Origins and evolution of the Western diet: health implications for the 21st century[1,2]

Loren Cordain, S Boyd Eaton, Anthony Sebastian, Neil Mann, Staffan Lindeberg, Bruce A Watkins, James H O'Keefe, and Janette Brand-Miller

ABSTRACT

There is growing awareness that the profound changes in the environment (eg, in diet and other lifestyle conditions) that began with the introduction of agriculture and animal husbandry ≈10 000 y ago occurred too recently on an evolutionary time scale for the human genome to adjust. In conjunction with this discordance between our ancient, genetically determined biology and the nutritional, cultural, and activity patterns of contemporary Western populations, many of the so-called diseases of civilization have emerged. In particular, food staples and food-processing procedures introduced during the Neolithic and Industrial Periods have fundamentally altered 7 crucial nutritional characteristics of ancestral hominin diets: *1*) glycemic load, *2*) fatty acid composition, 3) macronutrient composition, *4*) micronutrient density, *5*) acid-base balance, 6) sodium-potassium ratio, and *7*) fiber content. The evolutionary collision of our ancient genome with the nutritional qualities of recently introduced foods may underlie many of the chronic diseases of Western civilization. *Am J Clin Nutr* 2005;81:341–54.

KEY WORDS Westernized diets, chronic disease, processed foods, genetic discordance, hunter-gatherers, human evolution

EVOLUTIONARY DISCORDANCE

Evolution acting through natural selection represents an ongoing interaction between a species' genome and its environment over the course of multiple generations. Genetic traits may be positively or negatively selected relative to their concordance or discordance with environmental selective pressures (1). When the environment remains relatively constant, stabilizing selection tends to maintain genetic traits that represent the optimal average for a population (2). When environmental conditions permanently change, evolutionary discordance arises between a species' genome and its environment, and stabilizing selection is replaced by directional selection, moving the average population genome to a new set point (1, 2). Initially, when permanent environmental changes occur in a population, individuals bearing the previous average status quo genome experience evolutionary discordance (2, 3). In the affected genotype, this evolutionary discordance manifests itself phenotypically as disease, increased morbidity and mortality, and reduced reproductive success (1–3).

Similar to all species, contemporary humans are genetically adapted to the environment of their ancestors—that is, to the environment that their ancestors survived in and that consequently conditioned their genetic makeup (1–3). There is growing awareness that the profound environmental changes (eg, in diet and other lifestyle conditions) that began with the introduction of agriculture and animal husbandry ≈10 000 y ago occurred too recently on an evolutionary time scale for the human genome to adapt (2–5). In conjunction with this discordance between our ancient, genetically determined biology and the nutritional, cultural, and activity patterns in contemporary Western populations, many of the so-called diseases of civilization have emerged (2–12).

CHRONIC DISEASE INCIDENCE

In the United States, chronic illnesses and health problems either wholly or partially attributable to diet represent by far the most serious threat to public health. Sixty-five percent of adults aged ≥20 y in the United States are either overweight or obese (13), and the estimated number of deaths ascribable to obesity is 280 184 per year (14). More than 64 million Americans have one or more types of cardiovascular disease (CVD), which represents the leading cause of mortality (38.5% of all deaths) in the United States (15). Fifty million Americans are hypertensive; 11 million have type 2 diabetes, and 37 million adults maintain high-risk total cholesterol concentrations (>240 mg/dL) (15). In postmenopausal women aged ≥50 y, 7.2% have osteoporosis and 39.6% have osteopenia (16). Osteoporotic hip fractures are associated with a 20% excess mortality in the year after fracture

[1] From the Department of Health and Exercise Science, Colorado State University, Fort Collins (LC); the Departments of Radiology and Anthropology, Emory University, Atlanta (SBE); the Department of Medicine and UCSF/Moffitt General Clinical Research Center, University of California, San Francisco (AS); the Department of Food Science, RMIT University, Melbourne, Australia (NM); the Department of Medicine, Lund University, Sweden (SL); the Department of Food Science, Lipid Chemistry and Molecular Biology Laboratory, Purdue University, West Lafayette, IN (BAW); the Mid America Heart Institute, Cardiovascular Consultants, Kansas City, MO (JHO); and the Human Nutrition Unit, Department of Biochemistry, University of Sydney, Australia (JB-M).

[2] Address reprint requests to L Cordain, Department of Health and Exercise Science, Colorado State University, Fort Collins, CO 80523. E-mail: cordain@cahs.colostate.edu.

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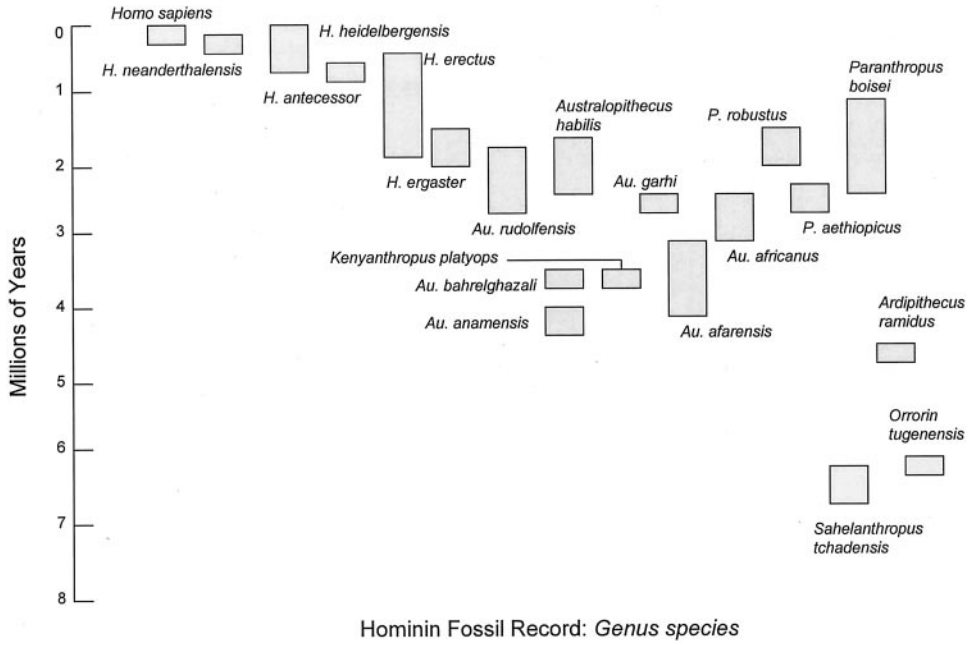

FIGURE 1. The hominin fossil record. Species are indicated with the dates of the earliest and latest fossil record. Adapted from Wood (19).

(17). Cancer is the second leading cause of death (25% of all deaths) in the United States, and an estimated one-third of all cancer deaths are due to nutritional factors, including obesity (18).

HOMININ DIETARY CHARACTERISTICS

In the 5–7 million-year period since the evolutionary emergence of hominins (bipedal primates within the taxonomic tribe hominini; note that the newer term *hominin* supplants the previous term, *hominid*) ≥20 species may have existed (**Figure 1**) (19). Similar to historically studied hunter-gatherers (20, 21), there would have been no single universal diet consumed by all extinct hominin species. Rather, diets would have varied by geographic locale, climate, and specific ecologic niche. However, there are universal characteristics of preagricultural hominin diets that are useful in understanding how the current Western diet may predispose modern populations to chronic disease. Increasingly, clinical trials and interventions that use dietary treatments with nutritional characteristics similar to those found in preindustrial and preagricultural diets have confirmed the beneficial health consequences predicted by the template of evolutionary discordance theory.

NUTRITIONAL CHARACTERISTICS OF PRE- AND POSTAGRICULTURAL DIETS

Before the development of agriculture and animal husbandry hominin dietary choices would have been necessarily limited to minimally processed, wild plant and animal foods. With the initial domestication of plants and animals, the original nutrient characteristics of these formerly wild foods changed, subtly at first but more rapidly with advancing technology after the Industrial Revolution. Furthermore, with the advent of agriculture, novel foods were introduced as staples for which the hominin genome had little evolutionary experience. More importantly, food-processing procedures were developed, particularly following the Industrial Revolution, which allowed for quantitative and qualitative food and nutrient combinations that had not previously been encountered over the course of hominin evolution.

In contrasting pre- and postagricultural diets, it is important to consider not only the nutrient qualities and types of foods that likely would have been consumed by preagricultural hominins but to also recognize the types of foods and their nutrient qualities that could not have been regularly consumed before the development of agriculture, industrialization, and advanced technology. Food types that would have generally been unavailable to preagricultural hominins are listed in **Table 1** (22–24). Although dairy products, cereals, refined sugars, refined vegetable oils, and alcohol make up 72.1% of the total daily energy consumed by all people in the United States, these types of foods would have contributed little or none of the energy in the typical preagricultural hominin diet (20). Additionally, mixtures of foods listed in Table 1 make up the ubiquitous processed foods (eg, cookies, cake, bakery foods, breakfast cereals, bagels, rolls, muffins, crackers, chips, snack foods, pizza, soft drinks, candy, ice cream, condiments, and salad dressings) that dominate the typical US diet.

Dairy foods

Hominins, like all mammals, would have consumed the milk of their own species during the suckling period. However, after weaning, the consumption of milk and milk products of other mammals would have been nearly impossible before the domestication of livestock because of the inherent difficulties in capturing and milking wild mammals. Although sheep were domesticated by ≈11 000 before present (BP) (25) and goats and cows by ≈10 000 BP (26, 27), early direct chemical evidence for dairying dates to 6100 to 5500 BP from residues of dairy fats found on pottery in Britain (28). Taken together, these data indicate that dairy foods, on an evolutionary time scale (Figure 1), are relative newcomers to the hominin diet.

TABLE 1
Food and food types found in Western diets generally unavailable to preagricultural hominins[1]

Food or food group	Value
Dairy products	*% of energy*[2]
Whole milk	1.6
Low-fat milk	2.1
Cheese	3.2
Butter	1.1
Other	2.6
Total	10.6
Cereal grains	
Whole grains	3.5
Refined grains	20.4
Total	23.9
Refined sugars	
Sucrose	8.0
High-fructose corn syrup	7.8
Glucose	2.6
Syrups	0.1
Other	0.1
Total	18.6
Refined vegetable oils	
Salad, cooking oils	8.8
Shortening	6.6
Margarine	2.2
Total	17.6
Alcohol	1.4
Total energy	72.1
Added salt, as sodium chloride	9.6[3]

[1] Data adapted from references 22–24.
[2] In the US diet.
[3] Salt from processed foods, table salt use, and cooking; in g/d.

