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Nutrigenomics: From Nutrition to Genes

It seems only yesterday that Watson and Crick announced the discovery of circular DNA isolated from *Escherichia coli*. Since this exciting advancement in the genetics era, new research has attempted to identify the genetic basis and molecular causes of chronic diseases. Recorded history acknowledges that dietary components contribute to cellular replication, growth, and apoptosis, yet the mechanisms remain in a maze in which the paths to healthiness wait to be revealed.

We now welcome an era of nutrigenomics, an exciting new multidisciplinary science that recognizes the potential of common nutrients to act as potent dietary signals that influence the metabolic behavior of cells (Fogg-Johnson and Kaput, 2003). More specifically, it has become clear that certain bioactive constituents of foods may alter gene expression at the cellular level by serving as ligands for transcription-factor receptors, by altering concentrations of substrates or intermediates, or by serving directly as signaling molecules. This awareness has given birth to the notion that foods might be “designed” or modified to directly support health, reduce the risk of diet-related diseases, and lead to individualized nutrition (Kaput and Rodriguez, 2004; German et al., 2004).

Epidemiological and controlled laboratory animal studies have identified types of specific dietary constituents and excess calories as the main culprits inducing or contributing to chronic diseases. Normal variations in genes among humans (i.e., single nucleotide polymorphisms, SNPs) and the difficulties of controlling or assessing what individuals eat confound the analyses of how diet affects health. The complexity is readily apparent when we consider that the human genome contains about 30,000 genes, approximately 3 billion base pairs, and more than 1.5 million SNPs. These numbers illustrate a new dimension to nutrition research.

Published research has demonstrated that mutations in more than 1,000 genes contribute to the development of congenital, chronic, and medically rare diseases. However, it appears that there are few research efforts that examine the role of diets on the activity of those genes. (Ordovas and Corella, 2004). There are several genes associated with familial hypercholesterolemia, an inherited disorder of lipoprotein metabolism, which may be

modulated by dietary and environmentally factors. At least 12 mutated genes alter many cellular functions that regulate glucose homeostasis among type 2 diabetics. Lactose intolerance, phenylketonuria, galactosemia, and celiac disease are examples of dynamic gene–nutrient interactions in health and disease through the life span. Obesity, diabetes, osteoporosis, cardiovascular disease, metabolic syndrome, cancers, and Alzheimer’s disease represent a few examples of possible genetic-linked diseases associated with polymorphisms.

Foods represent a complex matrix of nutritional components that can affect thousands of genes, genetic polymorphisms, and gene expression products recognized in this new nutrigenomics arena. As the pharmaceutical industry explores pharmacogenomics to discover drug targets, define drug efficacy, and reduce undesirable side effects in response to individual genetic variations within a human population, it is time for a revolutionary approach in nutrition to understand how foods interact at the cellular level among individual genotypes.

Similarly, our study of genomics within an agricultural setting will lead to cultivar selection that could lead to more healthful crops for a significant subset of the population (Watkins et al., 2001).

This understanding of individual genetic variation in humans and in cultivars is critical to further explain differences in nutrient requirements and how we can meet those needs. This, in turn, will lead to the development of “personalized” nutrition that delays the onset of disease and optimizes and maintains human health.

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Dietary Antioxidants—Risk or Relief?

Nutritional antioxidants have come under close scrutiny of late and are the subject of escalating debate. The alphabet soup of flavonoids, such as catechins (tea) and anthocyanins (wine and bilberries), occur naturally in virtually all foods and appear to be particularly abundant in fruits and vegetables. Notable examples and their sources include beta-carotene (sweet potatoes, squash, apricots, and pumpkin), lycopene (tomatoes, papaya, and blood oranges), lutein (spinach, kale, collard greens), vitamin C (citrus fruits), and vitamin E (almonds and other nuts, and corn and soybean oils).

An excellent recent study by Wu et al. (2004) indicated that the total antioxidant capacity of pecans, walnuts, and hazelnuts was very high, based in part on an in-vitro assessment of oxygen radical absorbance capacity (ORAC) and polyphenol content. Their results also suggested that grain-based foods, including some ready-to-eat breakfast cereals, are among the best sources of antioxidants, based on this assessment. Part of the challenge is to translate these in-vitro assessments into clinical relevance.

