Medium-chain triacylglycerols may not raise cholesterol

Dear Sir:

Although medium-chain triacylglycerols (MCTs; 8:0 and 10:0) historically have been considered nonlipemic for most individuals, the report by Asakura et al (1) suggests that MCTs may be hypercholesterolemic in subjects with hypertriglyceridemia. Although the authors emphasized the hypercholesterolemia induced when MCTs progressively replaced corn oil in the carefully manipulated diet of these subjects, an alternative conclusion would be that the removal of dietary linoleic acid (18:2) was the primary cause of the plasma cholesterol elevation. Patients were adapted to a low-fat diet (containing 22% of energy as fat) in which 100% corn oil represented about one-half (12%/22%) of the total fat energy, including ~8% of energy from 18:2. Progressive replacement of corn oil with MCTs resulted in <2% of energy from 18:2 in the final diet period (estimated as 20% of the intrinsic dietary fat) when 100% MCT was the added fat. This exchange progressively increased total cholesterol and triacylglycerol, with VLDL cholesterol and LDL cholesterol contributing equally to the elevation in total cholesterol, even though the increase in triacylglycerol was not significant. Thus, MCTs increased cholesterol in apolipoprotein B–rich lipoproteins as dietary 18:2 was reduced from 8% of energy to <2% of energy, the rise in total cholesterol being significant only when all the corn oil was removed. The background carbohydrate and other intrinsic fatty acids were constant and tended not to complicate interpretation here, which was a nice aspect of the study design.

The failure to alter plasma triacylglycerol values in this study likely reflects the fact that high-carbohydrate diets (22% of energy as fat in this case) are hypertriglyceridemic in their own right. Had the total fat provided 30–40% of energy, MCTs might have had a more favorable effect on triacylglycerol. More important is the fact that 18:2 is the principle dietary fatty acid responsible for reducing hepatic fatty acid and triacylglycerol synthesis as well as VLDL secretion induced by carbohydrate, and presumably, induced by MCTs acting like carbohydrate (2). It is well appreciated that 18:2 also can enhance impaired LDL receptor activity (3), and carefully controlled fatty acid exchanges showed that progressive decreases in 18:2 per se raise total cholesterol when diet saturated fatty acids (SFAs) are high but stable, ie, when 18:1 replaces 18:2 (4). In the relative absence of dietary cholesterol, the resulting increase in LDL reflects an overproduction of LDL more than impaired clearance (5). We described these fatty acid interrelations previously in terms of the 18:2 threshold, wherein a specific amount of 18:2 is required to protect against total cholesterol elevation during consumption of SFAs and cholesterol (6).

Examples of these fatty acid interrelations specifically involving MCTs were shown in normolipemic women (7) and hamsters (8). In fact, even when women were fed a low-18:2 diet (3% of energy), MCTs proved less cholesterolemic than a source of longer-chain SFAs (trilaurin). Furthermore, the hamster study found MCTs to be as cholesterol lowering as safflower oil in a cholesterol-free diet when 18:2 intake was adequate at 5% of energy.

Although the current data support the 18:2 threshold concept, they are not definitive because, as is often the case in such experiments, 2 important variables (MCTs and 18:2) were altered simultaneously in opposite directions. Thus, it is not clear which is to blame, rising MCTs or declining 18:2. But substantial evidence would argue the latter is most critical (6). A more definitive design would have kept 18:2 constant at 5–6% of energy and exchanged MCTs for 18:1 or carbohydrate, which are considered neutral. Furthermore, the clinical data cited in support of the cholesterol-raising nature of MCTs (9, 10), like the comparison in normolipemic women (7), suffer the same shortcoming as the present study, ie, 18:2 was lower (and below threshold) in the MCT diet period than in the control diet period. The clinically relevant point is that an adequate source of 18:2 needs to be supplied when MCTs, or even carbohydrate, replace other long-chain SFAs and monounsaturated fatty acids (5).

In summary, MCTs should not be considered as SFAs that raise total cholesterol and LDL. Nor do they represent a substitute for 18:2 that will effectively reduce circulating apolipoprotein B–rich lipoproteins in the absence of 18:2.

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Reply to KC Hayes

Dear Sir:

In our study of medium-chain triacylglycerols (MCTs) in hypertriglyceridemic individuals (1), we were disappointed to find that provision of MCTs as the major source of dietary fat did not lower plasma triacylglycerol concentrations, which was the major objective of the study, and in addition, had the inconvenience of raising plasma cholesterol. Hayes raises the possibility that a low-fat diet (carbohydrate- or MCT-rich) may correct the hypertriglyceridemia provided that an ideal proportion of 18:2 is added to the diet. This is an interesting suggestion that should be tested experimentally in humans no matter how convincing the animal data. Whatever answers one draws from future experiments on these proposed dietary modifications, the bottom line is that MCTs seem useless for the treatment of hyperlipidemia. In contrast, carbohydrate-induced hyperlipidemia, which is a well-known phenomenon that occurs in both healthy persons and in several cases of moderate hypertriglyceridemia, may benefit from Hayes’s interesting proposal because it would likely be circumvented by adding the right amount of 18:2 to a fat-free diet without raising, and probably lowering, plasma cholesterol.

