Efficacy of antiobesity therapies

Dear Sir:

In your June editorial, “Is Blockade of Pancreatic Lipase the Answer?” (1), you suggest that the success of the 2-y clinical trials of orlistat is diminished by the propensity of obese patients to regain weight. I disagree.

The North American Association for the Study of Obesity (NAASO) considers a weight loss of ≥5% to be clinically significant (2). In each of the published clinical trials of orlistat, the average weight loss for orlistat-treated patients at the end of the treatment period met or exceeded these guidelines.

The efficacy of antiobesity therapies must also be measured by evaluating outcomes other than weight loss. These include positive changes in serum lipids, blood pressure, fasting insulin concentrations, and glycemic control (3, 4). The clinical efficacy of orlistat is greatly enhanced by its effects on these outcomes.

As with other treatments for chronic illness, however, efficacy also demands patient compliance with prescribed treatment regimens. The fact that some patients outside the clinical trial environment may have less behavior-modification reinforcement than is provided by a controlled clinical setting should not undermine the potential benefits of orlistat to patients who are motivated to succeed.

In addition, you failed to acknowledge the intrinsic design of the study as a weight-regain study rather than a weight-loss study. The editorial suggests that the benefits of weight reduction may be erased over time. Yet, in the same issue of the Journal, Hill et al (5) present data showing that orlistat is significantly more effective than placebo in preventing weight regain.

Patients were prescribed a diet of higher energy value to ensure weight maintenance and those who gained weight were asked to maintain the higher weight. Despite the introduction of this bias, after 1 y of treatment with orlistat, nearly one-quarter of patients gained no weight at all or continued to lose weight (5). It is imperative to consider the intention of the initial study design when critiquing the findings of a study.

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REFERENCES

Benefits and risks of antiobesity agents

Dear Sir:

After successful weight loss, long-term weight maintenance is difficult and often not successful (1). Whereas recent studies (1, 2) indicate that long-term weight maintenance after very-low-energy diets that induce losses of >20 kg is better than after hypoenergetic diets that induce weight losses of ≤13 kg (3), <30% of successful weight losers maintain a weight loss of >10% of initial weight at 5 y (1, 2). The available data clearly indicate that we need more effective approaches to enable obese individuals to make the lifestyle changes required to successfully maintain a healthier weight long term.

In controlled clinical trials, adjunctive drug therapies, are accompanied by significantly greater weight losses (4–7) and significantly better weight maintenance (5, 6, 8) than placebo. The editorial by Halsted (9) suggests that the long-term safety of orlistat is not well established. However, 4 published trials of orlistat in nearly 4000 patients established orlistat as the medication with the longest and largest database of any antiobesity drug (5–8). In addition, antiobesity agents facilitate long-term weight maintenance and lifestyle changes such as a lower fat intake (10), intake of more vegetables and fruit (1, 2, 10), and more physical activity (10); the benefits may far outweigh the potential risks. Emerging data indicate that maintenance of significant weight loss is accompanied by significant improvement in blood pressure (11), serum lipids (11), and glycemic control in diabetes (12). Maintaining even modest amounts of weight loss significantly decreases the risk of developing coronary artery disease (14) and modest weight loss significantly reduces atherogenic risk factors (11–13).

Michael H Davidson
The value of orlistat for weight maintenance has been documented (5, 6, 8) as follows: 1) at 2 y of follow-up, 19% of orlistat-treated and 8% of placebo-treated subjects maintain a weight loss of 10% of initial body weight, and 2) weight regain at 1 and 2 y in orlistat-treated subjects is less than half that of placebo-treated subjects (15). Sustaining weight reductions of this magnitude is associated with significant reductions in cardiovascular disease risk factors. In addition, enabling persons to maintain lower weights is usually associated with improved lifestyles (ie, decreased fat intake). Because the side effects related to orlistat use are exaggerated with high fat intakes, it seems likely that orlistat use will have adjunctive value in decreasing fat intake (15). Thus, in our assessment, the potential benefits of orlistat use as an adjunct to weight maintenance exceed the hypothetical risks.

