Serum folate and homocysteine concentrations in large population samples of US ethnic and racial groups

Dear Sir:

Two papers, one reporting serum folate concentrations (1) and one reporting serum homocysteine concentrations (2) in large population samples of US ethnic and racial groups, appeared recently in the Journal. The largest difference in adjusted mean serum folate concentrations was between white (non-Hispanic) and Mexican American females (aged ≥17 y): 18.4 compared with 15.9 nmol/L, respectively (1). The geometric mean serum homocysteine concentrations for samples of the above populations (aged ≥12 y) were 7.9 and 7.4 μmol/L, respectively (2). The mean serum homocysteine value for Mexican American females was the lowest of the 6 sex and ethnic-racial sample means determined. Almost the same results are obtained if unadjusted means are compared or if only means from women aged 16 (or 17) to 49 y are compared. A qualitatively similar trend in the data is found when means from a sample of males from these 2 populations are compared. The trend for lower mean serum folate concentrations is apparently associated with the lower mean serum homocysteine concentrations.

The serum samples for these folate and homocysteine assays were collected from 1988 to 1991 and from 1991 to 1994, respectively. It is therefore difficult to conceive that large changes occurred in these populations during this relatively short time. The authors characterized their results as being "nationally representative results " (1) and "reference information . . . in a nationally representative sample" (2). Thus, one could conclude from the above that lower mean serum folate concentrations are associated with lower mean serum homocysteine concentrations when these 2 populations are compared. Yet this conclusion would be inconsistent with a body of literature reporting that relatively low serum folate concentrations (or low folate intakes) are strongly associated with relatively high serum homocysteine concentrations (3, 4). Perhaps other vitamins or nutrients or genetic factors completely reverse the powerful effect of folate nutriture on serum homocysteine concentrations in these populations.

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Reply to JE Baggott

Dear Sir:

Baggott questions why low mean serum folate concentrations are associated with low mean serum homocysteine concentrations in Mexican American women sampled in the third National Health and Nutrition Examination Survey (NHANES III), because lower serum folate concentrations are usually associated with increased circulating homocysteine concentrations (1, 2). Our response includes epidemiologic and statistical perspectives on the biology of homocysteine and its relation to folate and vitamin B-12 status.

Baggott's observation illustrates the difficulty in inferring associations between variables from group-level data, a phenomenon referred to as ecologic fallacy (3). First, several factors are determinants of circulating homocysteine concentrations (4). Folate status is one factor; others include vitamin B-12 status, vitamin B-6 status, genetic disorders, and metabolic disorders such as chronic renal disease. The relative importance of these factors varies significantly among population groups as well as individuals. Thus, it is highly unlikely that differences could be explained by measures of folate status alone.

For serum homocysteine, Jacques et al reported a significant age-sex interaction and also differences by race or ethnicity in females but not males (2). Because we presented folate concentration results for phase 1 and Jacques et al presented total plasma homocysteine concentration results for phase 2 of NHANES III, we thought it would be useful to present folate concentration data for phase 2 for participants aged ≥17 y (**Table 1**). In NHANES III, median serum vitamin B-12 concentrations in phase 2 were lowest for non-Hispanic whites, intermediate for

TABLE 1
Unadjusted mean and median concentrations of serum and red blood cell (RBC) folate, serum vitamin B-12, and total plasma homocysteine for participants aged ≥ 17 y in the third National Health and Nutrition Examination Survey, 1988–1994[1]

