High-protein diet, obesity, and the environment

Dear Sir:

Weigle et al (1) raise the intriguing question of whether high-protein diets are useful in preventing and treating excess body fat—a clinical issue that affects more than one billion people. They showed that a high protein intake reduces body weight by increasing satiety. Their study, together with the editorial by Astrup (2), raises the question of whether high-protein diets should be promoted in large numbers of people, particularly given the high protein intake typical of Western diets. Suffice it to note that the current estimated protein intake in the United States is already more than double the recommended amount (3). As a matter of fact, the human species is omnivorous and has developed very efficient adaptive physiologic mechanisms for fuel utilization, notwithstanding the feast or famine pendulum and that meat constituted the staple diet of our pre-Neolithic ancestors (4).

However, a meat-based diet—which has a high protein content—is largely less environmentally sustainable than is a vegetarian-based diet nowadays (5). A meat-based diet had little effect when the world's population numbered only a few million, unlike today when more than 6 billion individuals are competing for resources. Furthermore, a high-protein diet may have untoward effects, for example, on calcium and bone metabolism (6, 7).

In conclusion, the findings reported by Weigle et al confirm some basic physiologic concepts of human nutrition; a high-protein diet can have untoward effects, may be difficult to adhere to, and, most importantly, is not environmentally sustainable. Thus, caution should be exercised in applying the findings of Weigle et al in the clinical setting.

Neither author had a conflict of interest.

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Reply to F Contaldo and F Pasanisi

Dear Sir:

Contaldo and Pasinisi raise important questions about whether increases in the protein content of the diet should be recommended for the prevention and treatment of obesity. In my editorial I mainly addressed the potential health benefits of increasing the proportion of dietary energy provided by protein at the expense of a reduction in fat and carbohydrate sources that are less satiating. I can only agree that many other issues need to be taken into account, such as safety aspects, economy, and environmental issues, before such recommendations should be made.

In no way do I wish to suggest that overweight and obesity are "protein-deficiency conditions," but increasing the proportion of protein in the diet may be one way to attenuate the obesity problem in a sedentary population and, thereby, to help reduce many of the obesity-associated comorbidities. Current evidence from experimental and intervention studies suggests that an increase in the amount of energy provided by protein from the current 15–18% in most diets to 20–35% is associated with a spontaneous reduction in total energy intake and a weight loss of relevance for obese and diabetic subjects (1–4).

Contaldo and Pasinisi note that many individuals already consume high amounts of protein. It is obviously correct that even if a diet providing only 10% of calories from protein is consumed, it is still possible to get high amounts of protein if the total amount of calories consumed is high. However, evidence suggests that it is not just the absolute amount of protein (grams per day) consumed that is important, but that a high proportion of energy (% of calories) from protein is what results in a reduction in total caloric intake (1). Consequently, a high-protein diet may actually reduce the total amount of protein eaten, which is a highly relevant issue to be addressed in light of safety and environmental corollaries. Using data from the study by Due et al (1), I will provide an example to support the supposition that a high-protein diet does not necessarily result in an increase in total protein intake. An average obese individual has an energy requirement of 2500 kcal/d, which is provided by a diet in which 18% of the calories (or 107 g) come from protein. During the first 3 mo that the subjects consumed a high-protein diet providing 25% of calories from protein, the fat loss was consistent with an energy deficit of 700 kcal/d. Because energy requirements due to the

weight loss decreased by ≈100 kcal/d, the energy intake would have been ≈1700 kcal/d, of which 25% of energy (or 101 g) was protein.

Most experimental studies suggest that the replacement of some carbohydrate with protein has a neutral or even positive influence on inflammation and on risk factors for type 2 diabetes, cardiovascular disease, and osteoporosis (2–7). The increased protein content of the diet will normally be based on shellfish, fish, poultry, game, lean pork and beef, low-fat dairy products, lentils, and beans. However, our knowledge about the health effects of lean meat and dairy products is still limited. Whereas low-fat dairy products may be beneficial for preventing obesity, the metabolic syndrome, type 2 diabetes (8), and cardiovascular disease, there is concern that this food group may play a role in certain cancers. Similarly, processed meat may increase the risk of type 2 diabetes (9). Even so, on the basis of the available evidence, I find it difficult to warn individuals who will benefit from weight loss against replacing some of the less-nutritious carbohydrate with protein.

However, there are many aspects of high-protein diets that need to be addressed. We are currently running a large dietary intervention study (DiOGenes: Diet, Obesity and Genes) to identify the diet that is most effective for protecting against weight gain and weight regain in a susceptible population of obese and overweight individuals and their overweight children (10). This 6–12-mo dietary intervention will investigate the effect of different dietary components (high and normal protein contents and high- and low-glycemic-index carbohydrates) on weight-loss maintenance in 350 families in 8 European research centers. In particular, the safety and tolerability of high-protein diets in children will be addressed. Such a study would not have been initiated unless there was a need for more evidence before a higher-protein diet can be more widely recommended for weight control.

