Genetically unknown foods or thrifty genes?

Dear Sir:

Fox et al (1), after having compared Mexican Pima Indians with non-Pima Mexicans living in the same traditional environment, concluded that their own results do not support the hypothesis that hypoleptinemia, a relatively low resting metabolic rate, or both, are expressions of the "thrifty genotype," which is believed to account for the very high prevalence of obesity and type 2 diabetes in Pima Indians living in the United States. It is surprising that Fox et al (1), in view of both their findings and the fact that "Mexican Pima Indians are extremely lean compared with their American counterparts" (1), failed to draw the most obvious conclusion, namely, the confutation of the thrifty genotype hypothesis. Such a hypothesis, based as it is on the feast-or-famine tenet, is poorly convincing (2).

In fact, the existence of thrifty genes, fostered by past famines, is difficult to reconcile with the fact that the Nauruans and other Pacific populations who are highly prone to diabetes and obesity live in the thinly populated, tropical equatorial islands where a generous food supply is available year round (2). Furthermore, how can we reconcile the past famines experienced by populations in overcrowded Europe (which additionally does not offer tropical luxuriance) with the unusually low rate of diabetes in Europeans (2)?

A unifying hypothesis was recently proposed to explain both the dramatically increased prevalence of diabetes in populations who were virtually free from it until a few decades ago and its low prevalence in Europeans. The "genetically unknown foods" hypothesis (2) suggests that the recently adopted Western habits of consuming both high-fat meals and sucrose in solid form or in solutions with concentrations >4.18 MJ/L, which represents the physiologic limit imposed by evolution, largely account for the epidemic of diabetes in newly modernized populations, including American Pima Indians. These populations, which still have the original genotype of humankind, are metabolically unable to cope with those unnatural dietary habits, for which, conversely, Europeans have achieved passable, albeit incomplete, adaptation through millenary natural selection (2).

From an evolutionary standpoint, humankind's original genotype, which still characterizes Pima Indians as well as other New World populations (2), was metabolically molded by a low-energy-density, low-fat nutritional environment, where diets containing >10–15% fat were virtually impossible for millions of years (3, 4). Although this obviously does not imply any teleologic significance (5), which is absent indeed from evolutionary processes, it does clearly suggest that primitive, low-fat diets represent axiomatically ideal diets because they virtually designed and built humankind's metabolic physiology (6). Curiously, I found that this evolutionary axiom, which is often misunderstood and even questioned (7), becomes clearer to listeners when human metabolism is compared with an engine. It is evident that a motor designed and built for a specific fuel has maximal life and performance if it works with such fuel, which thus may be considered the ideal fuel for that motor. This motor, of course, can be damaged if the wrong fuel is put in the tank (8). Similarly, humans, metabolically shaped and built by low-energy-density, low-fat diets over millions of years, can only be damaged by Western nutritional extravagance (9), with diets that have an unnaturally high energy density and an absurdly high fat content (2, 6, 8, 9).

Even though we may dismiss any teleologic significance of primitive low-fat diets (5), we nevertheless should not overlook the fact that coronary artery disease mortality is 16.7-fold greater in the United States than in rural China, where fat intake is less than half and the mean cholesterol concentration is 3.28 mmol/L (127 mg/dL) compared with 5.24 mmol/L (203 mg/dL) (9). In view of this, one can hardly seriously hypothesize that cholesterol concentrations higher than those exhibited by both hunter-gatherer populations (4) and the rural Chinese (9) may confer some survival benefit (5).

Further evidence that the responsibility for both obesity and diabetes in American Pima Indians and in other newly Westernized populations has more to do with genetically unknown foods than with putative genetic variations comes from Stubbs et al (10), who recently reported that even European subjects, despite their relative adaptation to high-energy-density diets (2), are unable to defend energy balance, and thereby gain weight after switching from an ad libitum low-energy-density diet to a high-energy-density one. This is not surprising if we bear in mind that during the first 99% or more of humankind's life on earth, when populations existed as hunter-gatherers, high-energy-density, high-fat diets were virtually nonexistent (2–4, 6) and, therefore, such diets can only be viewed as unnatural and harmful nutrition (2, 6).