	European Americans	African Americans	Mexican Americans
Men			
Serum folate (nmol/L)			
Total			
Mean	14.5 ± 0.4 [3171]	11.0 ± 0.3 [2079]	11.4 ± 0.3 [2318]
Median	11.3 ± 0.4	8.8 ± 0.2	9.4 ± 0.3
Phase 1			
Mean	13.2 ± 0.4 [1823]	10.1 ± 0.2 [990]	10.4 ± 0.3 [1171]
Median	10.6 ± 0.3	8.2 ± 0.2	8.9 ± 0.3
Phase 2			
Mean	15.8 ± 0.8 [1348]	11.8 ± 0.4 [1089]	12.3 ± 0.5 [1147]
Median	12.1 ± 0.6	9.3 ± 0.3	10.0 ± 0.5
RBC folate (nmol/L)			
Total			
Mean	448.7 ± 7.4 [3182]	326.4 ± 4.0 [2095]	377.9 ± 7.9 [2289]
Median	397.0 ± 6.1	295.9 ± 4.7	341.1 ± 6.6
Phase 1			
Mean	439.3 ± 8.4 [1840]	325.9 ± 6.8 [1008]	364.3 ± 14.3 [1172]
Median	392.1 ± 10.5	299.1 ± 7.4	335.9 ± 13.0
Phase 2			
Mean	458.2 ± 17.2 [1342]	326.8 ± 6.4 [1087]	390.8 ± 12.3 [1117]
Median	403.3 ± 13.4	292.2 ± 5.8	351.0 ± 9.5
Vitamin B-12 (pmol/L)[2]			
Mean	328.2 ± 4.2 [1348]	419.0 ± 5.5 [1082]	382.1 ± 18.3 [1141]
Median	311.4 ± 5.0	384.3 ± 6.7	325.3 ± 7.1
Total plasma homocysteine (μmol/L)[2]			
Mean	10.7 ± 0.2 [1128]	10.6 ± 0.2 [958]	10.0 ± 0.2 [1049]
Median	9.5 ± 0.2	9.3 ± 0.1	9.1 ± 0.2
Women			
Serum folate (nmol/L)			
Total			
Mean	18.0 ± 0.5 [3643]	12.4 ± 0.3 [2517]	13.0 ± 0.4 [2321]
Median	13.3 ± 0.4	9.5 ± 0.1	10.3 ± 0.3
Phase 1			
Mean	16.4 ± 0.5 [1758]	11.8 ± 0.3 [1046]	12.0 ± 0.7 [1133]
Median	12.4 ± 0.4	9.1 ± 0.1	9.5 ± 0.6
Phase 2			
Mean	19.6 ± 0.7 [1885]	12.9 ± 0.3 [1471]	13.9 ± 0.6 [1188]
Median	14.0 ± 0.6	9.9 ± 0.3	10.9 ± 0.5
RBC folate (nmol/L)			
Total			
Mean	493.7 ± 8.5 [3661]	342.4 ± 4.4 [2533]	409.2 ± 10.2 [2298]
Median	428.8 ± 9.3	302.5 ± 4.7	362.5 ± 10.0
Phase 1			
Mean	483.4 ± 9.7 [1776]	342.7 ± 8.6 [1053]	393.7 ± 21.1 [1138]
Median	418.3 ± 11.3	306.1 ± 8.8	349.2 ± 18.6
Phase 2			
Mean	503.9 ± 15.5 [1885]	342.1 ± 6.8 [1480]	422.9 ± 16.0 [1160]
Median	444.8 ± 17.7	300.1 ± 7.4	377.4 ± 15.7
Vitamin B-12 (pmol/L)[2]			
Mean	342.4 ± 5.3 [1883]	414.6 ± 4.4 [1468]	616.9 ± 130.0 [1186]
Median	310.6 ± 5.4	385.6 ± —	342.9 ± —
Homocysteine (μmol/L)[2]			
Mean	9.1 ± 0.1 [1576]	8.9 ± 0.2 [1310]	7.7 ± 0.2 [1083]
Median	8.1 ± 0.1	7.8 ± 0.1	7.0 ± 0.1

[1] $\bar{x}$ or median ± SE; *n* in brackets.
[2] Results for phase 2 only.

Mexican Americans, and highest for non-Hispanic blacks (5). Also, although mean serum and red blood cell folate concentrations generally increased after the age of 20 y in adults, median serum vitamin B-12 concentrations were higher for the youngest age group (aged 4–5 y) and the serum vitamin B-12 distribution was highly skewed, especially among Mexican Americans (5). Because vitamin B-12 and several other factors affect circulating homocysteine concentrations, it is not surprising that the simple, expected relation between folate and homocysteine was not observed in all groups.

We calculated Spearman correlation coefficients between serum or red blood cell folate concentrations and total plasma homocysteine concentrations by ethnicity and sex (**Table 2**). Although some variation was present, all correlation coefficients were negative and the size of the correlation coefficients was generally similar. Thus, based on individual-level data, folate and vitamin B-12 concentrations were inversely related to total plasma homocysteine concentrations in all 6 groups.

TABLE 2
Unadjusted Spearman correlation coefficients between total plasma homocysteine concentrations and serum folate concentrations, red blood cell (RBC) folate concentrations, and vitamin B-12 concentrations for participants aged ≥17 y in the third National Health and Nutrition Examination Survey, 1988–1994

	European Americans	African Americans	Mexican Americans
Men			
Serum folate (nmol/L)	−0.42	−0.35	−0.38
RBC folate (nmol/L)	−0.37	−0.27	−0.25
Vitamin B-12 (pmol/L)	−0.35	−0.27	−0.25
Women			
Serum folate (nmol/L)	−0.44	−0.30	−0.35
RBC folate (nmol/L)	−0.31	−0.24	−0.24
Vitamin B-12 (pmol/L)	−0.30	−0.14	−0.13

On a biological level, the classic observation of Lewis et al (6) that plasma homocysteine concentrations are elevated in those who have plasma folate concentrations ≤14 nmol/L may also explain Baggott's observation. If serum folate concentrations are already sufficient to lower homocysteine nearly to its nadir (and 7.9 compared with 7.4 nmol/L is unlikely to be a biologically significant difference), then the observation can be explained physiologically and parsimoniously.