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provided certain brain-selective nutrients, such as docosahexaenoate, iodine, zinc, copper, and iron (2–4). The basis for this hypothesis is that terrestrial foods are deficient in iodine and contain little docosahexaenoate (only in animal tissue). Zinc, copper, and iron are more abundant and available from seafood than from plants. Dietary or genetically imposed deficiencies of all of these brain-selective nutrients leaves the modern human brain extremely vulnerable to subnormal development. Equally important is the issue of access to reliable sources of foods rich in brain-selective nutrients that required minimal effort to locate and consume. Such foods would have to be available for thousands of years before intelligence had risen sufficiently to conceive of and experiment successfully with true fishing or hunting and trapping of wild animals. The hominin fossil record shows that at least fish and shellfish—but probably also eggs, amphibians, and plants on lakeshores and seacoasts—provided an abundance of this important dietary stimulus for human brain evolution without special effort or substantial competition from predators (5).

If the nutrient and energy supplies were consistently inadequate in some geographic areas over thousands of years, human brain evolution would have faltered and long-term colonization of those areas would have ceased until the appropriate foods were found or supplements were invented. This is what happened most clearly with iodine deficiency, which affects more than a billion mostly vegetarian people in inland areas of all continents. Iodine is essential for energy metabolism, normal brain development, and fertility (6). People can survive even severe iodine deficiency but they cannot thrive or reproduce. In contrast, coastal peoples experience no known nutrient deficiencies affecting brain function. Hence, as we argued (2–4), marine, estuarine, and lacustrine locations probably favored human brain evolution by providing abundant energy and protein but, equally importantly, brain-selective nutrients.

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Reply to SC Cunnane

Dear Sir:

Our analysis was based on data derived from historically studied hunter-gatherers (Homo sapiens); hence, it may be inappropriate to assume, as Cunnane did, that Paleolithic hunter-gatherers would have maintained identical nutritional patterns characteristic of modern hunter-gatherers. During the Paleolithic period (a time period extending from roughly 2.6 million y ago until 10000 y ago), 3 hominid genuses (Australopithecus, Paranthropus, and Homo) that encompassed ≥11 separate species were simultaneously present (1). There is abundant evidence suggesting that the hominin’s diet was not static but, rather, evolved and varied throughout the Paleolithic period, depending on the species and the ecologic niche that was exploited. A common nutritional element of those hominid species that eventually led to anatomically modern humans was the inclusion of more energy-dense animal foods in their diet (2, 3). There is little or no fossil evidence to indicate that animal foods derived from the aquatic environment played a significant role in the diet of either early or later hominids until the Upper Paleolithic (35000–40000 y ago) period (4, 5). The fossil record shows that invertebrate shell refuse piles (middens) and fossilized fish remains associated with hominid occupation sites did not appear until the Upper Paleolithic period, concurrent with the technologic advent of hooks, lines, weirs, nets, and barbed spears (4, 5). Consequently, the high fish consumption (median: 26–35% of energy) we showed for 229 historically studied hunter-gatherers likely would not have been representative of Early (2.6 million y ago until 250000 y ago) and Middle (250000–40000 y ago) Paleolithic hominids. Hence, fish, shellfish, and other shore-based foods likely would have played a minor role in providing nutrients, including essential fatty acids, that were crucial for the rapid hominin brain expansion that occurred during the Early Paleolithic.

In regard to our estimation of the mean plant-food macronutrient profile (62% carbohydrate, 24% fat, and 14% protein), we clearly included vegetables in our estimates. Tubers, roots, bulbs, leaves, and flowers are plant-food categories and are included in Table 3 of our article; these categories would subsume such modern vegetables as potatoes (tubers), radishes (roots), onions (bulbs), lettuce (leaves), and broccoli (flowers). These food categories accounted for 29.3% of our entire wild plant food database and have a mean energy density of 4.18 kJ/g. As we mentioned in our article, hunter-gatherers collected plant-food species not randomly but in a fashion predicted by optimal foraging theory that would tend to maximize the ratio of energy capture to energy expenditure. Lipid-rich seeds and nuts (mean energy density: 13.14 kJ/g) would have been selected preferentially over vegetable foods when available. Hence, our weighting of the plant-food database in Table 3 of our article reflects the preferential foraging of these fat-containing plant foods by hunter-gatherers.