Cereals

Because wild cereal grains are usually small, difficult to harvest, and minimally digestible without processing (grinding) and cooking, the appearance of stone processing tools in the fossil record represents a reliable indication of when and where cultures systematically began to include cereal grains in their diet (7). Ground stone mortars, bowls, and cup holes first appeared in the Upper Paleolithic (from 40 000 y ago to 12 000 y ago) (29), whereas the regular exploitation of cereal grains by any worldwide hunter-gatherer group arose with the emergence of the Natufian culture in the Levant ≈13 000 BP (30). Domestication of emmer and einkorn wheat by the descendants of the Natufians heralded the beginnings of early agriculture and occurred by 10–11 000 BP from strains of wild wheat localized to southeastern Turkey (31). During the ensuing Holocene (10 000 y ago until the present), cereal grains were rarely consumed as year round staples by most worldwide hunter-gatherers (32, 33), except by certain groups living in arid and marginal environments (32, 34). Hence, as was the case with dairy foods, before the Epi-Paleolithic (10 000–11 000 y ago) and Neolithic (10 000 to 5500 y ago) periods, there was little or no previous evolutionary experience for cereal grain consumption throughout hominin evolution.

In Table 1, it is shown that 85.3% of the cereals consumed in the current US diet are highly processed refined grains. Preceding the Industrial Revolution, all cereals were ground with the use of stone milling tools, and unless the flour was sieved, it contained the entire contents of the cereal grain, including the germ, bran, and endosperm (35). With the invention of mechanized steel roller mills and automated sifting devices in the latter part of the 19th century (35), the nutritional characteristics of milled grain changed significantly because the germ and bran were removed in the milling process, leaving flour comprised mainly of endosperm of uniformly small particulate size (35, 36). Accordingly, the widespread consumption of highly refined grain flours of uniformly small particulate size represents a recent secular phenomenon dating to the past 150–200 y (35).

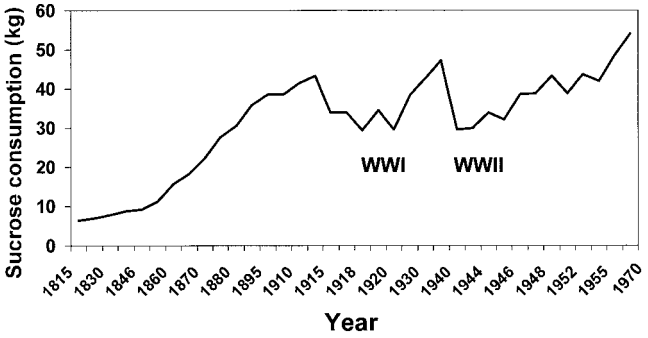

FIGURE 2. Per capita consumption of sucrose in England from 1815 to 1970. WWI, World War I; WWII, World War II. Adapted from Cleave (38).

Refined sugars

The per capita consumption of all refined sugars in the United States in 2000 was 69.1 kg, whereas in 1970 it was 55.5 kg (24). This secular trend for increased sugar consumption in the United States in the past 30 y reflects a much larger worldwide trend that has occurred in Western nations since the beginning of the Industrial Revolution some 200 y ago (37). The per capita refined sucrose consumption in England steadily rose from 6.8 kg in 1815 to 54.5 kg in 1970 (38), as shown in **Figure 2**. Similar trends in refined sucrose consumption have been reported during the Industrial Era for the Netherlands, Sweden, Norway, Denmark, and the United States (39).

The first evidence of crystalline sucrose production appears about 500 BC in northern India (37). Before this time, honey would have represented one of the few concentrated sugars to which hominins would have had access. Although honey likely was a favored food by all hominin species, seasonal availability would have restricted regular access. Studies of contemporary hunter-gatherers show that gathered honey represented a relatively minor dietary component over the course of a year, despite high intakes in some groups during short periods of availability. In the Anbarra Aborigines of northern Australia, average honey consumption over four 1-mo periods, chosen to be representative of the various seasons, was 2 kg per person per year (40). In the Ache Indians of Paraguay, honey represented 3.0% of the average total daily energy intake over 1580 consumer days (41). Consequently, current population-wide intakes of refined sugars in Westernized societies represent quantities with no precedent during hominin evolution.

In the past 30 y, qualitative features of refined sugar consumption have changed concurrently with the quantitative changes. With the advent of chromatographic fructose enrichment technology in the late 1970s, it became economically feasible to manufacture high-fructose corn syrup (HFCS) in mass quantity

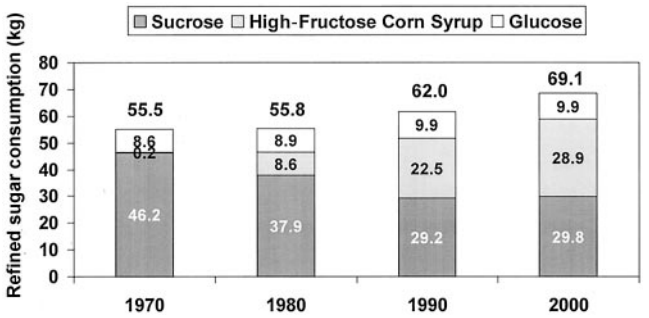

FIGURE 3. Per capita consumption of refined sugars in the United States from 1970 to 2000. Adapted from the US Department of Agriculture (24).

(42). The rapid and striking increase in HFCS use that has occurred in the US food supply since its introduction in the 1970s is indicated in **Figure 3**. HFCS is available in 2 main forms, HFCS 42 and HFCS 55, both of which are liquid mixtures of fructose and glucose (42% fructose and 53% glucose and 55% fructose and 42% glucose, respectively) (42). Increases in HFCS occurred simultaneously, whereas sucrose consumption declined (Figure 3). On digestion, sucrose is hydrolyzed in the gut into its 2 equal molecular moieties of glucose and fructose. Consequently, the total per capita fructose consumption (fructose from HFCS and fructose from the digestion of sucrose) increased from 23.1 kg in 1970 to 28.9 kg in 2000. As was the case with sucrose, current Western dietary intakes of fructose could not have occurred on a population-wide basis before industrialization and the introduction of the food-processing industry.

Refined vegetable oils

In the United States, during the 90-y period from 1909 to 1999, a striking increase in the use of vegetable oils occurred (**Figure 4**). Specifically, per capita consumption of salad and cooking oils increased 130%, shortening consumption increased 136%, and margarine consumption increased 410% (22). These trends occurred elsewhere in the world and were made possible by the industrialization and mechanization of the oil-seed industry (43). To produce vegetable oils from oil-bearing seeds, 3 procedures can be used: *1*) rendering and pressing, *2*) expeller pressing, and *3*) solvent extraction (43). Oils made from walnuts, almonds, olives, sesame seeds, and flax seeds likely were first produced via the rendering and pressing process between 5000 and 6000 y ago. However, except for olive oil, most early use of oils seems to have been for nonfood purposes such as illumination, lubrication, and medicine (43).

The industrial advent of mechanically driven steel expellers and hexane extraction processes allowed for greater world-wide

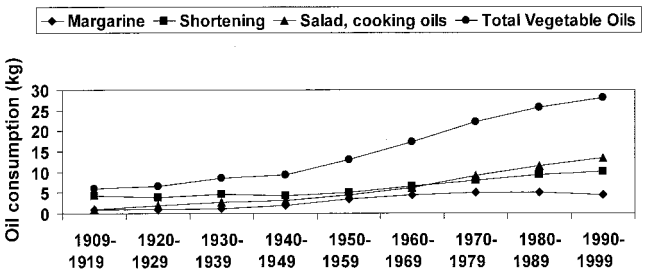

FIGURE 4. Per capita consumption of vegetable oils in the United States from 1909–1919 to 1990–1999. Adapted from Gerrior and Bente (22).

vegetable oil productivity, whereas new purification procedures permitted exploitation of nontraditionally consumed oils, such as cottonseed (43). New manufacturing procedures allowed vegetable oils to take on atypical structural characteristics. Margarine and shortening are produced by solidifying or partially solidifying vegetable oils via hydrogenation, a process first developed in 1897 (44). The hydrogenation process produces novel *trans* fatty acid isomers (*trans* elaidic acid in particular) that rarely, if ever, are found in conventional human foodstuffs (44). Consequently, the large-scale addition of refined vegetable oils to the world's food supply after the Industrial Revolution significantly altered both quantitative and qualitative aspects of fat intake.

Alcohol

In contrast with dairy products, cereal grains, refined sugars, and oils, alcohol consumption in the typical US diet represents a relatively minor contribution (1.4%) to the total energy consumed. The earliest evidence for wine drinking from domesticated vines comes from a pottery jar dated 7400–7100 y BP from the Zagros Mountains in northern Iran (45), whereas the earliest archaeologic indication of the brewing of beer and beer consumption dates to the late fourth millennium BC from the Godin site in southern Kurdistan in Iran (46). The incorporation of distilled alcoholic beverages into the human diet came much later. During the period from ≈800 to 1300 AD, various populations in Europe, the Near East, and China learned to distill alcoholic beverages (47).

The fermentation process that produces wine takes place naturally and, without doubt, must have occurred countless times before humans learned to control the process. As grapes reach their peak of ripeness in the fall, they may swell in size and burst, thereby allowing the sugars in the juice to be exposed to yeasts growing on the skins and to produce carbon dioxide and ethanol (48). Because of seasonal fluctuations in fruit availability and the limited liquid storage capacity of hunter-gatherers, it is likely that fermented fruit drinks, such as wine, would have made an insignificant or nonexistent contribution to total energy in hominin diets before the Neolithic (49).

Salt

The total quantity of salt included in the typical US diet amounts to 9.6 g/d (Table 1). About 75% of the daily salt intake in Western populations is derived from salt added to processed foods by manufacturers; 15% comes from discretionary sources (ie, cooking and table salt use), and the remainder (10%) occurs naturally in basic foodstuffs (50). Hence, 90% of the salt in the typical US diet comes from manufactured salt that is added to the food supply.

The systematic mining, manufacture, and transportation of salt have their origin in the Neolithic Period. The earliest salt use is argued to have taken place on Lake Yuncheng in the Northern Province of Shanxi, China, by 6000 BC (51). In Europe the earliest evidence of salt exploitation comes from salt mines at Cardona, Spain, dating to 6200–5600 BP (52). It is likely that Paleolithic (the old stone age which began 2.6 million years ago and ended 10 000–12 000 y ago) or Holocene (10 000 y ago to the present) hunter-gatherers living in coastal areas may have dipped food in seawater or used dried seawater salt in a manner similar to nearly all Polynesian societies at the time of European contact (53). However, the inland living Maori of New Zealand

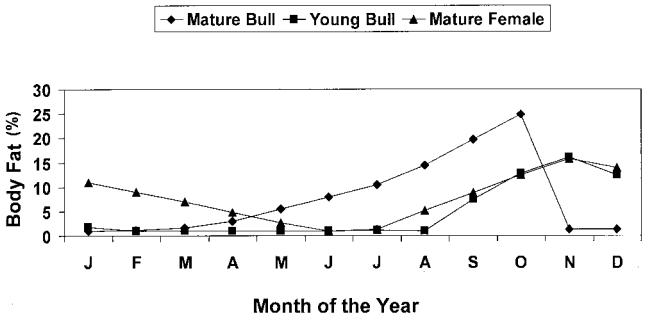

FIGURE 5. Seasonal fluctuations in percentage body fat in caribou. Adapted from Spiess (57).

lost the salt habit (53), and the most recently studied inland hunter-gatherers add no or little salt to their food on a daily basis (54). Furthermore, there is no evidence that Paleolithic people undertook salt extraction or took interest in inland salt deposits (55). Collectively, this evidence suggests that the high salt consumption (≈10 g/d) in Western societies has minimal or no evolutionary precedent in hominin species before the Neolithic period.