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Reply to JE Baggott

Dear Sir:

Baggott suggests that the data presented in 2 recent papers in the Journal (1, 2) conflict with the well-established inverse relation between circulating total homocysteine and folate concentrations (3–5). The basis of his assertion is the fact that Mexican American females in the third National Health and Nutrition Examination Survey (NHANES III) had on average lower serum total homocysteine concentrations (1) and lower serum folate concentrations than non-Hispanic white females (2). However, Baggott's statement that "The trend for lower mean serum folate concentrations is apparently associated with the lower mean serum homocysteine concentrations" is incorrect. In more recent analyses, higher serum folate concentrations were a strong predictor of lower total homocysteine concentrations in the NHANES III sample and this relation was not affected by race or ethnicity (6). When the relation between the logarithm of serum total homocysteine and the logarithm of serum folate was examined separately for Mexican American females, homocysteine concentrations were observed to be 16% lower with each doubling of serum folate concentrations ($P < 0.001$). Moreover, the difference in homocysteine concentration between Mexican American and non-Hispanic white females was independent of serum folate or vitamin B-12 concentrations. After adjustment for these vitamins as well as age and serum creatinine concentrations, the geometric mean total homocysteine concentration was 6% lower for Mexican American females than for non-Hispanic white females in the NHANES III sample, a small but significant difference ($P < 0.01$).

We have not yet identified the reason for the lower total homocysteine concentration in Mexican American females, but many factors other than folate and vitamin B-12 concentrations influence homocysteine concentrations. The large differences in homocysteine concentrations between males and females and young and old persons are not explained by circulating concentrations of folate or vitamin B-12 (6). Lifestyle factors and racial and genetic differences influence circulating total homocysteine

concentrations (7–10). Until the basis for the lower homocysteine concentrations in Mexican American females is examined, we only know for certain that the lower total homocysteine concentration in this population is not the result of higher serum folate and vitamin B-12 concentrations.

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The alcohol paradox

Dear Sir:

Jéquier's (1) recent editorial regarding the alcohol paradox notes that "epidemiologic evidence does not show a clear relation between daily alcohol energy intake and body weight." This is true with respect to men. However, large cross-sectional epidemiologic surveys show that women who are moderate drinkers tend to be much lighter than women who do not drink (2, 3). In a cohort of nearly 90 000 women participating in the extensive Nurses' Health Study, the average body mass index (BMI) of women who were moderate drinkers (1–2 drinks daily) was ≈15% lower than that of nondrinkers—even though self-reported daily energy consumption was higher for the drinkers (2). In the British Health Survey, women who were moderate drinkers were about half as likely to be obese as nondrinkers (3). Group differences in age, smoking habits, or physical activity do not appear to account for these remarkable (and remarkably overlooked) findings.

An explanation for this paradox may be readily at hand. Cross-sectional studies also show that moderate drinkers tend to be much more insulin sensitive than abstainers; this sensitivity is associated with lower fasting and postprandial insulin concentrations (4–6). Controlled studies documenting induction of insulin sensitivity by chronic ethanol consumption are lacking, but the magnitude of the sensitization associated with alcohol use is not likely to be explained by confounding factors. If we assume that the insulin sensitization produced by chronic ethanol ingestion is specific to skeletal muscle (perhaps induced by muscle metabolism of acetate?), the accompanying down-regulation of diurnal insulin secretion will diminish net insulin activity on adipocytes and hepatocytes, discouraging fatty acid storage while disinhibiting hepatic ketogenesis and gluconeogenesis, which are thermogenic.

Indeed, results of both clinical and animal research suggest that diminution of diurnal insulin secretion tends to promote leanness, independent of any effect on energy consumption (7). A decrease in insulin secretion may mediate, at least in part, reductions in body fat associated with exercise training, very-low-fat whole-food vegan diets, or administration of the drugs diazoxide, acarbose, and metformin. Arguably, the most effective strategy for achieving and maintaining leanness is to minimize daily insulin secretion within the context of a low fat intake.