In regard to the physiologic protein ceiling, we agree that Early Paleolithic hominids such as Homo habilis—because of their small size (male: height = 132 cm, weight = 37 kg), lack of effective weapons, and limited behavioral sophistication—would have been unsuccessful hunters of large herbivores and hence would have had only occasional access to “copious amounts of meat” as well as abdominal organs and depot fat. For the same reasons, these diminutive hominids would also have had little success in confrontational scavenging and stealing prey from large, carnivore-
rous predators. The fossil record indicates that the passive scavenging of the abandoned and defleshed long bones and skulls of herbivores with their intact contents of marrow and brain would have represented the primary large animal food source for early ancestral humans (6, 7). Hominids did not become successful hunters of large game until the Middle to Upper Paleolithic period.

The evolution of a large metabolically active brain in our species required food sources that were energetically dense (2, 3) and that contained docosahexaenoic acid (22:6n-3) (8). Although East African freshwater fish are good sources of 22:6n-3 (549 mg/100 g), they are a poor energy source (498 kJ/100 g) (9) and are less energetically dense than is a mixture of wild, edible plants (540 kJ/100 g) consumed by hunter-gatherers (10). Scavenged marrow is a rich energy source (3289 kJ/100 g) and scavenged bone is a more concentrated source of 22:6n-3 (861 mg/100 g) than is East African freshwater fish. Because scavenged marrow is a more highly concentrated energy source (3289 kJ/100 g) than is freshwater fish (498 kJ/100 g), the energy return versus the energy expenditure for scavenged marrow bones would have far exceeded that available from the manual capture of freshwater fish. Furthermore, because the energy-protein ratio in African ruminant marrow (477 kJ/g protein) is almost 20 times greater than for African freshwater fish (27 kJ/g protein), fish consumption would have been constrained by the physiologic protein ceiling, whereas marrow consumption would not have been. Thus, when the option was available, scavenged marrow and the brain that was concurrently present in the skull of the defleshed skeleton would almost always have been chosen over active capture of either fish or aquatic invertebrates. Taken together, the data indicate that scavenged marrow from ruminant long bones would have represented the concentrated energy source required for hominin brain evolution and that the brains of scavenged skulls would have represented the predominant source of 22:6n-3.

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Reply to SC Cunnane

Modern humans are noted for their large brain but factors related to the brain’s evolution are imperfectly understood. Cunnane states that a “shore-based ecologic niche was uniquely able to stimulate expansion of the primate brain. . . .” In a previous article, Cunnane and others (1) described “the African savanna ecosystem of large mammals and primates [as] associated with a dramatic decrease in relative brain capacity associated with little docosahexaenoic acid” (DHA; 22:6n-3). Abundant long-chain polyunsaturated fatty acids (LCPUFAs), particularly DHA and arachidonic acid (AA; 20:4n-6) are regarded as absolute requirements for advanced neural growth in humans and other mammals (1–3).

Because tropical freshwater fish and shellfish and many marine fish offer plentiful preformed DHA, Cunnane et al propose that the lacustrine and marine food chain was being extensively exploited at the time cerebral expansion took place in the ancestral line leading to modern humans (1, 2). I found little evidence to support this.

Members of the genus Homo have always been distinguished by a large brain relative to body size (4, 5). Data suggest that the major increase in encephalization in Homo occurred during the Middle Pleistocene, 600–150 thousand years before present (BP) (4). Well before this, overall body size and degree of sexual dimorphism in Homo had arrived at essentially the modern level (5). By 150–100 thousand years BP, absolute brain size in Homo appears to have been within the modern range, whether Homo is viewed as a single or multiple species (4, 5).

The first evidence supporting the systematic use of coastal resources is dated between 127 and 57 thousand years BP (5). If consumption of coastal resources underlies expansion of the mod-
ern human brain, what factors explain the precipitous increase in brain size on 3 different continents by members of the genus *Homo* well before evidence for the exploitation of shore-based resources? If humans in the African Rift Valley consistently utilized lacustrine resources (2), why the long period of stasis in human encephalization between 1800 and 600 thousand years BP (4)?

Another puzzle concerns the technologic explosion (5)—a burst of creativity in anatomically modern humans that appears to have begun fairly abruptly in the Late Paleolithic period some 40 thousand years BP and involved the dramatic acceleration of cultural evolution. This technologic explosion was not accompanied by any increase in human brain size and thus some other factor, possibly the development of fully modern language, has been suggested to underlie it (5).

Taken together, the fossil and archaeologic records suggest that the modern physical form of our species evolved before the modern capacity for culture (5). Although the question of where and when anatomically modern humans originated remains unresolved (5), data do not suggest any causal association between the exploitation of aquatic foods and human brain expansion.

