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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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Hunter-gatherer diets—a shore-based perspective

Dear Sir:

Cordain et al (1) estimated that Paleolithic hunter-gatherers would have consumed as much animal food as possible. I support the inclusion of fish and shellfish in Cordain et al's estimate of animal food intake because I believe that fish, shellfish, and other shore-based foods were crucial for human brain evolution (2–4). I have 2 comments about the reference values Cordain et al used for plant and animal macronutrient composition.

First, their reference macronutrient values for plant foods were 62% carbohydrate, 24% fat, and 14% protein. The list of food types for which this reference macronutrient profile was obtained did not include vegetables (*see* Table 3 of reference 1). In commonly available databases of the macronutrient contents of plant foods other than nuts and seeds, the fat content rarely seems to exceed 1% by weight. Does this imply that Cordain et al's macronutrient database does not really represent most plant foods or, alternatively, that nuts and seeds are interpreted to represent most plant foods consumed? Even if plant foods in the Paleolithic period did contain an average of 24% of energy as fat by proximate analysis, this value needs to be corrected downward by ≈30% to yield the content of actual fatty acids that are available for energy from plant material other than nuts. Was this correction made?

Second, Cordain et al emphasized the risk of protein toxicity by referring extensively to the outcome of the consumption of large amounts of meat containing <5% fat by weight. Lean muscle tissue is 2–3% fat, but animal organs other than muscle, which tend to be 5–10% fat, would also have been consumed. Body fat itself would also have been eaten. Furthermore, hominids would have faced fierce competition from carnivores for the copious amounts of meat needed to be eaten to induce protein toxicity; therefore, protein toxicity probably did not occur often, and certainly not for extended periods.

As Milton's (5) editorial points out, it makes empirical sense that foods of relatively high nutrient and energy densities would be consumed when available. However, Milton says that "Hunter-gatherers were not free to determine their diets, rather it was their predetermined biological requirements for particular nutrients that constrained their evolution. At the same time, these dietary needs apparently allowed for selection to favor increased brain size in the human lineage and the concomitant development of technologic, social, and other abilities directed at securing these nutrients" (5). Modern humans in a totally free-choice situation ultimately choose a diet that is complete in energy and nutrients. Those who cannot choose freely often develop malnutrition or specific nutrient deficiencies. Many factors, including climate, competition, and food availability would have been constraints affecting the daily or seasonal diet of hunter-gatherers; in that sense they may not have been totally free to determine their diets. However, in my view, it was the discovery of and adaptation to a high-quality shore-based diet that was a major determinant of the rate and extent of human brain evolution, not the other way around as implied by Milton (5).

We argue that the shore-based ecologic niche was uniquely able to stimulate expansion of the primate brain because, in addition to being a plentiful supply of dietary energy and protein, it

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 have been 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 hominid 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 10 000 y ago), 3 hominid genera (*Australopithecus*, *Paranthropus*, and *Homo*) that encompassed ≥ 11 separate species were simultaneously present (1). There is abundant evidence suggesting that the hominid'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 (35 000–40 000 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 250 000 y ago) and Middle (250 000–40 000 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 hominid 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 brain 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 hominid 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 archaeological 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 ω 3 fatty acids in the human liver is very active and capable of providing the high levels of long ω 3 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 hominid 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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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 must be in place before we can make recommendations to patients or to the general public. There is still more to learn about soy.

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Carlton M Colker

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 \approx 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 ISP or casein did not receive a mix of the 2 proteins. Given that only the macronutrient and isoflavone contents of the diet were quantified and that actual meat, soy, or other lipid-affecting nutrients were not evaluated, the authors' conclusions become weak. Furthermore, the conclusion that ingesting \geq 20 g ISP/d instead of animal protein for 6 wk reduces non-HDL cholesterol is both misleading and inaccurate.

In the apparent zeal of the authors to show the positive effect of small, daily servings of soy on lipid profiles, they mistakenly labeled non-HDL cholesterol. The authors state that non-HDL cholesterol equates to subtracting HDL from total cholesterol (TC), the error is within the framework of labeling non-HDL as VLDL + LDL cholesterol. Simply stated, the authors had the means to measure actual VLDL and LDL because they had measured TC, HDL, triacylglycerol, lipoprotein(a), apolipoprotein A-I, and apolipoprotein B. Thus, with all of the technical machinery available to the authors for firsthand measurement of these various lipids, 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 for the treatment of mild to moderate hypercholesterolemia

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Reply to DS Kalman and CM Colker

Dear Sir:

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 \approx 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-