

Dietary treatment of iron deficiency?

Dear Sir:

We read with great interest the article by Patterson et al (1) published recently in the Journal. In the conclusion of their abstract, the authors purport to have shown that “in iron-deficient women of childbearing age, a high-iron diet produced smaller increases in SF [serum ferritin] than did iron supplementation but resulted in continued improvements in iron status during a 6-mo follow-up.”

Certainly, the iron-deficient women in the diet group were advised to consume a diet high in absorbable iron for the first 12 wk of the study. However, they did not do this. Throughout the 12-wk intervention, there was no significant increase in either heme or nonheme iron intake; nor were there any significant changes in the intakes of vitamin C, meat, alcohol, phytate, calcium, or tea. Furthermore, 6 mo after the end of the formal intervention, bioavailable iron intake was, if anything, lower than at baseline; yet, the diet group’s serum ferritin concentration was slightly (2.1 $\mu\text{g/L}$) higher at the end of the 12-wk intervention and moderately higher (4.2 $\mu\text{g/L}$) 6 mo after the intervention. Given that any change in the intake of dietary iron or its absorption modifiers throughout the 9-mo study was negligible, what could account for the increase in serum ferritin concentration?

It is possible that at the end of the 12-wk intervention, women in the diet group chose to take or were prescribed an iron supplement because they knew that they were iron deficient and had not received an iron supplement during the study. It is also possible that because serum ferritin is an acute-phase reactant, the small increase in mean serum ferritin concentration at follow-up resulted from the inclusion of one or more individuals with a serum ferritin concentration that was elevated because of infection.

The absence of a true control group makes it particularly difficult to conclude that the changes in serum ferritin concentration were the result of an improvement in diet. The cornerstone of scientific research into the effects of diet on nutritional status is the randomized controlled trial in which participants are randomly assigned to treatment or control groups. Without an iron-deficient control group, it is difficult to quantify the effects on iron status of factors beyond the investigators’ control. For instance, it is well known that if a group of individuals is identified on the basis of a low biochemical index measured on one occasion, a subsequent measurement is likely, by chance, to be higher (ie, closer to the mean) even in the absence of any intervention effect. The only way to determine whether the increase in serum ferritin concentration in the iron-deficient diet group in this study was real, and not merely the result of a phenomenon such as regression to the mean, would be to compare it to changes in serum ferritin concentration in an iron-deficient control group. Concern about the ethics of not treating women with iron deficiency could have been minimized

by recruiting women with low serum ferritin concentrations but normal hemoglobin concentrations.

In conclusion, the article does not show that dietary change is an effective treatment for iron deficiency. Rather, it strongly shows the difficulties that even motivated volunteers experience in attempting to modify their diets to increase iron absorption and suggests that iron supplementation is the most effective treatment for iron deficiency.

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Extra dietary copper inhibits LDL oxidation

Wan et al (1) fed cocoa powder and dark chocolate to subjects for 4 wk and found that LDL oxidation was inhibited in vitro. This favorable effect on cardiovascular risk status was attributed to flavonoids, a group of polyphenolic compounds with antioxidant characteristics. An increase in dietary copper during this experiment may have contributed to their results.

The Western diet often is low in copper: approximately one-third of 849 diets that were analyzed provided 1 mg/d (2). The interquartile range was 0.91–1.86 mg/d. Milk chocolate and cocoa powder are in the upper quartile of 235 foods evaluated by Lurie et al (3), ranking 186 and 232, respectively, in copper concentration. Calculations using Lurie et al’s values for chocolate and cocoa powder of 2.86 and 50.0 $\mu\text{g/g}$, respectively, show that these supplements would have added nearly 1.15 mg Cu to the basal diet each day. Dark chocolate contains more copper than does light chocolate and would have increased this estimated amount even more. It seems likely that the total daily intake of copper might have been 3 times the daily estimated average requirement (0.7 mg) or twice the recommended dietary allowance (0.9 mg) for adults (4).