The idea that the African savanna could not support large-brained species (1, 2) seems inaccurate. No evidence suggests that primates in this environment have brains smaller for their body mass or a lower encephalization quotient (6) than do their counterparts in tropical forests. In fact, the savanna baboon (*Papio* spp.) and savanna-woodland vervet (*Cercopithecus aethiops*) have relatively large brains and high encephalization quotients compared with most African forest primates (6). Nor is it the case that all large savanna species have small brains relative to their body mass. Elephants, for example, have brains that, over the course of their evolution, “were enlarged even beyond the extent expected for their large bodies” (6).

Where do humans get the LCPUFAs that are so critical in brain development? Preformed LCPUFAs can be obtained from foods, or LCPUFAs can be synthesized in the mammalian liver from dietary precursors, ie, the essential fatty acids linoleic acid and α-linolenic acid. Tissues of the eye and brain can also synthesize DHA if the appropriate precursors are available (7). In humans, a progressive increase in fatty acid length and degree of unsaturation from maternal liver to placenta, fetal liver, and fetal brain has been documented (3). The direct incorporation of dietary LCPUFAs in the developing brain was also shown (3). Full-term infants can synthesize DHA, and human breast milk contains both linoleic acid and α-linolenic acid as well as LCPUFAs, including DHA (8, 9).

Although the conversion of α-linolenic acid to DHA in humans is stated to be weak (2), “elongation and desaturation of ω3 fatty acids in the human liver is very active and capable of providing the high levels of long ω3 PUFA required by the developing brain” during the crucial stage of brain development (3). Although n−3 deficiency can be induced in humans by a very poor supply of α-linolenic acid or an excessive supply of linoleic acid relative to α-linolenic acid, the possibility of n−3 fatty acid deficiency in the wild-food diets of evolving humans seems unlikely “because of the abundance of these fatty acids in nature, their small minimum requirements and the enzyme preference for the linolenate family” (3).

The “aquatic foods argument” also offers no real explanation for why these foods stimulated human brain expansion. In this Lamarckian scenario, the quiescent brain appears to be waiting patiently for humans to discover aquatic foods and then, eureka, the brain is free to enlarge and modern humans result. Not only are the selective pressures involved in this scenario unspecified, no information is provided as to how these large-brained humans were then able to provide DHA and other brain-specific nutrients for themselves or their developing offspring once they moved away from lacustrine or shore-based environments.

Dietary pressures appear to have been a major stimulus in human evolution (10). The association of stone tools with the earliest evidence for hominin exploitation of meat and marrow from large terrestrial ungulates strongly suggests that even the earliest humans used extrasomatic (cultural) innovations to help them solve immediate dietary problems (11). The brains, flesh, liver, tongue, marrow, and other parts of wild terrestrial mammals would have served as a concentrated source of many essential nutrients required by early humans, including LCPUFAs (12, 13). Because wild animals consume diets with very low ratios of n−6 to n−3 fatty acids, their tissues have relatively high proportions of n−3 fatty acids, including eicosapentaenoic acid (a precursor of DHA) and DHA (12, 13) and wild-plant foods would provide α-linolenic acid and linoleic acid.

Archaeologic evidence testifies to the increasing technologic proficiency and continuous exploitation of terrestrial mammals by members of the genus *Homo* over the course of their evolution (5). Calculations indicate that a diet composed of 35% terrestrial animal matter and 65% terrestrial plant matter would have provided more than adequate raw material for brain-building purposes, not only sufficient amounts of DHA but also of AA and docosatetraenoic acid (14). As highly opportunistic foragers, ancestral humans likely would have exploited aquatic foods whenever possible, but such foods seem unnecessary for brain expansion in the human lineage.

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There is still more to learn about soy

Dear Sir:

Teixeira et al (1) concluded that “consuming as little as 20 g soy protein/d instead of animal protein for 6 wk reduces concentrations of non-HDL cholesterol and apo B by ≈2.6% and 2.2%, respectively.” This appears to be an incorrect conclusion considering the data and discussion put forth by these authors. In keeping with the given protocol of evaluating the effects of various levels of soy protein supplementation (soy with or without casein) in moderately hypercholesterolemic adults, their conclusion does not match the test. Specifically, the group who received 20 g isolated soy protein (ISP) also received 30 g casein; additionally, only the groups who received either 50 g casein; and apolipoprotein B. Thus, with all of the technical machinery available to the authors for firsthand measurement of the various lipoproteins, it is questionable for them to put forth that observed changes in mathematically determined VLDL and LDL are accurate and truly reflective of the non-HDL lipid pool. Although it can be said that 65–70% of TC is carried as LDL, 10–15% as VLDL, and 20% as HDL and that there are various subfractions of LDL, we cannot accept the conclusion of the authors as a true measurement of non-HDL cholesterol (2).