Even though most of the metabolic energy derived from ethanol is presumably available to participate in feedback control of appetite, ethanol itself may have an appetite-stimulating effect, as recently shown in this Journal (8). Nevertheless, epidemiologic analysis suggests that chronic alcohol consumption tends to quell carbohydrate cravings, most notably in women (2). Thus, although alcohol use tends to increase daily energy consumption in both sexes, it does so more markedly in men, which perhaps explains why alcohol promotes leanness in women but not in men. Note, however, that men drinkers are no heavier than nondrinkers despite decidedly higher energy intakes (from food plus ethanol).

Although down-regulation of insulin secretion should promote fat oxidation, the immediate effect of ethanol ingestion is a selective inhibition of fat oxidation (9). This may explain why the BMI of women in the highest category of alcohol consumption tended to be higher than that of women who drank more moderately (2). Theoretically, the minimal daily dose of ethanol that produces substantial insulin sensitization should have the

most favorable effect on body composition—and should be reasonably safe from the standpoint of risks of breast cancer, hypertension, and liver damage while promoting vascular health.

The effect of alcohol on body composition in women may be of more than just cosmetic significance. In the Nurses' Health Study, women who had ≥2 drinks daily were 70% less likely to develop diabetes than nondrinkers during 4 y of follow-up (10). The authors of this study used statistical corrections for BMI to conclude that the true reduction in risk associated with alcohol was 40%, but this correction may not have been appropriate if alcohol use was primarily responsible for the lower BMI of the drinkers. Thus, the direct insulin-sensitizing effect of ethanol and its longer-term favorable effect on body weight may collaborate to substantially reduce diabetes risk in women.

Jéquier is absolutely right to call for longer-term studies of the metabolic effects of ethanol ingestion; the short-term studies completed to date only deepen the sense of paradox. In all probability, a better understanding of the long-term adaptive response to regular alcohol consumption will enable a definitive resolution of this issue.

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Reply to MF McCarty

Dear Sir:

I thank McCarty for his comments on my editorial (1). McCarty emphasizes a sex difference in the relation between daily alcohol energy intake and body weight: in men, there is no clear relation, whereas in women, moderate drinkers tend to be lighter than nondrinkers (2). The paradox that I mentioned, ie, an increased alcohol-induced energy intake without weight gain, is even more evident in women than in men because moderate alcohol intake seems to induce a decrease in body weight in women. If these large cross-sectional epidemiologic surveys (2) are correct, the only explanation for this finding is that a moderate alcohol intake increases energy expenditure in women more so than in men.

How can alcohol intake stimulate energy expenditure? McCarty mentions that cross-sectional studies also show that moderate drinkers are more insulin sensitive than nondrinkers (3, 4). He suggests that down-regulation of diurnal insulin secretion in moderate alcohol drinkers might disinhibit hepatic ketogenesis and gluconeogenesis, which are thermogenic processes. These metabolic explanations are unlikely to be true for the following reasons:

1) Ketogenesis is a moderately thermogenic pathway (5) and is more sensitive to the inhibitory action of insulin than muscle glucose uptake is sensitive to the stimulatory action of the hormone.
2) Gluconeogenesis is a highly thermogenic pathway but it is unlikely that it is stimulated in moderate alcohol consumers because alcohol inhibits gluconeogenesis (6).
3) Although cross-sectional epidemiologic surveys suggest that light-to-moderate alcohol intake is associated with enhanced insulin sensitivity (3, 4), metabolic studies in healthy volunteers show an alcohol-induced impairment in glucose metabolism caused by a decreased tissue sensitivity to insulin (7, 8).
4) McCarty's statement that "both clinical and animal research suggest that diminution of diurnal insulin secretion tends to promote leanness" raises the question of what comes first: low insulin secretion is more likely a consequence of an energy deficit (ie, from hypoenergetic diets or physical activity of long duration) than the cause of the energy deficit.

How can we solve the paradox in women of an increased alcohol-induced energy intake associated with a reduced body weight, if alcohol has only a moderate thermogenic effect? A recent paper by Levine et al (9) showed that nonexercise activity thermogenesis (NEAT) may play a major role in body weight regulation in response to chronic excesses in energy intake. This type of activity includes strolling around and movements of the limbs with little displacement of the body's center of gravity, ie, various types of activity referred to as fidgeting (10). Levine et al (9) clearly showed that a large portion of the variability in energy storage during an 8-wk overfeeding study in healthy volunteers was accounted for by changes in NEAT. If a moderate alcohol intake activates NEAT, this may be the most likely explanation of the above-cited paradox. Why this alcohol-induced increase in energy expenditure could be more important in women than in men remains to be elucidated.