Although copper salts (at 10 $\mu\text{mol/L}$) and LDL are highly reactive in vitro, this phenomenon is probably irrelevant to

human physiology because copper ions are virtually nonexistent (1 amol/L) in vivo (5–7). Indeed, after providing copper supplementation to middle-aged subjects, Rock et al (8) found that the subjects' erythrocytes were more resistant to oxidation in vitro. Although this improvement occurred without an increase in the activity of superoxide dismutase (EC 1.15.1.1), an enzyme that provides defense against oxidative damage, the results may indicate that the subjects ordinarily ate too little copper and had other means of defense.

Perhaps the usual copper intakes of the subjects studied by Wan et al were too low also. Their basal diet probably was low in copper because it excluded beans and soybeans, 2 foods in the top quartile (*see* above). Control of the diets for copper intake as well as for intakes of caffeine, cholesterol, fat, and fiber would have been informative because the increased copper intake from chocolate seems smaller than some beneficial amounts given by Rock et al (8). Perhaps chocolate enhances the absorbability of copper.

Copper is an antioxidant nutrient for cardiovascular health (7) and has no prooxidant activity at a considerably higher intake (8) than that given by Wan et al. Diets low in copper are suggested as an explanation for much of the epidemiology and pathophysiology of ischemic heart disease (9). Chocolate is a pleasant dietary supplement.

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Reply to LM Klevay

Dear Sir:

Klevay raises a very good question about whether or not copper could have contributed to the results of the lipid oxidation potential in the Cocoa and Dark Chocolate Study reported by researchers at Pennsylvania State University (1). Using nutrient database values, we calculated the copper content of the diets and report the following.

The base diet (averaging the 6 menus), at 2500 kcal/d, provided 0.844 mg Cu/d. (Note that not all foods in the menus have reported copper content; therefore, the total for the base diet and the experimental diet could be higher but would increase by the same amount.) The recommended dietary allowance for copper is 0.9 mg/d; therefore, the diets essentially provided the recommended dietary allowance for this micronutrient (94%). The addition of the dark chocolate (16 g/d) contributed an additional 0.128 mg Cu/d, and the cocoa powder (22 g/d) contributed, depending on the nutrient database used for values, between 0.17 and 0.83 mg Cu/d to the diets.

Therefore, the total copper content of the cocoa–dark chocolate diets was ≥ 1.14 mg Cu/d and could have been as much as 1.80 mg Cu/d. The difference between the control diet and the experimental diet was ≥ 0.298 and perhaps as much as 0.961 mg Cu/d.

Of note is that the base diet was adequate in copper. Whether the addition of the copper from the cocoa and dark chocolate was significant and whether it contributed to the effects on LDL oxidation would need to be tested. However, it is certainly possible that the copper contributed in some way to the overall antioxidant potential of the diets and the subsequent serum antioxidant capacity.

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Population estimates of folate intake from food analyses

Dear Sir:

In their article on the folate intakes of the adult Dutch population, Konings et al (1) presented calculations of folate intake based on the folate contents of foods determined by liquid chromatography (LC). The dietary folate intake of the Dutch population was estimated to be $182 \pm 119 \mu\text{g}/\text{d}$. The limitations of their study, and hence possible biases in the final estimates of folate intake, require comment.

In comparison with other published data on folate intakes in European populations, the intakes presented by Konings et al (1) seem low. In the study by de Bree et al (2), average folate intakes in European populations were reported to be 291 and 247 $\mu\text{g}/\text{d}$ for males and females, respectively. As part of the European Union's fifth framework project, "Folate: From Food to Functionality and Optimal Health" (3), folate intakes for populations in 7 European countries (Finland, Germany, Italy, the Netherlands, Spain, Sweden, and the United Kingdom) were estimated on the basis of each country's food consumption and food-composition data. Dietary folate intakes ranged from 217 to 310 $\mu\text{g}/\text{d}$, the average being $285 \pm 30 \mu\text{g}/\text{d}$ for males and $230 \pm 20 \mu\text{g}/\text{d}$ for females.