The author had no conflict of interest related to the topic of this letter.

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Reply to F Contaldo and F Pasanisi

Dear Sir:

Contaldo and Pasanisi offer thoughtful insights into the current global obesity epidemic in regard to food sustainability and the efficacy and health effects of diets high in protein. We acknowledge the complexity of the environmental issues related to the depletion of resources and population growth as well as the social and cultural implications driving food intake and physical activity.

A goal of our study design (1) was to examine the role of protein in body weight regulation. The study diets were created to measure a difference between a moderate-protein diet (15% of energy) and a high-protein diet (30% of energy). The protein foods used in the diets were obtained from both animal and vegetable sources to offer variety and appeal to a diverse population; our experience with study subjects indicates that a diet containing a wide variety of foods is essential for compliance. Our biggest challenge was to keep the fat content of the diet at 20% of energy while we increased the protein content and kept the carbohydrate content constant. To this end we used fat-free and low-fat dairy foods, egg whites, soy protein, and lean meats.

We appreciate the concerns of Contaldo and Pasanisi about the health effects of high-protein diets in regard to calcium and bone metabolism. We concluded in our article that it is essential to study the effects of protein-rich diets on renal function and calcium balance before recommending a high-protein diet for weight loss for the population at large (1). Perhaps the DiOGenes (Diet, Obesity, and Genes) trial described in Astrup's editorial (2) will begin to provide these answers.

We hereby affirm that none of the authors had a financial, employment, or promotional conflict of interest relevant to the submission of this letter.

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Assessment of biomarker selection in selenium-deficiency disease

Dear Sir:

Setting a standard for selenium status evaluation can be vexing. For example, in a recent article in the Journal, Xia et al (1) concluded that the use of glutathione peroxidase as an index of selenium status may not be appropriate. They found that full expression of selenoprotein P (SeP) requires a greater selenium dietary exposure than does full expression of plasma glutathione peroxidase activity. This implies that SeP is a better indicator of selenium nutritional status than is glutathione peroxidase (1). SeP is the transporter of selenium in serum (2, 3) and plays important roles in selenium tissue regulation (4–6). However, from the perspective of selenium-related disease assessments, even changes in SeP concentrations may not be useful. A low selenium status obtained with the use of glutathione peroxidase or SeP as indicators in clinical trials did not clearly predict Keshan disease in selenium-deficienct areas in China (7). Because SeP is more sensitive to selenium depletion than are other selenoproteins, it may be too sensitive for use as a standard. Turnover rates differ among selenoproteins (8, 9), which suggests that the regulating mechanisms also differ (10); in some tissues, the mechanisms of selenium use can be differentially sustained during dietary selenium depletion (11). Thus, evidence of selenium deficiency according to an arbitrary standard does not necessarily lead to a clinical prediction, even though the activity of a given selenium-containing enzyme may be reduced. Thus, the evaluation is less robust if it is based on only one criterion. Practical experience also showed that the assessment of selenium status should be carried out separately for different tissues (12). Adoption of SeP as the principal standard for selenium status evaluation does not adequately focus on the clinical specificities of different selenium-responsive diseases. In summary, biomarkers should be selected to match the characteristics of different selenium-responsive diseases.

The author had no conflicts of interest.

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Reply to XL Wang

Dear Sir:

Wang raises the issue of which criteria should be used to determine the selenium requirement and argues that selenoprotein P might not be the best biomarker for this assessment. Considerable controversy exists over the selenium intake needed for optimal health, as indicated by Wang, and a framework for discussion of this topic is needed.

Many years ago, Keshan disease was shown by Chinese investigators to be a disease that required selenium deficiency for its occurrence (1). It was not reported from locations where selenium intakes were $\geq$17 μg/d (2). Assertions have been made that other pathological conditions are related to selenium deficiency, but, so far, evidence for this remains circumstantial. Thus, available evidence supports the hypothesis that a selenium intake $\approx$20 μg/d is required to prevent Keshan disease, the only known selenium-deficiency disease.

Inferences that much higher selenium intakes protect against cardiovascular disease and cancer have been drawn from results of epidemiologic studies. Intervention trials are needed (and some are underway) to assess these claims and to determine whether these high-selenium supplements are safe (3). This is an area of research that is active and important. At present, however, the data available are largely observational and do not allow firm recommendations for selenium intake.

Our study addressed the use of selenium biomarkers to assess selenium nutritional status (4). It is generally accepted that selenium exerts its biological actions through selenoproteins. Selenoproteins subserve many biochemical functions and are essential for life. As Wang points out, a hierarchy of the selenoproteins exists, and some are maintained better than others as the selenium supply diminishes (5). It appears that the selenoproteins most essential for life have higher positions in the hierarchy than do those that are less essential. Thus, the ideal biomarker by which to assess full expression of all selenoproteins would be the selenoprotein with the lowest position in the hierarchy. In studies conducted in rats, liver glutathione peroxidase appears to occupy the lowest position in the hierarchy and is therefore the ideal biomarker in that species (6).

