## Dietary fat affects obesity rate

Dear Sir:

Recently, we published a paper in the Journal titled "Dietary Fat Intake Does Affect Obesity!" (1). This was in response to an earlier paper published by Willett titled "Is Dietary Fat a Major Determinant of Body Fat?" (2). The editorial written about our paper was also prepared by Willett (3) and deserves rebuttal because it was essentially a critique of parts of our article.

Our paper attempted to use epidemiologic data to counter similar data that Willett used in his argument published earlier in the Journal (2). We stated, "Ecologic studies…[are] useful for raising hypotheses" but they have far too many weaknesses to be used for more than that. We went on to refute each of Willett's examples with examples that we felt were more appropriate. Our rebuttal of Willett's use of median body mass index and weight and his selection of correlational analyses from China are the 2 areas that he focused on in his editorial.

Our analysis presented regression results relating overweight prevalence data from a wide range of countries to the proportion of energy from fat to show that there appears to be a progression from lower to higher fat intake that is correlated with the percentage of individuals who are overweight. We never stated that this showed causation; rather, as the above quote and others would show, we were cautious in using such data.

In the editorial by Willett (3), he presented correlation coefficients between dietary fat and obesity from 65 rural Chinese counties, a study that related household dietary intake data with adult body mass indexes. We rebutted this by presenting data from a nationwide longitudinal study of the effects of diet and activity on Chinese adults. Willett claimed that we did not control for a range of confounders and he noted quite correctly that "in China…dietary fat has increased concurrently with increases in wealth and food availability, reductions in infectious disease, and declines in physical activity… it is implausible that many Chinese would voluntarily resume the diets they consumed during times of poverty." We agree. In fact, in many papers we have modeled the structure of these relations from income changes to diet and activity to changes in prevalence of overweight. We were only contesting the point in his piece that stated, "in China no correlation was found between dietary fat intakes…and body weight" (2).

Note that we examined the effect of changes in diet while controlling for physical activity, smoking, sex, age, and residence. This powerful fixed-effects approach addresses his concerns. Elsewhere, we addressed his concerns in more detail (4, 5). He noted that the size of the coefficient of energy from fat (using adjustment and partitioning methods) was small. He is correct. We would expect this because we were looking at the effect of fat while controlling for energy intake, as we showed in the paper.

One of the more important contributions to our conclusion was the meta-analysis of the 28 clinical trials. Willett (2) selected 6 of these studies to make his point—we felt this was an inappropriate way to analyze the data. We took all extant published work, omitted 1 trial that was clearly an outlier (although it benefited our argument), and did a weighted regression of the others to show a small effect of the reduction in the proportion of energy from fat on weight loss. Willett pointed out that we overlooked the study by Knopp et al (6) in which low-fat diets (22–27% of energy) were given to hyperlipidemic men. A weight loss of 6 kg was seen in the heavier group of men with combined hyperlipidemia eating 25% fat compared with a loss of 2–3 kg in the other groups. We did not find this study when we prepared the database for our work.

Since that time, a 6-mo multicenter trial in 400 overweight men and women reported a significantly greater weight loss of 0.94–1.81 kg associated with a decrease in fat intake of 7.9–10% of energy. The control groups in this study gained 0.82–0.18 kg during the same interval. Whether the low-fat diet had complex or simple carbohydrates made no significant difference. These data were presented at the Eighth International Congress of Obesity (WHM Saris, A Astrup, AM Prentice, FJ Zunft, X Formiguera, unpublished observations, 1998).

Willett did not address the range of experimental animal and human studies we reviewed, in particular, he did not comment on those that showed the ways that reducing fat with fat modifiers or other means does not lead to full energy compensation. This led to our major point. We did not expect the thermic effect of fat reduction to be important. Rather, we felt that changing the fat content of food had a major effect on energy density, and in turn, this significantly affected total energy intake. In other words, our main argument is that the effect of energy density on food intake affects total energy intake. We used a set of animal and human studies to address this topic. Willett's editorial did not address this half of our paper.

In summary, we never expected a strong effect of reduction in fat intake while keeping energy constant and we reviewed a range of experimental data to back up this point. Thus, we would agree with Willett on that point. However, as we noted, controlling fat intake is an important element of our effort to reduce total energy intake. To prevent the increase in the prevalence of obesity, controlling the fat in the diet is an important component. Most importantly for those in the United States and other high-income countries, we concluded that "to reduce the prevalence of obesity, there must be an increase in energy expenditure, a reduction in total energy intake, or both. This goal can be facilitated by reducing the amount of fat in the diet."