In addition, an intercomparison study of suitable methods of analysis for food folates was organized by using 4 certified reference materials (CRMs): CRM 121 (whole-meal flour), CRM 421 (milk powder), CRM 485 (mixed vegetables), and CRM 487 (pig's liver). Nine project participants and the National Food Administration (Sweden) analyzed the samples. To increase the number of comparable results, the data from Konings previous publication (4) were included. The number of accepted results was 7–9 for each

CRM, 3–4 of which were obtained by a microbiological assay (MA) and 4–5 by HPLC. One of the HPLC laboratories used microbiological detection (LC-MA). In addition, 2 HPLC laboratories determined 5-methyltetrahydrofolate only. The certified values for total folate in these CRMs were obtained by MA by a group of experienced laboratories (5).

Our findings indicate the current status of food folate analysis in Europe. The results obtained by HPLC were 27–40% lower than the microbiological results, except for pig's liver. Indeed, Konings et al also reported a difference of the same magnitude (23–27%) between the results by LC and those by MA. The within-laboratory variation was generally small (3–11%), whereas the between-laboratory variation was large (7–51%). Generally, folic acid and 5-methyltetrahydrofolate could be determined with satisfactory accuracy but no agreement was found for the other vitamers.

The distribution of the folate vitamers and the total folate content of CRM 485 (mixed vegetables) are presented in **Figure 1**. The sum of folate vitamers was 73% of the microbiologically determined folate content for mixed vegetables but only 60% for whole-meal flour. The distribution patterns from CRMs containing several vitamers (whole-meal flour and pig's liver) varied considerably from one laboratory to another.

There are several possible explanations for the observed discrepancy. Some of the peaks in HPLC chromatograms were often masked, which made identification and accurate quantification difficult. The existence of unidentified compounds, either folate or nonfolate, was common. It is known, for example, that 5-formyltetrahydrofolate and 10-formyltetrahydrofolate can convert to 5,10-methylenetetrahydrofolate under acidic conditions ($\text{pH} < 2$) used in the current HPLC mobile phases. 5,10-Methylenetetrahydrofolate does not have sufficient fluorescence to be quantified accurately. However, alternate detec-

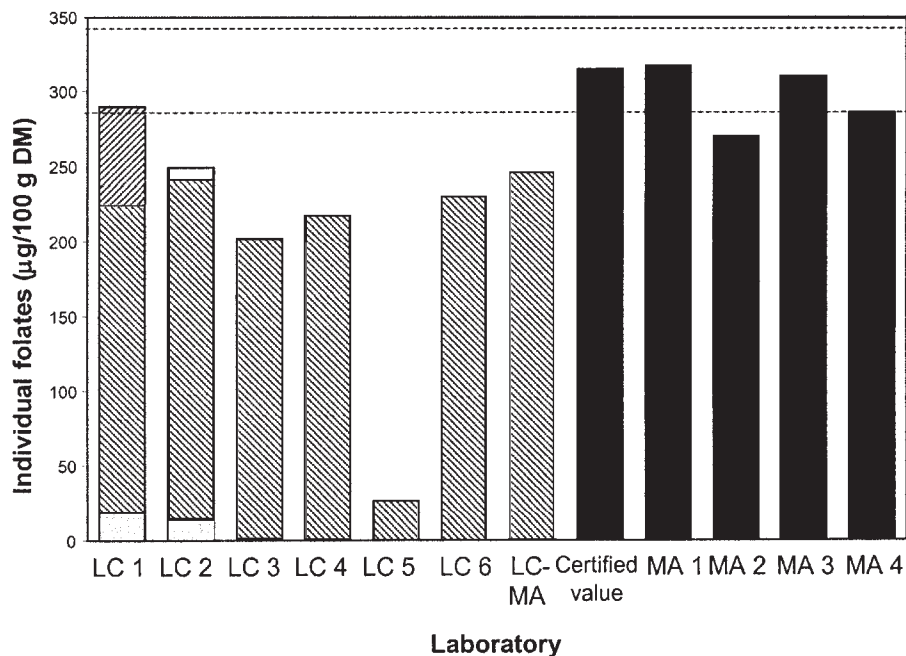


FIGURE 1. The total folate content (■), determined by microbiological assay (MA) in 4 laboratories and individual folate contents (□, folic acid; ▨, 5-HCO-H₄-folate; ▩, 5-CH₃-H₄-folate; ▧, H₄-folate) determined by HPLC (LC) in 6 laboratories of certified reference material 485 (mixed vegetables) in the European intercomparison study. The SD of the certified value is indicated by the horizontal dashed lines. The results of Konings (4) are included in LC 3. LC-MA, HPLC with microbiological detection; DM, dry matter.