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Reply to R Baschetti

Dear Sir:

Baschetti favors the "genetically unknown foods" hypothesis as an explanation for data presented in our November article comparing resting metabolic rate and plasma leptin concentrations between Mexican Pima Indians and non-Pima Mexicans (1). While we concluded that neither of these factors are expressions of the "thrifty genotype", purported to explain the high prevalence of obesity and type 2 diabetes in Pima Indians living in the United States, our findings do not disprove the "thrifty genotype" hypothesis.

The thrifty genotype hypothesis, first proposed by Neel (2), is based on the observation that susceptibility to develop type 2 diabetes appears to be genetically determined. Therefore, although currently disadvantageous, the diabetes genotype must have enhanced survival at some point in the past, thereby promoting its evolutionary selection. One of the environmental changes that has made the genotype detrimental in current times is the switch from feast and famine conditions to those of constant feasting. The ready availability of food with high energy density is proposed as a trigger to the metabolic changes leading to diabetes.

Baschetti dismisses the "thrifty genotype" explanation as poorly convincing, particularly with regard to Pacific Island populations suffering epidemic levels of type 2 diabetes, since food in that region has long been available year round. Similarly, he argues, Europeans have low rates of diabetes despite the fact they have experienced famines in the past.

We disagree with Baschetti with respect to the totality with which dietary changes explain the propensity toward diabetes. High fat diets alone do not explain the large variability in diabetes prevalence between populations. For example, Baschetti's "genetically unknown foods" hypothesis does not elucidate why Alaska Natives with their high fat diet have little diabetes (3) while the disease is rampant among the Pimas of Arizona. More likely, populations vary in the spectrum of genes that interact with the environment and determine that population's liability to type 2 diabetes.

For Pacific Island populations, explanations for the thrifty genotype have been proposed based on body size and composition. Houghton (4) hypothesized that cold, long and inhospitable oceanic voyages gave a survival advantage to those Polynesians with a large body size. A high fat-free mass would generate more heat, and a stocky frame, with a lower surface area to body mass ratio, would minimize heat loss. In contrast, Europeans appear to represent a low risk population. As suggested by Swinburn (5) the unique history of Europe may have reduced the frequency of diabetes-enhancing genes or promoted genes that protect against type 2 diabetes.

While we agree that high-fat diets rich in cholesterol contribute to the difference in coronary artery disease mortality between the US and rural China, the logic that this negates the "thrifty gene" hypothesis eludes us. Furthermore, Stubbs' data (6) that Europeans are unable to defend energy balance when provided a high-energy density diet can be readily explained by the fact that the current level of energy expenditure is insufficient to match the increased energy intake. It is not necessary to invoke the "genetically unknown foods" hypothesis to explain this finding either.

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Validation of dietary patterns assessed with a food-frequency questionnaire

Dear Sir:

In their recent article, Hu et al (1) identified dietary patterns using factor-analyzed data from food-frequency questionnaires (FFQs) and they assessed the validity of these patterns in part by examining their association with patterns identified by using factor-analyzed dietary-record data. Their use of dietary-record data to assess the validity of dietary patterns requires comment. Specifically, although dietary records are an acceptable gold standard for validating FFQs for measuring food or nutrient intake, the same strategy does not provide an equivalent validation of dietary patterns. To the extent that dietary records provide more accurate estimates of food intake, they also allow more precise estimation of factor scores than do FFQs. By conducting a factor analysis to identify dietary patterns, however, Hu et al essentially created two factor–analytically derived scales to measure intakes from Western and prudent dietary patterns, with each food or food group representing one (differentially weighted) item in each scale. Validation of FFQ-based dietary patterns against dietary-record-based patterns with use of scales derived from factor analysis based on the same food items is comparable with validation of a scale against the same scale with individual items measured more accurately. In essence, the validation strategy presumes that the item-level data are valid and uses these data rather than an independent indicator of each food pattern.

