable individual variability in response to whole grains and dietary fiber and the incidence of colorectal cancer. They also emphasize the importance of prospective epidemiological research among study groups that fully represent the dynamics of the general population, and the importance of understanding the physiochemical nature of dietary components. Clearly, dietary fiber is not equivalent to whole grains.

• **Making Changes.** Regular consumption of whole grains is part of a healthy lifestyle. That lifestyle change begins in the schools with the introduction of favorable sensory characteristics of whole-grain products. Continued clinical research, development of new whole-grain products, implementation of novel food technologies, and improved consumer education represent strong opportunities that will provide a new life for whole grains and a better quality of life for consumers.

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Energy Conundrum

As global concerns grow over obesity, the food industry's marketing of "energy" is both puzzling and challenging. In the United States, the energy drink business experienced significant growth in sales and product types in recent years, reaching $3.5 billion in revenue in 2005. These products convey both directly and indirectly the promise of mental alertness, raw muscle power, and sexual prowess through the addition of "pharmaceutically charged" ingredients, which when consumed in a bolus may contribute to an array of increased health risks as well as benefits.

For example, caffeine levels, which often exceed the amount in a cup of coffee, may be a potent stimulant of the central nervous system (to keep one awake and alert), and function as a natural diuretic and natriuretic. Caffeine may also contribute to episodes of tachycardia or periods of an elevated pulse.

Taurine, a sulfur amino acid synthesized within our body, is frequently referred to as a conditionally essential nutrient during periods of physical stress and illness, and may affect cardiac contractility (Baum and Weiss, 2001). This amino acid presents pharmacological properties that mimic some of the actions of angiotensin converting enzyme (ACE) inhibitors, which are the frontline drugs in treating heart disease (Schaffer, Lombardini, and Azuma, 2000).

The dynamics of these kinds of energy, the sometimes exotic ingredients, and emerging health concerns have triggered numerous regulatory guidelines. While the U.S. Food and Drug Administration has not issued any regulatory warning letters relative to energy drinks, Health Canada recommends that daily consumption be limited to 500 mL while the agency investigates reports of adverse events associated with consuming these drinks. France, Denmark, Norway, and Sweden have banned energy drinks!

Energy balance is essential for maintaining health. An imbalance of energy typically contributes to increased adiposity and numerous complications and increased health risks associated with cardiovascular disease, Type 2 diabetes, and cancer (Wolfgang and Lane, 2006; Rankinen and Bouchard, 2006). Energy status is naturally monitored and regulated through the expression and secretion of an array of neuropeptides that influence food intake and energy expenditure. Food-derived peptides inhibit fatty acid synthesis and produce metabolic effects similar to leptin. These effects influence energy balance, resulting in reduced food intake and subsequent weight reduction as evidenced in diet-induced or *ob/ob* obese animal models.

Energy intake or eating behavior traits may be linked to genetic heritage. Family and twins studies suggest a strong familial relationship and genetic effect on eating behavior traits (van den Bree, Eaves, and Dwyer, 1999). Similar relationships exist for eating disorders anorexia nervosa, bulimia nervosa, and binge eating.

Future molecular genetic studies may identify and map more than the eight specific chromosomal regions that influence relevant dietary traits. Human studies to confirm and translate these observations and to assess their impact on gene expression and behavior are essential. Such studies may offer significant opportunities for the food industry in the global obesity issue, while stimulating an alternative design to energy drinks.

Without detailing commonplace branding and advertising practices, it should suffice to note that colorful, distinctive cans and text embodying extreme sport and wild "kicks" on many other dimensions seem unprecedented as effective marketing. As we explore the potentials of foods and food supplements with frank medical impact, we really must think about our responsibility to public health, as well. The food industry is not and should not be a value-neutral enterprise focused only on the bottom line. Now, as we evolve toward a "medical food technology" or "clinical food science," we must look to creating, defining, and sustaining just what is efficacious and safe. **FT**

An imbalance of energy typically contributes to increased adiposity*...and increased health risks associated with cardiovascular disease, Type 2 diabetes, and cancer.*

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Just a Pinch, Please

Hypertension, defined as blood pressure of 140/90 or greater, is the leading cause of mortality and a significant cardiovascular disease risk factor worldwide, according to a 2003 report by the World Health Organization (www.who.int/cardiovascular_diseases/guidelines/hypertension_guidelines.pdf). Increasing longevity coupled with prevalence of contributing factors such as obesity, diabetes, atherosclerosis, thyroid dysfunction, dyslipidemia, inactivity, smoking, and stress only serve to highlight the importance of hypertension.