tion systems, such as electrochemical or mass spectrometry, have been developed (6).

There is also the possibility that the bacteria used in the MA gave unequal responses to the different vitamers or can be affected by some nonfolate compounds in the samples. However, the latter was evaluated on the basis of the combined LC-MA results. The data clearly show the absence of any nonfolate peaks with organism activity.

We conclude that the MA is preferred for the determination of the total folate content of foods, especially if data on individual folates is not considered necessary. Furthermore, we stress the need for careful validation of HPLC methods. Given the considerable, yet unidentified, difference between the microbiological and HPLC data, we advise caution when estimating dietary folate intakes at the population level.

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Reply to Kariluoto et al

Dear Sir:

We appreciate the reaction from Kariluoto et al regarding our paper (1), particularly on the population intakes, which are based on newly established food folate data. We completely agree that this is an important issue. Kariluoto et al referred to an estimated intake of $182 \pm 119 \mu\text{g/d}$ for a population aged 1–92 y and compared these data with data for adults. Our estimated intakes were 173 and 215 $\mu\text{g/d}$ for women and men, respectively.

Kariluoto et al reported that as a part of the European Union's fifth framework project, baseline folate intakes for populations across 7 European countries were studied by using data based on each country's food-composition data. An important problem with estimating folate intakes is the lack and the unreliability of the data on folate content in food-composition tables (2). Additionally, in 1996, a European working group, "COST 99," compared folate data in food-composition tables for some vegetables, milk, bread, and cereals from 7 European countries. Total folate was measured by microbiological assay (MA). These food folate data showed a 2–3-fold variation (PM Finglas, unpublished observations, 1996), which indicates that folate intakes cannot be compared between countries.

In an intercomparison study that analyzed 4 certified reference materials (CRMs), estimated folic acid and 5-methyltetrahydrofolate contents were comparable in 4–5 laboratories, but no agreement in the other vitamers was found. Other than our previously published results (3), no other participating laboratory used affinity chromatography as a cleanup step before the final determination of all vitamers with HPLC. Selhub (4) and Pfeiffer et al (5) used this technique successfully earlier. It must be stressed that only this cleanup procedure is suitable for determining the folate content in food-sample extracts when HPLC is used. Anion-exchange purification alone or solid-phase extraction leaves many interfering compounds in the chromatogram, which hampers interpretation and accurate quantitation (3, 6).

It is not correctly stated by Kariluoto et al that 5-formyltetrahydrofolate, 10-formyltetrahydrofolate, or both convert to 5,10-methylenetetrahydrofolate under acidic conditions. In particular, 10-formyltetrahydrofolate could be converted to 5,10-methylenetetrahydrofolate rapidly (ie, on column conversion) because of the low pH of the mobile phase (5).

5-Formyltetrahydrofolate also undergoes formation of 5,10-methylenetetrahydrofolate in acidic media, although at a much slower rate (5). Thus, the acidic mobile phase used is fully suitable for separation and quantification of 5-formyltetrahy-

drofolate, as shown previously by Gregory et al (7). The presence of 5,10-methenyltetrahydrofolate in our HPLC procedure was not determined by fluorescence detection as suggested by Kariluoto et al but was quantified by diode-array detection when present (3). 10-Formyltetrahydrofolate is completely oxidized to 10-formyldihydrofolate or 10-formylfolic acid during food preparation (8). The purpose of our study was to analyze food products in the form they are consumed. Both vitamers could be quantified with the system we used (1, 3).