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Blockade of pancreatic lipase

Dear Sir:

Despite the fact that Xenical (orlistat; Hoffmann–La Roche, Nutley, NJ) has been evaluated in >17000 individuals worldwide, and is now being prescribed to >100000 patients, you (1) question the safety of pancreatic lipase blockade in the treatment of obesity. In doing so, you contradict the findings of the Journal’s invited editorial writer (2)—a fellow gastroenterologist who, after careful review of the submitted scientific article and several previously published clinical trials, failed to identify a safety risk secondary to fat malabsorption when orlistat is used as directed. Similarly, your stance runs counter to decisions by the Food and Drug Administration and drug control authorities in many other nations to approve orlistat for prolonged use.

That the safety and efficacy of obesity medications are held to a higher standard of proof than that applied to other drugs used for treating chronic conditions is perplexing. In particular, I question why the Editor-in-Chief has not cited medica-
tions with known adverse effects on the gastrointestinal tract, eg, insulin sensitizers for the treatment of diabetes and antiinflammatory drugs for the treatment of arthritis, to name only 2. Clinical trials for drugs such as these typically run for just a few months.

No obesity medication approved for prolonged use has resulted in death or organ failure, even in instances of voluntary recall. For editorializing of this kind to thus be credible, the standard of evidence for doubt must exceed that used to establish safety. It took but a brief review of Moran et al’s (3) article to dismiss it as a rationale for questioning orlistat’s safety in obesity treatment. Perhaps a more pertinent study would be one that investigates why editors feel compelled to challenge not only the management of obesity but the very existence of the disease itself (4–7).

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Reply to MH Davidson, JW Anderson, EC Konz, and GL Blackburn

Davidson points out that the achievements of the orlistat trials must be weighed within the context of each experiment. I agree. Yet in the JAMA trial in which he is lead author, only a 3% difference in percentage of initial weight lost over 1 y separated the orlistat group (10%) and the placebo group (7%). This difference was produced under experimental conditions of high-intensity (monthly or less) dietary education and surveillance of all subjects, a procedure that goes beyond the typical standard of care for obesity management in most medical practices (1). In the trial published in the Journal (2), the bias was in selection of subjects who already had proven their ability to lose weight with diet restriction; diets were then prescribed for the 1-y drug trial that met the realistic conditions required to maintain metabolic balance according to each subject’s individual needs.

In response to Davidson as well as to Anderson and Konz, the central point of my editorial remains (3). Specifically, if 24% of subjects in the trial published in this journal either stabilized or continued to lose weight while receiving 120 mg orlistat 3 times daily, the overwhelming majority, 76%, regained weight despite this—hardly a ringing endorsement of the drug (2). Whether long-term use of orlistat will have a salutary effect on lifestyle is purely conjectural.

Blackburn objects to my notes of caution on the long-term safety of orlistat, yet many of his arguments reinforce my points. First, the available drug trials are of relatively short duration compared with the long-term use that doubtless will be made of orlistat by a target population of predominantly pre- and postmenopausal obese women already at risk for bone depletion. It is hardly likely that orlistat will be “used as directed,” because a cursory Internet search identifies > 4000 web sites from which orlistat can be purchased without a physician evaluation, personal prescription, or physician surveillance. Albeit an imperfect simile, the cited study on bone disease associated with long-term steatorrhea in chronic pancreatitis provides a cautionary model for the potential risks of iatrogenic orlistat-induced pancreatic insufficiency and steatorrhea (4). Second, nonsteroidal antiinflammatory drugs for arthritis treatment provide an excellent example of a class of drugs for which a very common side effect—unexpected and potentially life-threatening gastrointestinal bleeding—only became apparent after millions of prescriptions were filled and patients took the medication for many years (5). Third, I would be remiss in my editorial responsibilities if I failed to question the opinions of my colleagues, whether or not they carry the same specialty editorial responsibilities if I failed to question the opinions of my colleagues, whether or not they carry the same specialty

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Orlistat and weight loss

Dear Sir:

The welcome article by Hill et al (1) appears at first blush to be merely one small step removed from the still conventional notion that restricting energy intake well below that needed for satiety will yield long-term weight control. After all, Hill et al used fairly severe energy restriction (4180 kJ/d below estimated energy requirements) throughout the 6-mo lead-in period. Closer examination of the study, however, shows that it may actually represent 2 conceptual leaps that promise to advance the field of weight control.