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## Reply to GA Bray and BM Popkin

Dear Sir:

The arguments of Bray and Popkin (1) overemphasize effects that are minor and quite possibly only artifacts, but in the end we agree on much. Their analysis of Chinese data indicating that a major change in fat intake is associated with a minuscule 0.03-point difference in body mass index (in $kg/m^2$) supports rather than refutes my conclusion that dietary fat is not a major determinant of body fat. The unpublished abstract of a European trial that they cite purporting a 1–2-kg effect of fat reduction in obese patients is similar to other short-term studies, but longer-term studies show no progressive effect and even regression after 6 mo. Even if this difference in weight were maintained, it is not clinically important and probably not even perceptible or measurable in an individual obese person. Admonishing individuals to make major changes in lifestyle when the effects are so small puts our credibility at risk.

Bray and Popkin argue that it was "inappropriate" for me to present data only for the 6 studies lasting ≥1 y. However, they combined long-term and short-term studies, even though they acknowledged that they showed different outcomes. When these studies are combined, the results are dominated by the much larger number of short-term studies, which leads to misleading conclusions about the long-term effects of dietary fat, which is the real outcome of interest. I specifically noted the report by Knopp et al (2) because it was large and lasted 1 y; it thus provides an independent test of the prediction from the Bray and Popkin meta-analysis. Their prediction was completely refuted. Bray and Popkin highlighted the reported 6-kg weight loss in the smaller subgroup of men with combined hyperlipidemia eating a 25%-fat diet. However, this is a typographical error (R Knopp, personal communication, 1999), which is implied by its inconsistency with the corresponding figure and the statement in the text that "greater fat restriction was not associated with greater weight reduction" (2). The correct weight loss was 3.2 kg, which is compared with 1.8 kg in the highest-fat group and 2.8 kg in the medium-fat group.

I did not address animal studies or short-term human studies of modified-fat products, both because of space constraints and the doubtful relevance to long-term effects of dietary fat in humans. If we want to know the long-term effects of reducing dietary fat in humans, the most relevant studies are long-term, randomized trials of dietary fat reduction in humans; these consistently show effects that are either null or very small.

Bray and Popkin concluded that "…our main argument is that the effect of energy density of foods affects total energy intake" and that a reduction in total energy intake "can be facilitated by reducing the amount of fat in the diet." Our exchange has moved us forward, because there does seem to be agreement that, within the range of realistic diets, differences in thermic effects between fats and carbohydrates do not seem to be important for weight control. They do not discuss but appear to accept the unimportance of the fat-partitioning hypothesis of weight regulation, which predicts that body fat will be proportional to the percentage of energy from dietary fat because only energy intake from carbohydrate is regulated. This is firmly refuted by the data from long-term trials that indicate that major changes in the percentage of energy from fat have little if any effect on body fat. However, if energy density is the central dietary factor in determining body weight, then the focus on fat alone is too narrow because it ignores carbohydrates, the major source of energy in almost all human diets. Although pure fat is more energy dense than pure carbohydrate, we eat these as complex foods. The food industry has shown that almost any food can be created in a low-fat version that is just as energy dense as the high-fat form. Without an equal emphasis on excess energy from both carbohydrate and fat, we will surely get more of the same.

Finally, Bray and Popkin's conclusion about energy density must be regarded as an interesting but unproven hypothesis. This should not serve as a basis for individual dietary advice nor policy without evidence from long-term human studies. I suspect the hypothesis may prove to be overly simplistic.

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## Soy, soy phytoestrogens (isoflavones), and breast cancer

Dear Sir:

McMichael-Phillips et al (1) found that daily consumption (60 g) of a soy-protein product containing 45 mg isoflavones for 2 wk stimulated DNA synthesis in breast cells taken from biopsies of premenopausal women with benign and malignant breast disease. These findings suggest that soy may actually exert estrogenic rather than antiestrogenic effects on breast tissue. This is not the first human study to suggest such an effect. Petrakis et al (2) found that in premenopausal women, daily soy consumption for 4 mo was associated with an increase in breast nipple fluid aspirate secretion and breast cell hyperplasia. However, this study did not include a control group and fluid secretion increased in women even after soy feeding was discontinued. Nevertheless, both studies raise important questions about the effect of soy isoflavones on breast tissue.