It is not clear from Kariluoto et al's letter why the absence of bacterial growth by nonfolate compounds was based only on the results of 2 CRMs instead of the 4 CRMs used in the intercomparison study. This does not necessarily mean that the response of bacteria to nonfolate compounds is absent in all food matrices. According to Kariluoto et al, liquid chromatography-microbiological assay (LC-MA) showed the absence of any nonfolate peaks with organism activity, and all other peaks with microbiological activity add up to the same amount as found by HPLC in other analyses (Figure 1 of Kariluoto et al's letter). This does not explain the discrepancy between the results by HPLC and MA. One would expect equal amounts between results of LC-MA and MA if MA is preferred as the standard method. According to these results, HPLC is preferred to MA as the standard method.

The determination of folates by MA is grounded on biological activity, whereas the determination by HPLC is grounded on the actual detection of separate folate vitamers. Problems with the response of *Lactobacillus casei* to different folate vitamers, as reported by Phillips and Wright (9), and the influence of nonfolate compounds on the bacterial growth response are still not refuted and might explain the difference between the HPLC and MA results.

New, accurate food-composition data for folates are needed. Our study (1) was the first comprehensive assessment of a large range of folate-containing foods. Furthermore, this study showed the effect of new analytic data for folates, including identification and quantification. In light of current knowledge, we determined all relevant folates in foods with reliable and reproducible results (3).

With regard to the relative importance of accurate food folate data, because they are frequently used in epidemiologic analyses in which intakes are related to disease endpoints, we recommend the standardization of methods for the determination of folate in foods to ensure accurate quantification of total folate contents. HPLC should be the method of choice.

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Lessons learned in iron intervention trials

Dear Sir:

The December 2001 issue of the Journal featured the coincident publication of 3 articles related to anemia and its partition between iron deficiency and non-iron deficiency origins among African preschoolers living in areas of endemic malaria (1-3). Our attention was drawn to the article concerning an iron-supplementation intervention trial (3), which reported difficulties and caveats reminiscent of an experience of ours in Guatemala (4).

In the planning of their study, Zlotkin et al (3) approached their power and sample-size assumptions in the following manner: "On the assumption of 90% cure rates in the drops group and 80% in the sprinkles group and with a type I error set at 0.05 and a 0.9 probability of detecting a true difference, the final sample size estimate was 286 subjects per group." They expected up to 90% of anemic Ghanaian infants and toddlers to have iron deficiency and iron-responsive anemias. This expectation raises 2 points in our minds. The first of these points is that such an expectation conflicts with the sense of the introductory section of their paper, where they state, "... we tested the hypothesis that the response to treatment of anemia would be better with 2 mo of treatment with microencapsulated ferrous fumarate sachets daily than with ferrous sulfate drops..." (3). Both of these statements use wording that seems to refer to a one-tailed test, but with the latter statement inclining toward superiority for the sprinkles and the former statement inclining toward a 10% better efficacy for the drops. Thus, it is important that the authors clarify whether the study was powered for a one-tailed or two-tailed test of the hypothesis of dif-

ference and that they specify how many degrees of freedom were assumed for the statistical comparison. This is not to question their conclusion of no difference between 58% and 56% recovery rates, but to address a conceptual point. If a one-tailed test were conducted as stated with the power assumptions, then no conclusions of superiority for sprinkles could have been possible; one would be testing an asymmetric hypothesis to find either 1) that the ferrous sulfate was 10% better than fumarate or 2) that it was not.

The second point relates to their assumptions about the magnitude of the response to anemia treatment. The actual findings in their study fell far short of their expectations for a cure rate: in the 2-mo trial, 80 mg microencapsulated ferrous fumarate added to porridge (sprinkles) cured 56.3% of the anemia, and 40 mg ferrous sulfate in elixir (iron drops) cured 57.7% of the anemia. The optimistic interpretation of this finding is that 40% of the children were compromised in their ability to respond to iron because their anemia was due to malaria, another infection, or some other micronutrient deficiency. Thus, in fact, 100% of the “truly responsive” candidates in both wings of the intervention trial were cured by the iron treatments. Such a direct and simple interpretation could be seen as being bolstered by the coincident findings in malarial areas of Kenya (1) and the Ivory Coast (2) that 22% and 44%, respectively, of the subjects with anemia did not have iron deficiency and by the authors’ own findings that malaria-infected children have a 23% lower chance of responding to iron treatments than do children without malaria (3).