Certainly, the role of soy and soy protein as medicinal foods deserves more independent prospective trials to further determine both the risks and benefits of including this food in the Western diet. However, before we accept generalized conclusions such as those made in Teixeira et al’s article, we must insist on a strong body of evidence. Such a body of evidence may have resulted from a misunderstanding on their part of our results of our study, in fact, provide additional support for the FDA-approved health claim.

We reassert our conclusion that “as little as 20 g soy protein/d instead of animal protein for 6 wk reduces concentrations of non-HDL cholesterol and apo B by ≈2.6% and 2.2%, respectively” (1). We fully agree with Kalman and Colker that there is much more to learn about soy. However, a strong body of evidence from several laboratories, including a meta-analysis, already exists on the effects of soy protein on blood lipids (2–4). The Food and Drug Administration (FDA) reviewed the extensive literature published on this subject and in October of 1999 approved a health claim for foods containing soy protein (5). The qualifying amount of soy protein approved in this health claim (25 g) is similar to and consistent with the amount of soy protein shown to decrease blood lipids in our paper (20 g). Therefore, the results of our study, in fact, provide additional support for the FDA-approved health claim.

The comment of Kalman and Colker regarding our conclusion may have resulted from a misunderstanding on their part of our study design. In our study, the control group received 50 g casein (ie, no replacement). For all other groups, different amounts of casein (20, 30, 40, and 50 g) were replaced by equivalent amounts of isolated soy protein, so that the total protein intake remained constant. Therefore, our conclusion about the replace-
ment of animal protein with soy protein was indeed consistent with our data and study design. The comment of Kalman and Colker regarding nutrient analysis is also incorrect. Besides the analysis of macronutrients and isoflavones, we also calculated total cholesterol and saturated, monounsaturated, and polyunsaturated fat, as stated in the paper. Soy intake was also known because the only form of soy consumed was the one provided in the test protein (1).

Regarding the non-HDL-cholesterol values, non-HDL cholesterol is by definition any cholesterol that is not associated with HDL particles, and it corresponds to the cholesterol from all apolipoprotein B–containing lipoproteins [ie, VLDL, IDL, LDL, and lipoprotein(a)] (6). We labeled non-HDL cholesterol as VLDL + LDL cholesterol because the traditional definition of LDL entails LDL + IDL + lipoprotein(a) (7). We chose to report non-HDL cholesterol because it has been shown to be a good indicator of coronary heart disease (6).

We agree that measuring actual concentrations of LDL and VLDL cholesterol separately would provide additional useful information, especially because LDL cholesterol is used historically to determine risk of coronary heart disease (8). LDL cholesterol is also commonly determined through use of the Friedewald formula (9). However, it is well known that this formula is not accurate if triacylglycerol concentrations are >4.66 mmol/L (400 mg/dL) (10). Moreover, when triacylglycerol concentrations are between 2.3 and 4.5 mmol/L (200–400 mg/dL), LDL-cholesterol values obtained by the Friedewald formula show considerable variability as compared with those from ultracentrifugation (10). Most patients in our study fell into 1 of the 2 previous categories, so we chose not to use the Friedewald formula.

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Macronutrient estimations in hunter-gatherer diets

Dear Sir:

We disagree with the editorial (1) that accompanied our recent article on hunter-gatherer plant-animal subsistence ratios (2). Milton appears to have misinterpreted our findings as well as Lee’s (3) original analysis of the Ethnographic Atlas (4).

Within the nutritional community, it is common knowledge that the quantitative and qualitative lipid composition of domesticated meats is vastly different from that found in wild game. Game meat contains lower proportions of fat, especially saturated fat, than does meat from grain-fed domesticated animals, even on a whole-carcass basis (5). Nowhere in our article did we recommend that people should eat high-fat, domesticated livestock. Our take-home messages were that hunter-gatherer diets were higher in protein and lower in carbohydrate than are current Western diets or dietary guidelines and that this macronutrient balance may provide insight into potentially therapeutic diets. If any implication were to be inferred, it would be that dietary fat should emulate fat sources found in game meat and organs (high in n–3 fats, low in n–6 fats, and high in monounsaturated fats).