Essential or primary hypertension accounts for approximately 90–95% of the patients diagnosed with this condition, the precise etiology of which is unknown. Most hypertensives are sodium-insensitive, i.e., reducing dietary table salt does not reduce blood pressure or alter renal hemodynamics or proximal sodium reabsorption. The rest are sodium-sensitive, with compromised kidney ultrafiltration or tubular sodium reabsorption.

Secondary hypertension accounts for 5–10% of the diagnosed cases of hypertension. There are many identifiable causes, including increased cardiac output, increased vascular resistance, or both. Regardless, the course of therapy of those diagnosed with essential and secondary hypertension requires a modified lifestyle and antihypertensive medications.

Despite food industry efforts to reduce sodium in a wide range of foods, hypertension is increasing in the United States (Hajjar and Kotchen, 2003) but is more prevalent in Europe than in the U.S. (Wolf-Maier et al., 2003). Geographic differences, cultural diversity, and traditions in Europe contribute to regulatory inconsistencies (Brandsma, 2006).

Hypertension is** not a discrete disease ... but rather **a multifaceted risk factor ... for cardiovascular disease.

The United Kingdom's Food Standards Agency recommended that consumers reduce daily salt intake from 9 g to 6 g by 2010 (www.salt.gov.uk/index.shtml) and thus cut the risk of stroke and heart attacks. This move, however, was compromised by FSA's misleading claim that reduced salt alone was responsible for decreased blood pressure in a small clinical study. Critical examination of the study showed that other factors, including changes in lifestyle and increased consumption of fruits and vegetables, may have contributed to the apparent decrease in blood pressure.

The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure in 2004 emphasized the use of antihypertensive medications (www.nhlbi.nih.gov/guidelines/hypertension/jnc7full.htm). However, JNC7 called for increased physical activity and increased consumption of fruits and vegetables, low-fat dairy products, and foods rich in potassium and calcium as part of a weight-reduction program. It also appeared to bend to political currents in commenting that despite the years of research discounting the clinical importance of the sodium-hypertension relationship, it may still be prudent to limit sodium intake as a prophylactic measure, even among normotensive individuals.

In the salt-hypertension debate, the failure to apply scientific rigor is startling, e.g., the failure to distinguish between systolic and diastolic hypertension, the failure to place blood pressure trends in the wider context of heart rate and fitness, and the erroneous tendency to utilize hypertension as a proxy for cardiovascular disease.

The International Food Information Council in 2005 reviewed the technological challenges associated with reducing sodium in the food supply and noted sodium's importance in a healthy diet and its role in food preservation and the potentiation of food flavors (www.ific.org/publications/reviews/sodiumir.cfm).

The food industry's energetic response to the apparent sodium and hypertension relationship has not decreased the prevalence of elevated blood pressure. Considering that obesity and sedentary recreation contribute to more than 90% of hypertension cases, it is time that the food industry, in collaboration with the health care community, increase efforts in consumer education in essential lifestyle modifications.

As the health care community develops therapeutic options and the food industry develops dietary opportunities to curb acute and chronic disease through functional foods, we are reminded that hypertension is not a discrete disease or clinical end point, but rather a multifaceted risk factor pitted in myth-information as a surrogate for cardiovascular disease. **FT**

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Medical Foods and Irritable Bowel Syndrome

Irritable bowel syndrome (IBS)—also referred to as spastic colon, mucous colitis, spastic colitis, nervous stomach, and irritable colon—affects nearly 20% of the adult population. It is a multifaceted functional disorder without any discrete structural abnormality or biochemical or organic cause. It occurs more frequently in women (14–24%) than in men (5–19%) and typically presents before 35 years of age. It is not life-threatening and does not contribute to the development of inflammatory bowel disease or cancer.

Approximately 70% of those presenting symptoms associated with IBS do not seek medical attention. The predominant symptom is abdominal pain, bloating, and gastrointestinal discomfort, which may be relieved with bowel movements. Symptoms are idiosyncratic, ranging from constipation or infrequent bowel movements to diarrhea. Some individuals have episodes of constipation and diarrhea, with intervening periods of GI quiescence.

Many theories for the causes of IBS have been advanced, leading to a variety of therapeutic approaches. Some research suggests IBS is predominately a colon motility disorder, or an illness associated with the secretion of the neurotransmitter serotonin, which is frequently elevated among individuals with a stressful lifestyle. GI infection may make the intestine more reactive to mild stimulation or stress. The problem is so vexing that fringe and sometimes harmful alternative approaches have blossomed into big business.

IBS symptoms are frequently exacerbated by large meals, colon bloating, certain medications (e.g., antibiotics), some foods (e.g., grains, dairy, or alcohol), caffeinated beverages, physical or emotional stress, and level of physical exercise. Some research suggests that women may experience increased symptoms during their menstrual periods, implying that reproductive hormones may play a role.