These antioxidants may have a role in protecting cells from molecules known as reactive oxygen species (ROS) or free radicals, which have been implicated in the etiology of various malignancies, coronary artery disease, diabetic vasculopathy, and aging. The National Cancer Institute has reviewed a number of completed and clinical trials in progress (NCI, 2004) and concluded, in essence, that inconsistent data preclude anything but the recommendation that a healthy diet should include a variety of fruits and vegetables in moderate quantities.

The American Heart Association (www.americanheart.org/presenter) similarly finds no evidence to support antioxidant supplements, and continues to recommend a balanced diet including five daily servings of fruits and vegetables. Omenn et al. (1996a, b) reported that beta-carotene and vitamin A supplements were associated with a higher incidence of lung cancer in relatively high-intensity smokers than in controls. There have also been at least two studies that have found that antioxidant supplements, specifically vitamins E (400 IU twice a day, BID) and C (500 mg BID), beta-carotene (12.5 mg BID), and selenium (50 µg BID), and selenium may interfere with the protective effect of statin agents, such as Zocor, and HDL levels (Cheung et al., 2001; Brown et al., 2001).

In-vitro evidence and observational studies to date underscore

the benefits derived from food-derived antioxidants and undermine the role of some antioxidant-laden dietary supplements. Some relatively small clinical studies among high-risk individuals, however, such as those recently described by Richer et al. (2004), Sesso et al. (2004), and Block et al. (2004) are clinically provocative. For example, the evidence by Richer et al. suggests that visual function in patients with age-related macular degeneration may be improved by supplementation with 10 mg of lutein/day over a 12-month period. Sesso et al. described data from the Women's Health Study that indicated that higher plasma lycopene concentrations were associated with a lower risk of cardiovascular disease in women. Block et al. noted that when active smokers supplemented their diet with vitamin C (515 mg/day) during a 2-month study period, one of the plasma indicators of inflammation, namely C-reactive protein, decreased significantly.

Despite these potential benefits associated with a reduction in health risks, all of the investigators stipulated the need for additional clinical research to understand mechanisms of action, assess long-term effects, and validate these potential benefits in the general population. This is particularly important when considering the large number of middle-aged, those more senior in age, and the overweight/obese individuals who are consuming multiple medications, including statins to reduce their blood cholesterol levels.

Clearly, more rigorous study is indicated before antioxidant supplements can be recommended for those at risk for chronic disease such as cancer, vascular disease, and age-related conditions. The recent meta-analysis by Bjelakovic et al. (2004) suggests that pharmacological doses of beta-carotene, vitamins A, C, and E, and selenium supplements may not decrease one's risk of gastrointestinal cancers. On the other hand, the accompanying editorial by Forman and Altman (2004) asserts that the apparently negative impact of these nutrients is not convincing.

One of the key findings of the Dietary Guidelines Advisory Committee (2005) is that Americans should increase their daily intake of fruits and vegetables, whole grains, and nonfat or low-fat milk and milk products, so that we can increase our consumption of vitamins A, C, and E, as well as calcium, potassium, magnesium, and fiber. This recommendation incorporates the Advisory Committee's recognition that these foods provide physiological doses of diverse micronutrients as part of a balanced

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diet, and that the lifelong practice of balance, moderation, and variety beginning at childhood can contribute to a reduced risk of chronic disease. This finding also emphasizes that the specific roles of antioxidant compounds remains largely unknown from a clinical perspective, and that the doses and forms of these antioxidants that may reduce or even exacerbate one's risk of disease remain to be determined.

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Dietary Supplements and Sports Performance

At the 2004 Olympic games, athletes gave world record-breaking performances. Success at this level of sport competition is dependent primarily on genetic endowment of morphologic, psychologic, physiologic, and metabolic traits specific to a given sport, combined with superior training to optimize these traits. However, many athletes attempt to go beyond their endowments and training and use various techniques and substances, particularly nutritional strategies, in attempts to gain a competitive advantage.

In general, a diet that is optimal for health is also optimal for sports performance. A diet rich in fruits, vegetables, whole grains, lean meats, and low-fat dairy products that stresses variety, balance, and moderation will provide an adequate intake of carbohydrate, essential fatty acids, protein, vitamins, minerals, and water necessary to prevent a nutrient deficiency that could impair performance.

