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 axiomatic 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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REFERENCES

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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**REFERENCES**