Standard management of IBS includes dietary and drug intervention. Most individuals with IBS can benefit from gradual increased intake of dietary fiber and water intake, consumption of 3–6 low-fat meals, minimal intake of alcoholic and caffeinated beverages, and gradually restricted intake of fructose and sorbitol or lactulose (if chronic constipation is a problem).

There is some evidence that microbial overgrowth, particularly in the small bowel, may be resolved through increased use of some strains of probiotics that modulate inflammatory responses and promote digestion of dietary components such as lactose and fiber. Reports of dramatic and apparently enduring clinical responses to probiotics have been thrown into question and have frustrated patients and clinicians because of the huge and growing spectrum of commercially available organisms. Quality and quantity may vary significantly depending on strain, manufacturer, age, packaging, recommended dose, and whether the probiotic matrix consists of single or multiple organisms, with or without a fructooligosaccharide substrate.

Peppermint oil and peppermint tea are traditional medicines that contain an array of phenolic constituents, may relax the GI tract (slow motility), and exert local analgesic and anesthetic effects. Human clinical studies that support the animal studies and traditional use of peppermint in treating IBS are limited. Some animal studies and traditional use indicate that the sedative *Salvinorin A*, a neoclerodane from Mexican mint, has had some success in managing IBS-associated pain.

Available are medications that regulate motility and promote restoration of normal bowel contraction (*Dicetel, Modulon, Zelnorm*); antidiarrheal drugs aimed at preventing cramps (*Immodium, Lomotil, Levsin, Bentylol*) and controlling stool frequency; digestive enzymes (*Cotazyme, Creon, Pancrease, Ultrase*) intended to relieve symptoms by facilitating digestion in the small intestine, especially if pancreatic insufficiency is contributing to the symptoms; analgesics that increase pain threshold; and possibly selective serotonin reuptake inhibitors (*Prozac, Paxil, Zoloft*). In some cases, tricyclic antidepressants (*Amitril, Norpramin*) and psychological therapy are components of the treatment strategy.

Continuous research will enhance our understanding of the disease process, and strict adherence to dietary regimens and medication therapies will result in significant improvement. The development of medical foods now provides another form of dietary support for IBS patients. The appearance of cultured milk products enriched with proprietary strains of probiotic organisms designed in the laboratory to "regulate" disordered bowel function may well mark the arrival of a new and important era in the production and marketing of foods with potent clinical applications. **FT**

The development of medical foods now provides ***another form of dietary support for IBS patients.***

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Beyond Statins: Modulating Inflammation

Food and nutrition have long been discussed in the context of how certain dietary components may modulate oxidative stress or inflammation. The prospect of suppressing inflammation has been seen as a means of attacking one of the true "final common pathways" of the entire spectra of pathology. Whether it is aging, infection, cancer biology, or wound repair, inflammation remains central to the disease and healing processes.

There is growing evidence that the anti-inflammatory or immunomodulatory effects of the statin drugs (also known as HMG-CoA reductase inhibitors) such as *Lipitor*®, *Zocor*®, and *Mevacor*® may be at least as important therapeutically as their direct effect on decreasing plasma cholesterol and low-density lipoproteins to reduce the risk of myocardial infarction and stroke and retard the progression of atherosclerosis.

Thus, we increasingly face the need to rigorously define inflammation at the tissue and organ levels, delineate the role of inflammation in the physiology of both illness and health, and finally, and critically review what we know and what we need to know about nutrition, dietary components, and inflammation.

Inflammatory and anti-inflammatory processes are multifaceted and involve a cascade of biological events. In fact, inflammation protects the body against infection and injury and participates in transient wound healing and tissue repair processes. For example, the inhibition of cyclooxygenase-2 (COX-2), an enzyme that is activated in inflammation and causes the presentation of inflammatory evidence—i.e., local heat, redness, swelling, pain, and altered function—is facilitated by non-steroidal anti-inflammatories (NSAIDs) such as *Celebrex*® and *Prexige*®. During the past two years, NSAIDs like *Vioxx*® and *Bextra*® have been withdrawn from the market because of increased gastrointestinal and cardiovascular risks.

There is emerging evidence that ***statin drugs and dietary components may modulate the inflammatory processes.***

While controversy and review continue even regarding the non-specific NSAIDs such as ibuprofen and naproxen, there is emerging evidence that statin drugs and dietary components may modulate the inflammatory processes. Statin drugs may reduce the incidence of ischemic stroke, probably through antithrombotic mechanisms, and reduce the symptoms of rheumatoid arthritis through proangiogenic effects on neovascularization leading to tissue repair.

Some dietary components may have similar effects. Twelve scientific, peer-reviewed publications since 1999 suggest that curcumin, the major yellow pigment in turmeric, curry, and mustard, may potentiate apoptosis or inhibit growth of selected cancer cells and function as a COX-2 inhibitor in several in-vitro and animal models. The effects in mice and rats were observed with dietary curcumin from 0.05% to 2%. Topical or oral application of curcumin following chemically induced skin or liver cancer resulted in anti-carcinogenic effects.