The first advance is the use of a clinical strategy that honors the growing literature on the role of the gut in satiety. Recent empirical findings suggest that satiety is influenced by the nature of the energy ingested (2) and by the form in which the energy is found (3). Such evidence suggests that much of the variance in satiety can be explained by activities in the gut rather than in the brain. Hill et al showed that the use of a lipase inhibitor to reduce fat absorption to 19–22% of absorbed energy results in a daily energy deficit of 544–774 KJ/d (130–185 kcal/d) compared with placebo. The consistently lower weight regain associated with continued orlistat use suggests that the brain was unable to compensate fully for the 30% of fat energy not absorbed during the 1 y of orlistat use.

Although impressive conceptually, this new gut-level pharmacologic strategy appears to yield a modest practical benefit (only 1.3 kg more sustained weight loss than placebo), possibly obtained at some risk of long-term harm and at relatively great cost. The full power of potential nonpharmacologic, alternative approaches to weight control has yet to be evaluated experimentally. Retrospective results of the observational study, the National Weight Control Registry (NWCR) (which Hill originated with Rena Wing), however, showed that a 30-kg weight loss could be maintained for ≥ 5 y by including not only a fat intake 30% lower than that of the average American (≈24% of energy from fat) but also a diet substantially higher in nutrient density (4). Shick et al (5) inferred from the increased nutrient density that the NWCR weight-loss maintenance diet was relatively high in fruit, vegetables, and fiber. A concurrent finding from this same study
suggested that long-term maintenance of weight loss requires unusually high levels of physical activity (equivalent to walking 45 km/wk). But proportional reductions in these recommended lifestyle choices still produce measurable long-term weight-control benefits in less-selected US adults: eating a lower-fat diet somewhat higher in fruit, vegetables, and fiber and engaging in as little as 4 h of moderate physical activity per week (6).

The second conceptual advance is the illustration that effective, short-term, temporary shaping of qualitative food choices can influence long-term behavioral success at reducing excess energy intake. Hill et al observed that patients taking orlistat early in the trial quickly learned not to exceed the recommended fat intake if they wanted to avoid unpleasant gastrointestinal events. Nearly all (95%) patients assigned to the orlistat condition reported unpleasant gastrointestinal events early in the trial but quickly learned how to avoid such events. Hill et al’s Figure 3 appears to show that the orlistat group decreased their dietary fat intake 5-fold more than did the placebo group, from week 2 of orlistat therapy to 1 y of follow-up. Is this sharper decline significant? If so, might it not be reasonably conjectured that orlistat serves as a behavioral analogue to antabuse by making dietary relapses back to high-fat meals unpleasant? This inadvertent aversive therapy effect could help to explain why, in the European orlistat trial (7), taking patients off orlistat during the second year did not impair the weight-control advantage obtained while receiving orlistat during year 1. This result suggests that orlistat therapy could be withdrawn after 1 y with only a partial return of the fat absorption level observed at baseline.

These important conceptual advances, if confirmed, should stimulate increased behavioral research on how qualitative differences in foods relate to variations in satiety and how best to motivate the eating of high-satiety foods. When obtained in minimally processed, natural foods, the constituents water and fiber hold particular promise for contributing to satiety (8). Such issues as meal frequency and starch resistance (9) have yet to be investigated thoroughly with respect to long-term weight control. Finally, there has been remarkably little research on the potential for daily physical activity to influence adherence to a diet of high-satiety foods, especially fruit and vegetables, despite some cross-sectional evidence of dose–response relations (10).

While these theoretical issues are being sorted out by the researchers, the clinician would do well to recommend a sustainable version of the nutrient-rich, high-activity NWCR weight-control strategy before considering the use of orlistat. Not only does the NWCR strategy yield maintenance of far greater excess weight loss long-term than was shown so far for orlistat, but it also yields salubrious increases in micronutrients. The use of orlistat, by contrast, is associated with significant, unavoidable losses of fat-soluble micronutrients, with unknown long-term consequences for health.

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Reply to WJ McCarthy

Dear Sir:

McCarthy makes several interesting points about our study of the lipase inhibitor orlistat for the prevention of weight regain. Some of these issues were discussed previously in a letter by McCarthy (1) to the Editor of The Lancet and in the response to McCarthy by Sjöström et al (2).