Fatty domestic meats

Before the Neolithic period, all animal foods consumed by hominins were derived from wild animals. The absolute quantity of fat in wild mammals is dependent on the species body mass –larger mammals generally maintain greater body fat percentages by weight than do smaller animals (21, 56). Additionally, body fat percentages in wild mammals typically vary by age and sex and also seasonally in a cyclic waxing and waning manner with changing availability of food sources and the photoperiod (**Figure 5**) (57, 58). Hence, maximal or peak body fat percentages in wild mammals are maintained only for a few months during the course of a year, even for mammals residing at tropical and southern latitudes (59). In mammals, storage of excess food energy as fat occurs primarily as triacylglycerols in subcutaneous and abdominal fat depots. The dominant (>50% fat energy) fatty acids in the fat storage depots (adipocytes) of wild mammals are saturated fatty acids (SFAs), whereas the dominant fatty acids in muscle and all other organ tissues are polyunsaturated fatty acids (PUFAs) and monounsaturated fatty acids (MUFAs) (11). Because subcutaneous and abdominal body fat stores are depleted during most of the year in wild animals, PUFAs and MUFAs ordinarily constitute most of the total carcass fat (11). MUFAs and PUFAs are the dominant fats in the edible carcass of caribou for all 12 mo of the year, as illustrated in **Figure 6** (11, 60–65). Because of the seasonal cyclic depletion of SFAs and enrichment of PUFAs and MUFAs, a year-round dietary intake of high amounts of SFAs would have not been possible for preagricultural hominins preying on wild mammals. Even with selective butchering by hominins, in which much of the lean muscle meat is discarded, MUFAs and PUFAs constitute the greatest percentage (>50% of energy as fat) of edible fatty acids in the carcass of wild mammals throughout most of the year (Figure 6).

Beginning with the advent of animal husbandry, it became feasible to prevent or attenuate the seasonal decline in body fat (and hence in SFAs) by provisioning domesticated animals with stored plant foods. Furthermore, it became possible to consistently slaughter the animal at peak body fat percentage. Neolithic advances in food-processing procedures allowed for the storage of concentrated sources of animal SFAs (cheese, butter, tallow, and salted fatty meats) for later consumption throughout the year.

Technologic developments of the early and mid 19th century—such as the steam engine, mechanical reaper, and railroads—allowed for increased grain harvests and efficient transport of both grain and cattle, which in turn spawned the practice of feeding grain (corn primarily) to cattle sequestered in feedlots (66). In the United States before 1850, virtually all cattle were free range or pasture fed and were typically slaughtered at 4–5 y of age (66). By about 1885, the science of rapidly fattening cattle in feedlots had advanced to the point that it was possible to produce a 545-kg steer ready for slaughter in 24 mo and that exhibited "marbled meat" (66). Wild animals and free-range or pasture-fed cattle rarely display this trait (11). Marbled meat results from excessive triacylglycerol accumulation in muscle interfascicular adipocytes. Such meat has a greatly increased

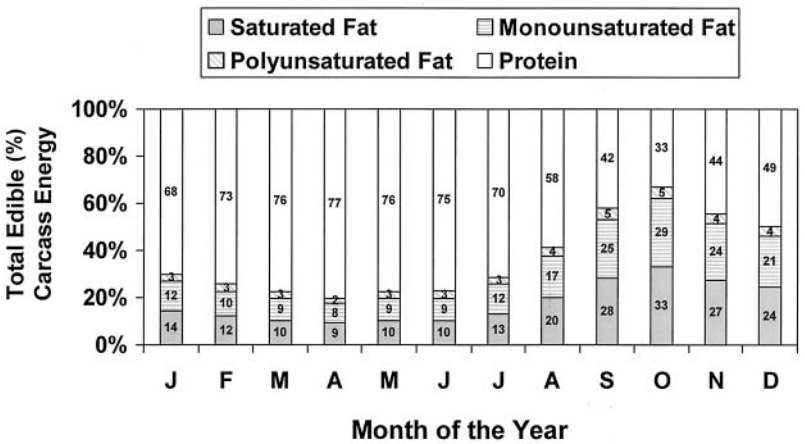

FIGURE 6. Seasonal variation in mean percentage body fat for mature male, immature male, and mature female caribou (57). Total body fat and total body protein, as a percentage of energy, were calculated from the respective mean values by weight by using the cubic regression equations developed by Cordain et al (20). The edible carcass mass was calculated by subtracting the mass of the bones (minus marrow), hide, hooves, antlers, blood, urine, and gastrointestinal contents from the total live weight. The mass of the edible organs and tissues were calculated from the allometric relation between body mass and organ and tissue mass (60–63). Edible carcass fatty acid composition was calculated by multiplying tissue and organ mass by fatty acid composition (% mass) in these tissues from values for caribou or similar ruminant species (11, 64, 65).

SFA content, a lower proportion of n−3 fatty acids, and more n−6 fatty acids (11, 65).

Modern feedlot operations involving as many as 100 000 cattle emerged in the 1950s and have developed to the point that a characteristically obese (30% body fat) (67) 545-kg pound steer can be brought to slaughter in 14 mo (68). Although 99% of all the beef consumed in the United States is now produced from grain-fed, feedlot cattle (69), virtually no beef was produced in this manner as recently as 200 y ago (66). Accordingly, cattle meat (muscle tissue) with a high absolute SFA content, low n−3 fatty acid content, and high n−6 fatty acid content represents a recent component of human diets (11).

HEALTH RAMIFICATIONS OF FOODS IN THE NEOLITHIC AND INDUSTRIAL ERAS

The novel foods (dairy products, cereals, refined cereals, refined sugars, refined vegetable oils, fatty meats, salt, and combinations of these foods) introduced as staples during the Neolithic and Industrial Eras fundamentally altered several key nutritional characteristics of ancestral hominin diets and ultimately had far-reaching effects on health and well-being. As these foods gradually displaced the minimally processed wild plant and animal foods in hunter-gatherer diets, they adversely affected the following dietary indicators *1*) glycemic load, *2*), fatty acid composition, *3*) macronutrient composition, *4*) micronutrient density, *5*) acid-base balance, *6*) sodium-potassium ratio, and *7*) fiber content.

Glycemic load

The glycemic index, originally developed in 1981, is a relative comparison of the blood glucose raising potential of various foods or combination of foods based on equal amounts of carbohydrate in the food (70). In 1997, the concept of glycemic load (glycemic index x the carbohydrate content per serving size) was introduced to assess blood glucose raising potential of a food based on both the quality and quantity of dietary carbohydrate (71). **Table 2** shows that refined grain and sugar products nearly always maintain much higher glycemic loads than unprocessed fruits and vegetables. Unrefined wild plant foods like those available to contemporary hunter-gatherers typically exhibit low glycemic indices (73).

Acute elevations in blood glucose concentrations, along with increases in hormones secreted from the gut, stimulate pancreatic insulin secretion causing an acute rise in blood insulin concentrations. Consumption of mixed meals containing protein and fat combined with carbohydrate may lower the total glycemic and insulinemic response of the carbohydrate food alone (74). Nevertheless, it is established that repeated consumption of high glycemic index, mixed meals results in higher mean 24 h blood glucose and insulin concentrations when compared with low glycemic index, mixed meals of identical caloric content (75, 76).

Within the past 20 y, substantial evidence has accumulated showing that long term consumption of high glycemic load carbohydrates can adversely affect metabolism and health (71, 77, 78). Specifically, chronic hyperglycemia and hyperinsulinemia induced by high glycemic load carbohydrates may elicit a number of hormonal and physiologic changes that promote insulin resistance (71, 77, 78). Chronic hyperinsulinemia represents the primary metabolic defect in the metabolic syndrome (79). Diseases of insulin resistance are frequently referred to as "diseases of civilization" (5, 78, 79) and include: obesity, coronary heart

TABLE 2
Glycemic indexes and glycemic loads of various food groups[1]

	Glycemic index	Glycemic load[2]
Grain products		
Rice Krispies cereal[3]	82	72.0
Cornflakes[3,4]	81	70.1
Rice cakes[5]	78	63.6
Shredded wheat cereal[6]	75	62.0
Graham wafers[7]	74	56.8
Cheerios cereal[8]	74	54.2
Rye crisp bread[9]	64	52.6
Vanilla wafers[7]	77	49.7
Stoned Wheat thins[7]	67	41.9
Corn chips[10,11]	63	39.9
Muesli bar[12]	61	39.3
Bagel	72	38.4
Doughnuts	76	37.8
White bread	70	34.7
Whole-wheat bread	71	32.7
All-bran cereal[3,4]	42	32.5
Sugar, sweets		
Jelly beans	78	72.6
Lifesavers[13]	70	67.9
Table sugar (sucrose)	65	64.9
Mars bar[14,15]	65	40.4
Vegetables		
Baked potato	85	21.4
Sweet potato	61	14.8
Yam	37	8.4
Rutabaga	72	6.3
Beets	64	6.3
Carrots	47	4.7
Fruit		
Banana	52	11.9
Grapes	46	8.2
Kiwi fruit	53	7.5
Pineapple	59	7.3
Apple	38	5.8
Pear	38	5.7
Watermelon	72	5.2
Orange	42	5.0
Dairy foods		
Ice cream	61	14.4
Yogurt, low-fat	27	5.3
Skim milk	32	1.6
Whole milk	27	1.3

[1] Data adapted from reference 72.
[2] Glycemic load = glycemic index × carbohydrate content (in 100-g portions); the glycemic reference is glucose with a glycemic index of 100.
[3] Kellogg's Inc, London.
[4] Kellogg's Inc, Auckland, Australia and Battle Creek, MI.
[5] Rice Growers Co-op, Leeton, Australia.
[6] Nabisco Brands Ltd, Toronto.
[7] Christie Brown and Co, Toronto.
[8] General Mills Inc, Mississauga, Canada.
[9] Ryvita Company Ltd, Poole, United Kingdom.
[10] Smith's Snack Food Co, Adelaide, Australia.
[11] Old El Paso Foods Co, Mississauga, Canada.
[12] Uncle Toby's, North Ryde, Australia.
[13] Nestlé, Rhodes, Australia.
[14] Mars Confectionery, Ballarat, Australia.
[15] M & M Mars, Hackettstown, NJ.

disease (CHD), type 2 diabetes, hypertension, and dyslipidemia [elevated serum triacylglycerols, small-dense, LDL cholesterol and reduced HDL cholesterol]. It is likely that the metabolic syndrome may extend to other chronic illnesses and conditions that are widely prevalent in Western societies, including: myopia (80), acne (81), gout (79), polycystic ovary syndrome, epithelial cell cancers (breast, colon, and prostate), male vertex balding, skin tags and acanthosis nigricans (78). Diseases of insulin resistance are rare or absent in hunter-gatherer and other less westernized societies living and eating in their traditional manner (5, 21, 82, 83).