The ability to assess the validity of dietary patterns measured by factor analysis is limited by our understanding of what dietary patterns actually represent. Nutritional anthropologists have researched numerous dimensions of intake patterns—how foods are organized into dishes and dishes into meals, which foods are integral to the meal, and even the time, place, and context in which meals are eaten (2). Measuring patterns by using factor-analyzed FFQ responses assumes that patterns can be characterized adequately by food-intake frequencies and their intercorrelations. Although this method may capture enough variation in eating habits to render measurement of other dimensions unnecessary, examining dimensions of dietary patterns other than with the use of food-frequency data may provide valuable additional information in some instances. For example, effects on iron bioavailability of concurrent consumption of meats as absorption enhancers or phytates as absorption inhibitors (3) illustrate the potential importance of considering the organization of foods into meals. Whether scales derived from factor analysis based on food frequencies alone are acceptably valid measures of actual dietary patterns, therefore, remains to be evaluated. Identifying a more appropriate gold standard for validation will require a more complete conception of what the Western and prudent dietary patterns actually are. Indeed, the greater challenge may be to gain a more complete a priori understanding of dietary patterns before trying to measure them, thus raising the possibility of measuring dietary patterns directly rather than relying on ad hoc interpretations of dietary data.

Hu et al's analysis does provide evidence of food groupings that might have been anticipated a priori. The finding of similar patterns across methods also provides evidence of the reproducibility of their approach. As such, their evaluation showed that FFQs can be a useful and convenient source of dietary data for measuring dietary patterns, even though they were not originally intended for dietary-pattern measurement.

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Reply to M Tseng

Dear Sir:

We thank Tseng for her interest in our paper on validation studies of dietary patterns assessed with a food-frequency questionnaire (1). We agree that there is no gold standard for assessing dietary patterns. Nevertheless, the consistency of major dietary patterns assessed with food-frequency questionnaires and multiple, weekly dietary records suggests the usefulness of factor-analytic approaches for assessing dietary patterns. More importantly, dietary patterns were reasonably correlated with plasma biochemical measures of cardiovascular disease and nutrient intakes, further suggesting the validity of the method. The ultimate test of validity, however, lies in whether dietary patterns can independently predict disease outcomes. Analyses are underway to examine the relation between major dietary patterns assessed with food-frequency questionnaires and the incidence of cardiovascular disease.

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Very-low-fat diets do not necessarily promote small, dense LDL particles

Dear Sir:

Dreon et al (1) concluded that "There is no apparent lipoprotein benefit of reduction in dietary fat from 20–24% to 10% in men with large LDL particles…." They also suggest that switching from an average American diet to a very-low-fat diet "in a subset of men who convert to phenotype B, [is] suggestive of an increase in coronary disease risk." However, Ornish et al (2) observed regression of atherosclerosis in subjects consuming a very-low-fat (VLF) diet even though their serum triacylglycerol concentrations increased and their HDL-cholesterol concentrations decreased (lipoprotein changes often associated with an increase in small dense LDL particles, also known as pheno- type B or pattern B). In contrast, Ornish et al (2) observed the progression of atherosclerosis in subjects consuming a more moderate-fat diet, even in those subjects who were taking cholesterol-lowering drugs. Many years ago, Morrison (3) showed a dramatic reduction in both cardiovascular disease and in all-cause mortality in subjects consuming a VLF diet compared with those consuming an average American diet. We know of no comparable clinical trials showing that diets with ≥20–30% of energy as fat lead to regression of atherosclerosis, a reduction in all-cause mortality, or both. Should suggestive evidence from Dreon et al's short-term trial outweigh evidence from these much longer clinical trials with harder endpoints (eg, overall mortality and cardiovascular disease mortality)?

There is little doubt that pattern B is associated with an increased risk of atherosclerosis in people who eat a moderate-to-high-fat diet. But what is the evidence that a change in LDL status from pattern A to pattern B as a result of restricting dietary fat promotes atherosclerosis?

A low HDL-cholesterol concentration is associated with an increased risk of ischemic heart disease (IHD), and restriction of dietary fat generally leads to a drop in HDL cholesterol. However, in countries where VLF diets are the norm, the incidence of IHD is much lower than in the United States, despite significantly lower HDL-cholesterol concentrations. In hamsters, it was shown that reverse cholesterol transport is not impaired by fat restriction despite a nearly 50% reduction in HDL (4). Perhaps there are other metabolic changes associated with the change to pattern B when fat is restricted that reduce the risk of atherogenesis when a VLF diet is consumed? For example, Parks et al (5) showed a significant reduction in the susceptibility of LDL to oxidation in subjects consuming a diet containing 10% of energy as fat (10%-fat diet) even though there was little change in LDL particle size.