The study by McMichael-Phillips et al is particularly noteworthy, assuming that the increased DNA synthesis reflects an increase in cell proliferation. Increased cell proliferation has traditionally been considered a marker for increased cancer risk. However, this notion was challenged recently, at least with regard to the colon (3). In addition, as discussed below, there is reason to question whether the increased breast cell proliferation in response to soy consumption should be interpreted in a unfavorable light.

In the assessment of cancer risk, cell proliferation is only one side of the equation, the other being apoptosis. Illustrative of the need to look at both sides of the equation is the finding that the nonsteroidal antiinflammatory drug sulindac enhances cell proliferation in 1,2-dimethylhydrazine-treated mouse colonic mucosa, but inhibits 1,2-dimethylhydrazine-induced colon tumors (4). Moorghen et al (4) suggest that sulindac inhibits carcinogenesis despite the increase in cell proliferation because proliferation in this case is a compensatory response to an even larger increase in apoptosis. Because genistein, the primary isoflavone in soybeans, causes apoptosis in breast cancer cells in vitro, perhaps a similar phenomenon occurs with soy in vivo as it does with sulindac. Consistent with this suggestion is recent research showing that soy isoflavones markedly inhibited transplantable murine bladder cancer; however, although cell proliferation decreased slightly, apoptosis increased as much as 2–3-fold (5).

As pointed out by McMichael-Phillips et al, the short-term nature of their study is an important consideration, especially because of a report showing that tamoxifen increased pS2 expression (suggesting an estrogenic effect) in the breast tissue of breast cancer patients after 6 wk of administration but that this effect was reversed after 6 mo of treatment (6). Related to this finding is the finding that chronic exposure to isoflavones in vitro down-regulates the estrogen receptor. If down-regulation takes >2 wk to occur in people eating soyfoods, any effect on cell proliferation would not have been detected by McMichael-Phillips et al. Similarly, the increase in follicular phase length in response to soy consumption that has been observed by some investigators would not be apparent after only 2 wk of soy feeding. Increasing follicular phase length could decrease breast cancer risk in the long term.

Although 2 recent studies failed to show an effect of soy on cycle length, soy was found recently to favorably affect estrogen metabolism in premenopausal women—increasing the urinary ratio of 2- to 16α-hydroxylated estrogens and of 2- to 4-hydroxylated estrogens (7). Again, this change in estrogen metabolism would likely not occur rapidly enough to affect cell proliferation after only 2 wk of soy feeding.

Overall, there are inconsistent data regarding the likely estrogenic and antiestrogenic effects of soy on breast tissue. In vitro studies suggest that the isoflavones are estrogenic, not antiestrogenic. Although partial and pure antiestrogens demonstrate antiestrogenic effects in vitro, in vitro systems are incomplete and may not permit an antiestrogenic effect of isoflavones to be observed. Studies involving intact adult animals have not shown that soy feeding increases chemically induced mammary cancer, rather, most show substantial cancer inhibition—generally a 50% reduction in tumor number has been observed.

On a more cautionary note, Hsieh et al (8) found that dietary genistein stimulated the growth of MCF-7 cells implanted subcutaneously into ovariectomized nude mice, although growth stimulation was considerably less than that observed for 17β-estradiol (8). However, there are concerns about whether results from this model can be extrapolated to either premenopausal or postmenopausal women. In contrast with the results of Hsieh et al, Shao et al (9), in a short-term study, found that in intact mice given 17β-estradiol subcutaneously, genistein markedly inhibited breast cancer cell growth in vivo.

The complexity of the findings for isoflavones, as shown by these studies (8, 9), was also illustrated by the findings of Foth and Cline (10) in ovariectomized cynomolgus monkeys. They found that in animals not given estradiol, soy feeding produced a nonsignificant increase in mammary cell proliferation but significantly antagonized the stimulatory effects of estradiol on mammary cell proliferation.

Finally, genistein exposure for just a few days during the neonatal and prepubertal periods has been shown to reduce chemically induced mammary cancer in rodents later in life. The proposed mechanism of action seems to involve an estrogenic effect of genistein on mammary tissue, resulting in enhanced mammary tissue development and differentiation. Thus, in young animals, an estrogenic effect of soy on breast tissue may result in a decreased breast cancer risk.

In conclusion, there are insufficient data on which to draw definitive conclusions about the effects of soy consumption on breast tissue in either pre- or postmenopausal women. Epidemiologic data show some support for a protective effect of soy against breast cancer (primarily premenopausal breast cancer) and, importantly, no epidemiologic studies found an increased breast cancer risk associated with soy consumption. However, it is not clear whether these epidemiologic data, which involved primarily Asian women, can be used to assess the effect of adult soy consumption on breast cancer risk in Western populations. The recent findings by McMichael-Phillips et al should serve as a stimulus for much needed research into the effects of soy on breast tissue.

