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PURPOSE AND OBJECTIVES

Many diseases, including most leading causes of death, are influenced by diet. Physicians in all specialties, especially those in primary care, have a crucial role to play in preventing chronic diseases. After reading this article, physicians should be able to describe the various dietary fats and their role in disease, make educated recommendations regarding dietary fiber, sodium, calcium, vitamin D, and folic acid, be aware of the current thinking on antioxidants, and understand the J-shaped curve related to alcohol consumption

DISCLOSURE

In publishing this article in *Southern Medical Journal*, the Southern Medical Association recognizes educational needs of physicians in all specialties, especially those in primary care, for current information regarding dietary guidelines for the prevention of chronic diseases. In this article, authors may have included discussions about drug interventions, whether Food and Drug Administration approved or unapproved. Therefore, it is incumbent on physicians reading this article to be aware of these factors in interpreting the contents and evaluating recommendations. Moreover, views of authors do not necessarily reflect the opinions of the Southern Medical Association. Every effort has been made to encourage the author to disclose any commercial relationships or personal benefit that may be associated with this article. If the author disclosed a relationship, it is indicated below. This disclosure in no way implies that the information presented is biased or of lesser quality.

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The primary purpose of this article in the *Journal* is education. Information presented and techniques discussed are intended to inform physicians of medical knowledge, clinical procedures, and experiences of physicians willing to share such information with colleagues. It is recognized that a diversity of professional opinions exists in the contemporary practice of medicine that influences the selection of methods and procedures. The views and approaches of authors are offered solely for educational purposes. The Southern Medical Association disclaims any and all liability for injury or other damages to any individual reading this article and for all claims that may result from the use of techniques and procedures presented in it.

CURRENT CONCEPTS

Dietary Guidelines for Chronic Disease Prevention

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ABSTRACT: In developed nations, diet is related directly or indirectly to the most prevalent chronic diseases. Research has helped clarify diet-disease relationships and enabled the promulgation of dietary recommendations for chronic disease prevention. We reviewed epidemiologic study results, clinical trial data, and general dietary recommendations from various agencies to develop a set of overall dietary guidelines for the prevention of the most common chronic diseases in the United States, including coronary heart disease, hypertension, cancer, and osteoporosis. Intake of monounsaturated fats, fiber, calcium, vegetables and fruits, and whole grains should be promoted. Consumption of saturated and *trans* fats, sodium, and refined grains should be minimized. Moderation in alcohol and caloric intake should be encouraged. Although research into associations between diet and disease is constantly in flux, our guidelines are based on replicated findings and provide a starting point for assisting patients in improving their diets.

MOST LEADING CAUSES of adult deaths in developed nations—including coronary heart disease (CHD), cancer, and stroke—are influenced by diet. Other diseases associated with significant morbidity, including hypertension, diabetes mellitus, obesity, and osteoporosis, are also closely linked with dietary intake, as an etiologic or exacerbating factor.

One of the seminal reports on the association between diet and disease was a review by Doll and Peto[1] in 1981, in which the authors estimated that at least 35% of cancer deaths might be attributable to diet. Since that time, countless descriptive and analytic epidemiologic studies have attempted to clarify the link between diet and CHD, cancer, and a variety of other chronic diseases, with varying degrees of success. While nutritional epidemiology is an inexact science, certain findings have been consistently reproduced in multiple studies and serve as the foundation for formulating dietary recommendations for the general population.

Dietary recommendations to promote health and prevent disease are summarized by the US Departments of Agriculture and Health and Human Services in *Nutrition and Your Health: Dietary Guidelines for Americans.*[2] The fourth edition of these guidelines was published in 1995 (Table 1). These guidelines, as well as other official recommendations (Table 2), attempt to distill years of research into the association between diet and disease into recommendations that can be readily implemented. Although rather vague, they provide a starting point for assisting patients in making healthful changes in their diets, with the goal of preventing or postponing the most common chronic diseases affecting Americans. More specific recommendations (which are more useful in a clinical setting), and the evidence supporting them, are presented here.

DIETARY FATS

Observational epidemiologic studies and primary prevention clinical trials have shown a positive association between serum cholesterol

TABLE 1. Dietary Guidelines for Americans[2]

Eat a variety of foods.
Balance the food you eat with physical activity—maintain or improve your weight.
Choose a diet with plenty of grain products, vegetables, and fruits.
Choose a diet low in fat, saturated fat, and cholesterol.
Choose a diet moderate in sugars.
Choose a diet moderate in salt and sodium.
If you drink alcoholic beverages, do so in moderation.

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TABLE 2. Sources of Dietary Recommendations for Chronic Disease Prevention

Healthy People 2000: National Health Promotion and Disease Prevention Objectives. US Department of Health and Human Services, 1990 (DHHS Publication No. [PHS] 91-50212)
Diet and Health: Implications for Reducing Chronic Disease Risk. National Research Council, 1989
Food, Nutrition and the Prevention of Cancer: a Global Perspective. World Cancer Research Fund and the American Institute for Cancer Research, 1997
Guidelines on Diet, Nutrition, and Cancer Prevention: Reducing the Risk of Cancer With Healthy Food Choices and Physical Activity. American Cancer Society, 1996
Dietary Guidelines for Healthy American Adults. A Statement for Health Professionals From the Nutrition Committee. American Heart Association, 1996
Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). National Cholesterol Education Program, 1994
The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, 1997
National Institutes of Health Consensus Statement on Optimal Calcium Intake, 1994
Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: Executive Summary. Expert Panel on the Identification, Evaluation, and Treatment of Overweight in Adults, 1998
Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantothenic Acid, Biotin, and Choline. Institute of Medicine, 1998
Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride. Institute of Medicine, 1997
The Food Guide Pyramid. US Department of Agriculture, 1992 (Home and Garden Bulletin No. 252)
The Mediterranean Diet Pyramid. Oldways Preservation & Exchange Trust and Harvard School of Public Health, 1994