Atherosclerosis, an inflammatory disease which may result from endothelial dysfunction, may be modulated by a variety of dietary flavonoids through the inhibition of tumor necrosis factor alpha (TNF-α, also known as cachexin or cachectin) activity and expression, and possibly through the inhibition of nitric oxide production by macrophages. TNF-α, a cytokine involved in systemic inflammation, is released by white blood cells, endothelial cells, and several other tissues in the course of damage or insult.

Some metabolites of eicosapentaenoic acid (EPA), found in some fish oils, may inhibit several inflammatory control steps, such as the transcription of nuclear factor kappa B (NF-κB), a pro-inflammatory factor found in all cell types, and thus prevent the activation of inflammatory genes and block the terminal stages of arachidonic acid synthesis from its precursors. There is preliminary in-vitro evidence that extracts of some herbs, such as the stinging nettle (*Urtica dioica*) and cat's claw (*Uncaria tomentosa*), may function as COX-2 inhibitors.

These are interesting observations that require clinical evaluation, development of appropriate biomarkers, determination of dose–effect relationships, and certainly regulatory guidance. In addition, advances in bioactive dietary components require development of validated chemical analysis tools and procedures for the identification and quantification of these substances.

Enhanced understanding of these aspects of dietary components and inflammatory processes may expand our understanding of acute and chronic pathologies and health-modulating processes, and lead to the development of foods and food systems which will present fewer contraindications than are experienced with the use of some pharmaceutical products. **FT**

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by Roger Clemens & Peter Pressman

The Struggle to **Defeat Cancer**

Few struggle with the war against cancer more than the half-million families affected by cancer deaths annually than Dr. Judah Folkman, whose 1971 landmark publication launched one of the most significant research battles against cancerous tumors. Tumor growth requires endothelial cell proliferation and its own network of blood vessels, a process known as angiogenesis. The concept of controlling tumor growth through anti-angiogenic therapy has dominated cancer research strategies in major medical centers for three decades.

***Controlling tumor growth through anti-angiogenic therapy** has dominated cancer research strategies....*

Approved for clinical use in the United States are angiogenesis inhibitors for treatment of metastatic cancer of the colon or rectum, advanced pancreatic and lung cancer, and neovascular (wet) age-related macular degeneration. This approach of clinical therapy with the co-administration of anti-neoplastics such as 5-fluorouracil, have markedly increased patient survival with minimal side effects.

Angiogenesis is not particularly evident in the mature adult, except for the female reproductive system, which undergoes cyclic changes associated with intense growth of new blood vessels. Significant angiogenic changes also occur in the mammary gland, mostly following childbirth, and in the placenta during pregnancy. These angiogenic dynamics are intricately controlled by many factors, among them promoters like vascular endothelial growth factor (VEGF), placental growth factor (PlGF), transforming growth factor (TGF)-β1, and fibroblast growth factors (FGF), which are balanced by a myriad of endogenous anti-angiogenic factors. Angiotensin and endostatin are just two of the 27 endogenous angiogenesis inhibitors that have been identified. Approximately 60% of the nearly 200 different types of human cancers express VEGF. Thus, anticancer activity is often focused on the inhibition of synthesis, receptor blockage, and interruption of expression of VEGF, FGF, and TGF isoforms.

Emerging evidence suggests that some dietary components may exert pharmacological functions and modulate angiogenesis and proliferation of tumor cells. Aged garlic extract has been shown to inhibit growth of HT29, SW480, and SW620 colorectal cancer cells and their angiogenesis (Matsuura et al., 2006). The *c9,t11* form of conjugated linoleic acid (CLA) inhibited angiogenesis, induced apoptosis of adipocytes, and decreased serum VEGF in mice (Masso-Welch et al., 2004). The oral administration of green tea polyphenols to mice reduced the incidence , multiplicity, and growth of UVB-induced tumors by enhancing the expression of select matrix metalloproteinases and VEGF, while inhibiting the expression of proliferating cell nuclear antigen (Mantena et al., 2005). Pharmacological doses of dietary soy polyphenols inhibited the proliferation and angiogenesis of prostate cancer in mice and the growth of LNCaP human prostate cancer cells while increasing apoptosis and reducing the vascular density in the tumor bed (Zhou et al., 1999). The chemopreventive observations of two pools of selenium metabolites, namely hydrogen selenide and methylselenol, may be related to the inhibition of tumor-associated angiogenesis and apoptosis (Jian et al., 2004).