Milton’s editorial repeated the same error that has occurred continually in the anthropologic community since Lee published his work 32 y ago (3). Lee did not report the total food intakes derived from animal sources because he did not sum hunted and fished animal foods. This is one of the reasons our reanalysis of Lee’s (3) original analysis of the Ethnographic Atlas is original and noteworthy. Although we did not report it in our article, we analyzed Lee’s sample of 58 hunter-gatherer societies as a subset and obtained results almost identical to those of our analysis of the entire sample (n = 229). The dependence on hunted and fished foods for subsistence was 86–100% (modal value) and 66–75% (median value). Milton’s statement that “emphasis on hunting occurred only in the highest latitudes” is also inaccurate because our analysis of Lee’s
data showed that there is no correlation (Spearman’s rho = 0.01) between dependence on hunting and latitude; on the contrary: as intakes of plant food decrease with increasing latitude, intakes of fish food increase and of hunted animal food stay constant—the same conclusion we reached with our original analysis. The editorial emphasizes the importance of animal foods in hunter-gatherer diets by citing 2 extreme and nonrepresentative societies, the !Kung and the Hazda, both of which have been shown by the Ethnographic Atlas and modern quantitative studies to maintain high plant-animal subsistence ratios (67:33 and 56:44, respectively). Of the 229 hunter-gatherer societies listed in the Ethnographic Atlas, only 1 other society maintains a plant-animal subsistence ratio as high as that of the !Kung and only 13% maintain a ratio as high or higher than that of the Hazda. A compilation of the few available quantitative dietary studies in hunter-gatherers showed a plant-animal subsistence ratio of 41:59 (6), which is similar to the aggregate value (45:55) we reported in our article.

Increases in low-fat dietary protein at the expense of carbohydrate may have therapeutic effects. Wolfe and Piche (7) showed that the replacement of dietary carbohydrate with low-fat, high-protein animal foods improved blood lipids (LDL, VLDL, total cholesterol, triacylglycerol, and the ratio of total to HDL cholesterol). Furthermore, increased dietary protein may reduce the risk of coronary heart disease (8) and reduce serum homocysteine concentrations (9) while facilitating weight loss (10) and improving insulin metabolism (11).

Again, we do not recommend increases in intakes of domesticated animal fat, only of lean protein from lean animals, preferably protein that may also contain significant amounts of n−3 and monounsaturated fat such as that found in game meat. Consumption of low-fat dietary protein at the expense of carbohydrate is the nutritional pattern that is consistent with our species’ evolutionary history and represents a viable dietary option for improving health and well-being in modern people. Further research is needed before this dietary pattern can be recommended without reservation, particularly in subjects with preexisting kidney disease.

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Reply to L Cordain et al
Dear Sir:

In their article in the March 2000 issue of the Journal (1), and now in their letter to the Editor, Cordain et al discussed plant-animal subsistence ratios and likely macronutrient intakes (percentage of energy) in recent hunter-gatherer societies. They concluded that, worldwide, most hunter-gatherer societies derived >50% of dietary energy from animal foods and suggested that “the universally characteristic macronutrient consumption ratios of hunter-gatherers in which protein is elevated at the expense of carbohydrate” may have therapeutic health effects for modern humans.

As discussed in my March 2000 editorial on this topic (2), hunter-gatherer societies, both recent and ancestral, displayed a wide variety of plant-animal subsistence ratios, illustrating the adaptability of human metabolism to a broad range of energy substrates. Because all hunter-gatherer societies are largely free of chronic degenerative disease, there seems little justification for advocating the therapeutic merits of one type of hunter-gatherer diet over another.

What general features of hunter-gatherer diets might contribute to this lack of degenerative disease? One important feature may be that many wild foods consumed by hunter-gatherers are similar or identical to foods consumed by their prehuman
ancestors. Thus, it could be said that human biology is adapted to characteristics of a wide range of wild plant and animal foods but apparently is less well adapted to characteristics of many contemporary Western foods.

Most wild foods have a low energy density compared with the refined foods of Western nations. Muscle tissue of wild prey is consistently low in fat and fat depots tend to be very small in most wild animals (3). Most wild fruit is hexose dominated (4), and wild plant foods tend to have a low glycemic index (5) and, often, considerable dietary fiber (4, 5). Such features, in combination with the slow transit of ingesta characteristic of humans (4), should make it difficult for hunter-gatherers to digest more than a limited quantity of these wild foods each day (2). In effect, then, most hunter-gatherers have a natural barrier between themselves and chronic dietary or energy excess.

In contrast, contemporary Western populations live surrounded by volumetrically concentrated foods that are high in sugar and fat and that can be ingested in enormous quantities. It is extremely easy for individuals in Western nations to consume far more energy each day than they expend. Although often stated, it bears repeating that this Western dietary pattern, in combination with a largely sedentary lifestyle, appears to contribute to many chronic degenerative diseases that affect Western nations but are largely or completely absent in hunter-gatherer and similar societies (2, 6), regardless of the macronutrient ratio or principal energy source.

To derive their conclusions on hunter-gatherer diets, Cordain et al (1) used Murdock’s *Ethnographic Atlas* (7). Despite its general utility, the Atlas provides, at best, a “quantitative overview” (1) of the dietary behaviors of recent (largely 20th century) hunter-gatherers and “in almost all cases represents subjective approximations by Murdock of the ethnographer’s or anthropologist’s original observations” (1).