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Meta-analysis of the cholesterol-lowering effects of dietary fiber

Dear Sir:

In a search of MEDLINE (National Library of Medicine, Bethesda, MD) for articles published from 1966 to June 1996, Brown et al (1) found 67 controlled trials of pectin, oat bran, guar gum, or psyllium that met their 6 rather arbitrary criteria. This appeared to be an adequate number of studies at first, but in retrospect was an incomplete systematic review because the literature was not searched thoroughly and the rejection criteria were too exclusive. Four years ago (2), I found 22 human trials with pectin, 50 with guar gum, 39 with oatmeal, and 28 with psyllium that reported effects on plasma lipids—a total of 139 controlled trials with viscous fibers!

Concerning pectin, the first clear finding of a plasma cholesterol–lowering effect was by Keys et al (3). Their study was well designed, but was not included in Brown et al's meta-analysis, presumably because it was published in 1961 (although another paper of Keys et al published in 1957 was cited) or because it measured only total cholesterol. Kay and I (4) published our first controlled trial with pectin (21 d of pectin feeding preceded and followed by 14-d control periods) in this Journal in 1977 and Judd and I (5) published another human study with pectin (a crossover design comparing diets high and low in methoxyl pectins) in the *British Journal of Nutrition* in 1982. Neither of these carefully conducted studies appeared in Brown et al's meta-analysis.

In addition, the findings of our metabolically controlled trial of oat fiber published in this Journal (6) was also missing from Brown et al's meta-analysis. In this trial, subjects were fed rolled oats (125 g) for 21 d, preceded and followed by 14-d control periods. Blood samples were taken for plasma lipid measurement on the last 3 d of each period. Furthermore, we controlled for the content of polyunsaturated fatty acids in the rolled oats by adding simulated oat oil to the control diets.

A meta-analysis can only be as good as the efficiency of the literature search and the usefulness of the rejection criteria (7).

The mean plasma cholesterol–lowering effect of pectin (based on only 7 studies) calculated by Brown et al was twice as high per gram of fiber as the effect of the other 3 viscous fibers studied. The value I (2) calculated from a larger number of studies was lower than this and, not surprisingly, Brown et al did not find the pectin value to be significantly different from their mean estimates for the other 3 viscous fibers.

As for the mechanism of action of viscous fibers, Kay and I (4) reported significant increases in fecal neutral steroid and bile acid excretion in subjects who consumed citrus pectin (15 g/d) as part of a metabolically controlled diet for 3 wk. Subsequently, in another study, Judd and I (5) found little difference between the effect on plasma cholesterol of high and low methoxyl pectin consumption. In addition, it was reported that pectin was fully effective in the treatment of patients with familial hypercholesterolemia who were already taking the bile acid–binding resin cholestyramine (8). Therefore, it appears that one mechanism of action of viscous fibers is dependent on viscosity, but not on chemical binding, in the small intestine. Zhang et al (9) in Gothenburg found increased excretion of bile acids in ileostomy subjects fed oat bran. The alternative feedback effect of increased volatile fatty acid production has not yet been shown directly. Lactulose has been shown to increase colonic fermentation but not to lower plasma cholesterol (10) and oral propionate also did not change plasma cholesterol concentrations (11).

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Reply to AS Truswell

Dear Sir:

We agree with Truswell that a comprehensive literature search is central to a high-quality meta-analysis. However, we disagree with his statement that our meta-analysis was incomplete. We searched the MEDLINE (National Library of Medicine, Bethesda, MD) database (from January 1966 through June 1996) for literature with the following medical subject headings: "dietary fiber," "cereals (corn, oat, rye, millet, rice, and wheat)," "oat bran", "oatmeal," "gums," "guar," "pectin," "fruit," "vegetables," "psyllium (*Plantago ovata* husk and seeds)," "blood cholesterol," and "hyperlipidemia." We reviewed 162 clinical studies reporting the effects of soluble fiber on blood cholesterol, including 49 studies of oat products, 26 of psyllium, 20 of pectin, and 57 of guar (1). As stated in our paper, most of the studies excluded lacked either random allocation to low- and high-fiber diets or a randomized crossover between the 2 diet periods. For instance, Truswell cites 2 of his studies that each began with a 14-d control diet followed by a high-fiber diet of either pectin (2) or of oats (3) and that concluded with a 14-d control diet. We did not include either of these studies in the meta-analysis because the order of the control and fiber diets was not randomly assigned.