Angiogenesis has a critical role in arthritis, atherosclerosis, and age-related macular degeneration, recurrent squamous cell carcinoma, and perhaps even obesity. The clinical literature suggests the treatment of these conditions and the concomitant administration of food-derived compounds at pharmacological or supraphysiological doses can significantly raise endostatin and lower VEGF levels in joint fluids and plaques while decreasing the progression of disease.

Preliminary findings such as these, and results from phase III clinical studies may demonstrate that the clinical utility of the inhibition of angiogenic factors is not limited to cancer. These kinds of research may enhance our understanding of the biological mechanisms of vascularization and cell proliferation and how those mechanisms are modulated by dietary components. **FT**

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Epigenetics: **Influencing Health Inheritance**

Twenty-five years ago, Doll and Peto (1981) published their milestone epidemiological estimates of avoidable risks and prevention of the cancer burden in the United States. Since then, many environmental and lifestyle factors beyond tobacco, diet, and infections have been associated with additional emerging pathologies such as heart disease, stroke, obesity, diabetes, and hypertension.

Forty years earlier, Waddington (1942) defined *epigenetics*, which stresses that gene expression, not DNA sequence, is critical to advancing our understanding of genomic imprinting, which is evident in many aspects of the management of human health and disease This genomic imprinting is notable during critical or sensitive periods of development of the common diseases noted above. These periods include intrauterine life, the first 12 months of life, preschool through school age, and adolescence. However, the genetic influences do not discount the influence of other determinants during these periods, such as biological, environmental, and behavioral. In the pediatric population, for example, these represent periods of potential abnormal weight gain, which may lead to adolescent obesity.

There are many clinical disorders of imprinted genes, exemplified by the phenotypes of Prader-Willi syndrome, which is characterized by excessive appetite and lack of satiation during childhood. This condition presents progressive obesity and subsequent risks of heart disease, diabetes, and life-threatening illnesses. These kinds of genetic abnormalities are associated with uniparental disomy, which is the inheritance of two chromosomes from one parent and none from the other (see www.geneimprint.com).

***Genomic imprinting ... is evident** in many aspects of the management of human health and disease.*

Atherosclerotic cardiovascular disease, the leading cause of death in the U.S., has a long preclinical phase which reflects pathological changes during childhood and perhaps even during postnatal development. A composite or cluster of related risk factors, such as obesity, insulin resistance, dyslipidemia, and hypertension, contribute to this disease, which is now termed metabolic syndrome. Genetic predisposition, nutrition programming, and environmental influences are the primary mechanisms through which the phenotypes of cardiovascular disease and metabolic syndrome are demonstrated.

The notion that nutritional perturbations during early critical periods of development may cause long-term changes in the development and adverse outcomes during the adult years was originally advanced by Barker et al. (1989). This debate between the fetal-origins hypothesis and the developmental model of adult disease focuses on fetal growth and birth weight. During these critical periods of prenatal and postnatal growth, a variety of genotypes for insulin and insulin-like growth factor—IGF-1 expressed by the infant or IGF-2 expressed maternally—may predispose infants to insulin resistance, diabetes, obesity, and cardiovascular disease in later life. In addition, the extent to which maternal nutrition affects the fetal-origins hypothesis deserves further assessment.

Caloric restriction, inadequate micronutrients and trace elements, therapeutic drugs, utero-placental circulation, and pre-implantation are other perturbations that influence the development of health and adult disease. Each of these perturbations affects placental, maternal, fetal, neonatal, and postnatal epigenetics, which in turn affect all of the human organ systems as well as vasculogenesis and angiogenesis. These perturbations may well contribute to an array of pathologies, including cardiovascular disease, diabetes, dyslipidemia, and obesity.

The intersection of food science, nutrition, and medicine is increasingly being recognized as a model of critical components and challenges related to over- and undernutrition during prenatal life and manifestations during the adult years. Management of epigenetic information and identification of epigenetic markers are crucial for the most meaningful identification and assessment of gene expression and variation. These data will lead to a much greater understanding of the complexity of diseases, especially as people age, and will drive development of food products that reduce the risk of chronic disease for future generations. **FT**

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by Roger Clemens & Peter Pressman

Bioterrorism: Not a Dead Issue

The furor over the prospect of United States ports being operated by a Middle Eastern company, the detection of a suspicious substance in the Russell Senate Office Building, and the ricin scare at the University of Texas make it abundantly clear that bioterrorism is still very much a concern, despite legislative and institutional safeguards already in place.

Not long ago, as he resigned as Secretary of Health and Human Services, Tommy Thompson said that he worried on a daily basis about the vulnerability of our food supply to terrorist action, despite the Bioterrorism Act's requiring registration of food production facilities and meticulous tracking and recordkeeping of the origin and shipping of food.