We agree with McCarthy’s comments that dietary fat specifically is an appropriate target in obesity management, in addition to total energy intake, and that the gut may be an important target of medical therapy that may be attacked with virtually no systemic side effects. Although we did not obtain any data regarding satiety in our study, the fact that self-reported dietary intakes were fairly stable over 1 y and were not significantly different between the orlistat and placebo groups supports McCarthy’s suggestion that the brain does not appear to compensate for the 30% malabsorption of dietary fat produced by orlistat. However, we would like to point out that Figure 3 in our paper (3) does not indicate that orlistat treatment reduced the subjects’ fat intake 5-fold more than placebo, as he states in his letter. Indeed, according to self-reported intakes, the 2 treatment groups consumed similar amounts of dietary fat and the lesser weight regain in the orlistat group was attributable to the mechanism of action of the drug, which effectively converted a 30%-fat diet to a 24%-fat diet by rendering one-third of the fat energy unavailable for storage or utilization. Thus, the difference...
between the treatment groups was attributable to the pharmacologic effect of orlistat on the absorption of dietary fat rather than to an aversive effect that drove the dietary fat intake of the orlistat-treated patients below that of the placebo group. However, it is possible that avoidance of gastrointestinal side effects could play a role in controlling consumption of dietary fat in excess of the recommended 30%.

We agree that weight loss without the use of medication would be optimal. In clinical practice, however, some patients cannot achieve and most patients cannot sustain long-term weight loss. Orlistat is intended for use as an adjunct to a program of diet and exercise. It is not meant to take the place of a program of lifestyle and behavioral changes. Whereas the difference in weight loss maintained between the placebo and orlistat groups appears modest, previously published studies of orlistat use showed that small weight losses can be clinically significant in preventing relapse of obesity-related complications (4, 5). Furthermore, categorical analysis of the percentage of patients who lost >10% of initial body weight with orlistat shows that, as with many drugs, some patients do extremely well, whereas others may not (5). In clinical practice, for example, we do not continue to give an antihypertensive agent that does not lower blood pressure; additional or alternative treatment options are considered. We suspect the same will be true of antiobesity agents, including orlistat; patients who are successful will continue to use them, and those who are not may require additional counseling, dietary advice, or therapies. Last, although there is great value in identifying factors related to successful weight management, one should cautiously compare the 30-kg weight loss sustained over 5 y in the cohort of patients enrolled in the National Weight Control Registry (6) with other obesity treatments because the former is a self-selected population whose experience may not be typical of that of most obese adults.

Obesity is a disorder of overnutrition. There are no data that we are aware of to support the suggestion that consuming a diet containing 30% fat coupled with lipase inhibition to block the absorption of one-third of dietary fat energy is different from simply consuming a diet that is ~20–25% fat with respect to the micronutrient content or fat-soluble vitamin contents. Diets containing similar amounts of dietary fat have not been shown to produce micronutrient or vitamin deficiencies (7).

Finally, we concur with McCarthy that there is a need for further research regarding satiety. We also agree that there are many areas of future research that could potentially improve the long-term efficacy of obesity treatment, including the extent to which orlistat therapy may act as a deterrent to dietary fat consumption in some patients, interactions between dietary intake and exercise, and existing and future pharmacologic options.

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REFERENCES

Protein, fat, and ischemic heart disease

Dear Sir:

Hu et al (1) write that “a high dietary protein intake is often accompanied by increases in saturated fat and cholesterol intakes.” The statement has an interesting logic. Either it is correct, and their finding that a high protein intake correlates with reduced risk of ischemic heart disease contradicts the connection of dietary saturated fat to this disease, or it is not correct. This puzzle has a simple solution: the connection between dietary saturated fat and ischemic heart disease does not exist (2).

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Reply to OH Holmqvist

As shown in Table 1 of our article (1), protein intake, especially animal protein, is positively associated with saturated fat because major sources of protein such as red meat also contain high amounts of saturated fat. Therefore, our multivariate analyses
controlled for saturated fat intake. We previously published results on saturated fat intake and risk of coronary heart disease in the Nurses’ Health Study (2). In this study, 5% of energy from saturated fat, compared with an equivalent amount of energy from carbohydrates, was associated with a nonsignificant 17% greater risk of coronary disease (relative risk: 1.17; 95% CI: 0.97, 1.41; P = 0.10). In metabolic studies, replacing carbohydrates with saturated fat increases not only plasma LDL cholesterol, but also HDL cholesterol (3). The weak effect observed in prospective studies is consistent with the possibility that the proportional increase in plasma HDL-cholesterol concentrations produced by saturated fatty acids largely compensates for the adverse effects of these fatty acids on LDL concentrations.