concentration and the incidence of and mortality from CHD.[3] Low-density lipoprotein (LDL) is the major cholesterol-carrying lipoprotein particle in circulation. It is also the major atherogenic lipoprotein in humans, with serum concentration of LDL-cholesterol (LDL-C) positively associated with the risk of CHD. For every 1 mg/dL increase in LDL-C, the risk of CHD increases by 1% to 2%.[4] The mechanism behind the atherogenicity of LDL has been elucidated in recent years and involves the oxidation of LDL—specifically, the peroxidation of polyunsaturated fatty acids (PUFAs) in LDL particles.[5,6]

High-density lipoprotein (HDL) is involved in reverse cholesterol transport, carrying cholesterol from peripheral tissues to the liver for metabolism or excretion. It is an antiatherogenic lipoprotein, with serum concentrations of HDL-cholesterol (HDL-C) inversely proportional to the risk of atherogenesis. A 1 mg/dL increase in HDL-C concentration is associated with a 2% to 3% decrease in the risk of CHD.[7] Lower HDL-C concentration is a risk factor for CHD even when total cholesterol concentration is not elevated.[8]

Triglyceride (triacylglycerol, TG) is the main form of dietary fat. Triglyceride concentration is also positively associated with the risk of CHD; however, it may not be an independent risk factor.[9] High TG concentration may promote atherogenesis by inducing the formation of small, dense LDL particles, which are especially atherogenic.[10] Hypertriglyceridemia is also associated with low HDL-C concentration and increased blood coagulability.[9]

Within populations, mean total serum cholesterol concentration is proportional to the percentage of energy consumed as fat, despite the fatty acid composition.[11] Thus, the National Cholesterol Education Program (NCEP) recommends limiting total fat to ≤30% of total energy.[12] A further reduction in fat intake may confer additional cardiovascular benefits, but these are probably minimal.[13] While ultra low-fat (approximately 10% of total energy) diets have been shown to lower cholesterol concentrations,[14] long-term adherence to such diets may be difficult for most individuals. Also, when dietary fat intake is severely restricted (with calories replaced by carbohydrates), serum TG concentration may be increased and HDL-C concentration decreased.[15] However, there is evidence that when individuals are gradually introduced to a low-fat (20%), high-carbohydrate (65%) diet, a reduction of serum total cholesterol and LDL-C may be achieved without the development of carbohydrate-induced hypertriglyceridemia.[16] Data from the third National Health and Nutrition Examination Survey show that fat intake currently comprises on average 34% of total energy intake in the United States.[17]

Dietary fat is not a single entity but consists of various fatty acids and cholesterol. The type of fat consumed appears to be more important than overall fat intake for cholesterol reduction. Saturated fatty acids (SFAs) are the major serum cholesterol-raising fatty acids in the diet.[18] A diet high in SFAs will raise LDL-C, and to a lesser extent HDL-C.[19] Palmitic acid (found in meats, butter, and tropical oils and the principal SFA in the diet) is primarily responsible for this effect. Lauric and myristic acids (found in tropical oils) also raise cholesterol concentration. Stearic acid (the primary fatty acid in chocolate) has not been shown to elevate cholesterol concentration significantly.[20] The current NCEP recommendation is to limit saturated fat intake to 8% to 10% of energy and to

<7% if there is an inadequate serum cholesterol response. Applying the 7% limit to all individuals may help to maximize cardiovascular benefits. To reduce intake of saturated fat, patients should be advised to decrease their consumption of meat in general (especially fattier cuts of beef and dark poultry meat) and full-fat dairy products. Emphasize beans, grains, and vegetables, and encourage patients to shift dietary emphasis from animal to plant sources of protein.

Polyunsaturated fatty acids are classified as n-6 or n-3 fatty acids, depending on the location of the first double bond. The primary n-6 fatty acid is linoleic acid, an essential fatty acid found in plant oils such as corn oil. Substitution of linoleic acid for SFAs results in decreased total cholesterol, LDL-C, and HDL-C.[21] In fact, replacing saturated fats in the diet with unsaturated fats may ultimately have the same effect on CHD risk as replacing fat calories with those from carbohydrates. Relative to monounsaturated fatty acids (MUFAs), some studies have shown that PUFAs may decrease LDL-C slightly,[21] though other studies have shown no significant difference in their cholesterol-lowering abilities.[22]

The main dietary n-3 PUFA is linolenic acid, found in soybean, canola, and fish oils. Linolenic acid also lowers LDL-C when substituted for SFAs. However, the main effect of linolenic acid is the reduction of plasma TG concentration.[23] In addition, linolenic acid is elongated in the body to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). These long-chain fatty acids may decrease the risk of thrombosis and lower blood pressure.[24] These n-3 fatty acids may also inhibit cardiac arrhythmias.[25] Fish oils are also rich in EPA and DHA. Low rates of CHD in countries with high fish consumption suggest that eating fish may protect against heart disease. Although one large prospective study (the Health Professionals Follow-up Study) found no evidence of an association between intake of either marine n-3 fatty acids or fish and the risk of CHD,[26] subjects in the US Physicians' Health Study who consumed fish at least once per week had half the risk of sudden cardiac death compared with men who consumed fish less than once per month.[27] An increased consumption of fish can be recommended, especially as a substitute for beef, with its high SFA content. However, a recommendation for fish oil capsules cannot be made at present, primarily because of their high susceptibility to peroxidation.