Indeed, the coordinated efforts of the Federal Bureau of Investigation, U.S. Dept. of Homeland Security, U.S. Dept. of Agriculture, and Food and Drug Administration, in conjunction with industry through the Strategic Partnership Program Agroterrorism Initiative, appear to provide a reassuring response.

Nevertheless, when queried about our worries involving the vulnerabilities, preparation for, and response set of the health care system to terrorist assault on the food supply, the director of the Homeland Security National Center for Food Protection and Defense stated that "we do not have any special projects or information on threats or vulnerabilities to food or medicine in the health care system."

Clearly, despite the considerable good work that has gone into laying some of the foundation of our response to the specter of bioterrorism, there is more to be done, and quickly. A Midwestern Multi-State Consortium for security, threat detection, and response in agriculture was launched in 2004 but was supported with a budget allocation of only $2 million.

In response to a request from the HHS Office of Emergency Preparedness (OEP), the Institute of Medicine (IOM) was charged to assess the effectiveness of the Metropolitan Medical Response System (MMRS), which attempts to enhance the preparedness of major U.S. cities with regard to the health and medical consequences of attack or threatened attack with chemical, biological, or radiological agents.

The IOM report said that OEP must be empowered to take a stance that fosters voluntary collaboration and be willing and able to enforce integration of local, state, and federal services as a pressing societal need for coping with inevitable future acts of terrorism. It added that it is critical that OEP develop an essential and rational approach that is rigorous and continue to evaluate and improve its response program.

IOM also said that the enhanced organization and cooperation demanded by a well-functioning MMRS program will permit a unified preparedness and public health system with immense potential for improved responses not only to a wide spectrum of terrorist acts but also to mass-casualty incidents of all varieties.

*Despite the **considerable good work [in] response to the specter of bioterrorism,** there is more to be done, and quickly.*

The White House noted in 2002 that many of our health care systems, facilities, and institutions need improved defense against biological terrorism. It said that national efforts to strengthen infrastructure at the state and local levels were needed to improve bioterrorism responsiveness at the national level, and recommended implementing an aggressive research program directed at developing vaccines, medications, and diagnostic protocols.

This "early warning" initiative addressed concern that our health care system is inadequate to serve large numbers of victims and contagious patients, coordinate emergency information, coordinate regional health care organizations, and provide appropriate personnel training in the management of bioterrorism.

In 2005, the Texas Medical Association updated its bioterrorism toolkit for physicians and their patients (www.texmed.org/Template.aspx?id=2500). The toolkit includes protocols for the diagnosis, reporting, etiology, and management of anthrax, botulism, smallpox, and plague.

Plant viruses, phages, fungi, and bacteria will likely continue to be far more readily obtainable than virulent pathogens that may have been packaged in various delivery systems in military laboratories.

The agricultural and food industries are arguably responsible for more activism and productivity in public health research and development than either academia or the federal government. The private sector is challenged again to demonstrate the strength, vision, and adaptive capacity that reside in American capitalism, to help us fight and prevent terrorist attack, meaningfully and incisively address threat detection and assessment, and develop coordinated and informed response.

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by Roger Clemens & Peter Pressman

Women's Health—Fat Chance?

Recent wildly contradictory headlines from the clinical literature question what the public is to believe, how clinical investigators and research funding agencies adjust and conceive hypotheses and study designs, and what health professionals are to recommend to consumers and patients.

The mixed messages include "fat is risky" and "fat is good." Clearly, the real questions are how do we read the simplistic and sensational headlines and how do we interpret the studies? How do we maintain some measure of balance in the evidence based on what data may be valuable and relevant?

Let's examine ... the evidence relative to women's health and diet.

Let's examine some of the evidence relative to women's health and diet.

The Nurses' Health Study, launched by the National Institutes of Health in 1976, intended to investigate the long-term consequences of oral contraceptives, was modified in 1980 and 1989 because of the compelling evidence linking diet, nutrition, and lifestyle to the development of chronic disease. Subsequent followup among 125,000 premenopausal women initially free of cardiovascular disease, diabetes, and cancer suggested (1) that an inverse relation existed between polyunsaturated fat intake and coronary heart disease risk, particularly among younger or overweight women, and (2) that intakes of total fat and fiber were not significantly related to risk of breast cancer, yet vegetable fat, vitamin E, and fiber intakes during adolescence were inversely associated with risk of proliferative benign breast disease.

The Women's Health Initiative, consisting of major clinical trials and large observational studies funded by NIH, examined nearly 50,000 postmenopausal women relative to dietary and behavioral intervention and the risk of cancer and cardiovascular disease. Recent headlines based on clinical results from this initiative (see the February 8, 2006, issue of *JAMA*) indicated that after an average eight years of followup on these women, a low-fat, high-fiber dietary intervention did not yield a significant reduction in breast cancer, colon cancer, or heart disease. These conclusions require several points of clarification, critical assessment of the data, and closer examination of the disease process.