In addition to high-glycemic-load carbohydrates, other elements of Neolithic and Industrial Era foods may contribute to the insulin resistance underlying metabolic syndrome diseases. Milk, yogurt, and ice cream, despite having relatively low glycemic loads (Table 2), are highly insulinotropic, with insulin indexes comparable with white bread (84). Fructose maintains a low glycemic index of 23 and a low glycemic load, but paradoxically it is routinely used to induce insulin resistance in laboratory rodents at high (35–65% of energy) dietary concentrations (85, 86). Diets containing lower concentrations (20% of energy) of fructose worsened insulin sensitivity in hyperinsulinemic men (87); more recently it was shown that fructose infusions in healthy men and women induce insulin resistance (88). Dietary fructose may contribute to insulin resistance via its unique ability among all sugars to cause a shift in balance from oxidation to esterification of serum nonesterified free fatty acids (89, 90).

In the typical US diet, sugars with a high glycemic load (HFCS 42, HFCS 55, sucrose, glucose, honey, and syrups) now supply 18.6% of total energy, whereas refined cereal grains with a high glycemic load supplies 20.4% of energy (Table 1). Hence, ≥ 39% of the total energy in the typical US diet is supplied by foods that may promote the 4 proximate causes of insulin resistance: chronic and substantial elevations in plasma glucose (91, 92), insulin (93, 94), VLDL (95), and free fatty acid (96) concentrations. Although sugars and grains with a high glycemic load now represent a dominant element of the modern urban diet, these foods were rarely or never consumed by average citizens as recently as 200 y ago.

Fatty acid composition

Chemically, fats are defined as acylglycerols—compounds in which a fatty acid molecule (acyl group) is linked to a glycerol molecule by an ester bond. Almost all dietary and storage fats are triacylglycerols, compounds in which 3 fatty acid molecules are bound to a single glycerol molecule. Fatty acids fall into 1 of 3 major categories: *1*) SFAs, *2*) MUFAs, and *3*) PUFAs. Additionally, essential PUFAs occur in 2 biologically important families, the n−6 PUFAs and the n−3 PUFAs. Substantial evidence now indicates that to prevent the risk of chronic disease, the absolute amount of dietary fat is less important than is the type of fat (97). Beneficial health-promoting fats are MUFAs and some PUFAs, whereas most SFAs and *trans* fatty acids are detrimental when consumed in excessive quantities (97). Furthermore, the balance of dietary n−6 and n−3 PUFAs is integral in preventing the risk of chronic disease and promoting health (97–99).

The Western diet frequently contains excessive saturated and *trans* fatty acids and has too little n−3 PUFAs than n−6 PUFAs (97–99). High dietary intakes of SFAs and *trans* fatty acids increase the risk of CVD by elevating blood concentrations of total and LDL cholesterol (97, 100–102). n−3 PUFAs may reduce the risk of CVD via many mechanisms, including reductions in ventricular arrhythmias, blood clotting, serum triacylglycerol concentrations, growth of atherosclerotic plaques, and blood pressure (98). A 20% reduction in overall mortality and a 45% reduction in sudden death after 3.5 y were reported in subjects with preexisting CVD when given 850 mg n−3 fatty acids, either with or without vitamin E (103). Higher dietary intakes of n−3 fatty acids are also therapeutic in preventing or ameliorating many inflammatory and autoimmune diseases (99). Low- (22% energy) and high- (39% energy) fat diets that had identical ratios of PUFAs to SFAs, n−6 PUFAs to n−3 PUFAs, and MUFAs to total fat produced no significant differences in total or LDL cholesterol after a 50-d trial (104). These data support the notion that fat quality is more important than fat quantity in regard to CVD risk.

Although much of the early work on the link between diet and CVD focused primarily on dietary fats and their effect on total and LDL-cholesterol concentrations, there are many other dietary elements that can operate synergistically to promote atherosclerosis. As was previously mentioned, carbohydrates with a high glycemic load encourage a proatherogenic blood profile by elevating triacylglycerols and small-dense LDLs, while reducing HDL cholesterol. Atherosclerosis is not just a "plumbing" problem involving excessive LDL cholesterol in the blood from excessive dietary SFAs, but also from chronic inflammation, which is essential in the formation of atherosclerotic plaques (105). A recent study suggested that the blood concentration of the inflammatory marker C-reactive protein (CRP) is a stronger predictor of CVD than is LDL cholesterol (106). High-glycemic-load diets are associated with increased concentrations of CRP (107), as are low dietary intakes of n−3 PUFAs (108), and diets that encourage weight loss reduce CRP (109) concentrations. These studies indicate how multiple interrelated qualities of Western diets and recently introduced Neolithic and Industrial Era foods may drive a variety of mechanisms that promote the development of chronic diseases.

The 6 major sources of SFAs in the United States diet are fatty meats, baked goods, cheese, milk, margarine, and butter (110). Five of these 6 foods would not have been components of hominin diets before the advent of animal husbandry or the Industrial Revolution. Because of the inherently lean nature of wild animal tissues throughout most of the year (Figure 5) and the dominance of MUFAs and PUFAs, high dietary levels of SFAs on a year-round basis (Figure 6) could not have exerted adverse selective pressure on the hominin genome before the development of agriculture.

The advent of the oil-seed processing industry at the beginning of the 20th century significantly raised the total intake of vegetable fat (Figure 4), which directly increased the dietary level of n−6 PUFAs at the expense of a lowered level of n−3 PUFAs because of the inherently higher concentrations of n−6 PUFAs and lower concentrations of n−3 PUFAs in most vegetable oils (111). The trend toward a higher ratio of n−6 to n−3 PUFAs was exacerbated as meat from grain fed cattle and livestock became the norm in the US diet over the past 100 y (11, 66). In the current US diet, the ratio of n−6 to n−3 PUFAs has risen to 10:1 (112), whereas the ratio in hunter-gatherer diets predominant in wild animal foods (20, 21) has been estimated to be between 2:1 and 3:1 (11, 111).

The invention of the hydrogenation process in 1897 (44) allowed vegetable oils to become solidified and marketed as shortening or margarine and as foods containing hydrogenated vegetable oils. The hydrogenation process introduced a novel *trans* fatty acid (*trans* elaidic acid) into the human diet, which elevates blood cholesterol concentrations and leads to an increased risk of CVD (113). *trans* Fatty acids in the US diet are now estimated to constitute 7.4% of the total fatty acid intake (114).

Macronutrient composition

In the present US diet, the percentage of total food energy derived from the 3 major macronutrients is as follows (23): carbohydrate (51.8%), fat (32.8%), and protein (15.4%). Current advice for reducing the risk of cardiovascular disease and other chronic diseases is to limit fat intake to 30% of total energy, to maintain protein at 15% of total energy, and to increase complex carbohydrates to 55–60% of total energy (115, 116). Both the current US macronutrient intakes and suggested healthful levels differ considerably from average levels obtained from ethnographic (20) and quantitative (21) studies of hunter gatherers in which dietary protein is characteristically elevated (19–35% of energy) at the expense of carbohydrate (22–40% of energy) (20, 21). Although the macronutrient compositions of hominin diets during the Paleolithic period cannot be directly determined, recent isotopic data from Neanderthal (117) and Upper Paleolithic European (118) skeletons support the notion that protein consumption may have been substantially higher than current values.

An increasing body of evidence indicates that high-protein diets may improve blood lipid profiles (119–123) and thereby lessen the risk of CVD. Wolfe and Giovannetti (121) have shown that the isocaloric substitution of protein (23% of energy) for carbohydrate in moderately hypercholesterolemic subjects resulted in significant decreases in total, LDL, and VLDL cholesterol and triacylglycerols and an increase in HDL cholesterol. Similar beneficial blood lipid changes have been observed in type 2 diabetic patients in conjunction with improvements in glucose and insulin metabolism (119, 120). Furthermore, high-protein diets have been shown to improve metabolic control in patients with type 2 diabetes (119, 120, 124). In obese women, hypocaloric, high-protein diets improved insulin sensitivity and prevented muscle loss, whereas hypocaloric, high-carbohydrate diets worsened insulin sensitivity and caused reductions in fat-free mass (125).

Epidemiologic evidence supports the clinical data, which shows a cardiovascular protective effect of dietary protein. Protein intake has been shown to be inversely related to CVD in a cohort of 80 082 women (126). Dietary protein is also inversely related to blood homocysteine concentration (127), an independent risk factor for CVD. Meat-eating populations have been shown to maintain lower plasma homocysteine concentrations than nonmeat eaters (128, 129). In numerous population studies, summarized by Obarzanek et al (130), higher blood pressure has been associated with lower intakes of protein. A 4-wk dietary intervention of hypertensive subjects showed that a high-protein diet (25% energy) was effective in significantly lowering blood pressure (131). Furthermore, many population studies have established that stroke mortality is inversely related to protein intake (132, 133).

Because protein has >3 times the thermic effect of either fat or carbohydrate (134) and because it has a greater satiety value than do fat or carbohydrate (134, 135), increased dietary protein may represent an effective weight-loss strategy for the overweight or obese. Recent clinical trials have shown that calorie-restricted, high-protein diets are more effective than are calorie-restricted, high-carbohydrate diets in promoting (136–138) and maintaining (139) weight loss in overweight subjects while producing less hunger and more satisfaction (140).

TABLE 3
Percentages of all individuals aged ≥ 2 y not meeting 100% of the 1989 US recommended dietary allowances[1]

Nutrient	Value
	%
Vitamin B-12	17.2
Niacin	25.9
Phosphorus	27.4
Riboflavin	30.0
Thiamine	30.2
Folate	33.2
Vitamin C	37.5
Iron	39.1
Vitamin B-6	53.6
Vitamin A	56.2
Magnesium	61.6
Calcium	65.1
Zinc	73.3

[1] Values are the 2-d average of data collected from 1994 to 1996 (23).

Micronutrient density

Refined sugars are essentially devoid of any vitamin or mineral (64). Accordingly, the consumption of refined sugar or foods containing refined sugar reduces the total vitamin and mineral (micronutrient) density of the diet by displacing more nutrient-dense foods. A similar situation exists for refined vegetable oils, except that they contain 2 fat-soluble vitamins (vitamin E and vitamin K) (64). Because vegetable oils and refined sugars contribute ≥36.2% of the energy in a typical US diet (Table 1), the widespread consumption of these substances—or foods made with them—has considerable potential to influence the risk of vitamin and mineral deficiencies.

