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 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 fished food increase and of hunted animal food stay constant—the same conclusion we reached with our original analysis. The editorial deemphasizes 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" agriculturalists 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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## No advantage of using ferrous bisglycinate as an iron fortificant

Dear Sir:

In the June 2000 issue of the Journal, Bovell-Benjamin et al (1) compared the absorption of iron from ferrous sulfate, ferrous bisglycinate, and ferric trisglycinate added to a whole-maize meal. They concluded that iron absorption was better from ferrous bisglycinate than from ferrous sulfate or ferric trisglycinate and that ferrous bisglycinate was an effective and safe source of iron that was particularly useful as an iron fortificant in diets rich in phytate. Their other main conclusion was that iron from ferrous bisglycinate does not exchange in the intestinal nonheme-iron pool with the iron from maize or ferrous sulfate.

In comparisons of iron absorption from meals, the percentage absorption, based on tracer methodology, needs to be multiplied by the amounts of iron present in the corresponding labeled pools. Bovell-Benjamin et al concluded that iron from ferrous bisglycinate does not exchange with the iron from maize or ferrous sulfate. This conclusion was based on observations that, when the same amounts of iron as ferrous sulfate and ferrous bisglycinate were given separately together with the maize meal, iron absorption was 1.7% and 6.0%, respectively; when the same amounts of iron were added to the same maize meal, absorption of the tracers was 1.0% and 6.8%, respectively. The authors combined the mean percentage absorption in their studies 1A and 1B, which were then 1.3% and 6.4%, respectively, indicating a 4.7 times greater absorption of iron from ferrous bisglycinate ($P < 0.05$). It is not clear how the conclusion of "no exchange" was drawn between the labels in the intestinal pool in study 1B. However, because the absorption studies were done in the same subjects, the data can be analyzed in a way that is more sensitive and specific by comparing the absorption in the same subjects and not in 2 groups of subjects. The mean absorption of iron from the tracer for ferrous sulfate given alone with maize was 1.7% (study 1A); when ferrous sulfate was given together with maize and ferrous bisglycinate (study 1B) the absorption was lower (1.0%). These mean values suggest that the absorption was different in the 2 studies. When we compared more correctly the individual ratios in absorption of the ferrous sulfate tracer in studies 1A and 1B, this mean ratio was 1.653 ($t = 2.436$, $P = 0.0375$). 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, $t = -0.299$, $P = 0.77$). This implies *1*) that the absorption of iron from the nonheme-iron pool dropped by ≈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 bisg-