Unfortunately, a more complex and pessimistic interpretation seems to be more logical; this interpretation even challenges the possibility of attributing any specific fraction of the anemia response to the iron treatments in the absence of concurrent observations on a third treatment wing, which serves as a placebo control. The authors address this issue in their statement: “Because it would be unethical to provide a placebo to a child with anemia, we did not include a placebo control” (3). Such a proclamation of ethical absolutism could be taken more seriously had it not come from 2 of the institutions that conducted one of the largest placebo-controlled trials of vitamin A and child morbidity and mortality ever conducted (5, 6). Are we to accept that 2 mo of observation of children with hemoglobin in the 70–99-g/L range is unethical, but it is acceptable to follow children at risk of hypovitaminosis A for an entire year in a placebo trial with mortality among the outcome variables? The consequence of this doctrine for anemia research in Ghana would mean that any field team in that country must surely bring liters of iron drops along with the HemoCue apparatus and lancets in their backpacks, because teams would be obliged to treat almost all comers after any survey. This drawback is especially valid if one realizes that newer international standards for “anemia” in this age group have a cutoff of 110 g/L (7). If 65% of Ghanaian infants and toddlers in this region have a hemoglobin below the 100-g/L anemia definition used to enroll a presumably iron-responsive sample (3), over 90% might be classified as anemic with the more conventional 110-g/L criterion. It would be worth knowing what treatment, if any, was offered by Zlotkin et al to those children found on initial screening to be in the <70-g/L range of hemoglobin (ie, severely anemic) and those found to be in the 100–109.9-g/L range (ie, mildly anemic by international standards).

Without a placebo group, moreover, we are at a loss to assess the attributable efficacy of either form of iron in this study (3). Because all the children were chosen to be in the lower part of the hemoglobin distribution, mathematical regression to the mean would account

for some of the test-retest increment in hemoglobin concentration. This regression-to-the-mean term, moreover, might be larger than anticipated, given the fact that capillary finger-stick samples were used. Morris et al (8) examined the reliability (within-individual variability) of measurements of hemoglobin concentrations in capillary blood. From samples taken from the same persons, either concurrently from different anatomical sites or on consecutive days, they showed that concentration measurements in capillary blood have lower reproducibility than do those in venous blood, which is attributable to larger biological variation with peripheral sampling than with venous sampling. Hence, those children admitted into the eligible study pool on the basis of a hemoglobin concentration just below 100 g/L at baseline might have a hemoglobin concentration just above the criterion level at the second measurement merely because of the inherent unreliability of capillary samples (8). Another reason for the improved anemia status of the subjects may simply have been the development of the subjects during the 2 mo of the study; anemia rates tend to improve with age after infancy. Moreover, the effects of regression to the mean or asymmetrical diagnostic misclassification, in addition to developmental changes, could account for some of the observed improvements in the rates of anemia; thus, to determine the true degree of improvement in anemia attributable to the iron treatment, there would have to be a no-treatment (placebo) wing in the study design.