Cis-monounsaturated fatty acids have been the subject of great interest in the lipid literature. The only nutritionally important MUFA is oleic acid, abundant in olive and canola oils and also in nuts. Because MUFAs are present in relatively high amounts in the traditional Mediterranean diet (mainly due to the liberal use of olive oil), and regions consuming this diet generally have lower rates of CHD, it has been speculated that MUFAs are cardioprotective.[28] Monounsaturated fatty acids were originally shown to lower both LDL-C and HDL-C when replacing SFAs in the diet, generally to the same extent as when SFAs are replaced by PUFAs.[29] Further studies replacing SFAs with MUFAs have shown no decrease in HDL-C, while some have shown increases in HDL-C.[30] The response of HDL-C to high-MUFA diets may depend on the PUFA content of the diet. If PUFAs provide more than about 8% to 10% of total energy, the reduction in LDL-C in response to high-MUFA diets may be offset by a reduction of HDL-C.[22]

Compared with high-carbohydrate diets, those that include liberal amounts of olive oil as the primary source of fat result in an equivalent drop in LDL-C, but also an increase in HDL-C.[31] Monounsaturated fatty acids may also decrease serum glucose and TG concentrations in type II diabetics.[32] Monounsaturated fatty acids may have the additional advantage of decreasing the susceptibility of LDL to oxidative modification, while LDL oxidizability is enhanced by enrichment with PUFAs, at least in vitro.[33] First-pressed extra virgin olive oil contains appreciable amounts of polyphenolic compounds, which have inhibited the oxidation of LDL in vitro.[34] Extra virgin olive oil also contains other antioxidants, such as tocopherols and flavonoids, which may account for some of its purported beneficial effects. A MUFA intake of 13% of total energy, at the expense of SFAs, should be recommended.

In summary, one might reasonably recommend the following dietary fatty acid composition in light of the currently available evidence: SFAs, 7% of total energy; PUFAs, 10%; and MUFAs, 13% (assuming fat intake of 30% of total energy). While precise adherence to these percentages is not critical, they are presented to reinforce the notion that MUFAs and PUFAs should be the primary fatty acids in the diet, with much smaller amounts of SFAs.[35]

Trans-monounsaturated fatty acids (TFAs) are produced through the hydrogenation of PUFAs, converting them from liquid oils into

semisolid fats for use in commercially prepared foods. Hydrogenation results in the formation of *trans* double bonds, and the resulting TFAs resemble SFAs in conformation. Partially hydrogenated fats are found in shortenings, margarines, snacks, crackers, cookies, and in fast-food service fats and oils.[36] Studies have shown that TFAs increase LDL-C to levels similar to those produced by SFAs, but also decrease HDL-C concentration, potentially making them more atherogenic than SFAs.[37] *Trans*-monounsaturated fatty acids have been associated with an increased risk of CHD in epidemiologic studies,[38] though they have not been studied to the same extent as other fatty acids. While research into the health effects of TFAs continues, their intake should be limited until such time that official dietary recommendations can be made. Manufacturers were recently mandated to list TFA content on nutrition labels, which will make monitoring their intake simpler than in the past. Generally, it can be inferred that foods containing partially hydrogenated oils contain TFAs.

Dietary cholesterol is positively associated with both serum cholesterol concentration[39] and CHD risk.[40] However, dietary cholesterol has less effect on serum cholesterol than do SFAs or PUFAs. Cholesterol is found only in foods of animal origin (primarily egg yolks, fatty meats, and dairy products). Dietary cholesterol should be limited to ≤300 mg/day or to ≤200 mg/day in hyperlipidemic individuals with an inadequate serum cholesterol response.[12]

Dietary fat may be related to the development of other chronic diseases. International correlational studies show that countries with higher per capita intakes of fat, especially animal fat, have higher incidence rates of certain cancers, including breast, colon, prostate, and pancreas.[41] Migrational studies show that when individuals move from a country of low fat intake to one of high fat intake, the risk of some cancers increases.[42] The results of case-control and cohort studies have generally not been as convincing. The relation between breast cancer and fat intake, in particular, is slightly tenuous, with large prospective studies failing to find a correlation with total fat or saturated fat.[43] Epidemiologic studies indicate that colon cancer is linked to high consumption of animal fat, though the results are slightly equivocal.[44] Any connection between fat and cancer may actually be due to the confounding effect of energy. However, because decreasing fat intake (particularly saturated fat intake) may reduce the risk of certain cancers, and because doing so will provide documented cardiovascular benefits, this should be recommended without hesitation.

DIETARY FIBER

Dietary fiber refers to plant materials that are not readily digestible by enzymes in the human gut. Water-soluble fibers include pectins, gums, mucilages, and some hemicelluloses. Insoluble fibers include cellulose and other hemicelluloses. Fiber has several well-documented physiologic effects in the gastrointestinal tract that may influence the occurrence and course of several chronic disorders.