Sports supplements account for almost 10% of dietary supplements sold in the United States. In a 2000 joint statement, the American College of Sports Medicine, American Dietetic Association, and Dietitians of Canada indicated that dietary supplements might be required by some athletes, such as those in weight-control sports. However, depending on the specific requirements of a given sport, some sports supplements may be used in attempts to enhance performance.

Sports supplements may be classified in four categories. Here's an example of each:

• **Supplements that perform as claimed.** Creatine, as creatine monohydrate, is one of several supplements that can enhance performance. Creatine supplementation has been shown to increase muscle supplies of creatine phosphate (PCr), a compound necessary for rapid ATP resynthesis during very high-intensity exercise. Numerous major reviews, including a meta-analysis and a monograph, support the effect of creatine supplementation to enhance performance in short-duration, high-intensity exercise tasks such as cycle ergometer sprint protocols, and sprint running. Combined with resistance training, it also consistently appears to increase muscle mass and muscle strength. Yet, long-term effects of taking creatine have not been established.

• **Supplements that may perform as claimed.** Glycerol, when mixed and consumed with water, may result in greater fluid re-

tention that may increase plasma volume and total body water, with potential beneficial effects for performance and temperature regulation during exercise in the heat. Research findings are inconsistent, but several well-controlled studies have found that glycerol hyperhydration may improve cardiovascular responses, temperature regulation, and cycling exercise performance under warm/hot environmental conditions. Reviewers differ as to whether glycerol supplementation enhances sports performance, and additional research is needed to resolve the equivocal findings.

• **Supplements that do not perform as claimed.** Ginseng contains a wide variety of chemical substances, some theorized to enhance sports performance by various means. Some early research indicated that ginseng supplementation could enhance sports performance, but these studies employed improper research methodology. Contemporary studies and comprehensive reviews overwhelmingly indicate that ginseng supplementation has no beneficial effect on cardiovascular,

metabolic, or psychologic responses to either submaximal or maximal exercise performance, or on maximal performance capacity.

• **Supplements that have been banned.** Ma huang is herbal ephedrine, an ingredient which has been associated with significant health risks, such as hypertension, tachycardia, and death. Ephedrine use is prohibited by the World Anti-Doping Agency (WADA) and the National Collegiate Athletic Association (NCAA).

Most sports supplements do not improve performance, but some may. However, individuals may respond differently to various nutritional strategies or dietary supplements, so athletes and their advisors must be prepared to individualize a dietary regimen to optimize both training and performance. Most sports supplements are safe and permissible. However, excessive intake of many supplements, even vitamins, may pose significant health risks. The U.S. Anti-Doping Agency (USADA) and NCAA warn that dietary supplements, transdermal patches, and topical creams may contain prohibited substances, and that athletes are at risk of testing positive for banned substances and thus committing a doping violation.

Athletes will benefit most from consumption of a balanced and varied healthful diet. ●

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Men's Health—An Opportunity for the Food Industry

The Women's Health Initiative has focused national attention on medical problems affecting more than half the female population. Disease specific to males may now deserve some additional emphasis. Prostatic disease, for example, especially among men over 65 years of age, is a serious clinical concern that may be one target for the food industry.

Nearly 100% of all males over 50 years of age present symptoms associated with benign prostatic hyperplasia (BPH)—noncancerous prostate enlargement and cell proliferation. While most men develop BPH, approximately 1 out of 6 males are at risk for developing prostate cancer over their lifetime (Epperly and Moore, 2000). Prostate cancer remains the second leading cause of death among men.

A diagnosis of BPH is based on histological evidence and gland volume, typically >30 mL. The clinical diagnosis of BPH is presumptive, based on three basic symptoms: irritation, obstruction, and infection.

Current medical literature is replete with discussion of dietary approaches to the prevention and management of BPH. These include a variety of food components as well as plant and herbal extracts frequently found in dietary supplements. Food components include resveratrol, soy, tomatoes, and n-3 fatty acids. Among the more popular dietary supplements are saw palmetto, prunus, nettle root, and milk thistle.