The vitamins and minerals most frequently lacking in the US diet are listed in **Table 3**. At least half the US population fails to meet the recommended dietary allowance (RDA) for vitamin B-6, vitamin A, magnesium, calcium, and zinc, and 33% of the population does not meet the RDA for folate. Adequate dietary intake of both folate and vitamin B-6 prevents the accumulation of homocysteine in the bloodstream. Elevated blood concentrations of homocysteine represent an independent risk factor for the development of CVD, stroke, and deep vein thrombosis (141, 142).

The nutrient density in various food groups for the 13 vitamins and minerals most frequently lacking in the US diet are contrasted in **Table 4** (64, 143, 144). Because whole grains and milk maintain the next to the lowest nutrient density rankings, displacement of fruit, vegetables, lean meats, and seafood by these 2 staple food groups lowers the overall micronutrient density in the diet. Wild plant foods known to be consumed by hunter-gatherers generally maintain higher micronutrient concentrations than do their domesticated counterparts (4, 145), as does the muscle meat of wild animals (64). Consequently, the Neolithic introduction of dairy foods and cereal grains as staples would

TABLE 4
Mean nutrient density of various foods groups (418-kJ samples)[1]

	Whole grains ($n = 8$)	Whole milk ($n = 1$)	Fruit ($n = 20$)	Vegetables ($n = 18$)	Seafood ($n = 20$)	Lean meats ($n = 4$)	Nuts and seeds ($n = 10$)
Vitamin B-12 (μg)	0.00 [4]	0.58 [5]	0.00 [4]	0.00 [4]	7.42 [7]	0.63 [6]	0.00 [4]
Vitamin B-3 (mg)	1.12 [4]	0.14 [1]	0.89 [3]	2.73 [5]	3.19 [6]	4.73 [7]	0.35 [2]
Phosphorus (mg)	90 [3]	152 [5]	33 [1]	157 [6]	219 [7]	151 [4]	80 [2]
Riboflavin (mg)	0.05 [2]	0.26 [6]	0.09 [3]	0.33 [7]	0.09 [4]	0.14 [5]	0.04 [1]
Thiamine (mg)	0.12 [5]	0.06 [1]	0.11 [3]	0.26 [7]	0.08 [2]	0.18 [6]	0.12 [4]
Folate (μg)	10.3 [4]	8.1 [2]	25.0 [6]	208.3 [7]	10.8 [3]	3.8 [1]	11.0 [5]
Vitamin C (mg)	1.53 [3]	74.2 [5]	221.3 [7]	93.6 [6]	1.9 [4]	0.1 [1]	0.4 [2]
Iron (mg)	0.90 [4]	0.08 [1]	0.69 [2]	2.59 [7]	2.07 [6]	1.10 [5]	0.86 [3]
Vitamin B-6 (mg)	0.09 [3]	0.07 [1]	0.20 [5]	0.42 [7]	0.19 [4]	0.32 [6]	0.08 [2]
Vitamin A (RE)	2 [2]	50 [5]	94 [6]	687 [7]	32 [4]	1 [1]	2 [3]
Magnesium (mg)	32.6 [4]	21.9 [2]	24.6 [3]	54.5 [7]	36.1 [6]	18.0 [1]	35.8 [5]
Calcium ((mg)	7.6 [2]	194.3 [7]	43.0 [4]	116.8 [6]	43.1 [5]	6.1 [1]	17.5 [3]
Zinc (mg)	0.67 [4]	0.62 [3]	0.25 [1]	1.04 [5]	7.6 [7]	1.9 [6]	0.6 [2]
Sum rank score	44	44	48	81	65	50	38

[1] Food types within food groups are based on the most commonly consumed foods in the US diet (135, 136). Values in brackets represent relative ranking (7 = highest; 1 = lowest). The micronutrient concentrations for each food group were derived from reference 64. RE, retinol equivalents.

have caused the average micronutrient content of the diet to decline. This situation worsened as cereal milling techniques developed in the Industrial era allowed for the production of bread flour devoid of the more nutrient-dense bran and germ (35). The displacement of more nutrient-dense foods (eg, fruit, vegetables, lean meats, and seafood) by less-dense foods (refined sugars, grains, vegetable oils, and dairy products) and the subsequent decline in dietary vitamin and mineral density has far reaching health implications—consequences that not only promote the development of vitamin- deficiency diseases but also numerous infectious and chronic diseases (7).

Acid-base balance

After digestion, absorption, and metabolism, nearly all foods release either acid or bicarbonate (base) into the systemic circulation (146, 147). As shown in **Table 5**, fish, meat, poultry, eggs,

TABLE 5
Potential net acid (or base) loads of 17 food groups[1]

	Net acid load[2]	Net acid load[2]	Potassium	Protein	Protein
	mEq/418 kJ	*mEq/10 460 kJ*	*mEq/418 kJ*	*g/418 kJ*	*g/100 mEq potassium*
Acid-producing foods					
Fish ($n = 8$)	14.6	398	8.1	16.8	207
Meat ($n = 3$)	12.4	342	7.6	18.4	242
Poultry ($n = 2$)	7.8	227	4.7	13.4	287
Egg ($n = 1$)	7.3	215	2.4	8.3	339
Shellfish ($n = 3$)	7.3	215	18.4	18.0	159
Cheese ($n = 9$)	3.3	115	0.8	7.1	982
Milk ($n = 4$)	1.3	64	6.4	5.7	90
Cereal grains ($n = 7$)	1.1	60	2.6	3.2	153
Near-neutral foods					
Legumes ($n = 6$)	−0.4	24	12.6	10.6	100
Base-producing foods					
Nut ($n = 6$)	−1.1	6	3.8	2.5	86
Fresh fruit ($n = 11$)	−5.2	−98	9.4	1.6	16
Tuber ($n = 2$)	−5.4	−102	11.8	2.2	18
Mushroom ($n = 1$)	−11.2	−247	62.3	25.7	41
Root ($n = 5$)	−17.1	−395	34.3	6.8	21
Vegetable fruit ($n = 1$)	−17.5	−404	35.5	5.6	15
Leafy greens ($n = 6$)	−23.4	−553	43.5	10.0	24
Plant stalks ($n = 1$)	−24.9	−590	54.8	4.6	8

[1] Daily net acid load per 10 460-kJ hypothetical diet, for which a single food group is solely consumed; 32.9 mEq/d was added to baseline to account for diet-independent organic acid production. For example, the total net endogenous acid production for a 10 460-kJ diet of cereal grains = (1.1 mEq) × (10 460 kJ/418 kJ) + 32.9 mEq = 60.4 mEq/d.

[2] Calculations were made with the use of previously described procedures (148). Positive and negative values represent acid-producing and base-producing equivalents, respectively.

shellfish, cheese, milk, and cereal grains are net acid producing, whereas fresh fruit, vegetables, tubers, roots, and nuts are net base producing. Legumes yield near-zero mean acid values, which reflects an overlapping distribution from slightly net acid producing to slightly net base producing. Not shown in Table 5 are energy-dense, nutrient-poor foods such as separated fats and refined sugars that contribute neither to the acid nor the base load. Additionally, salt is net acid producing because of the chloride ion (146).

The typical Western diet yields a net acid load estimated to be 50 mEq/d (148). As a result, healthy adults consuming the standard US diet sustain a chronic, low-grade pathogenic metabolic acidosis that worsens with age as kidney function declines (146, 149). Virtually all preagricultural diets were net base yielding because of the absence of cereals and energy-dense, nutrient-poor foods—foods that were introduced during the Neolithic and Industrial Eras and that displaced base-yielding fruit and vegetables (147). Consequently, a net base-producing diet was the norm throughout most of hominin evolution (147). The known health benefits of a net base-yielding diet include preventing and treating osteoporosis (150, 151), age-related muscle wasting (152), calcium kidney stones (153, 154), hypertension (155, 156), and exercise-induced asthma (157) and slow the progression of age- and disease-related chronic renal insufficiency (158).

Sodium-potassium ratio

The average sodium content (3271 mg/d) of the typical US diet is substantially higher than its potassium content (2620 mg/d) (23). Three dietary factors are primarily responsible for the dietary ratio of sodium to potassium, which is >1.0. First, 90% of the sodium in Western diets comes from manufactured salt (sodium chloride); hence, the sodium content of naturally occurring foods in the average US diet (≈330 mg) is quite low. Second, vegetable oils and refined sugars, which are essentially devoid of potassium, constitute 36% of the total food energy. The inclusion of these 2 foods into the diet displaces other foods with higher potassium concentrations and thereby reduces the total dietary potassium content. Third, the displacement of vegetables and fruit by whole grains and milk products may further reduce the potassium intake because potassium concentrations in vegetables are 4 and 12 times those in milk and whole grains, respectively, whereas in fruit the potassium concentration is 2 and 5 times that in milk and whole grains (64). Taken together, the addition of manufactured salt to the food supply and the displacement of traditional potassium-rich foods by foods introduced during the Neolithic and Industrial periods caused a 400% decline in the potassium intake while simultaneously initiating a 400% increase in sodium ingestion (4, 12, 159).

The inversion of potassium and sodium concentrations in hominin diets had no evolutionary precedent and now plays an integral role in eliciting and contributing to numerous diseases of civilization. Diets low in potassium and high in sodium may partially or directly underlie or exacerbate a variety of maladies and chronic illnesses, including hypertension, stroke, kidney stones, osteoporosis, gastrointestinal tract cancers, asthma, exercise-induced asthma, insomnia, air sickness, high-altitude sickness, and Meniere's Syndrome (ear ringing) (160–170).

Fiber content

The fiber content (15.1 g/d) (23) of the typical US diet is considerably lower than recommended values (25–30 g) (116). Refined sugars, vegetable oils, dairy products, and alcohol are devoid of fiber and constitute an average of 48.2% of the energy in the typical US diet (Table 1). Furthermore, fiber-depleted, refined grains represent 85% of the grains consumed in the United States (Table 1), and because refined grains contain 400% less fiber than do whole grains (by energy), they further dilute the total dietary fiber intake. Fresh fruit typically contains twice the amount of fiber in whole grains, and nonstarchy vegetables contain almost 8 times the amount of fiber in whole grains on an energy basis (64). Fruit and vegetables known to be consumed by hunter-gatherers also maintain considerably more fiber than do their domestic counterparts (145). Contemporary diets devoid of cereal grains, dairy products, refined oils and sugars, and processed foods have been shown to contain significantly more fiber (42.5 g/d) than either current or recommended values (159).