The consumption of insoluble fiber, particularly cellulose, tends to normalize large bowel function, decreasing transit time in constipation and increasing it in certain conditions characterized by chronic diarrhea.[45] Dietary cellulose increases stool weight and bulk but can result in dry stools. The addition of a soluble fiber such as pectin increases the water content of stools, providing for easier evacuation. A diet low in fiber may play a role in the pathogenesis of diverticulosis. Increasing both soluble and insoluble fiber in the diet will produce bulky, soft stools, facilitating defecation and reducing intracolonic pressure in this disorder.[46]

Pioneering studies by Burkitt[47] more than 20 years ago first suggested that fiber intake was inversely related to the risk of colorectal cancer because of the virtual absence of colorectal cancer in native Africans consuming high-fiber diets. Populations with a higher per capita intake of fiber generally have a lower incidence of colorectal cancer compared with those with a lower intake, such as in the United States. However, epidemiologic studies of dietary fiber and colorectal cancer have been inconclusive. A prospective study using the Nurses' Health Study cohort found no association between fiber intake and the risk of colorectal cancer or adenoma.[48] Two recent clinical trials found that increasing the intake of total fiber and insoluble fiber did not influence the risk of recurrent colorectal adenomas.[49,50] The anticarcinogenic effects previously attributed to fiber may in fact be due to the effects of the nonfiber constituents of fruits and vegetables with possible anticancer properties, such as antioxidant vitamins and minerals. In addition, high fiber intake is generally associated with lower energy intake, which may also decrease cancer risk indepen-

dently and confound the relation between fiber and colorectal cancer.

Most soluble fibers reduce plasma total cholesterol and LDL-C concentrations, an effect confirmed in a recent meta-analysis of 67 controlled trials.[51] Pectins, psyllium, gums (including guar and locust bean), mucilages, algal polysaccharides, and some hemicelluloses lower total cholesterol and LDL-C without affecting HDL-C.[52] Reported reductions in total plasma cholesterol after supplementation with soluble fiber such as oat bran have been as high as 25% but are usually in the range of 5% to 10%. High intake of fiber from cereal sources was associated with a reduced risk of CHD in the Nurses' Health Study, though the magnitude of reduction was more than would be expected from effects on serum cholesterol alone.[53]

There is limited evidence that fiber intake may play a role in other diseases. High fiber intake may have a beneficial effect on blood pressure. Dietary fiber was inversely associated with the risk of hypertension in the Health Professionals Follow-up Study.[54] Water-soluble fiber, especially gel-forming pectins and gums, blunts the postprandial glycemic and insulinemic responses in normal and diabetic individuals and may have a role in the prevention and treatment of diabetes mellitus and insulin resistance.[55] High intake of fiber has been associated with a reduced risk of cancer of hormonal tissues, including the breast and ovary.[56,57]

Because of its documented role in maintaining normal bowel function and possible role in disease prevention, adequate fiber intake should be encouraged. Most authorities recommend an intake in the range of 25 to 30 g/day or 10 to 13 g/1,000 kcal,[58] though a recent review by Wolever and Jenkins[59] recommended an intake of 15 to 20 g/1,000 kcal. Mean dietary fiber intake in the United States is only about 14 to 15 g/day,[60] which is characteristic of populations consuming a high proportion of refined grains. Fiber intake should be in the ratio of insoluble to soluble of 3:1, which approximates that found in nature.

Because some of the purported benefits of high-fiber foods may be due to components other than fiber, high-fiber foods, rather than isolated fiber, should be recommended whenever possible. However, the addition of wheat or cereal bran, the most concentrated sources of fiber, may be necessary for achieving the recommended intake. Recommend foods high in fiber—whole fruits over juices, whole grains over refined grains, etc. Pectin is found in fruits and vegetables, especially apples, oranges, strawberries, and carrots. Gums are found in oat bran, barley, and legumes. Whole wheat flour, wheat bran, and vegetables are good sources of cellulose, while hemicellulose is found in wheat bran and whole grains. Consumption of liberal amounts of water should be encouraged when adding fiber to prevent fecal impaction. High-fiber foods should be added gradually to the diet to minimize gastrointestinal symptoms, which may include flatulence, borborygmus, cramps, and diarrhea.

SODIUM

The role of sodium in the pathogenesis of hypertension remains slightly controversial. Hypertension is extremely rare in primitive societies with low salt intake, as is the rise in blood pressure with age commonly seen in industrialized societies with high salt intake. Results from the Intersalt study[61] showed a small correlation between both systolic and diastolic blood pressure and average sodium intake in 52 different populations. Numerous other observational studies have also shown a positive association between sodium intake and systolic and diastolic blood pressure. However, these studies must be weighed against those showing a low prevalence of hypertension in vegetarians and nondrinkers with high sodium intakes, suggesting that other dietary factors may play a more important role in the development of hypertension than does salt. In a meta-analysis of clinical trials of sodium reduction and hypertension, hypertensive patients decreased their blood pressure by a mean 4.9/2.6 mm Hg through sodium reduction, while nonhypertensive subjects decreased their blood pressure by about half this amount.[62] Although these are not large reductions on an individual level, they could have a substantial impact on the prevalence of hypertension at the population level.

The relationship between sodium and blood pressure is not a simple one. While some individuals respond to excess sodium with an increase in blood pressure (designated "salt-sensitive"), others do not. Approximately 30% to 50% of hypertensive patients and 15% to 33% of normotensive individuals are salt-sensitive.[63,64] Along with hypertensives in general, African Americans and the elderly appear to be particularly salt-sensitive. Unfortunately, although methods for ascertaining salt sensitivity have been proposed,[65] they are generally slow, cumbersome, expensive, and impractical in a clinical setting.