Resveratrol and its *trans* isomer are phytoestrogens found in the skin of red grapes. There is emerging evidence that resveratrol suppresses the expression and function of a variety of androgen-regulated genes, including the androgen receptor in at least one prostate cancer cell line. Preliminary in-vitro research suggests that these grape skin extracts possess antioxidant and antiproliferative properties, and that resveratrol may promote nitric oxide production, thus mitigating some of the potential sequelae associated with BPH and prostate cancer treatment (Bhat et al., 2001).

Soybean-derived products such as soy "milk" and tofu contain an array of phytoestrogens. One of the best studied is the isoflavone genistein. While the most intriguing data are derived from human histoculture studies (and thus must be interpreted carefully), there is epidemiologic evidence that the relatively low prevalence of prostate disease in Asia may be associated with high dietary soy consumption. Apart from inhibition of multiple hormone-dependent and hormone-independent prostate cancer cell

lines, there is evidence that other soy-derived isoflavones and their metabolites may be more active in suppression of tumor growth and inflammation.

Several recent prospective surveys suggest that a high intake of cruciferous vegetables may offer some protection against prostatic disease. The polyphenols in fruits, vegetables, red wines, coffee, tea, and even juices may be responsible for some of these

effects. For example, lycopene, a carotenoid found in high amounts in tomatoes and tomato products, typically concentrates in the prostate and retinal tissues (Clinton, 1998). Again, epidemiologic data among Mediterranean populations are intriguing, implying an inverse association between the consumption of high proportions of lycopene-containing foods, thus possibly reducing oxidative stress, and lower rates of prostate disease. However, the overall data are inconclusive, especially when considering advanced prostatic cancer in older men.

Numerous clinical studies suggest that the consumption of n-3 fatty acids, specifically eicosapentaenoic and docosahexaenoic acids (EPA and DHA), from fish and plant sources may contribute to a healthy heart. These fatty acids also inhibit prostatic cell proliferation, yet dietary α -linolenic acid may increase growth of these cells, and possibly contribute to BPH. Future dietary studies that assess the risk of BPH and prostatic disease could contribute to our understanding of the dynamics of this disease process, and lead to additional food products and public health intervention strategies (Leitzmann et al., 2004).

Prostate disease will affect nearly every male who lives beyond 50 years. Whole foods and food components from fruits and vegetables, including phytoestrogens, antioxidants, selected fatty acids, and other macronutrients, may be useful adjuncts in limiting the risk of prostatic enlargement and BPH.

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Is Glucosamine a Remedy or a Risk?

Osteoarthritis is the most common form of arthritis, affecting 40% of those over 60 years of age. It is the leading cause of physical disabilities, especially among older adult women. This senior population group dominates the United States demographics, and more than 60% of those 45–74 years of age are overweight (BMI > 25), a significant risk factor for diabetes, cardiovascular disease, hypertension, and arthritis-related disabilities.

Many of those diagnosed with osteoarthritis often take glucosamine—self-prescribed or advised by orthopedists—to reduce the symptoms associated with degenerative joint disease and arthralgia. However, the American College of Rheumatology in 2000 indicated that such advice was premature based on the body of scientific evidence.

An emerging issue surrounding the efficacy and utility of glucosamine is that it may contribute to insulin resistance and type 2 diabetes. Insulin resistance is a serious precursor to diabetes that affects 80 million in the U.S. This is a chronic condition typically characterized by dyslipidemia, elevated blood pressure, an android pattern of body fat distribution, and glucose intolerance. The latter clinical presentation may be the vulnerable mechanism through which continuous glucosamine challenge perturbs glucose metabolism and leads to type 2 diabetes.

At the heart of this issue is the potential impact of glucosamine on multiple tissues and organ systems. These multiple involvements amplify the clinical significance of potential health risks associated with obesity, insulin resistance, and type 2 diabetes. In addition, there is evidence that glucosamine can (1) increase oxidative injury and stress to pancreatic β cells (the cells responsible for insulin production) and may contribute to their deterioration and dysfunction, and (2) impair mobilization of glycogen (the storage form of glucose) from the liver, thus contributing to hepatic steatosis or non-alcoholic fatty liver disease (Cooksey et al., 1999).