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## Provitamin A food sources and serum retinol

Dear Sir:

We are writing in regard to the paper by de Pee et al, "Orange Fruit is More Effective than are Dark-green, Leafy Vegetables in Increasing Serum Concentrations of Retinol and β-Carotene in Schoolchildren in Indonesia" (1). Although the data presented appear sound, we caution readers that the conclusion stated in the title with respect to retinol is not supported by the data. The data presented in Figure 1 of the article indicate that there was no statistically significant difference in the change in serum retinol concentrations between the treatment group who consumed fruit and the treatment group who consumed vegetables. In addition, because baseline (pretreatment) serum retinol concentrations were at the low end of the normal range (≈0.70 μmol/L) and because serum retinol is a rather weak indicator of vitamin A status, the modest increases in retinol after the consumption of both vegetables and fruit (≈0.07 and 0.12 μmol/L, respectively) further suggest that there was no nutritional difference shown between these 2 sources of provitamin A carotenoids on vitamin A status. It was shown in this article that fruit was more effective than were vegetables in increasing serum β-carotene concentrations. However, the serum β-carotene concentration is not an accurate indicator of vitamin A status.

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## Reply to EH Harrison and JC Smith

Dear Sir:

The remark by Harrison and Smith that there was no significant difference in serum retinol response between the vegetable and fruit groups is correct. However, analysis of duplicate portions showed that the vegetable group had received more provitamin A than the fruit group [684 compared with 535 retinol equivalents (RE)/d]. When corrected for this difference of intake, the difference in the change in serum retinol concentration between the fruit group and the vegetable group was 0.064 μmol/L, which is similar to the difference found between the vegetable group and the control group (0.07 μmol/L).

Accounting for the difference in the amount of carotenoids provided, we derived the following retinol conversion factors (μg β-carotene equivalent to 1 RE) for fruit and for leafy vegetables and carrots: 12 (95% CI: 6, 29) and 26 (95% CI: 13, 76), respectively. The factor for vegetables is more than twice as high as that for fruit, but the ranges overlap. The ranges were based on the 95% CIs of the serum retinol responses and on the average amounts of retinol and provitamin A carotenoids provided. If we had accounted for the precise variation in carotene content of the foods provided, the differences in the amounts eaten by individual children, and other factors that affect carotene bioavailability and bioconversion, the ranges would have been even larger.

However, when factors are used for converting provitamin A intake to vitamin A, an average value is required. We are confident that the conversion factors we derived represent the general difference between fruit and vegetables. However, as also mentioned in our article, the real conversion factor for specific foods under specific circumstances depends on many factors. Our confidence is based not only on the results of our study. Another study, conducted in breast-feeding women in Vietnam, found similar conversion factors: 12 for fruit and 28 for vegetables (1). The fact that the serum β-carotene response was better for fruit than for vegetables (5.7 times higher when corrected for the amount of β-carotene provided) means that the bioavailability of the most important provitamin A carotenoid was better from fruit. Thus, for fruit, bioconversion rather than bioavailability did not seem to have been optimal. Perhaps the conversion rates would be more efficient if the vitamin A status is lower, when the same amount of fruit is consumed in smaller portions throughout the day, or if both conditions exist. Thus, although we agree that serum β-carotene is not an indicator of vitamin A status, it indicates the potential for increasing vitamin A status when bioconversion could be optimized.

With regard to the remark that the serum retinol concentration is a rather weak indicator of vitamin A status, we note that the currently recommended conversion factors for calculating the retinol equivalence of provitamin A are also based on the results of studies that compared changes in serum retinol concentrations after different sources of vitamin A were consumed. However, as discussed in our paper, the magnitude of the difference and the range of estimates of bioavailability and bioconversion still have to be established more accurately and precisely. This will require the use of other techniques, such as those involving stable isotopes, which are currently being applied in our laboratories (2) and in those of others.