Nevertheless, because most Americans consume sodium in great excess of physiologic requirements, and because there are no adverse effects associated with moderate sodium restriction in otherwise healthy individuals, a reduction in sodium intake to ≤2,400 mg/day should be recommended to most individuals as a preventive measure.[66] This is the equivalent of 6 g of table salt (approximately 1 teaspoon). Only about 5% to 10% of sodium consumed occurs naturally in foods (primarily in meat). The rest is added during cooking or at the table (20% to 40%) or is consumed in processed foods (30% to 70%). Significant sodium reduction can be achieved by removing the salt shaker from the table, restricting the amount of salt used in cooking, and limiting the consumption of processed and fast foods. Foods associated with excessive saltiness (eg, pretzels and potato chips) often contain much less sodium than foods with "hidden" sodium, such as bread and canned vegetables and soups. In summary, although the role of sodium restriction in the prevention of hypertension in normotensive individuals has yet to be thoroughly established, it is prudent to recommend moderate sodium restriction for most individuals.

An increase in potassium intake appears to provide some protection from the deleterious effects of a high-sodium diet in humans.[67] Although evidence suggests that dietary potassium supplementation lowers blood pressure in established hypertension,[68] its role in the prevention of hypertension in normotensive individuals has not been established. Therefore, potassium supplementation for the prevention of hypertension is not currently recommended. However, the liberal intake of potassium-rich fresh fruits and vegetables (including bananas, orange juice, prunes, and dried beans) should be encouraged in otherwise healthy individuals. Processed fruits and vegetables are generally depleted of potassium and higher in sodium compared with their fresh counterparts, resulting in much lower potassium-to-sodium ratios.

CALCIUM AND VITAMIN D

Calcium is an integral component of bone in the form of hydroxyapatite, a crystalline structure of calcium phosphate in an organic matrix of collagenous protein. Calcium is an essential nutrient, required for the formation of bone and the maintenance of normal bone structure. Two periods that may have an impact on the risk of osteoporosis, and during which optimal calcium intake is critical, have been identified. The first is before age 30, particularly before age 20. During this period, a positive balance is the norm, with bone formation exceeding resorption. Peak bone mass is attained largely during this period, with little bone mass added after age 30. Optimal calcium intake in childhood and young adulthood is therefore crucial to achieving peak adult bone mass. Recognizing this, the Dietary Reference Intake (DRI) for this age group has been set at 1,300 mg.[69] The National Institutes of Health (NIH) Consensus Development Conference on Optimal Calcium Intake[70] recommended a calcium intake of 1,200 to 1,500 mg/day in adolescents and young adults to achieve peak adult bone mass. Results of dietary surveys show that average calcium intake in girls and young women is often less than 900 mg/day,[60] seriously compromising the accrual of bone mass.

After age 30 and before menopause in women and before age 50 in men, bone mass remains relatively stable, with bone resorption approximating new bone formation. The DRI for this age group is 1,000 mg/day, an amount that will help maintain adequate bone mass during this period.

The second critical period of calcium intake occurs after menopause in women. Corresponding to the fall in circulating estrogen heralding the onset of menopause is an increased rate of bone resorption relative to new bone formation. This imbalance may continue for 8 to 10 years and result in a 15% to 20% loss of accrued bone mass.[71] Adequate calcium intake during this period and in the years after the immediate postmenopausal period should be emphasized to help minimize loss of bone mass, though the effects of calcium on bone mass are less than that of estrogen replacement therapy (ERT).[71] The DRI for women in this age group is 1,200 mg/day. The NIH Consensus Development Conference recommended an intake of 1,000 mg/day for women older than 50 years of age who are receiving ERT and 1,500 mg/day for women older than 50 who are not receiving ERT. Inadequate calcium intake is also associated with reduced bone mass in men, and optimal calcium intake should also be emphasized in men. The DRI for men in this age group is 1,200 mg/day. Average calcium intake in this age group is typically around 600 mg/day.[60]

Deficient calcium status in adults older than 65 years is common due to decreased calcium intake and absorption and decreased vitamin D intake and synthesis. Increased calcium in-

take in this age group may also reduce bone loss and decrease the incidence of fractures.[72] Recognizing this, the NIH Consensus Development Conference recommended an intake of 1,500 mg/day in this age group for men and women, somewhat higher than the DRI of 1,200 mg/day.

Low calcium intake has been implicated in the etiology of other chronic diseases. Data from observational studies have suggested an inverse association between calcium intake and blood pressure.[73] Results from several double-blind, placebo-controlled clinical trials have been equivocal, with some showing modest reductions in both systolic and diastolic blood pressure and others showing little, if any, effect of calcium from foods or supplements on blood pressure.[74] There are insufficient data at this time to warrant a recommendation for increased calcium intake solely for the prevention of hypertension. However, because it has been suggested that the threshold of calcium intake below which the risk of elevated blood pressure increases sharply is 400 to 600 mg/day, dietary calcium recommendations for the prevention of osteoporosis would likely be adequate for blood pressure lowering. There is also epidemiologic evidence that high calcium intake may decrease the risk of colorectal cancer.[75] Calcium supplementation was associated with a moderate reduction in the risk of recurrent colorectal adenomas (precursors to cancer) in a recent clinical trial.[76] Low calcium intake was associated with an increased risk of ischemic stroke in the Nurses' Health Study cohort.[77] Contrary to previous reports, high calcium intake may actually help prevent nephrolithiasis, possibly by maintaining a lower rate of parathyroid hormone secretion.[78]

Nonfat or low-fat (1% fat) dairy products such as milk and yogurt are excellent sources of calcium due to their high calcium content. Calcium from vegetables such as broccoli, cabbage, and greens is absorbed to a higher degree than calcium from dairy sources, but their relatively low calcium contents can make obtaining adequate calcium strictly from vegetable sources difficult.[79] In addition to foods containing naturally occurring calcium, more and more calcium-fortified foods and beverages are appearing in the marketplace. Calcium supplements (in the form of carbonate or citrate) may be necessary to ensure adequate intake in cases of inadequate intake from foods.