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Animal protein and ischemic heart disease

Dear Sir:

The important paper by Hu et al (1) on findings from the Nurses’ Health Study (NHS) deserves comment, especially now that these findings have been publicized in the popular media (2). In my opinion, several highly questionable interpretations of the data have been made. The study by Hu et al purports to show, in contrast with previous evidence, that increased consumption of animal protein is associated with decreased risk of ischemic heart disease (IHD), although this observation is only marginally significant.

The importance of this paper can hardly be overemphasized. It not only reports evidence mostly contrary to the existing literature, but also reveals an important shortcoming of this widely reported study, both in the experimental design and in the method of analysis. Dietary protein (as quintile means) ranged from 14.7% to 24.0% of energy and an overwhelming 80% of this protein was from animal sources; these findings suggest the consumption of a virtually carnivorous diet. This becomes even more evident in view of the relatively high intake of total fat (36–41% of energy, as quintile means) and the very low intake of fruit and vegetables and dietary fiber of the study cohort. Even the intake of protein in the lowest quintile was ≈50% more than recommended (3), perhaps close to 90–100% more than the requirement when the unusually high concentration of high-efficiency animal protein and the statistical construction of the recommended dietary allowances are taken into account.

This dietary experience contrasts sharply with the findings of the original international correlation studies (4, 5) that showed impressive associations between selected dietary factors and chronic degenerative diseases. The contrast between the diets of the cohorts in the international correlation studies and in the NHS can be illustrated by comparing the respective protein-fat associations in these cohorts. The correlation of total fat with animal protein in the international correlation study diets was ≈90–95%, whereas in the NHS dietary range, the correlation was small and nonsignificant (∼15%). Furthermore, both animal fat and animal protein, but not plant fat, were found to be tightly associated with breast cancer in the international correlation studies.

These earlier findings from the international correlation studies suggest that the incidence of chronic degenerative disease was associated with animal-based food consumption over a broad range of intakes—from very low amounts—at the expense of plant-based food consumption, and not necessarily with the consumption of any particular nutrient or nutrient group. The NHS dietary experience, in contrast, differs because of the uniformly high consumption of animal-based foods, thus severely limiting a meaningful investigation of the comprehensive effects either of this food group or of individual foods and related nutrients within this group. As for virtually every other study of Western subjects, the NHS therefore does not permit a discriminating analysis of the diet-disease associations originally observed in the international correlation studies; the necessary range of intake of these foods and their respective nutrients is missing. Not only is the detection of meaningful disease-related associations for individual foods and their indicator nutrients compromised, but the prospect of making paradoxical observations is increased and the investigation of the more comprehensive dietary effects is ignored.

Although the statistical method used in this study is popular and well accepted, it is also based on the highly unlikely assumption that the independent effects of individual nutrients are primarily and comprehensively responsible for the multiplicity of disease outcomes. This method originally was meant for testing the safety and efficacy of pharmaceuticals, not for evaluating the comprehensive effects of multiple dietary and nutritional components. In the study by Hu et al, for example, inclusion of various “known” risk factors in the analytic model cannot eliminate the problem of residual confounding, as is often implied. Also, as shown in Table 4 of the article, the group in the highest quintile of protein intake and at lowest risk for IHD also paradoxically smoked less, consumed less alcohol, exercised more, had lower body mass, and consumed more fruit, vegetables, dark bread, dietary fiber, folate, and polyunsaturated fat but less white bread, sweets, and desserts than the groups who consumed less protein—factors for which significant trends among quintiles of protein intake were seen and which are thought to be protective of IHD. In contrast, the high-protein consumers also had a longer history of hypertension and more family history of IHD, with each factor presumably contributing to increased IHD risk.