A recent 90-day study among 22 well-controlled diabetics (mean age 68.6 years) suggested that daily supplementation with 1,500 mg of glucosamine did not significantly alter hemoglobin A_{1c} (HbA_{1c}) concentrations (Scroggie et al., 2003). HbA_{1c}, a clinical indicator of glycemic control among diabetics and the main outcome measure of the study, calls into question the validity of the conclusions that glucosamine does not alter glucose metabolism in those with type 2 diabetes. While this biomarker certainly

evaluates serum glucose stability, it is conventional wisdom that HbA_{1c} is neither a sensitive nor a specific indirect indicator for insulin resistance.

Jain and McCormick (2004) pointed out that the well-controlled diabetic population studied by Scroggie et al. actually reflected unique subjects who had the capacity for a compensatory endogenous insulin response to the possible amplification in insulin resistance with oral glucosamine challenge. The authors cautioned that Scroggie et al.'s findings may be applicable only to early or well-controlled diabetics and not to a more representative obese population at risk to hyperglycemia, insulin resistance, type 2 diabetes, and osteoarthritis.

The National Research Council's report on assessing the safety of dietary supplements (NRC, 2004) stated that there are many unresolved issues surrounding glucosamine, as well as many opportunities for future research. One of the unresolved issues centers on glucosamine intake possibly being associated with insulin resistance and liver disease. From a public health perspective, the report suggests that our knowledge of glucosamine impact on children and during pregnancy and lactation is unknown, and thus may place these vulnerable populations at risk for these conditions. Our understanding of the long-term consequences of glucosamine intake beyond three years, especially among pre diabetics and diabetics, is uncertain, and our comprehension of glucosamine metabolism remains unclear.

While glucosamine may provide some clinical benefits in terms of bone and joint health, there are also emerging risks with respect to obesity, diabetes, and liver disease that are associated with consuming pharmacological doses of this supplement.

Our understanding of the long-term consequences of glucosamine intake . . . is uncertain. . . .

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Clinical Value of Glycemic Index Unclear

The concept that foods have different glycemic effects was advanced more than 20 years ago by Otto et al. (1981), and use of glycemic index as a possible tool for the management of type 1 diabetes and dyslipidemia was introduced nearly two decades ago by Jenkins (1985). Reports within the past several years suggest that an elevated glycemic index may be associated with increased risk of myocardial infarction, endometrial cancer, and insulin resistance and may be important in the treatment or prevention of chronic disease, including obesity.

On closer examination of the relationship between glycemic index and disease and a broad review of the scientific evidence of central pathways that regulate food intake and energy homeostasis, however, it becomes clear that it is premature to advise the general public and most patients to avoid foods with a high glycemic index.

Numerous factors affect the reproducibility of glycemic index (GI). For example, the GI of a food or meal in the morning following an overnight fast differs from that after lunch or dinner. The ripeness of fruit, the physical form and chemical nature of food, the type, processing, and preparation of the food, the combination of macronutrients within the food, including protein, fat, carbohydrate, and fiber, and even acidity influence GI (Pi-Sunyer, 2002).

Structural relationships, applied processing technologies (thermal and nonthermal), and the amount of water are among the many parameters that account for at least 25% variation in GI among carbohydrate-containing foods. For example, the amylose and amylopectin in potatoes and the D-glucose and mixture of 1-4 and 1-6 glucose linkages in different kinds of rice and pastas influence GI (Wolever et al., 2001).

Since it appears that GI is dependent on the processing, storing, ripening, curing, and cooking of a food, no one food has a single or definitive GI. In fact, a specific and standard GI value for a given food runs counter to our current understanding of these variations and misleads consumers and the food industry.

The popularization of GI as a potentially useful tool in reducing risks and preventing some chronic diseases such as obe-

sity is confounded by the virtual absence of supporting clinical data. In general, some would suggest that high-GI foods increase food intake as a result of elevated glucose and possibly excessive post-prandial insulin response. The best long-term studies indicate no difference in weight gain between groups consuming high-GI and low-GI diets.