Optimal calcium utilization is dependent on adequate vitamin D status. The major vitamin D metabolite, $1,25(OH)_2D_3$, facilitates calcium absorption in the intestine. Therefore, optimal vitamin D status should be ensured through dietary intake and ample exposure to sunlight. The current DRI for vitamin D is 5 μg/day (200 IU/day) up to age 50, 10 μg/day (400 IU/day) from 51 to 70 years of age, and 15 μg/day (600 IU/day) thereafter in men and women. However, studies have shown that up to 20 μg/day (800 IU/day) improves calcium balance and may help reduce the risk of fractures in the elderly, who are at increased risk of vitamin D deficiency due to decreased intake and exposure to sunlight.[80] Excessive vitamin D intake (≥50 μg/day) can result in hypercalcemia and hypercalciuria and should be avoided.[81] The main dietary sources are vitamin D-fortified dairy products, though certain fish, such as salmon and sardines, contain substantial amounts. Supplements may be necessary when dietary intake and sun exposure are limited.

While it is generally accepted that calcium intake is inversely associated with the incidence of fractures, some studies have failed to show a protective effect of dietary calcium, especially dairy calcium, on fracture risk.[82] One possible explanation for this is the finding that protein, including that associated with dairy products, is positively associated with urinary calcium excretion. At a calcium intake of 800 mg/day, increasing the intake of animal protein from 60 to 100 g/day (a moderate amount in the typical US diet) increases the calcium requirement from 840 to 1,680 mg/day.[83] Sodium intake is also positively correlated with urinary calcium excretion, and increasing sodium intake by 2.3 g/day has the same effect on calcium requirement as the 40 g/day increase in protein intake described.[83]

DIETARY ANTIOXIDANTS

Antioxidants have received much attention in the scientific and popular literature and media over the past several years. A substantial fraction of the general population regularly consumes antioxidant vitamins. However, the results of some studies suggest that supplementation with antioxidants may be of dubious benefit and may actually be harmful in some individuals.

Free radicals are predominantly reactive oxygen species that are byproducts of exogenous or endogenous oxidation reactions.[84] Free radical damage has been implicated in the pathogenesis of several diseases. The postsecretory oxidation of LDL by oxygen free radicals results

in the unregulated uptake of cholesterol in arterial walls, accelerating the atherosclerotic process. Cumulative oxidative damage to DNA may be associated with the rise in cancer risk that occurs with increasing age.[85] Excess production of free radicals may also contribute to tissue damage in rheumatoid arthritis, inflammatory bowel diseases (including Crohn's disease and ulcerative colitis), cataracts, macular degeneration, and neurodegenerative diseases and may be a major contributor to the aging process.[85]

The body has an antioxidant defense system to keep free radical damage in check. This includes antioxidant nutrients, which can directly scavenge free radicals, inactivating them. These include α-tocopherol, the most active and abundant vitamin E isomer and the major lipid-soluble antioxidant vitamin present in all cellular membranes, and ascorbic acid (vitamin C), a water-soluble antioxidant. β-Carotene (a provitamin A carotenoid) and flavonoids (phenolic compounds found in plants) have shown antioxidant activity in vitro, but their importance as antioxidants in vivo is still under investigation.

Because nutrients such as α-tocopherol and ascorbic acid have antioxidant activity in vivo, it has been proposed that increased intake of these nutrients through diet or supplements may reduce the incidence or delay the onset of diseases such as CHD and cancer. Vitamin E initially showed the most promise in the prevention of CHD. Being lipid-soluble, α-tocopherol is present in LDL particles and inhibits the oxidation of LDL particles both in vitro and in vivo.[86] Several large cohort studies have shown significant reductions in the incidence of cardiac events in men and women taking high-dose vitamin E supplements (approximately 200 to 400 mg/day).[87,88] However, the largest and longest randomized clinical trial of high-dose vitamin E supplementation conducted to date, the Heart Outcomes Prevention Evaluation (HOPE) study, did not corroborate these findings. The results revealed no effect of supplementation with 400 IU of vitamin E/day for a mean of 4.5 years on myocardial infarction, stroke, or death from cardiovascular causes in men or women.[89] There was no decrease in major coronary events and only a minor decrease in the incidence of angina pectoris with α-tocopherol supplementation in male smokers in the Alpha-tocopherol Beta-carotene Cancer Prevention Study (ATBC).[90,91] While α-tocopherol supplementation reduced the rate of nonfatal myocardial infarction in patients with angiographically proven coronary atherosclerosis in the Cambridge Heart Antioxidant Study,[92] it had no effect on morbidity and mortality after myocardial infarction in the GISSI-Prevenzione trial.[93] Therefore, there are not adequate data to recommend vitamin E supplementation for the primary or secondary prevention of atherosclerosis at this time. Vitamin E intake from foods such as fruits, vegetables, and nuts has been shown to be inversely associated with the risk of CHD in some studies[94] but not in others.[95] Nevertheless, the consumption of these foods should be encouraged because of the multitude of nutrients they contain.

High dietary β-carotene intakes have been associated with a decrease in cardiac events in some observational studies.[95] However, the results of clinical trials have generally been negative. The ATBC study revealed no effect of β-carotene supplementation on cardiovascular mortality, major coronary events, or angina pectoris.[90,91,96] There is not justification to recommend β-carotene or other carotenoids for the prevention of CHD.