Within a dietary range in which one food group so predominates, it makes no sense to me that it is possible to reliably
Mal product consumption and disease rates. However, internal cholesterol intakes. In the conclusion, we cautioned the application of improved blood lipid profiles when protein replaces carbohydrates (3). In the conclusion, we cautioned the application of improved blood lipid profiles when protein replaces carbohydrates (3). In the conclusion, we cautioned the application of improved blood lipid profiles when protein replaces carbohydrates (3). In the conclusion, we cautioned the application of improved blood lipid profiles when protein replaces carbohydrates (3).

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Nurses' Health Study (2). By analyzing repeated measures of dietary data over 14 y of follow-up, we firmly rejected the hypothesis that high protein intakes increase the risk of ischemic heart disease. In contrast, our data suggest a modest inverse association between animal product consumption and risk of heart disease or major cancers (4).

Prospective cohort studies of individuals, in which diet is assessed before the occurrence of disease, are typically considered to be the strongest nonrandomized design because it is possible to control for other known risk factors. One common misconception is that the dietary experience of a single population in a typical prospective cohort study is too homogeneous to detect associations with disease risk. In the Nurses’ Health Study, however, we identified several important dietary factors for risk of ischemic heart disease, including trans fatty acids (5), the ratio of polyunsaturated to saturated fat (5), α-linolenic acid (6), cereal fiber (7), nuts (8), whole-grain products (9), and fruit and vegetables (Kumudi unpublished observations, 2000).

Because high protein intakes are associated with other dietary variables and lifestyle factors, we conducted careful statistical analyses to adjust for these variables. However, the multivariate relative risks were similar to the age-adjusted ones, suggesting that confounding by other dietary variables and lifestyle factors was likely to be minor. Also, in stratified analyses according to levels of smoking and exercise and intakes of dietary fat and fiber, the modest inverse association with dietary protein persisted. Campbell suggests that the independent effects of various nutrients cannot be teased out because of their high correlations. This assertion is not substantiated by our analyses showing opposite associations with risk of coronary heart disease for different types of dietary fat that are intercorrelated (5). The large sample size, the long follow-up, and the multiple dietary measurements made in the Nurses’ Health Study provide high power to examine independent effects of many individual nutrients. Although we agree that overall dietary patterns are also important in determining disease risk (10), we believe that identification of associations with individual nutrients should be the first step because it is the specific compounds or groups of compounds that are fundamentally related to the pathophysiology of the disease. Specific components of diet can be modified, and individuals and the food industry are actively doing so. Understanding the health effects of specific dietary changes, which Campbell refers to as “reductionism,” is therefore an important undertaking.

**Reply to TC Campbell**

Dear Sir:

Although dietary protein has been the focus of controversy regarding several popular diets, scientific data on the effects of protein intake on the development of chronic disease are limited. International studies suggest a positive correlation between animal protein intake and ischemic heart disease rates across countries (1). Therefore, we tested this hypothesis directly in the Nurses’ Health Study (2). By analyzing repeated measures of dietary data over 14 y of follow-up, we firmly rejected the hypothesis that high protein intakes increase the risk of ischemic heart disease. In contrast, our data suggest a modest inverse association for both animal and vegetable protein intake. This finding is compatible with results of metabolic studies indicating improved blood lipid profiles when protein replaces carbohydrates (3). In the conclusion, we cautioned the application of these findings to public dietary advice because a high dietary protein intake is often accompanied by high saturated fat and cholesterol intakes.

Campbell questioned the validity of our findings because they contradict the results of international correlation studies on animal product consumption and disease rates. However, international correlations such as those cited by Campbell are intractably confounded by other dietary and lifestyle factors associated with economic affluence in different countries; differences in physical activity, body fat, and smoking are particularly important. Also, the food disappearance data used in most of the calculations may be more indicative of food wastage within a country than actual consumption. Correlational studies conducted within a country can usually provide more credible data than international comparisons because of relatively homogeneous populations and the possibility of collecting data on potential confounding variables at individual levels. A survey of 65 counties in rural China, however, did not find a clear association between animal product consumption and risk of heart disease or major cancers (4).

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Geriatric cachexia: a role for magnesium deficiency as well as for cytokines?