Truswell is concerned that our inclusion criteria may have been too restrictive. We assessed the influence of certain inclusion criteria on the results by relaxing some of the inclusion criteria in secondary analyses that were reported in our paper. For example, 3 trials [including 1 published by Judd and Truswell in 1982 (4)] that did not use a true low-fiber control but rather compared the effects of high doses with lower doses of the same fiber were included in a secondary analysis. Although the report of the cholesterol-lowering effect of pectin (15 g/d) by Keys et al (5) did not specifically state that the order of treatments was randomized, the investigators administered the pectin and control diets in reverse order to compensate for potential carryover effects. When we included this study in a secondary analysis, the mean total cholesterol–lowering effect of pectin was similar to that of other fibers (-0.04; 95% CI: -0.01, -0.09), making it appear even less likely that type of fiber could have accounted for a significant amount of heterogeneity among the different studies. However, it is possible that small differences in the response of cholesterol (-0.02 to -0.03 mmol/L per gram dietary fiber) to different fibers may not be detectable. In addition to the secondary analyses in the published report, we also performed analyses to include trials in which the background diet was not well characterized or controlled (6–13). The results from these analyses were not materially different from the primary analysis. The mechanism by which fiber lowers blood cholesterol remains unknown. We thank Truswell for his comments on the mechanism of action of viscous fibers.

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Fat malabsorption in cystic fibrosis patients

Dear Sir:

We read with great interest the recent paper by Kalivianakis et al (1), who traced the gastrointestinal handling and postprandial partitioning of a labeled fatty acid to determine the extent to which the steatorrhea exhibited by patients with cystic fibrosis (CF) during habitual pancreatic enzyme replacement therapy (PERT) could be attributable to fat malabsorption. Malabsorption is a term widely used in clinical practice and is usually considered to be synonymous with increased stool losses. In clinical practice,

there is often a failure to differentiate between dietary residue that is not absorbed as a result of poor digestion and thereby is not presented in a form that could be absorbed by the body (ie, maldigestion) from a failure in the absorptive capacity of the gastrointestinal tract (ie, malabsorption). We addressed this issue using ^{13}C-labeled fatty acids and triacylglycerols in an attempt to improve the nutritional management of CF patients on the basis of our own reports of stool energy and lipid losses in CF patients during their habitual PERT (2, 3). Although we do not wish to comment on the study design, we do feel that the conclusions presented in Kalivianakis et al's study are not consistently supported by their own observations and warrant further examination.

Kalivianakis et al concluded that the continuing fat malabsorption in CF patients receiving PERT was not due to insufficient lipolytic enzyme activity, but to incomplete intraluminal solubilization of long-chain fatty acids, reduced mucosal uptake, or both. Two lines of reasoning led to their conclusion. First, because no relation was observed between the recovery of label in breath after 1,3-distearyl,2[1-^{13}C]octanoyl glycerol ingestion and gross lipid excretion in the stool, the authors concluded that increased stool lipid losses were probably not related to defective lipolysis (ie, maldigestion). However, in the absence of direct measurements of recovery of label in stool, the authors assumed that the sole determinant of differences in the recovery of label in breath was the extent of digestion within the gastrointestinal tract. In other words, once absorbed, the oxidation of the labeled fatty acid was uniform and consistent and not influenced by nutritional status and metabolic demands. Second, after ingestion of [^{13}C]linoleic acid ([^{13}C]LA), a strong relation was observed between the concentration of labeled fatty acid in the circulation 8 h later and gross lipid excretion in the stool. Justification that this finding differentiates between pancreatic insufficiency and deficient intestinal uptake is restricted to a single brief report (abstract) of lipid malabsorption studies conducted in rats (4). The assumption was that poor lipid absorption would be reflected in a delayed or lower concentration in the circulation and that factors that may influence the removal of labeled fatty acid from the circulation are unimportant in determining the concentration of fatty acid in the circulation. In the absence of control data, analysis was restricted to differences within the group of CF patients.

We used a direct approach to determine the availability of dietary lipid on the basis of recovery of label in stool in patients with CF and compared the results with those from healthy volunteers to differentiate between maldigestion and malabsorption. Using this approach, we showed that the recovery of ^{13}C label in the breath after oral administration of [1,1,1-^{13}C]tripalmitin presented within an emulsion to patients with CF receiving habitual PERT was not related (inversely or otherwise) to the recovery of ^{13}C label in the stool and did not reflect the extent to which labeled triacylglycerols are digested and absorbed (5). This may have been due, at least in part, to lower oxidation of the labeled fatty acids after absorption in CF patients than in control subjects. Furthermore, the recovery of label in stool after oral administration of nonesterified [1-^{13}C]palmitic acid was paradoxically lower in patients with CF than in control subjects, implying that the availability of long-chain fatty acids after digestion was either the same as or possibly even greater in patients with CF (6).