The preponderance of scientific literature supports the view

What is important in weight loss is the caloric content of food, not the source of its carbohydrate content or its impact on insulin response within a given individual.

that the use of GI as a biomarker and management tool in chronic disease states and obesity is limited and unique to individual responses. The best scientific evidence and clinical experience to date suggest that what is important in weight loss is the caloric content of food, not the source of its carbohydrate content or its impact on insulin response within a given individual. Other threats to the validity of any simplified construct involving GI and weight loss include the fact that GI has an enormously variable impact on metabolism, depending on many factors, including an individual's weight, age, sex, physical activity level,

general health, antecedent diet, the type of food and how it was processed and prepared, and variable rates at which aspects of digestion and gut motility occur.

There remain too many uncertainties regarding the validity of GI to label foods "good" or "bad." Examination of the broad range of apparent GI quintiles in the Nurses' Health Study and among men in the Health Professionals' Follow Up Study suggests that it is both impractical and unreasonable to drive the GI down in the general population. In light of the current medical and scientific evidence, it seems irrational at this time to advocate GI as a prophylactic public health measure and to advise the avoidance of certain carbohydrates (Sievenpiper and Vuksan, 2004).

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Low-Carb Craze Unwarranted

Low-carbohydrate diets have developed into a multimillion-dollar industry. They promise healthy, rapid, and indulgent weight loss for relentless dieters. This is especially remarkable, since no randomized, controlled clinical trials evaluated its efficacy until 2003.

Foster et al. (2003) conducted a one-year, multi-center study among 63 obese men and women with a body mass index (BMI) greater than 30. The results demonstrated greater weight loss on the low-carbohydrate diet within the first six months than on a conventional diet of 1,200–1,800 kcal/day, but this apparent difference did not continue through the remainder of the study period.

Of particular interest is that the frequently observed dyslipidemia (elevated cholesterol, depressed HDL, increased LDL) associated with moderate overweight was not resolved between the study groups, and the post-prandial glucose and insulin levels did not differ. These results were also confounded with poor compliance and high attrition.

A review of the literature from January 1966 through February 2003 (Bravata et al., 2003) indicates that there is not a clear consensus as to what amount of carbohydrates consumed daily constitutes a low-carbohydrate diet; and that there is insufficient evidence to make recommendations for use of low-carbohydrate diets, especially among subjects older than 50 years of age or for more than 90 days. Among the reviewed studies, participant weight loss while using low-carbohydrate diets was principally associated with decreased caloric intake and diet duration but not with reduced carbohydrate content.

While clinical and scientific impression is that any diet that ensures caloric restriction—e.g., limits food choices—will promote weight loss, the overwhelming popular trend continues to emphasize regimens organized around high-fat, high-protein content. Popularity of this dietary strategy persists despite available evidence suggesting that long-term safety and improved compliance are strongly associated with *moderate* fat balance and variety in a diet regimen (Freedman et al., 2001).

In discussing variety, it is worth noting the popular impression that the prevalence of refined sugar and fast-food is causally linked to obesity. Epidemiological data refute this assertion dramatically. World Health Organization data (DeOnis and Blössner, 2000) demonstrate that some of the highest rates of childhood

obesity occur in developing countries and Eastern Europe, where access to refined sugar and processed food is virtually nonexistent.

Thus, calories do count, the source of those calories may not require conformation to some extreme ideal, and most diet algorithms that effectively reduce caloric intake do result in weight loss. Achieving and maintaining a healthy weight over a meaningful duration is another matter. Medically supervised, safe and effective weight reduction is not an acute event,

but a chronic process that includes simultaneous caloric restriction (through a diet that truly facilitates compliance) and regular physical activity (Freedman et al., 2001).

Never before in history have we enjoyed such quality, quantity, and variety of food, but we have a growing responsibility to develop and market foods that reduce the risk of acute and chronic disease. We've gone beyond basic nutrition and are responding to consumer demands for rapid adjuncts to health. In the face of these unprecedented market pressures, it is essential that food

industry innovation be scientifically based and medically well founded. The evidence demands critical examination and rational decisions rather than implicit promotion of fads and crazes.

Obesity prevention and health improvement are everyone's responsibilities. These include "model" eating habits and moderate exercise. In conjunction with evidence-based, clinically validated dietary regimens, what seems essential are partnerships among academic institutions, food industry members, regulatory agencies, and popular media that promote healthy diets and appropriate levels of physical activity.

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This is the first of a continuing series of articles that will provide medical and scientific perspectives on the relationship of food, medicine, and public health.