Dear Sir:

Thank you for publishing the fine review of geriatric cachexia by Yeh and Schuster (1). They stated that prostaglandin E2 (PGE2) and the proinflammatory cytokines interleukin 1 (IL-1), IL-6, and tumor necrosis factor α (TNF-α) are involved in biological processes related to the disorder. They implicated oxygen free radicals in the pathogenesis of cachexia by noting that TNF-α increases protein oxidation and that cachectic patients often experience a loss in body protein and an accelerated mobilization and oxidation of energy substrates. Cytokines have complex roles in the cause of cachexia because they rarely act alone, usually acting in conjunction with other cytokines (1), prostaglandins (1), or oxygen free radicals (2). Cytokines may inhibit feeding by causing nausea and vomiting and decreased gastric motility and gastric emptying (1).

Geriatric cachexia is associated with anorexia, involuntary weight loss, infections, decubitus ulcers, malnutrition, cognitive and psychiatric disorders, and even death (1). Yeh and Schuster stated that, of these conditions, only malnutrition is amenable to medical intervention. I propose that magnesium replacement therapy be considered as a therapy in geriatric cachectic patients found to be magnesium deficient.

Magnesium is the fourth most abundant cation in the body and the second most abundant intracellular cation (3). It is an activator in ~300 enzyme systems that are critical to cellular metabolism (4). Magnesium is essential in reactions involving ATP, which is required for glucose utilization, muscle contraction, and the synthesis of fat, protein, nucleic acid, and coenzymes (4). Other functions of magnesium include neurochemical transmission, skeletal muscle contraction, cardiac homeostasis, and the maintenance of normal intracellular concentrations of other cations (3).

Magnesium depletion is associated with biochemical and clinical derangements (3–5), which include impaired anabolic processes manifested by low serum albumin and serum protein concentrations and a decreased growth rate (5). Magnesium deficiency may contribute to cardiac arrhythmias, skeletal and respiratory muscle weakness, and seizures (3). Several mediators associated with the pathogenesis of cachexia are increased in magnesium deficiency (1). These include the inflammatory cytokines IL-1, IL-6, and TNF-α (2); PGE2 (6); and oxygen free radicals (2). In magnesium deficiency, not only are free radical concentrations higher than normal, but tissue concentrations of the antioxidants vitamin E, ascorbate, and glutathione are lower than normal; thus, endogenous antioxidant capacity is reduced, predisposing magnesium-deficient tissues to subsequent oxidative stress (2). The cytokine substance P, which increases early in magnesium deficiency, may lead to oxidative injury and appetite suppression, possibly contributing to the reduced food intake and weight loss that characteristically occur in experimental animals within 2 wk of dietary magnesium restriction (2).

Two surveys showed suboptimal magnesium intake among free-living adults in the United States. One survey, sponsored by the US Department of Agriculture (7), showed magnesium intakes that were 61.7% of the recommended dietary allowance (RDA: 8) among elderly people from food-insufficient households. A second study was conducted among well-educated, middle-to-upper class, community-dwelling volunteers in the Baltimore Longitudinal Study of Aging (9). In both men and women, median daily dietary intakes of magnesium failed to meet the 1989 RDA. Forty percent of the men and ~50% of the women consumed less than two-thirds of the RDA for magnesium. There is no information concerning the incidence of hypomagnesemia or of its associated mortality among hospitalized patients. In their study of an inner-city, medically disadvantaged, indigent population, Rubeiz et al (3) detected hypomagnesemia at the time of admission in 18% of ward and in 20% of intensive-care-unit patients. The mortality rates of the 2 groups of patients were approximately twice (P < 0.01) the rates of the normomagnesemic groups. They cited one study that reported low serum magnesium concentrations in up to 65% of intensive-care-unit patients, and another study that showed a higher mortality rate in hypomagnesemic postoperative patients than in their normomagnesemic counterparts.

Cognitive disorders, psychiatric disorders, and mental depression are occasional features of cachexia (1) and may be associated with hypomagnesemia (10). Levine et al (10) showed that patients with acute depressive disorders had elevations in the ratio of calcium to magnesium in both serum and cerebrospinal fluid. Hypomagnesemic patients have reported confusion, disorientation, agitation, hallucinations, and depression. Magnesium has been effective in alleviating depressive and manic symptoms in rapidly cycling bipolar disorders (10).
Possibly, magnesium deficiency contributes to diminished host defenses in the elderly (1). Elin (5) showed profound immunosuppressive capability in magnesium-deficient mice that had low numbers of antibody-synthesizing cells and low serum immunoglobulin concentrations. He cited studies in magnesium-depleted rats with decreased serum γ globulin and immunoglobulin G concentrations.