Therefore, we were surprised to find that despite measuring the excretion of ^{13}C label in stool using gas chromatography–combustion isotope ratio mass spectrometry, the authors failed to take these observations into account when drawing their conclusions. As evident in their Table 2, stool [^{13}C]LA expressed as a percentage of the administered dose was low and varied between 0.0% and 1.8%. In other words, because almost 100% of the labeled fatty acids were absorbed, there was no evidence of malabsorption. Note that such an apparently high availability of long-chain polyunsaturated fatty acids was also seen in healthy men (99–100% of administered dose) in the only other reported study in which the availability of [^{13}C]LA was determined from stool losses (7). The absorption of [^{13}C]LA in CF patients in Kalivianakis et al's study was also similar to what we observed for nonesterified [1-^{13}C]palmitic and oleic acids (>98% of administered dose) in healthy volunteers (8). Our impression is that, having failed to show any association between [^{13}C]LA excretion and total fat in stool, the authors overlooked the only direct measure of fatty acid availability. It is probably not surprising that no association was observed given that there was so little label in the stool yet stool lipid losses varied markedly.

Therefore, although we do not dismiss the possibility that there may be problems associated with the intraluminal solubilization or reduced mucosal uptake of long-chain fatty acids, we feel that the authors could have reflected on this apparent dichotomy in their own observations.

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Reply to J Murphy et al

Dear Sir:

We are grateful for the comments of Murphy et al concerning the metabolic handling of lipids labeled with stable isotopes in relation to our recently published study (1). Murphy et al feel that the conclusions presented in our study are not consistently supported by our own observations, nor by previous observations (2, 3). The reservations of Murphy et al concern an important issue for all studies in which labeled compounds are used, namely, does the metabolic fate of a labeled compound reflect that of the (unlabeled) bulk of this compound? Murphy et al raise 3 issues in this respect: *1*) the oxidation of [1-^{13}C]octanoate from 1,3-distearoyl,2[1-^{13}C]octanoyl glycerol ([^{13}C]MTG) in our study, *2*) the relation between the plasma concentration of [^{13}C]linoleic acid ([^{13}C]LA) and deficient intestinal fatty acid uptake in our study, and *3*) the recovery of ^{13}C-labeled lipids from the feces of control and cystic fibrosis patients in previous studies (2, 3). These 3 aspects will be discussed below in turn.

The [^{13}C]MTG breath test was described originally and validated by Vantrappen et al (4). In healthy subjects and in patients with pancreatic disease, a strong correlation was observed between the 6-h cumulative expiration of $^{13}CO_2$ and lipase activity in the duodenum after maximal pancreatic stimulation (r = 0.89). Nevertheless, we appreciate the concern of Murphy et al that the oxidation of labeled fatty acids may not be uniform and consistent and may be influenced by nutritional status and metabolic demands. In a previous study, we examined in healthy adults the determinants of the $^{13}CO_2$ response with the [^{13}C]MTG breath test (5). It appeared that standardization of the test, particularly with respect to physical activity, was warranted. Because the [^{13}C]MTG breath test was used under these standardized conditions in our study, which were virtually identical to the conditions originally described by Vantrappen et al, we do not believe that differences in oxidation rates per se significantly affected our main conclusions.

After their intestinal absorption, medium-chain fatty acids, such as octanoate, are transported in plasma predominantly bound to albumin, are rapidly cleared from plasma, and are subsequently readily oxidized. The postabsorptive metabolism of long-chain fatty acids, such as linoleate and palmitate, is significantly different from that of medium-chain fatty acids, includes the assembly into lipoproteins, and is much less characterized by oxidation. To obtain information on the intestinal absorption of long-chain fatty acids, we developed stable-isotope methods that do not depend on the eventual oxidation of absorbed tracer compounds, but rather on the appearance of the label in an earlier metabolic compartment, ie, the plasma. In permanently bile-diverted rats, an accepted animal model for impaired long-chain fatty acid solubilization, plasma concentrations of [^{13}C]LA between 1 and 4 h after its enteral administration were closely related to the efficacy of gross fat absorption and to fecal fat excretion (r = 0.84) (6). We agree with Murphy et al that the specificity of such tests of long-chain fatty acid absorption is demonstrated by the independence of the results from pancreatic insufficiency. We showed recently that postabsorptive plasma concentrations of enterally administered [^{13}C]palmitate, another stable, isotopically labeled long-chain fatty acid, were virtually identical in control rats and in rats treated with the intestinal lipase inhibitor orlistat; these rats absorbed only 32.8 ± 3.7% of ingested dietary fats (7). These observations indicate that postabsorptive plasma concentrations of enterally administered, ^{13}C-labeled long-chain fatty acids are specifically and significantly related to the efficacy of their intestinal solubilization and uptake. Although we agree with Murphy et al that the removal of labeled fatty acids from the circulation may interfere, present data indicate that, at least in the time scales and fat absorption models studied so far (bile-diverted rats, orlistat-treated rats, pediatric cystic fibrosis patients) (1, 6, 7), their relative contribution to ^{13}C-labeled plasma concentrations appears to be minor.