In addition, it would be incorrect to generalize from Dreon et al's results and conclude that all VLF diets inevitably lead to an increased number of small, dense LDL particles (pattern B). Indeed, at the Pritikin Center we found that the LDL status of 6 of 22 subjects actually changed from pattern B to pattern A (a predominance of large LDL particles) while consuming a VLF diet, which is the exact opposite of the trend observed by Dreon et al (6). There are several possible factors that may have contributed to the opposite trends observed during the 2 diets, even though both provided ≈10% of energy as fat. One reason we saw a trend away from pattern B at the Pritikin Center is exercise. Exercise tends to raise HDLs and lower triacylglycerols and thus may also reduce the predominance of small, dense LDL particles. However, there are 3 possible differences between Dreon et al's 10%-fat diet and the 10%-fat diet we used or in the way the diets were fed that might explain the opposite trends observed.

1) Dreon et al's higher-fat diet actually had 50% more fiber than their 10%-fat diet, but our 10%-fat diet had much more fiber than either of Dreon et al's diets. Because dietary fiber improves blood lipids (7) and most high-fat foods are low in fiber, it seems odd that the higher-fat diet of Dreon et al would contain more fiber than their 10%-fat diet. The unusually low-fiber content of Dreon et al's VLF diet would also have biased their results against the VLF diet.
2) Those who advocate a VLF diet to treat and prevent IHD generally recommend a high fiber intake and a reduction in dietary cholesterol and animal protein. However, Dreon et al's VLF diet not only had less fiber but also had at least as much cholesterol (and presumably animal protein) as their more moderate-fat diet. Again, these differences would tend to reduce the efficacy of Dreon et al's VLF diet for treating dyslipidemia compared with the kind of VLF diets typically advocated for the treatment and prevention of IHD.
3) Finally, those who advocate VLF diets also generally recommend that they be consumed ad libitum. As Dreon et al noted, "…the tendency for ad libitum consumption of low-fat diets to promote weight loss need[s] to be considered." Why was it not considered in their experimental design? This is important because extra energy and an increased body weight increase the size of small, dense LDL particles (8). Indeed, Dreon et al's data showed that their subjects actually consumed 14% more energy with the VLF diet than with their usual diet. Would not the extra 1548 kJ/d (370 kcal/d) provided by Dreon et al's VLF diet than by their moderate-fat diet have caused more adverse effects on blood lipids and again biased the results against the VLF diet? It has been shown that the presumably adverse metabolic effects on blood lipids associated with VLF diets compared with higher-fat diets largely disappear when both diets are fed ad libitum rather than isoenergetically (9). Few people adhere long term to diets with a prescribed energy level that differs significantly from what their appetite demands (10), which makes the results of short-term studies with a controlled energy intake of limited clinical value.

If the point of Dreon et al's study is that a VLF, energy-dense, low-fiber diet consisting largely of refined sugars and white flour is of questionable value for many, if not most, normolipidemic individuals, we agree. However, if Dreon et al believe that their data show that a more vegetarian, high-fiber, VLF diet is likely to increase atherosclerosis and IHD in normolipidemic individuals relative to an average American diet, we disagree. The peculiar nature of the VLF diet used in Dreon et al's study coupled with the fact that it provided a higher energy intake than the subjects' usual diet make it inappropriate to suggest or imply that all VLF diets promote pattern B, an increased risk of IHD, or both.

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Reply to JJ Kenney et al

Dear Sir:

Kenney et al allude to studies in which there was apparent clinical benefit of programs incorporating very-low-fat diets for the management of coronary artery disease. A recent scientific advisory statement by the American Heart Association Nutrition Committee addressed the current evidence for effects of very-low-fat diets on heart disease risk (1). The statement points out that there are not adequate grounds for ascribing these effects to low fat intake per se, because, as pointed out by Kenney et al, these effects are generally accompanied by other potentially healthful behavioral and dietary changes (2, 3). Moreover, the clinical benefits of these programs have been evaluated either principally or exclusively in groups of patients with preexisting coronary artery disease, many of whom have had abnormal lipoprotein profiles (1–3).