Once again, the displacement of fiber-rich plant foods by novel dietary staples, introduced during the Neolithic and Industrial periods, was instrumental in changing the diets that our species had traditionally consumed—a diet that would have almost always been high in fiber. Soluble fibers (those found primarily in fruit and vegetables) modestly reduce total and LDL-cholesterol concentrations beyond those achieved by a diet low in saturated fat and fiber, by slowing gastric emptying, may reduce the appetite and help to control caloric intake (171). Diets low in dietary fiber may underlie or exacerbate constipation, appendicitis, hemorrhoids, deep vein thrombosis, varicose veins, diverticulitis, hiatal hernia, and gastroesophageal reflux (172).

SUMMARY

In the United States and most Western countries, diet-related chronic diseases represent the single largest cause of morbidity and mortality. These diseases are epidemic in contemporary Westernized populations and typically afflict 50–65% of the adult population, yet they are rare or nonexistent in hunter-gatherers and other less Westernized people. Although both scientists and lay people alike may frequently identify a single dietary element as the cause of chronic disease (eg, saturated fat causes heart disease and salt causes high blood pressure), evidence gleaned over the past 3 decades now indicates that virtually all so-called diseases of civilization have multifactorial dietary elements that underlie their etiology, along with other environmental agents and genetic susceptibility. Coronary heart disease, for instance, does not arise simply from excessive saturated fat in the diet but rather from a complex interaction of multiple nutritional factors directly linked to the excessive consumption of novel Neolithic and Industrial era foods (dairy products, cereals, refined cereals, refined sugars, refined vegetable oils, fatty meats, salt, and combinations of these foods). These foods, in turn, adversely influence proximate nutritional factors, which universally underlie or exacerbate virtually all chronic diseases of civilization: *1*) glycemic load, *2*) fatty acid composition, *3*) macronutrient composition, *4*) micronutrient density, *5*) acid-base balance, *6*) sodium-potassium ratio, and *7*) fiber content. However, the ultimate factor underlying diseases of civilization is the collision of our ancient genome with the new conditions of life in affluent nations, including the nutritional qualities of recently introduced foods.

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REFERENCES

1. Gould SJ. The structure of evolutionary theory. Cambridge, MA: Harvard University Press, 2002.
2. Boaz NT. Evolving health: the origins of illness and how the modern world is making us sick. New York: Wiley & Sons, Inc, 2002.
3. Nesse RM, Williams GC. Why we get sick. The new science of Darwinian medicine. New York: Times Books, 1994.
4. Eaton SB, Konner MJ. Paleolithic nutrition. A consideration of its nature and current implications. N Engl J Med 1985;312:283–9.
5. Eaton SB, Konner M, Shostak M. Stone agers in the fast lane: chronic degenerative diseases in evolutionary perspective. Am J Med 1988;84:739–49.
6. Cordain L, Gotshall RW, Eaton SB. Physical activity, energy expenditure and fitness: an evolutionary perspective. Int J Sports Med 1998;19:328–35.
7. Cordain L. Cereal grains: humanity's double edged sword. World Rev Nutr Diet 1999;84:19–73.
8. Cohen MN. Health and the rise of civilization. London: Yale University Press, 1989.
9. Abrams HL. The relevance of Paleolithic diet in determining contemporary nutritional needs. J Appl Nutr 1979;31:43–59.
10. Truswell AS. Diet and nutrition of hunter-gatherers. In: Health and disease in tribal societies. New York: Elsevier; 1977:213–21.
11. Cordain L, Watkins BA, Florant GL, Kehler M, Rogers L, Li Y. Fatty acid analysis of wild ruminant tissues: evolutionary implications for reducing diet-related chronic disease. Eur J Clin Nutr 2002;56:181–91.
12. Frassetto L, Morris RC Jr, Sellmeyer DE, Todd K, Sebastian A. Diet, evolution and aging—the pathophysiologic effects of the post-agricultural inversion of the potassium-to-sodium and base-to-chloride ratios in the human diet. Eur J Nutr 2001;40:200–13.
13. Hedley AA, Ogden CL, Johnson CL, Carroll MD, Curtin LR, Flegal KN. Prevalence of overweight and obesity among US children, adolescents, and adults, 1999–2002. JAMA 2004;291:2847–50.
14. Allison DB, Fontaine KR, Manson JE, Stevens J, VanItallie TB. Annual deaths attributable to obesity in the United States. JAMA 1999;282:1530–8.
15. American Heart Association. Heart and stroke statistics—2004 update. Dallas: American Heart Association, 2003.
16. Siris ES, Miller PD, Barrett-Connor E, et al. Identification and fracture outcomes of undiagnosed low bone mineral density in postmenopausal women. Results from the National Osteoporosis Risk Assessment. JAMA 2001;286:2815–22.
17. National Osteoporosis Foundation. Osteoporosis: review of the evidence for prevention, diagnosis, and treatment and cost-effectiveness analysis. Osteoporos Int 1998;8(suppl):S1–88.
18. American Cancer Society. Cancer facts & figures 2004. Atlanta: American Cancer Society, 2004.
19. Wood B. Palaeoanthropology: hominid revelations from Chad. Nature 2002;418:133–5.
20. Cordain L, Brand Miller J, Eaton SB, Mann N, Holt SHA, Speth JD. Plant to animal subsistence ratios and macronutrient energy estimations in world wide hunter-gatherer diets. Am J Clin Nutr 2000;71:682–92.
21. Cordain L, Eaton SB, Brand Miller J, Mann N, Hill K. The paradoxical nature of hunter-gatherer diets: meat based, yet non-atherogenic. Eur J Clin Nutr 2002;56(suppl):S42–52.
22. Gerrior S, Bente L. Nutrient content of the U.S. food supply, 1909-99: a summary report. Washington, DC: US Department of Agriculture, Center for Nutrition Policy and Promotion, 2002. (Home Economics report no. 55.)
23. US Department of Agriculture, Agricultural Research Service. Data tables: results from USDA's 1994-96 Continuing Survey of Food Intakes by Individuals and 1994-96 Diet and Health Knowledge Survey. ARS Food Surveys Research Group, 1997. Internet: (available under "Releases"): http://www.barc.usda.gov/bhnrc/ foodsurvey/ home.htm (accessed 11 May 2004).
24. US Department of Agriculture, Economic Research Service. Food Consumption (per capita) data system, sugars/sweeteners. 2002. Internet: http://www.ers.usda.gov/Data/foodconsumption/datasystem.asp (accessed 11 May 2004).
25. Hiendleder S, Kaupe B, Wassmuth R, Janke A. Molecular analysis of wild and domestic sheep questions current nomenclature and provides evidence for domestication from two different subspecies. Proc R Soc Lond B 2002;269:893–904.
26. Luikart G, Gielly L, Excoffier L, Vigne J, Bouvet J, Taberlet P. Multiple maternal origins and weak phylogeographic structure in domestic goats. Proc Natl Acad Sci U S A 2001;98:5927–32.
27. Loftus RT, Ertugrul O, Harba AH, et al. A microsatellite survey of cattle from a centre of origin: the Near East. Mol Ecol 1999;8:2015–22.
28. Copley MS, Berstan R, Dudd SN, et al. Direct chemical evidence for widespread dairying in prehistoric Britain. Proc Natl Acad Sci U S A 2003;100:1524–9.
29. Wright K. The origins and development of ground stone assemblages in Late Pleistocene Southwest Asia. Paleorient 1991;17:19–45.
30. Bar-Yosef O. The Natufian culture in the Levant, threshold to the origins of agriculture. Evol Anthropol 1998;6:159–77.
31. Salami F, Ozkan H, Brandolini A, Schafer-Pregl R, Martin W. Genetics and geography of wild cereal domestication in the near east. Nat Rev Genet 2003;3:429–41.
32. Keeley LH. The use of plant foods among hunter-gatherers: a cross-cultural survey. In: Anderson PC, ed. Prehistoire de l'agriculture. Nouvelles approches experimentales et ethnographiques. (Prehistoric agriculture. New experimental approaches and ethnography.) Paris: National Center for Scientific Research, 1992:29–38 (in French).
33. Eaton SB. Humans, lipids and evolution. Lipids 1992;27:814–20.
34. Harlan JR. 1992. Wild grass seed harvesting and implications for domestication. In: Anderson PC, ed. Prehistoire de l'agriculture. Nouvelles approches experimentales et ethnographiques. Paris: National Center for Scientific Research, 1992;21–7.
35. Storck J, Teague WD. Flour for man's bread, a history of milling. Minneapolis: University of Minnesota Press, 1952.
36. Nelson JH. Wheat: its processing and utilization. Am J Clin Nutr 1985;41:1070–6.
37. Galloway JH. 2000. Sugar. In: Kiple KF, Ornelas KC, eds. The Cambridge world history of food. Vol 1. Cambridge: Cambridge University Press, 2000:437–49.
38. Cleave TL. The saccharine disease. Bristol, United Kingdom: John Wright & Sons, Ltd, 1974;1974:6–27.
39. Ziegler E. Secular changes in the stature of adults and the secular trend of modern sugar consumption. Z Kinderheilkd 1967;99:146–66.
40. Meehan B. Shell bed to shell midden. Canberra, Australia: Australian Institute of Aboriginal Studies, 1982.
41. Hawkes K, Hill K, O'Connell JF. Why hunters gather: optimal foraging and the Ache of eastern Paraguay. Am Ethnologist 1982;9:379–98.
42. Hanover LM, White JS. Manufacturing, composition, and applications of fructose. Am J Clin Nutr 1993;58(suppl):724S–32S.
43. O'Keefe SF. 2000. An overview of oils and fats, with a special emphasis on olive oil. In: Kiple KF, Ornelas KC, eds. The Cambridge world history of food. Vol 1. Cambridge, United Kingdom: Cambridge University Press, 2000:375–97.
44. Emken EA. Nutrition and biochemistry of trans and positional fatty acid isomers in hydrogenated oils. Annu Rev Nutr 1984;4:339–76.
45. McGovern PE, Voigt MM, Glusker DL, Exner LJ. Neolithic resinated wine. Nature 1996;381:480–1.
46. Rudolph MH, McGovern PE, Badler VR. Chemical evidence for ancient beer. Nature 1992;360:24.
47. Comer J. Distilled beverages. In: Kiple KF, Ornelas KC, eds. The Cambridge world history of food. Vol 1. Cambridge, United Kingdom: Cambridge University Press, 2000:653–64.
48. Newman J. Wine. In: Kiple KF, Ornelas KC, eds. The Cambridge world history of food. Vol 1. Cambridge, United Kingdom: Cambridge University Press, 2000;730–7.
49. Eaton SB, Shostak M, Konner M. The paleolithic prescription. New York: Harper and Row Publishers, 1988.
50. James WP, Ralph A, Sanchez-Castillo CP. The dominance of salt in manufactured food in the sodium intake of affluent societies. Lancet 1987;1:426–9.