In his 1968 analysis of hunter-gatherer diets, Lee (8) reclassified some Atlas data and also excluded mounted hunters with guns and “casual” agriculturists from his database. In Lee’s opinion, only 24 societies from all of Africa, Asia, Australia, and South America could be classified as hunter-gatherers, whereas North America alone contained >80% (135) of the 165 “hunting” societies listed in the Atlas.

In contrast, in their analysis, Cordain et al (1) identified 229 hunter-gatherer societies in the *Atlas*; they also combined 2 of Lee’s discrete categories (hunting and fishing) to estimate the total contribution of animal foods to energy subsistence. Given the uneven quality of most dietary data in the *Atlas*, the overrepresentation of hunter-gatherer societies from more temperate locales and the differences in classification and data analysis between these authors, different conclusions seem inevitable and all conclusions appear to merit closer study.

The !Kung and Hazda, dismissed by Cordain et al as “unrepresentative,” differ from many hunter-gatherers listed in the Atlas precisely because they have been relatively well studied dietarily—in both cases, plant foods contributed the bulk of daily energy intake. Examination of the literature suggests that hunter-gatherers throughout the world took full advantage of any dependable sources of dietary energy in their environment (9–11), even devising complex technologies to secure energy from potentially toxic plant sources such as acorns and cycads (10, 11). Such dependable plant foods, in turn, tended to be relied on heavily for dietary energy. For this reason, Cordain et al’s comments on the “low carbohydrate content of wild plant foods” seem largely beside the point—what is key is the steady availability of energy from 1 or 2 reliable wild-plant staples. To secure a dependable source of dietary carbohydrate, some hunter-gatherers, such as the Mbuti (Africa) and the Maku (South America), established symbiotic trade relationships with indigenous agriculturalists (12).

There seems little doubt that many hunter-gatherer societies had a high intake of animal protein (and animal foods) by present-day standards (1, 8, 13). However, this does not imply that such a dietary pattern is the most appropriate for human metabolism or that it should be emulated today. Past hunter-gatherers did not have unlimited dietary options but had to make the best of whatever was available in a particular habitat. The gut proportions of humans do not indicate a highly carnivorous diet; rather, they indicate adaptation to a diet made up of high-quality foods of all types and amenable to digestion primarily in the small intestine (14). Gut proportions of carnivorous mammals differ from those of humans (2). Food transit times in humans are very similar to those of apes and notably different from those of carnivores (2, 14).

To date, few genetic adaptations to diet have been identified in humans, suggesting that, in their evolution, humans tended to resolve dietary problems primarily by using technology rather than biology. The technologic abilities of humans derive from their unusually large, complex brain, a brain that, under normal conditions, is fueled by a steady supply of glucose. Consumption of digestible carbohydrate is the most efficient way for humans to obtain glucose for brain function. Potential alternatives—gluconeogenesis or the use of ketones to fuel the brain—represent alternative, more costly metabolic solutions.

Although Cordain et al noted a neutral or therapeutic effect for high protein intakes in some instances, Hu and Willard (15) recently cautioned application of their findings on heart disease and a high protein intake to public dietary advice because “a high dietary protein intake is often accompanied by high saturated fat and cholesterol intakes.” Given that most Westerners do not have access to wild game, this recommendation seems prudent. Certainly the average well-nourished, inactive American might benefit from reaching for 100 g lean protein rather than a 100-g cheese Danish, but foraging for a 100-g apple might prove to be the most therapeutic of all.

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**REFERENCES**


labels in the intestinal pool in study 1B. However, because the conclusion of “no exchange” was drawn between the absorption of iron from ferrous bisglycinate (FeNaEDTA) and ferrous sulfate in the same meals in study 1B (mean ratio: \( t = 0.044 \)). A corresponding comparison of ferrous bisglycinate in studies 1A and 1B showed that the absorption was the same when ferrous sulfate was given alone in study 1A and when given together with the same amount of ferrous sulfate in the same meals in study 1B (mean ratio: 0.956, \( t = 0.299 \)). This implies 1) that the absorption of iron from the nonheme-iron pool dropped by \( \approx 40\% \) (1/1.65) when ferrous sulfate was given together with ferrous bisglycinate and 2) that the percentage absorption of iron from a hypothetical chelate pool of ferrous bisglycinate was not influenced. The most obvious explanation is that some iron moved from “the ferrous bisglycinate pool” to the “maize pool,” which we know from several previous studies is uniformly labeled by the added ferrous sulfate.