We specifically selected a group of healthy men who, in previous studies, had maintained a normal lipid profile with predominantly large LDL particles (pattern A) while consuming diets containing 20–24% of energy as fat (4). The question that our study addressed was whether a diet with further short-term reductions in total fat intake, with substitution of carbohydrates, and with a total energy intake aimed at maintaining stable body weight, would confer favorable lipoprotein changes or result in a metabolic response leading to a shift to smaller LDL particles (pattern B) as we had observed in subsets of men switched from high-fat to lower-fat diets in previous studies (4, 5). Our findings, therefore, specifically relate to effects of very-low-fat, high-carbohydrate diets on lipoprotein profiles of men whose lipoprotein profiles suggest a low risk of cardiovascular disease. Although the average reported energy intakes of our subjects while consuming their usual diets were lower than those prescribed for the test diet, we observed no weight increases during the study and therefore ascribe the findings to underestimates of energy intake, which are commonly observed with data from food intake records.

As we pointed out, our findings did not address the potential benefits of such diets in men with metabolic traits indicating a higher risk of coronary artery disease (eg, elevated concentrations of total LDLs or LDL pattern B). Indeed, our earlier studies, as well as those of others (6), indicate that these higher-risk individuals, such as those with coronary disease studied by Ornish et al (2), tend to have greater benefits on lipoprotein profiles as a result of dietary fat restriction than do those with normal or low-risk lipoprotein profiles.

We strongly support the recommendation, as described elsewhere (7), that an overall dietary program to reduce cardiovascular risk should emphasize the intake of vegetables, fruit, and whole grains, incorporating an overall energy balance aimed at maintaining a healthy body weight. In this regard, our study was not designed to test these multiple components of an overall dietary program, but to isolate, as effectively as possible, the effects of reduced fat intakes and increased carbohydrate intakes. Although the experimental diet fell short of maintaining basal intakes of fiber and had a high content of simple sugars, our findings may have relevance to those in the population who achieve lower fat intakes by increasing their consumption of prepared low-fat foods with low fiber and high sugar contents and who do not succeed in reducing their total energy intakes. We are planning further studies that address to what extent our findings can be extended to other forms of dietary fat restriction, including diets with a high whole-grain content and in which energy intakes are ad libitum.

We believe that it is not necessary to reiterate that very-low-fat diets do not necessarily promote a pattern B lipid profile. In fact, as stated in our paper, we estimate that ≈33% of healthy American men do not express a pattern B lipid profile, even when consuming very-low-fat diets. We also emphasize that in deliberately maintaining stable body weights, we did not address the potential effects of weight reduction (with or without increased exercise) on cardiovascular metabolic risk factors and, in particular, the potential for attenuating or eliminating the adverse changes found in a subset of men whose LDL profile changed from pattern A to pattern B in the present study.

It is also not known to what extent our results may have differed with longer-term consumption of low-fat diets. Noteworthy, however, is that in at least one population with habitual fat consumption lower than that in the average American diet, peak LDL particle size

is also smaller (8), in a manner consistent with the predictions based on our short-term feeding studies. Because coronary artery disease risk in these populations is not high, we conclude, as did others (9), that a preponderance of small LDL particles (pattern B) may not confer increased coronary artery disease risk in the absence of elevated concentrations of these or other atherogenic lipoproteins.

We also note that the results of our short-term dietary challenge, while useful in identifying metabolic heterogeneity in the population, cannot yet be extrapolated to clinical outcomes (4). However, on the basis of the strong and well-established relations of lipoproteins to coronary artery disease risk, we feel that our results raise the important possibility that subsets of the healthy population, particularly those with normal lipid metabolic profiles, may not benefit from extreme dietary fat restriction and may even experience lipoprotein changes that would be expected to increase their risk of coronary artery disease.

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Erratum

Monsen ER. The ironies of iron. Am J Clin Nutr 1999;69:831–2.

On page 831, column 2, paragraph 4, sentence 1 should read as follows:

> Overall, however, the study, which was conducted at the US Department of Agriculture Grand Forks Human Nutrition Research Center, Grand Forks, ND, was well controlled.