51. Kurlansky M. Salt: a world history. New York: Walker and Company, 2002.
52. Weller O. The earliest salt exploitation in Europe: a salt mountain in the Spanish Neolithic. Antiquity 2002;76:317–8.
53. Norton SA. Salt consumption in ancient Polynesia. Perspect Biol Med 1992;5:160–81.
54. Denton D. The hunger for salt. An anthropological, physiological and medical analysis. New York: Springer, 1984.
55. Brothwell D, Brothwell P. Food in antiquity: a survey of the diet of early peoples. New York: Frederick A Praeger Publishers, 1969.
56. Pitts CG, Bullard TR. Some interspecific aspects of body composition in mammals. In: Body composition in animals and man. Washington, DC: National Academy of Sciences, 1968:45–70. (Publication 1598.)
57. Spiess AE. Reindeer and caribou hunters: an archaeological study. New York: Academic Press, 1979.
58. Mercer JG. Regulation of appetite and body weight in seasonal mammals. Comp Biochem Physiol Part C 1998;119:295–303.
59. Shackleton CM, Granger JE. Bone marrow fat index and kidney-fat of several antelope species from Transkei. S Afr J Wildl Res 1989;19:129–34.
60. Stahl WR. Organ weights in primates and other mammals. Science 1965;150:1039–42.
61. Calder WA. Size, function and life history. Cambridge, United Kingdom: Harvard University Press, 1984.
62. Meadows SD, Hakonson TE. Contributions of tissues to body mass in elk. J Wildl Manage 1982;46:838–41.
63. Hakonson TE, Whicker FW. The contribution of various tissues and organs to total body mass in mule deer. J Mammal 1971;52:628–30.
64. First Data Bank. Nutritionist V nutrition software, version 2.3. San Bruno, CA: First Data Bank, 2000.
65. Rule DC, Broughton KS, Shellito SM, Maiorano G. Comparison of muscle fatty acid profiles and cholesterol concentrations of bison, beef cattle, elk, and chicken. J Anim Sci 2002;80:1202–11.
66. Whitaker JW. Feedlot empire: beef cattle feeding in Illinois and Iowa, 1840-1900. Ames, IA: The Iowa State University Press, 1975.
67. Wells RS, Preston RL. Effects of repeated urea dilution measurement on feedlot performance and consistency of estimated body composition in steers of different breed types. J Anim Sci 1998;76:2799–804.
68. Pollan M. Power steer. New York Times Magazine. 2002. Internet: http://www.nytimes.com/2002/03/31/magazine/31BEEF.html (accessed 11 May 2004).
69. Kidwell B. All grass, no grain. Progressive Farmer Magazine, 8 October 2002: Internet: http://www.progressivefarmer.com/farmer/magazine/article/0,14730,355103,00.html (accessed May 11, 2004).
70. Jenkins DJ, Wolever TM, Taylor RH, et al. Glycemic index of foods: a physiological basis for carbohydrate exchange. Am J Clin Nutr 1981;34:362–6.
71. Liu S, Willett WC. Dietary glycemic load and atherothrombotic risk. Curr Atheroscler Rep 2002;4:454–61.
72. Foster-Powell K, Holt SH, Brand-Miller JC. International table of glycemic index and glycemic load values: 2002. Am J Clin Nutr 2002;76:5–56.
73. Thorburn AW, Brand JC, Truswell AS. Slowly digested and absorbed carbohydrate in traditional bushfoods: a protective factor against diabetes? Am J Clin Nutr 1987;45:98–106.
74. Wolever TM, Jenkins DJ. The use of the glycemic index in predicting the blood glucose response to mixed meals. Am J Clin Nutr 1986;43:167–72.
75. Jenkins DJ, Wolever TM, Collier GR, et al. Metabolic effects of a low-glycemic diet. Am J Clin Nutr 1987;46:968–75.
76. Miller JC. Importance of glycemic index in diabetes. Am J Clin Nutr 1994;59(suppl):747S–52S.
77. Ludwig DS. The glycemic index: physiological mechanisms relating obesity, diabetes, and cardiovascular disease. JAMA 2002;287:2414–23.
78. Cordain L, Eades MR, Eades MD. Hyperinsulinemic diseases of civilization: more than just syndrome X. Comp Biochem Physiol Part A 2003;136:95–112.
79. Reaven GM. Pathophysiology of insulin resistance in human disease. Physiol Rev 1995;75:473–86.
80. Cordain L, Eaton SB, Brand Miller J, Lindeberg S, Jensen C. An evolutionary analysis of the aetiology and pathogenesis of juvenile-onset myopia. Acta Opthalmol Scand 2002;80:125–35.
81. Cordain L, Lindeberg S, Hurtado M, Hill K, Eaton SB, Brand-Miller J. Acne vulgaris: a disease of western civilization. Arch Dermatol 2002;138:1584–90.
82. Schaeffer O. When the Eskimo comes to town. Nutr Today 1971;6:8–16.
83. Trowell HC. From normotension to hypertension in Kenyans and Ugandans 1928–1978. East Afr Med J 1980;57:167–73.
84. Ostman EM, Liljeberg Elmstahl HG, Bjorck IM. Inconsistency between glycemic and insulinemic responses to regular and fermented milk products. Am J Clin Nutr 2001;74:96–100.
85. Thorburn AW, Storlien LH, Jenkins AB, Khouri S, Kraegen EW. Fructose-induced in vivo insulin resistance and elevated plasma triglyceride levels in rats. Am J Clin Nutr 1989;49:1155–63.
86. Taghibiglou C, Carpentier A, Van Iderstine SC, et al. Mechanism of hepatic very low density lipoprotein overproduction in insulin resistance. J Biol Chem 2000;275:8416–25.
87. Reiser S, Powell AS, Scholfield DJ, Panda P, Fields M, Canary JJ. Day-long glucose, insulin, and fructose responses of hyperinsulinemic and non-hyperinsulinemic men adapted to diets containing either fructose or high-amylose cornstarch. Am J Clin Nutr 1989;50:1008–14.
88. Dirlewanger M, Schneiter P, Jequier E, Tappy L. Effects of fructose on hepatic glucose metabolism in humans. Am J Physiol Endocrinol Metab 2000;279:E907–11.
89. Mayes PA. Intermediary metabolism of fructose. Am J Clin Nutr 1993;58 (suppl):754S–65S.
90. Elliott SS, Keim NL, Stern JS, Teff K, Havel PJ. Fructose, weight gain, and the insulin resistance syndrome. Am J Clin Nutr 2002;76:911–22.
91. Rossetti L, Giaccari A, DeFronzo RA. Glucose toxicity. Diabetes Care 1990;13:610–30.
92. McClain PA. Hexosamines as mediators of nutrient sensing and regulation in diabetes. J Diabetes Complications 2002;16:72–80.
93. Del Prato S, Leonetti F, Simonson DC, Sheehan P, Matsuda M, DeFronzo RA. Effect of sustained physiologic hyperinsulinaemia and hyperglycaemia on insulin secretion and insulin sensitivity in man. Diabetologia 1994;37:1025–35.
94. Thomson MJ, Williams MG, Frost SC. Development of insulin resistance in 3T3–L1 adipocytes. J Biol Chem 1997;272:7759–64.
95. Zammit VA, Waterman IJ, Topping D, McKay G. Insulin stimulation of hepatic triacylglycerol secretion and the etiology of insulin resistance. J Nutr 2001;131:2074–7.
96. Boden G, Shulman GI. Free fatty acids in obesity and type 2 diabetes: defining their role in the development of insulin resistance and beta-cell dysfunction. Eur J Clin Invest 2002;32(suppl 3):14–23.
97. Institute of Medicine of the National Academies. Dietary fats: total fat and fatty acids. In: Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids (macronutrients). Washington, DC: The National Academy Press, 2002:335–432.
98. Kris-Etherton PM, Harris WS, Appel LJ. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. Circulation 2002;106:2747–57.
99. Simopoulos AP. Omega-3 fatty acids in inflammation and autoimmune disease. J Am Coll Nutr 2002;21:495–505.
100. Spady DK, Woollett LA, Dietschy JM. Regulation of plasma LDL-cholesterol levels by dietary cholesterol and fatty acids. Annu Rev Nutr 1993;13:355–81.
101. Mustad VA, Etherton TD, Cooper AD, et al. Reducing saturated fat intake is associated with increased levels of LDL receptors on mononuclear cells in healthy men and women. J Lipid Res 1997;38:459–68.
102. Stamler J, Daviglus ML, Garside DB, Dyer AR, Greenland P, Neaton JD. Relationship of baseline serum cholesterol levels in 3 large cohorts of younger men to long-term coronary, cardiovascular, and all-cause mortality and to longevity. JAMA 2000;19:284:311–8.
103. GISSI-Prevention Investigators. Dietary supplementation with n−3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Lancet 1999;354:447–55.
104. Nelson GJ, Schmidt PC, Kelley DS. Low-fat diets do not lower plasma cholesterol levels in healthy men compared to high-fat diets with similar fatty acid composition at constant caloric intake. Lipids 1995;30:969–76.
105. Rifai N, Ridker PM. Inflammatory markers and coronary heart disease. Curr Opin Lipidol 2002;13:383–9.
106. Ridker PM, Fifai N, Rose L, Buring JE, Cook NR. Comparison of