- Dietary interventions called for a fat reduction to less than 20% of total calories. In fact, the low-fat group reduced total fat intake from approximately 38% to nearly 29% of total energy.
- Within the low-fat group, there was a 9% lower risk for invasive breast cancer among women 50–79 years old during the followup period.
- Decreased energy from fat and increased vegetable, fruit, and grain intake did not significantly reduce the risk of invasive colorectal cancer in postmenopausal women. However, in secondary analysis among those using aspirin and hormone replacement therapy, there was a 9% reduction in the self-report of colorectal polyps or adenomas during the study period.
- Among the intervention group, there was an observed trend toward the reduction of cardiovascular disease risk among those consuming the lower levels of dietary fat and higher amounts of fruits and vegetables at year 1.
- Higher-carbohydrate, lower-fat dietary practices appeared to increase body weight or augment risk factors, such as elevated triglycerides and glucose associated with insulin resistance and diabetes.
- Dietary assessment did not differentiate among the various kinds of fat intake. However, there were reductions in saturated, *trans* fatty acids, polyunsaturated fat, and monounsaturated fat within the intervention group.
- Disease development is typically a long-term process, especially when considering some forms of cancer and cardiovascular disease, not to mention metabolic bone disease and diabetes. The dietary intervention of eight years is too short to adequately assess the potential clinical benefit of interventions on these disease processes.

Despite the methodologic limitations of epidemiologic research, these two large studies among women suggest that risk reduction of breast cancer and cardiovascular disease through dietary intervention and lifestyle modifications is meaningful and should begin during the earlier decades of life. Those modifications that help in maintaining a desirable body weight, remaining physically active, and following current dietary guidelines will be studied further and hopefully will be clarified and communicated to the public.

Reading and interpreting public health investigation is at least as challenging as conceiving and executing it. We must all focus critical eyes on data and on the complex relationships between variables, many of which are not intuitively obvious and which ultimately then justify the effort and funding of this kind of research. **FT**

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by Roger Clemens & Peter Pressman

Attaining Good Health Is Not Magic

The past year in foods, nutrition, medicine, and health brought us extremes. There were exciting, almost magical advances in applied biology and food technology, yet there continued to be fundamental and widespread misunderstanding and oversimplification in many Americans' pursuit of well-being.

• **Looking Back.** Last year was a year of good science and outrageous myth. Reducing risk and preventing illness were and continue to be two important objectives within the health care system. These objectives were wonderfully presented by Kaiser Permanente through animation and floral fantasy during the "It's Magic" 2006 Tournament of Roses Parade.

The commentary by Kaiser noted that attaining good health is not magic. Good health is realized daily by the choices we make in what we eat, what we teach our children, and what we demonstrate through our lifestyle. Nutritious food, exercise, and health choices represent the best combination for great health, according to the whimsical family of Peter Rabbit. Mother rabbit and the bunny family enjoy heaping basketfuls of freshly picked fruits, nuts, and vegetables. Despite this "eat right" model, there is little doubt that the American public was less discerning in 2005.

During 2005, Americans were presented with new dietary guidelines and "myPyramid" from the U.S. Dept. of Agriculture. These guidelines asked consumers to look at food from a different perspective—from the vantage point of health promotion and weight management, a notable shift from nutrient adequacy to weight management and reducing the risk of chronic disease.

Disturbingly, new ways of losing weight forever flowered without foundation, low-carbohydrate diets became the unwarranted craze, glycemic index foods were advocated in the absence of substantive clinical data, and "detox" regimens became an international phenomenon. The lure and myths of instant health and internal cleansing continue to compete with sound science and balance, moderation, and variety.

The lure and myths of instant health *... continue to compete with sound science....*

Some fundamental and clinical research findings on specific phytochemicals, such as polyphenols and carotenoids, were transformed and incorporated as excellent functional foods, while others lacked significant scientific agreement for qualified health claims. Omega-3 fatty acids, hormone replacement therapy, metabolic syndrome, cancer, neural tube defects, oral health, mental health, and obesity were topics of controversy and signs of promise upon examination of the dynamics of and interactions between food, medicine, and health during the past 12 months.

• **Looking Forward.** Nanotechnology, the science of the tiny, has a big future. This emerging molecular technology will likely revolutionize conventional food production, produce less waste, and require less energy, while yielding safe, sustainable "smart" foods like magic to reduce risk and even prevent disease.