Aside from the issues of quantification with regard to efficacy, we also encountered a problem in the authors’ evaluation of safety. The authors comment on the similarity of the 14.5% rate of diarrhea with the ferrous sulfate treatment and the 12.8% rate with the ferrous fumarate treatment (3). Although we can readily accept the conclusion of no difference between treatments with regard to diarrhea experience, the design does not provide sufficient evidence to safeguard against intrinsic adverse effects of microencapsulated ferrous fumarate. Only by knowing that a no-treatment group also had diarrhea incidence in this range could we exonerate the iron treatments of causing the gastrointestinal symptoms. With regard to the assumptions of safety for a new treatment, moreover, its comparison with a placebo is procedurally indispensable. Even if the authors offer us “efficacy relativism” in the conclusion on the basis of comparative effects with the proven therapy as the standard for anemia cure (3), we simply cannot accept this logic of “safety relativism” with regard to adverse effects. It would not be sufficient to argue that sprinkles are safe on the basis of the fact that they do not have any more adverse effects than the elixir form of ferrous sulfate. The latter is an old medication that may have been grandfathered into the pharmacopeia with safety criteria that we may not now accept for a new agent or format. For new questions of safety, comparison against no exposure would still seem to be needed at some point.

The final conundrum for the ethical imperative to treat all anemias on sight comes from the findings of the 3 previously mentioned African studies in malarial areas. In Kenya, 22% of anemic children with a median age of 19 mo did not have iron deficiency anemia (1); in the Ivory Coast, 44% of anemic children with a mean age of 49 mo did not have iron deficiency anemia (2); in Ghana, 40% of anemic children with a mean age of 13 mo did not have iron-responsive anemia (3). Malaria is not the only possible confounding factor. In our 10-wk, placebo-controlled intervention with heme iron and ferrous sulfate in children with a mean age of 21 mo in the nonmalarial Guatemalan highlands, ≈43% of anemic children (hemoglobin concentration <115 g/L) had no evidence of iron deficiency (4). Thus, if we are to believe Zlotkin et

al that “it would be unethical to provide a placebo to a child with anemia,” the question is what do we treat the child with to cure the anemia? Iron will work for some children, although we do not know a priori which ones; what do we offer to the rest, and when?

This is not just an ethical question for investigators and their populations, who are screened for eligibility on the basis of anemia. It underlies a very important program and policy issue for micronutrient deficiency interventions in developing (and developed) countries: when is an anemia a nutritional anemia, and when is a nutritional anemia an iron deficiency anemia? The results of all of the studies from Africa and Central America cited in this letter seem to converge toward a conclusion that “close to 100%” can no longer be the answer for either question. We may be obliged to do the “unthinkable,” namely, to screen and diagnose anemias *before* assigning treatments both in human research and in the public health domain. The experience reported in the articles from Kenya (1) and the Ivory Coast (2) provides a basis for such diagnostic screening.

Finally, the authors leave some numerical issues to be resolved. Although they reported screening 880 children and enrolling 557, in the side effects subsection of Results, they state, “Seventy-four percent (933 of 1277) of the mothers of children in the drops group,” and “Diarrhea was reported in 76 of 523 ... subjects in the drops group and in 62 of 486 ... in the sprinkles group.” These latter figures must represent typographical errors that were not detected in editing.

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Reply to NW Solomons and K Schümann

Dear Sir:

The major criticism by Solomons and Schümann of our recently published study (1) was our lack of a placebo control in the protocol, although their stance on this issue is equivocal, because they also criticize previous studies that included a placebo control. We stand firmly by our decision not to include a placebo control group. We recognize the extensive international debate on this issue (2, 3). In our study of infants in Ghana who had moderately severe anemia, subjects in a placebo group would have received no treatment, which is exactly what they would have received had they not been enrolled in the study. Yet, there is extensive literature on the adverse effects of moderately severe anemia (4). If the current local standard therapy is to do nothing, is it justifiable to include that standard therapy as a study arm? We agree with other ethicists that the standard of providing no less than people are able to get in their own country (which often is nothing) is a standard that is too low (S Benetar, unpublished observations, 2000). We strongly believe that, in clinical research, it is not ethical to offer a “treatment” of doing nothing just because that is what otherwise would be available to the population under study.