All this implies that the iron absorption from ferrous sulfate given with maize in study 1A was measured correctly. However, the absorption of iron from ferrous bisglycinate in study 1A cannot be calculated because we do not know 1) how much iron moved from ferrous bisglycinate to the nonheme-iron pool in maize, and thus 2) how much iron remained in chelate form. We know from study 2A that iron in ferrous bisglycinate is less well absorbed than is ferrous sulfate when given alone. It may be assumed that ferrous bisglycinate is partly dissociated and that an unknown, but possibly considerable, amount of iron is released into the nonheme-iron pool (maize-meal pool). An absolute condition in these kinds of tracer studies is to know the specific activity of the iron.

This would imply that it is impossible to estimate the total amounts of iron absorbed. Actually, the only way to correctly analyze the isotopic exchange between an iron compound and iron in a food is by comparing iron absorption from a biosynthetically radioiron-labeled food (eg, maize) and the iron compound to be tested. An incomplete isotopic exchange between iron in another iron chelate, FeNaEDTA, and biosynthetically radioiron-labeled maize was observed by several investigators (3–5). In unpublished studies in our laboratory we found an absorption ratio of 0.58 ± 0.044 between biosynthetically radioiron-labeled maize and the iron in FeNaEDTA (n = 10). All these results suggest that a fraction of iron chelates may form a separate pool, that some iron is dissociated and exchanges with the nonheme-iron pool, and that some unknown fraction is absorbed from a kind of possible mucosal-iron pool.

An interesting part of the discussion in the present study (1) addressed the process of absorption of iron from the intestines when strong iron chelates are also present. Our assumption is that there is a pool at the intestinal mucosal surface from which iron is taken up by special nonheme-iron receptors. This mucosal pool is directly connected with the nonheme, intraluminal nonheme-iron pool. In that pool, ferric iron is probably reduced to ferrous iron to be absorbable. Iron chelates such as ferrous bisgly-
lycinate and FeNaEDTA are present initially in an iron chelate pool that is connected both with the common nonheme intraluminal pool (where an isotopic exchange may take place) and directly with the mucosal nonheme-iron pool, where its iron may be released and absorbed. In this way, iron status influences the absorption from both the iron in the chelate pool (as reported here) and the iron in the usual intraluminal nonheme-iron pool. Such a hypothesis might explain many of the seemingly contradictory results.

On the basis of our analysis of the data presented, we cannot accept the main conclusions drawn by Bovell-Benjamin et al. There is no evidence to support the conclusion that ferrous bisglycinate is useful as an iron fortificant.

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Reply to L Hallberg and L Hulthén

Dear Sir:

Hallberg and Hulthén question the interpretation of our data that showed that ferrous bisglycinate is absorbed better from whole maize than is ferrous sulfate. Specifically, they question our conclusion that there was no exchange in the intestinal pool between iron from ferrous bisglycinate and iron from ferrous sulfate.

The basis of our conclusion is that absorption of iron from ferrous sulfate and ferrous bisglycinate was the same whether the labeled forms of these compounds were given separately or mixed together in the same meal. Our data were analyzed correctly because it is appropriate to control for the repeated-measures nature of the design. Also, because a log transformation was used, in effect the absorption ratios were compared, not the absolute values. As stated in our article, the average absorption of iron from ferrous sulfate was about one-fifth that of its absorption from ferrous bisglycinate ($P < 0.0001$).

What we did not do was use the repeated-measures procedure to examine the interaction between study and iron source. We have since used that procedure and found the interaction to be significant ($P = 0.01$). It is therefore appropriate to make a comparison of iron sources between studies. This comparison showed that iron absorption from the bisglycinate was the same in each trial ($P = 0.77$, Tukey’s test) but, as noted by Hallberg and Hulthén, the absorption from ferrous sulfate differed between studies 1A and 1B ($P = 0.04$). However, the results do not support their interpretation that there is an exchange between iron from ferrous bisglycinate and the nonheme-iron pool.

If the iron from these sources had exchanged in the intestinal pool there would have been a similar trend in iron absorption from both iron sources in studies 1A and 1B. In fact, the opposite occurred. As the geometric mean absorption ratio of iron from ferrous sulfate between studies 1A and 1B dropped to 0.59, a significant difference, it increased to 1.13 for ferrous bisglycinate, which was not significant. If, as Hallberg and Hulthén suggest, the explanation is that some iron moved from the ferrous bisglycinate into the “maize pool,” which is equilibrated with the ferrous sulfate iron, less label from bisglycinate would have been absorbed in study 1B, and there would have been less of a difference between the geometric absorption means. However, the means became more separated: the ratio of absorption of iron from ferrous bisglycinate to absorption of iron from ferrous sulfate in study 1A was 3.5 and increased to 6.8 in study 1B. In addition, even if the cause of the 41% lower absorption of iron from ferrous sulfate in study 1B was dilution with iron from ferrous bisglycinate, it still could not explain this amount of divergence. Importantly, care was taken to provide the same amount of iron as sulfate or bisglycinate, or both, so that the size of the intestinal iron pool was similar in the 2 studies.

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