The National Institutes of Health has expanded efforts to study medicine and health interactions by establishing and funding a national network of Nanomedicine Development Centers (NDCs). The goals of these intellectual and technological centers are to characterize quantitatively the *minute* nanoscale components of the cell and to precisely control and manipulate molecules and supramolecular assembles in living cells to improve human health (http://nihroadmap.nih.gov/). Interestingly, none of the NDC awards includes the potential application of nanoscience to agriculture, food science, food packaging, and nutrition as part of their pathways to discovery.

The significance of nanotechnology and even nanonutrition was emphasized in a recent report by Helmut Kaiser Consultancy (www.hkc22.com/nanofood.html). The report notes that the future of new food products and new processes from nanotechnology in agriculture, food science, and nutrition will improve safety and quality of foods while providing a means to customize and personalize a more healthful food supply. The report indicates that more than 200 global companies are active in nanotechnology research for the nanofood market, which is expected to reach $20.4 billion by 2010. The most-active food companies in the United States, China, and Japan will change the shopping baskets and meal profiles to deliver designer foods with greater capability and precision, lower costs, and improved sustainability. New nutrition delivery systems will bring active agents more precisely and efficiently to the body's systems and cells that need these substances, thus reducing the risk of disease through improved disease resistance at the nanoscale level.

Attaining good health is not magic. It is a challenge for all of us. Our tools to meet this challenge, such as nanotechnology, are becoming more powerful. **FT**

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by Roger Clemens & Peter Pressman

The Road to **Diabetes**

Examination of the Impaired Fasting Glucose data from the 1999–2000 National Health and Nutrition Examination Survey (NHANES) suggests that 27 million United States adolescents alone are at risk for developing diabetes and cardiovascular disease (Williams, 2005). The prevalence of diabetes in the U.S. in 2005 exceeds 20 million, or about 7% of the total population, with estimated annual health-care costs of approximately $132 billion.

Whether we are discussing type 1 diabetes, previously known as insulin-dependent diabetes mellitus, or type 2 diabetes, formerly called non-insulin-dependent diabetes mellitus, it is safe to assert that lifestyle changes are important disease-modifying variables.

Type 1 diabetes has been regarded as an autoimmune attack on the insulin-producing cells of the pancreas. This pathology, which accounts for 5–10% of all diagnosed cases of diabetes, does not have any known roads of prevention. Type 2 diabetes, which accounts for 90–95% of all diagnosed cases of diabetes, is driven by a resistance or insensitivity to adequate insulin. Type 2 diabetes is strongly associated with diet and exercise patterns, thereby providing a non-medical means of managing a potentially devastating and multifactorial illness.

Other provocative evidence from the Nurses' Health Studies suggest that increased duration of lactation is associated with a decreased risk of type 2 diabetes among young and middle-aged women (Stuebe, 2005).

Meanwhile, the impact that dairy food consumption may have on type 2 diabetes continues to stir considerable discussion within nutrition and medical communities. Recent statistical assessment of the prospective epidemiological Health Professionals Follow-up Study suggested that higher consumption of low-fat dairy products may lower the risk of type 2 diabetes among males 45–75 years old (Choi, 2005). Several mechanisms have been proposed to explain this observation, and several studies have been cited to counter these explanations.

Dairy products contain an array of components that may support the inverse relationship between dairy consumption and type 2 diabetes. (King, 2005). Notably, bioactive peptides with insulinotropic properties may augment insulin secretion and stimulate glucagon-like peptides that potentiate insulin activity. Magnesium may function as a mild calcium antagonist intracellularly and thus participate in the modulation of lipolysis and insulin sensitivity. Dairy consumption is also associated with a lower risk for hypertension and cardiovascular disease, which may be co-morbidities associated with type 2 diabetes. Independently, the increased intake of potassium and supplemental vitamin D intake associated with dairy foods have been linked with a lower incidence of type 2 diabetes and related health complications.

We are reminded that the 2005 *Dietary Guidelines for Americans* include a recommendation that Americans "consume 3 cups per day of fat-free or low-fat milk or equivalent milk products." The strength of clinical evidence regarding the inverse relationship of dairy product consumption and chronic disease is interesting, yet the mechanisms to explain the importance and complexity of this evidence still falls under the tentative umbrella of "emerging science."

Nonetheless, there is sufficient evidence to suggest that reducing the risk of type 2 diabetes and preventing the complications associated with this disease represent significant opportunities for the food industry to build a strong relationship with nutrition and health-care professionals. There is clinical evidence of foods that improve glycemic control, reduce blood pressure, lower risks of cardiovascular disease, and develop favorable serum lipid profiles in conjunction with appropriate physical activity.

It is interesting to note that among the 37 government-sponsored clinical trials on type 1 and type 2 diabetes, none has an objective to examine opportunities for dietary intervention per se. The value of continued research that integrates food science, nutrition, and health should not be underestimated. **FT**

Diet and exercise *[provide] a non-medical means of managing a potentially devastating and multifactorial illness.*

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