Only a few selenoproteins are easily accessible for measurement in humans, and liver glutathione peroxidase is not among them. Plasma (or serum) contains 2 selenoproteins—glutathione peroxidase 3 and selenoprotein P—that are readily accessible and easy to measure, and that is why we compared those 2 selenoproteins. Our study showed that selenoprotein P was lower in the hierarchy of

selenoproteins than was plasma glutathione peroxidase. Therefore, we concluded that selenoprotein P was a better biomarker for whole-body selenoprotein expression than was plasma glutathione peroxidase.

Two approaches are being used to determine the selenium nutritional requirement. One approach is disease-related and will require intervention trials to determine the selenium intake needed to prevent pathological conditions and ensure optimal health. At present, this approach supports an intake of ≈20 μg selenium/d to protect against Keshan disease. Intervention trials are being carried out to determine the effect of higher selenium supplements, and they may lead to an increase in this recommendation.

The second approach is the use of biomarkers for selenoproteins to assess the full expression of selenoproteins in the body. This approach was used in 2000 by the Institute of Medicine to support a dietary reference intake of 55 μg selenium/d, which is based on plasma glutathione peroxidase activity (7). The same glutathione peroxidase results were used by a Chinese panel to set a dietary reference intake of 50 μg selenium/d (8). When adequate data on optimization of selenoprotein P by selenium intake are available, the current recommendations will likely require an upward revision.

None of the authors had any conflict of interest.

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Do unsaturated fatty acids function as endogenous antibacterial and antiviral molecules?

Dear Sir:

The recent study in the Journal by Merchant et al (1) that showed that higher intakes of α-linolenic and *cis*-linoleic acids (ALA and LA, respectively) and fish may reduce the risk pneumonia is interesting but not surprising. Previously, I proposed that long-chain polyunsaturated fatty acids (LCPUFAs), such as γ-linolenic acid (GLA), dihomo-GLA (DGLA), arachidonic acid (AA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), may behave as endogenous antibacterial, antifungal, antiviral, and immunostimulating agents (2).

Kodicek (3) showed that both LA and ALA have a bacteriostatic effect on gram-positive and gram-negative bacteria. Lacey and Lord (4) observed that cultures of *Staphylococcus aureus* seeded onto human skin were rapidly killed after the skin was covered with ALA and suggested that ALA had all the attributes of an ideal antibacterial agent. A variety of bacteria were found to be sensitive to the growth-inhibitory actions of LA and ALA in vitro (5). Hydrolyzed linseed oil, which contains 52% ALA and pure LA, killed methicillin-resistant *Staphylococcus aureus* (6). Both LA and AA inactivated animal herpes, influenza, Sendai, and Sindbis viruses within minutes of contact (7). The oral administration of LA as safflower oil (which contains 76% LA) produced the remission of mycosis fungoides, a rare skin disease of viral etiology, in dogs; the remission correlated with an increase in plasma LA and AA concentrations (8). AA, EPA, and DHA induced the death of *Plasmodium falciparum* both in vitro and in vivo (reviewed in 9). Furthermore, both prostaglandin E_1 and prostaglandin A, which are derived from DGLA, AA, and EPA, inhibit viral replication and behave as antiviral compounds (10, 11). These observations suggest that both LCPUFAs and their products have antibacterial, antifungal, and antiviral actions. Both lymphocytes and macrophages contain significant amounts of LCPUFAs and are capable of releasing them with the appropriate stimulation. In addition, LCPUFAs stimulate NADPH-dependent superoxide production by macrophages, neutrophils, and lymphocytes, which is capable of killing the invading microorganisms (12). In view of these evidences, it is reasonable to believe that an increased intake of LA, ALA, EPA, and DHA protects against or reduces the risk of pneumonia.

Recent studies showed that AA, EPA, and DHA could give rise to antiinflammatory compounds such as lipoxins and resolvins, which are essential for the limitation and resolution of inflammation (13). These studies imply that a deficiency of lipoxins and resolvins could lead to the perpetuation of inflammation and tissue damage.

In light of these facts, it will be interesting to study whether a subclinical deficiency of LCPUFAs and a decreased formation of lipoxins and resolvins occurs in subjects who develop various types of pneumonia and its complications. Because LCPUFAs can inactivate enveloped viruses, including influenza (7), it is probably worthwhile to study the effect of various fatty acids on the bird flu virus and, if the fatty acids do inactivate the bird flu virus, to study whether increased intake of these fatty acids could reduce the risk of flu.

The author had no conflict of interest.

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