I suggest that magnesium deficiency in elderly patients contributes to cachexia. Magnesium deficiency puts the patient at risk of increased activity of damaging mediators that contribute to cachexia (eg, inflammatory cytokines, PGE₂, and oxygen free radicals) and it reduces the tissues’ antioxidant capacity. Magnesium deficiency may increase the risk for cognitive and psychiatric disorders, which may be amenable to magnesium therapy (10).

It may be prudent to evaluate the magnesium status of elderly patients with cachexia. If these subjects are magnesium deficient, magnesium supplementation may be beneficial because magnesium supplementation was shown to rapidly reverse the clinical symptoms (anorexia, apathy, weakness, and weight loss) of severely malnourished, magnesium-deficient children (11). However, numerous factors must be considered in geriatric cachexia. The chronicity of marginal or inadequate intakes of iron, calcium, magnesium, and zinc; the prolonged use of medications; and the reduced absorption or metabolism of nutrients may adversely affect the nutritional status of the elderly (9). The effects of magnesium supplementation late in the course of magnesium deficiency in the elderly are not known, but are worthy of investigation.

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Reply to JL Caddell

Dear Sir:

We thank Caddell for pointing out the important role of magnesium deficiency in cachexia. Although the focus of our review was on the cytokines themselves, we agree that there are numerous factors to be considered in geriatric cachexia (1). Inadequate food intake, reduced absorption, cytokine production, and medications can all affect the nutritional status of the elderly. Thi- azone diuretics and loop diuretics are among the most common medications taken by the elderly and they clearly can cause a loss of magnesium. This loss may be overlooked because of apparently normal serum magnesium concentrations. However, when skeletal muscle biopsies are performed, subnormal magnesium and potassium concentrations are found (2). Insufficient dietary supplies of magnesium may inhibit protein synthesis by decreasing serum insulin-like growth factor I (2). Therefore, minerals like magnesium and vitamins are important supplements in the treatment of cachexia.

We agree that magnesium deficiency may exacerbate the elevation of inflammatory cytokines caused by other etiologies. Furthermore, magnesium deficiency may decrease endogenous antioxidant capacity and diminish host defenses. Magnesium deficiency may play an essential role in cellular reactions and in immunoinflammatory processes (3). Magnesium deficiency can also affect mineral homeostasis, induce membrane damage, increase lipid peroxidation, and increase cytokine concentrations, thus reducing immunocompetence (4). Weglicki et al (5–7) found that dramatic elevations in interleukin 6, interleukin 1, and tumor necrosis factor α may promote cardiac lesions in magnesium-deficient rodents. This activation of immune cells probably occurs early in magnesium deficiency because magnesium-deficient rats that received magnesium-replacement therapy before endotoxin challenge had significantly lower tumor necrosis factor α production than controls (3). It was also noted that vitamin E supplements can prevent the occurrence of myocardium reperfusion injury, possibly through the restoration of endogenous antioxidant defenses in the hypomagnesemic state (7).

Stress and chronic inflammation, under conditions of mineral or antioxidant deficiency, probably further stimulate the secretion of catecholamines and cortisol, which then stimulate the release of cytokines. As we emphasized in our review, cytokines rarely act alone because they stimulate a variety of cell types to produce and secrete a cascade of other cytokines (1). All of these interactions point to the complex roles of cytokines in causing cachexia (1). The effects of magnesium supplementation, the use of antioxidants, as well as the use...
of cytokine inhibitors in the treatment of geriatric cachexia require further study.

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Adolphe Quetelet

Dear Sir:

I read with interest the supplement to the July 1999 issue of The American Journal of Clinical Nutrition, entitled “Assessment of Childhood and Adolescent Obesity.” Most of the authors used the body mass index as an assessment tool; Franklin used the Benn index. When Adolphe Quetelet proposed what is now known as the body mass index in his Physique Sociale in 1869, he indicated that it applied to adults (1, 2). During the developmental period of both sexes, the index was wt²/ht².

It might be interesting to re Crunch the numbers and see what results this produces. And, because what is now called the body mass index is rarely called Quetelet’s index, let’s honor the man who proposed both by naming the one for children and adolescents for Quetelet.

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