C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med 2002; 347:1557–65.
107. Liu S, Manson JE, Buring JE, Stampfer MJ, Willett WC, Ridker PM. Relation between a diet with a high glycemic load and plasma concentrations of high-sensitivity C-reactive protein in middle-aged women. Am J Clin Nutr 2002;75:492–8.
108. Madsen T, Skou HA, Hansen VE, et al. C-reactive protein, dietary n−3 fatty acids, and the extent of coronary artery disease. Am J Cardiol 2001;88:1139–42.
109. Tchernof A, Nolan A, Sites CK, Ades PA, Poehlman ET. Weight loss reduces C-reactive protein levels in obese postmenopausal women. Circulation 2002;105:564–9.
110. Subar AF, Krebs-Smith SM, Cook A, Kahle LL. Dietary sources of nutrients among US adults, 1989 to 1991. J Am Diet Assoc 1998;98: 537–47.
111. Cordain L. The paleo diet. New York: Wiley, Inc, 2002.
112. Kris-Etherton PM, Taylor DS, Yu-Poth S, et al. Polyunsaturated fatty acids in the food chain in the United States. Am J Clin Nutr 2000; 71(suppl):179S–88S.
113. Ascherio A, Hennekens CH, Buring JE, Master C, Stampfer MJ, Willett WC. Trans-fatty acids intake and risk of myocardial infarction. Circulation 1994;89:94–101.
114. Allison DB, Egan SK, Barraj LM, Caughman C, Infante M, Heimbach JT. Estimated intakes of trans fatty and other fatty acids in the US population. J Am Diet Assoc 1999;99:166–74.
115. US Department of Agriculture. The food guide pyramid. Center for Nutrition Policy and Promotion. 2000. Internet: http://www-.pueblo.gsa.gov/cic_text/food/food-pyramid/main.htm (accessed 11 May 2004). (Home and Garden Bulletin 252.)
116. Krauss RM, Eckel RH, Howard B, et al. AHA dietary guidelines: revision 2000: a statement for healthcare professionals from the Nutrition Committee of the American Heart Association. Circulation 2000;102:2284–99.
117. Richards MP, Pettitt PB, Trinkaus E, Smith FH, Paunovic M, Karavanic. I. Neanderthal diet at Vindija and Neanderthal predation: the evidence from stable isotopes. Proc Natl Acad Sci U S A 2000;97: 7663–6.
118. Richards MP, Hedges RM. Focus: Gough's Cave and Sun Hole Cave human stable isotope values indicate a high animal protein diet in the British Upper Palaeolithic. J Archaeol Sci 2000;27:1–3.
119. O'Dea K. Marked improvement in carbohydrate and lipid metabolism in diabetic Australian Aborigines after temporary reversion to traditional lifestyle. Diabetes 1984;33:596–603.
120. O'Dea K, Traianedes K, Ireland P, et al. The effects of diet differing in fat, carbohydrate, and fiber on carbohydrate and lipid metabolism in type II diabetes. J Am Diet Assoc 1989;89:1076–86.
121. Wolfe BM, Giovannetti PM. Short term effects of substituting protein for carbohydrate in the diets of moderately hypercholesterolemic human subjects. Metabolism 1991;40:338–43.
122. Wolfe BM, Giovannetti PM. High protein diet complements resin therapy of familial hypercholesterolemia. Clin Invest Med 1992;15: 349–59.
123. Wolfe BM, Piche LA. Replacement of carbohydrate by protein in a conventional-fat diet reduces cholesterol and triglyceride concentrations in healthy normolipidemic subjects. Clin Invest Med 1999;22: 140–8.
124. Seino Y, Seino S, Ikeda M, Matsukura S, Imura H. Beneficial effects of high protein diet in treatment of mild diabetes. Hum Nutr Appl Nutr 1983;37 A(3):226–30.
125. Piatti PM, Monti F, Fermo I, et al. Hypocaloric high-protein diet improves glucose oxidation and spares lean body mass: comparison to hypocaloric high-carbohydrate diet. Metabolism 1994;43:1481–7.
126. Hu FB, Stampfer MJ, Manson JE, et al. Dietary protein and risk of ischemic heart disease in women. Am J Clin Nutr 1999;70:221–7.
127. Stolzenberg-Solomon RZ, Miller ER III, Maguire MG, Selhub J, Appel LJ. Association of dietary protein intake and coffee consumption with serum homocysteine concentrations in an older population. Am J Clin Nutr 1999;69:467–75.
128. Mann NJ, Li D, Sinclair AJ, et al. The effect of diet on plasma homocysteine concentrations in healthy male subjects. Eur J Clin Nutr 1999; 53:895–99.
129. Mezzano D, Munoz X, Martinez C, et al. Vegetarians and cardiovascular risk factors: hemostasis, inflammatory markers and plasma homocysteine. Thromb Haemost 1999;81:913–7.
130. Obarzanek E, Velletri PA, Cutler JA. Dietary protein and blood pressure. JAMA 1996;275:1598–603.
131. Burke V, Hodgson JM, Beilin LJ, Giangiulioi N, Rogers P, Puddey IB. Dietary protein and soluble fiber reduce ambulatory blood pressure in treated hypertensives. Hypertension 2001;38:821–6.
132. Klag MJ, Whelton PK. The decline in stroke mortality. An epidemiologic perspective. Ann Epidemiol 1993;3:571–5.
133. Kinjo Y, Beral V, Akiba S, et al. Possible protective effect of milk, meat and fish for cerebrovascular disease mortality in Japan. J Epidemiol 1999;9:268–74.
134. Crovetti R, Porrini M, Santangelo A, Testolin G. The influence of thermic effect of food on satiety. Eur J Clin Nutr 1998;52:482–8.
135. Stubbs RJ. Nutrition Society Medal Lecture. Appetite, feeding behaviour and energy balance in human subjects. Proc Nutr Soc 1998;57: 341–56.
136. Skov AR, Toubro S, Ronn B, Holm L, Astrup A. Randomized trial on protein vs carbohydrate in ad libitum fat reduced diet for the treatment of obesity. Int J Obes Relat Metab Disord 1999;23:528–36.
137. Baba NH, Sawaya S, Torbay N, Habbal Z, Azar S, Hashim SA. 1999. High protein vs high carbohydrate hypoenergetic diet for the treatment of obese hyperinsulinemic subjects. Int J Obes Relat Metab Disord 1999;23:1202–6.
138. Layman DK. The role of leucine in weight loss diets and glucose homeostasis J Nutr 2003;133:261S–7S.
139. Westerterp-Plantenga MS, Lejeune MP, Nijs I, van Ooijen M, Kovacs EM. High protein intake sustains weight maintenance after body weight loss in humans. Int J Obes Relat Metab Disord. 2004;28:57–64.
140. Johnston CS, Tjonn SL, Swan PD. High-protein, low-fat diets are effective for weight loss and favorably alter biomarkers in healthy adults. J Nutr 2004;134:586–91.
141. Wald DS, Law M, Morris JK. Homocysteine and cardiovascular disease: evidence on causality from a meta-analysis. BMJ 2002;325:1202–8.
142. Meleady R, Graham I. Plasma homocysteine as a cardiovascular risk factor: causal, consequential, or of no consequence? Nutr Rev 1999; 57:299–305.
143. Kurtzweil P. Nutritional info available for raw fruits, vegetables, fish. FDA Consumer Magazine. May 1993. US Health and Human Services, Food and Drug Administration, Rockville, MD. Internet: http://www-.fda.gov/fdac/special/foodlabel/raw.html (accessed 11 May 2004).
144. US Department of Agriculture, Economic Research Service. 1999. America's eating habits: changes and consequences. Elizabeth Frazao, ed. Washington, DC. Internet: http://www.ers.usda.gov/ publications/ aib750/aib750app.pdf (accessed 11 May 2004). (Agriculture Information Bulletin No. 750.)
145. Brand-Miller JC, Holt SH. Australian aboriginal plant foods: a consideration of their nutritional composition and health implications. Nutr Res Rev 1998;11:5–23.
146. Frassetto LA, Todd KM, Morris RC, Sebastian A. Estimation of net endogenous noncarbonic acid production in humans from diet potassium and protein contents. Am J Clin Nutr 1998;68:576–83.
147. Sebastian A, Frassetto LA, Sellmeyer DE, Merriam RL, Morris RC. Estimation of the net acid load of the diet of ancestral preagricultural *Homo sapiens* and their hominid ancestors. Am J Clin Nutr 2002;76: 1308–16.
148. Lemann J. Relationship between urinary calcium and net acid excretion as determined by dietary protein and potassium: a review. Nephron 1999;81(suppl 1):18–25.
149. Frassetto L, Morris RC, Sebastian A. Effect of age on blood acid-base composition in adult humans: role of age-related renal functional decline. Am J Physiol 1996;271:1114–22.
150. Sebastian A, Harris ST, Ottaway JH, Todd KM, Morris RC Jr. Improved mineral balance and skeletal metabolism in post-menopausal women treated with potassium bicarbonate. N Engl J Med 1994;330: 1776–81.
151. Bushinsky DA. Metabolic alkalosis decreases bone calcium efflux by suppressing osteoclasts and stimulating osteoblasts. Am J Physiol 1996;271:F216–22.
152. Frassetto L, Morris RC Jr, Sebastian A. Potassium bicarbonate reduces urinary nitrogen excretion in postmenopausal women. J Clin Endocrinol Metab 1997;82:254–9.

153. Pak CY, Fuller C, Sakhaee K, Preminger GM, Britton F. Long-term treatment of calcium nephrolithiasis with potassium citrate. J Urol 1985;134:11–9.
154. Preminger GM, Sakhaee K, Skurla C, Pak CY. Prevention of recurrent calcium stone formation with potassium citrate therapy in patients with distal renal tubular acidosis. J Urol 1985;134:20–3.
155. Morris RC Jr, Sebastian A, Forman A, Tanaka M, Schmidlin O. Normotensive salt sensitivity: effects of race and dietary potassium. Hypertension 1999;33:18–23.
156. Sharma AM, Kribben A, Schattenfroh S, Cetto C, Distler A. Salt sensitivity in humans is associated with abnormal acid-base regulation. Hypertension 1990;16:407–13.
157. Mickleborough TD, Gotshall RW, Kluka EM, Miller CW, Cordain L. Dietary chloride as a possible determinant of the severity of exercise-induced asthma. Eur J Appl Physiol 2001;85:450–6.
158. Alpern RJ, Sakhaee S. The clinical spectrum of chronic metabolic acidosis: homeostatic mechanisms produce significant morbidity. Am J Kidney Dis 1997;29:291–302.
159. Cordain L. The nutritional characteristics of a contemporary diet based upon Paleolithic food groups. J Am Neutraceutical Assoc 2002;5:15–24.
160. Antonios TF, MacGregor GA. Salt—more adverse effects. Lancet 1996;348:250–1.
161. Massey LK, Whiting SJ. Dietary salt, urinary calcium, and kidney stone risk. Nutr Rev 1995;53:131–9.
162. Devine A, Criddle RA, Dick IM, Kerr DA, Prince RL. A longitudinal study of the effect of sodium and calcium intakes on regional bone density in postmenopausal women. Am J Clin Nutr 1995;62:740–5.
163. Gotshall RW, Mickleborough TD, Cordain L. Dietary salt restriction improves pulmonary function in exercise-induced asthma. Med Sci Sports Exerc 2000;32:1815–9.
164. Miller MM. Low sodium chloride intake in the treatment of insomnia and tension states. JAMA 1945;129:262–6.
165. Lindseth G, Lindseth PD. The relationship of diet to airsickness. Aviat Space Environ Med 1995;66:537–41.
166. Porcelli MJ, Gugelchuk GM. A trek to the top: a review of acute mountain sickness. J Am Osteopath Assoc 1995;95:718–20.
167. Thai-Van H, Bounaix MJ, Fraysse B. Meniere's disease: pathophysiology and treatment. Drugs 2001;61:1089–102.
168. Jansson B. Geographic cancer risk and intracellular potassium/sodium ratios. Cancer Detect Prev 1986;9:171–94.
169. Tuyns AJ. Salt and gastrointestinal cancer. Nutr Cancer 1988;11:229–32.
170. Carey OJ, Locke C, Cookson JB. Effect of alterations of dietary sodium on the severity of asthma in men. Thorax 1993;48:714–8.
171. Anderson JW, Smith BM, Gustafson NJ. Health benefits and practical aspects of high-fiber diets. Am J Clin Nutr 1994;59(suppl):1242S–7S.
172. Trowell H. Dietary fiber: a paradigm. In: Trowell H, Burkitt D, Heaton K, Doll R, eds. Dietary fibre, fibre-depleted foods and disease. New York: Academic Press, 1985:1–20.