Flavonoids in red wine have been proposed as one explanation for the "French paradox"—the relatively low cardiovascular mortality in France despite a relatively high intake of total and saturated fat[97]—in part due to their antioxidant activity.[98] However, data on flavonoids, as well as vitamin C, and CHD risk are generally lacking and slightly equivocal. It would be premature to recommend supplementation with either to prevent atherosclerosis.

Since a seminal report by Peto et al[99] in 1981 on the putative protective effects of dietary β-carotene on the incidence of cancer, countless observational studies have supported the notion that dietary and plasma carotenoids may decrease the risk of various human cancers, most notably lung cancer. However, the results of clinical trials of β-carotene supplementation have not been as promising. At best, the effects of β-carotene have been minimal. At worst, β-carotene may actually be associated with an increased cancer risk in certain groups, such as smokers. This occurred in the ATBC study. Results from one arm of the Physicians' Health Study, a double-blind clinical trial of supplementation with 50 mg of β-carotene on alternate days, showed no effect on cancer incidence.[100] Results of the few clinical trials of vitamin E and vitamin C in the prevention of cancer have also been slightly disappointing.

Despite these negative results, the quarter of the population with the lowest intake of fruits and vegetables has double the rate of the most common cancers, including genitourinary, gastrointestinal, and pulmonary malignancies.[85] Recent studies have shown that a diet rich in fruits and vegetables also protected against in vivo lipid peroxidation[101] and stroke.[102] The Dietary Approaches to Stop Hypertension (DASH) trial indicated that a diet rich in fruits and vegetables was associated with reductions in blood pressure.[103] However, it is premature to attribute these effects solely or even primarily to antioxidants in these foods. Besides vitamins, minerals, and fiber, fruits and vegetables also contain minor components (phytochemicals) that may have protective properties, including isothiocyanates and indoles, found in cruciferous vegetables; flavonoids, found in tea, wine, onions, soy, potatoes, and fruits; sulfides, present in onions and garlic; and terpenes, found in citrus oils.[104] This is why patients should be advised to increase their consumption of healthful foods, including fruits and vegetables, rather than specific nutrients, such as antioxidant vitamins. Patients should be advised to eat at least five to seven servings of fruits and vegetables each day, an amount that only about 20% of Americans currently consume on a regular basis.[105]

ENERGY

Excess caloric intake over time without a corresponding increase in energy expenditure results in the accumulation of excess body fat. At its extreme, the result is obesity, an abnormally high percentage of body fat. More than 50% of adults in the United States are either overweight (body mass index [BMI] ≥25) or obese (BMI ≥30), and the prevalence of obesity is on the rise.[106]

Excessive body fat and obesity, especially abdominal obesity, are risk factors for several diseases. In men and women, higher BMI and waist-to-hip ratio are associated with increased risk of hypertension and cardiovascular disease.[107-109] The results of several clinical trials, such as the Trials of Hypertension Prevention, have shown that weight loss results in modest reductions in blood pressure.[110] Obesity is also associated with glucose intolerance and insulin resistance and is a risk factor for type 2 diabetes mellitus.[111] This is especially true with abdominal obesity.[112] Weight loss improves glucose tolerance and decreases insulin resistance, reducing the risk and severity of diabetes.[113] Obesity increases the risk of gallbladder disease (including cholelithiasis), especially in women.[114]

Many common cancers may be related to excess caloric intake and obesity rather than to fat intake per se. High caloric intake has been associated in correlational studies with an increased prevalence of cancers of the breast, cervix, endometrium, ovary, gallbladder, and prostate.[115] Abdominal obesity in particular has been associated with an increased risk of breast cancer.[116] The risk of colon cancer has been associated with high caloric intake in prospective observational studies.[117]

Because of the evidence linking high caloric intake and obesity to several diseases, caloric intake should not exceed what is required to maintain a BMI of <25.[118] Weight loss to achieve this BMI should be the ultimate goal in overweight patients. However, even modest weight loss in obese individuals decreases disease risk. The clinician should aid the patient in identifying weight-loss programs that are based on sound scientific principles, incorporate diets that are safe and nutritionally adequate, and include behavior modification, aerobic exercise, and social support. Patients should avoid fad and novelty diets, weight-loss gimmicks, and short-term diets that advocate complete elimination or overconsumption of specific foods or whole food groups. Maintenance of weight loss should be emphasized in any program.

ALCOHOL

When represented as a curve, the relation of alcohol consumption to mortality is generally J-shaped, with abstainers experiencing slightly higher mortality rates than moderate drinkers, and heavy drinkers having much higher mortality rates than moderate drinkers or abstainers.[119] International correlational studies have consistently shown lower overall mortality in individuals consuming from one to two drinks per day. The protective effect of moderate ethanol consumption is primarily mediated through its effect on CHD risk. Several cohort studies have shown that the incidence of and mortality from CHD are diminished in moderate drinkers.[120-121] Moderate alcohol consumption (up to two drinks per day) has also been associated with a reduced risk of ischemic stroke in men and women.[122]

The possible beneficial effects of moderate ethanol intake must be weighed against the deleterious effects of higher intakes, including increased risk of hypertension, cardiomyopa-

thy, and hemorrhagic stroke. More than three drinks per day have been associated with a rise in blood pressure, and at more than four drinks per day, the average increase is 5 to 6 mm Hg in systolic pressure and 2 to 4 mg Hg in diastolic pressure.[123] Excess ethanol consumption is also associated with increased plasma TG concentration.