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## The dietary pyramid

Dear Sir:

The nutrition world should wake up to the revolutionary statement made by Willett (1) in a recent letter to the Editor: "if potatoes are to be included in the dietary pyramid, the appropriate place appears to be in the apex along with sweets, to be eaten only sparingly." The potato is a staple in many countries; here in Ireland especially, where the 150th anniversary of the Irish potato famine was just commemorated, such a statement needs careful consideration. It seems somewhat defeatist to accept that given our sedentary lifestyles, high-carbohydrate diets should be recognized as disadvantageous because of their frequent, but not constant, association with elevated plasma triacylglycerol, low plasma HDL cholesterol, and occasionally insulin resistance. These effects of high-carbohydrate diets are totally negated by moderate physical activity on the order of 30 min of accumulated brisk walking. To begin to accept that dietary guidelines be constructed to suit a sedentary and overweight culture is absolutely revolutionary and cannot be ignored. Nothing in public health nutrition is more urgent than the resolution of this matter. Without prejudice to the outcome of a high-level consultation on this issue, which I hope will be fostered immediately by some august and independent body, it is worth noting that every study of changes in proxies for physical inactivity (eg, number of cars per household or number of hours spent watching television) has shown attendant changes in the prevalence of obesity (2). The notion that the dietary guidelines be constructed to defend the automobile, the television, the computer game, and the town planning industry, while at the same time relegating the potato and presumably pasta, rice, and bread to the same level of the food pyramid as sweets, is so revolutionary that it is either daft or brilliant. Given the distinguished provenance of this wisdom, it is truly urgent that nutritionists resolve this issue now.

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## Reply to MJ Gibney

Dear Sir:

I appreciate Gibney's call to consider seriously the placement of potatoes at the apex of the dietary pyramid along with sweets, to be eaten sparingly. Of course, the humble potato deserves honor for keeping famine at bay in Ireland and in the United States during economic depressions, and it is a staple in some countries today. However, this does not necessarily mean that consumption of potatoes as a major energy source is optimal for health and longevity in contemporary Western societies. Nor does this history prove that potatoes have intrinsic positive health benefits, as is implied by their inclusion as a vegetable in the US dietary pyramid. Although the topic cannot be fully considered in the context of a letter, 2 general points deserve consideration.

First, as a major energy source, potatoes displace other foods with higher nutritional values, in particular, vegetables and whole grains. In a major review, Steinmetz and Potter (1) found consistent evidence that foods usually considered to be vegetables were associated with lower risks of cancer; in striking contrast, direct and inverse associations were seen with equal frequency for potatoes, as would be expected by chance. Similarly, in the extensive review of diet and cancer conducted by the World Cancer Research Fund (2), no evidence of benefit was seen for potato consumption, again in contrast with the findings for vegetables. Moreover, a large and consistent body of epidemiologic data shows that higher consumption of whole grains and cereal fiber (which will be low if potatoes are the staple carbohydrate) is associated with reduced risks of coronary artery disease (3).

Second, apart from preventing energy deficiency (hardly an issue in Western countries, where obesity is the dominant nutritional problem), potatoes have adverse metabolic effects on health. Carbohydrate ingestion per se is not harmful (virtually all diets will have carbohydrates as the major energy source), but some carbohydrate-containing foods are more healthful than others. Potatoes, along with white bread, have a nearly maximal glycemic index (4), higher than that of table sugar. Thus, these foods raise insulin concentrations and C-peptide excretion to a greater extent than do foods that contain identical amounts of carbohydrates but with lower glycemic indexes (5). Hyperinsulinemia is independently predictive of coronary artery disease risk (6) and is associated with hypertriglyceridemia and low HDL-cholesterol concentrations. In both men and women, consumption of potatoes is associated with higher risk of type 2 diabetes (7, 8). In contrast, consumption of cereal fiber and whole-grain foods is associated with reduced risk.

Gibney asserts that 30 min of brisk walking can totally negate the adverse metabolic effects of high-carbohydrate diets, but offers no evidence. Certainly, physical activity has many benefits, including reducing insulin resistance, and should lessen the adverse effects of a high glycemic load (9). However, adverse effects of high glycemic loads are likely to be present even with 30 min of walking, which is after all, modest compared with the physical activity of traditional agriculturalists. Specifically, to address the issue of these metabolic effects in the context of low insulin resistance, West et al (10) studied 8–9-y-old boys in 12 countries, including developing nations. Even in this group, the percentage of energy from carbohydrate intake was directly correlated with serum triacylglycerol concentrations and inversely correlated with serum HDL-cholesterol concentrations. Contrary to Gibney's implication, advocating the consumption of whole grains and vegetables is not a defense of inactivity; both good diets and regular exercise are essential for optimal health. In summary, abundant metabolic and epidemiologic evidence support the conclusion that those who consume potatoes (or white bread and white rice) as their staple would be healthier if they replaced, to the extent feasible, this source of carbohydrate with whole grains and vegetables.

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