On the basis of previous studies by Murphy et al, it is apparent that the recovery of [^{13}C] label in feces is not, or is only poorly, related to gross fecal fat excretion after enteral administration of trace amounts of stable isotopically labeled long-chain fatty acids (2, 3, 8). In our own studies, including our recently published study in this Journal, we confirmed their original observation: the 48- or 72-h recovery of 13C label in feces or in fecal fats does not reliably reflect the fate of unlabeled, gross amount of dietary fats (1, 6, 7). The reason for this apparent discrepancy may be related to the administration of a tracer lipid in a physicochemical form that differs from the matrix of unlabeled dietary fats. In addition, the small intestine has a considerable compensatory capacity to uphold quantitative fat absorption under widely variable conditions. For example, when there is impaired fat absorption from the proximal part of the intestine, where the predominant fraction of dietary fats is absorbed under physiologic conditions, the more distal sections of the small intestine may become recruited in fat absorption (9, 10). In our recently published study, however, we found a close correlation between the 8-h plasma concentration of [^{13}C]LA and the net, 72-h absorption of dietary fats (r = 0.88). On the basis of this and previous observations, we are confident that appearance of labeled fatty acids in the plasma compartment, within hours after its administration, more closely reflects rate-limiting steps in malabsorption of dietary fats when compared with the fraction of the tracer fatty acid that, after passage through the whole intestine, remains unabsorbed.

In our opinion, the recently obtained data strongly support the concept that incomplete intraluminal solubilization of long-chain fatty acids, their reduced mucosal uptake, or both processes together impair the absorption of dietary fats in pediatric cystic fibrosis patients (1). We do agree with Murphy et al that the application of stable-isotope tracers in biomedical investigations warrants a critical appraisal with respect to whether the metabolism of the tracer accurately reflects the physiologic process under study.

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Why cholesterol-lowering diets should still be encouraged in the face of effective pharmaceutical interventions

Dear Sir:

There are at least 5 more reasons, in addition to those mentioned by Denke (1) in her editorial, why cholesterol-lowering diets should still be encouraged in the face of effective pharmaceutical interventions. First, dietary choices are available to everyone, many times every day. Certainly, some cholesterol-lowering foods may be more expensive than their cholesterol-raising equivalents. However, many cholesterol-free, low-fat foods (especially plant-based foods that naturally have such characteristics) can be inexpensive, simple food choices. It is worth remembering that although the food technologies Denke mentions may solve some problems, they are unlikely to solve all diet-related problems and may create others.

Second, heart disease risk reduction is not limited to cholesterol lowering, and diets constructed to reduce cholesterol may also reduce other heart disease risks. For example, diets that emphasize intake of cholesterol-free plant products are also high in antioxidants. Furthermore, such diets tend to lower risks of other chronic diseases.

Third, diets are in the hands of individuals and do not require the intervention of a health care provider. This independence may be considered advantageous by some (although others might see the absence of health provider monitoring as a disadvantage).

Fourth, eating lower on the food chain, as occurs with many lower-fat and lower-cholesterol diets, has positive environmental benefits. For example, fewer resources are required to feed a pound of soy protein directly to a human than to feed it to a cow and produce a few ounces (estimates vary) of cow protein for human consumption.

Finally, everyone must eat, although not everyone must take drugs. Making the best of required choices seems an obvious step toward health promotion.

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Reply to E Frank

Frank raises additional considerations supporting dietary therapy. She is "preaching to the choir," but perhaps with MEDLINE (National Library of Medicine, Bethesda, MD) searches the message will be heard beyond the pews.

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Erratum

Note that the September 1999 supplement issue and the October 1999 issue have overlapping page numbers: 429S–634S and 429–579, respectively. However, the page numbers in the supplement issue end in an "S," which differentiates them from the page numbers in the October 1999 issue.