Ethanol consumption has been associated with an increased risk of certain malignancies, including oropharyngeal, laryngeal, and esophageal cancer.[124] Alcohol intake has also been positively associated with the risk of breast cancer in a dose-response relation.[125] Excessive ethanol consumption may also increase the risk of colorectal cancer and its precursor lesion, adenomatous polyps.[126]

Alcohol intake is a risk factor for osteoporosis, though moderate drinking was associated with higher bone density in women in one study.[127] Excessive ethanol consumption is a well-established risk factor for liver disease, including fatty liver, alcoholic hepatitis, and cirrhosis, and is associated with increased mortality from pancreatitis and gastritis.[128]

Because of the potential for abuse and the associated morbidity and mortality associated with excessive intake, the use of ethanol to decrease CHD risk should not be recommended to current nondrinkers. However, in the absence of medical contraindications, current drinkers need not necessarily be advised to abstain, but moderation should be emphasized. This translates into no more than one drink (12 oz beer, 4 oz wine, or 1 oz distilled spirits) per day for women and no more than two drinks per day for men.[66]

FOLIC ACID

Folic acid, a water-soluble vitamin required for several one-carbon transfer reactions, may play a role in the prevention of CHD. Moderate elevations of plasma homocysteine, a sulfur-containing amino acid, have been associated in epidemiologic studies with an increased risk of peripheral vascular and cerebrovascular disease and CHD.[129,130] Folic acid is required for the methylation reaction that converts homocysteine to methionine, another amino acid involved in one-carbon transfer reactions. Reduced plasma concentrations of folic acid can result in homocystinemia. In the Framingham Heart Study, folic acid status was strongly associated with plasma homocysteine concentrations,[131] as it was in the Hordaland Homocysteine Study.[132] Clinical trials have shown that folic acid supplementation decreases plasma homocysteine concentrations,[133] an effect that may be enhanced with the addition of vitamin B_{12}.[134] Data from the Nurses' Health Study showed a reduced risk of CHD among women in the highest quintile of folic acid intake from diet and supplements.[135]

Epidemiologic studies have also related folic acid deficiency to an increased prevalence of precancerous dysplastic changes in cervical and colorectal epithelium.[136,137] Women in the Nurses' Health Study had a significantly reduced risk of colon cancer after 15 years of folic acid supplement use.[138] The excess risk of breast cancer associated with alcohol consumption may be partially mitigated by adequate folate intake.[139]

Until the results of ongoing clinical trials of folic acid and vascular disease and cancer become available, adequate folic acid intake (400 μg/day) should be ensured through diet (especially fresh, dark-green leafy vegetables) and, if necessary, supplements. To help ensure adequate intake of folate (primarily for the prevention of neural tube defects), the US Food and Drug Administration mandated folic acid fortification of cereal and grain products beginning in 1998.[140] Adequate dietary intake of vitamins B_6 and B_{12}, involved in homocysteine metabolism, should also be ensured. Healthy dietary sources of vitamin B_6 include lean meats, whole-grain cereals, nuts, oatmeal, and bananas. Sources of vitamin B_{12} include fish, lean meats, and milk. Supplements may be used when adequate dietary intake is questionable.

SUMMARY

Americans have become slightly suspicious of nutrition research over the past several years. They have been confronted with contradictory advice based on incomplete data and isolated study findings. Rarely, if ever, should dietary recommendations be based on the results of one study. Each study should be considered a piece of the diet and disease puzzle. Patients must understand that positive results in one study must be confirmed in subsequent studies in different groups and under varying conditions before dietary recommendations can be made. Clinicians and patients alike must also understand that an association between a nutrient and disease is not the same as cause and effect, which seldom can be proved in nutritional epidemiology.

This being said, it is possible to make recommendations based on currently available

TABLE 3. Summary of Dietary Recommendations for Chronic Disease Prevention

Fat (% of total energy)	
Total	≤30
Saturated	7
Polyunsaturated	10
Monounsaturated	13
Cholesterol (mg/day)	≤300
If inadequate response	≤200
Dietary fiber (g/day)	25-30 (10-13 g/1,000 kcal)
Insoluble-soluble ratio	3:1
Sodium (mg/day)	≤2,400
Calcium (mg/day)	
Age 9-24 yr	1,200-1,500
Age 25-50 yr	1,000
Age 51-65 yr	1,200
Age >65 yr	1,500
Vitamin D (μg/day)	
Age 9-50 yr	5
Age 51-70 yr	10
Age >70 yr	15-20
Energy	To maintain BMI of <25
Folic acid (μg/day)	400
Fruits and vegetables (servings/day)	5-7
Alcohol (drinks*/day)	
Women	≤1
Men	≤2

*One drink = 12 oz beer, 4 oz wine, or 1 oz distilled spirits.
BMI = body mass index.

data. The guidelines contained in this review (Table 3) are based on the totality of the evidence. We have avoided the temptation to make recommendations based on provocative results that await substantiation. Perhaps the greatest challenge in the immediate future is finding effective ways to put these recommendations into practice. With this in mind, the US Department of Agriculture released the Food Guide Pyramid in 1992.[141] The pyramid summarizes in graphic format dietary recommendations from several organizations. It effectively portrays that vegetables, fruits, and grains (at the base of the pyramid) should make up the bulk of the diet, while meats, dairy products, and especially fats and sweets (at the tip of the pyramid) should be consumed in much smaller amounts. A version based on the Mediterranean diet, which more closely reflects dietary recommendations presented here, has also been developed.[142] The pyramids emphasize, as we should with our patients, that improving one's diet is a multifactorial process. In motivated individuals, the potential for disease prevention is substantial.

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