Solomons and Schümann make mention of earlier placebo-controlled vitamin A supplementation studies in Northern Ghana by members of our research group, which were conducted between 1988 and 1991 (5, 6). These studies formed part of a second generation of important field trials carried out in several countries that verified the landmark findings of Sommer et al (7). At that time, there was no global policy on universal vitamin A supplementation to children; nor was there a national program in Ghana. The protocols for these trials were reviewed and approved by the relevant ethics committees and the Ministry of Health of Ghana. We believe that it is unethical to withhold treatment of anemia today, and similarly, it would be unethical today to conduct a placebo-controlled trial of vitamin A supplementation in children. This issue begs the larger question of how to identify when the global scientific community has concluded that a specific research question has been adequately answered. In the case of treatment of iron deficiency anemia, we believe that the question has been answered and that further placebo-controlled confirmation studies are both unjustifiable and unethical.

Solomons and Schümann suggest that the biological impact of our not having included a placebo control group would place them at “a loss to assess the attributable efficacy of either form of iron in this study.” Statistically speaking, this is true, but is there any biological plausibility to their statistical contention? We believe there is very little. First, the study was of very short duration. What possible mechanisms would lead to significant improvement in anemia in a group receiving no intervention for 2 mo? Because we believe that the primary mechanism causing the anemia was a lack of bioavailable dietary iron, we would have to ask whether a no-intervention group could have rapidly improved their diet with more sources of bioavailable iron, such as meat or poultry. This could have happened if there had been a significant improvement

in the economic status of families in the region—for example, that resulting from the sudden discovery of gold or oil deposits. That did not happen, and, to the best of our knowledge, the economic standards of the communities in the region remained static (and very poor). Thus, we doubt that anemia would have improved if a no-intervention group had been included.

Regression to the mean might have accounted for some of the test-retest increment in hemoglobin concentrations, but true regression to the mean is a time-dependent statistical measure. Over the relatively short intervention Solomons and Schümann describe, regression to the mean would have been negligible. They also suggested that the wide biological variation in capillary finger-stick samples (wider than that in venous samples) might have contributed to the regression to the mean. Again, we disagree. Although we acknowledge the wider variation in capillary samples, the variation may result in either an overestimation or an underestimation of hemoglobin concentration (compared with concentrations in venous samples) and thus would not contribute to a regression to the mean (which would imply a bias only to higher hemoglobin values).

There is nothing in the literature to support Solomons and Schümann's contention that economically disadvantaged infants with anemia due to dietary inadequacy will rapidly improve with no intervention. Thus, although we cannot calculate the attributable change in incidence of anemia in the population we studied, we maintain that the argument against any treatment is fallacious.

Solomons and Schümann question our ability to comment on safety without having included a no-treatment group. They accuse us of "efficacy relativism." We are guilty as charged, but we would argue that we did not include a no-treatment group for the reasons previously outlined and, perhaps more important, that neither ferrous fumarate or sulfate needs the rigorous scrutiny of a "new treatment." Both have been used for decades with documentable side effects such as dark stools, strong metallic taste (ferrous sulfate), staining of teeth (ferrous sulfate drops), and change in gut flora but little else. In sprinkles, ferrous fumarate is coated with a thin layer of soybean lipid to mask the taste of the iron and to prevent changes in the color or taste of the food to which the sprinkles are added. But the form of iron (ferrous fumarate) is not new, and, indeed, in our reported study, given that the fundamental comparison was between the 2 formulations (ferrous sulfate and fumarate), the comparison of diarrhea prevalence was similarly valid.

Solomons and Schümann make the valid point that not all anemias, even in malaria-endemic areas, are due to iron deficiency. We totally agree. Some anemias may be due to blood loss from parasitic infection or to other nutrient deficiencies. One of the advantages of the sprinkles concept is that several micronutrients can be included in the sachet for delivery to the infant. In the current study, we included ascorbic acid to enhance iron absorption. In an ongoing project in Mongolia, we included vitamin D (in addition to iron, ascorbic acid, zinc, vitamin A, and folic acid) in the sachet, because, in Mongolia, anemia and vitamin D deficiency rickets are the 2 most prevalent nutritional problems in children. Thus, we agree with Solomons and Schümann that our study, along with the other studies cited in their letter, "underlies a very important program and policy issue for micronutrient deficiency interventions in developing (and developed) countries...." However, we disagree with their conclusion that "we may be

obliged ... to screen and diagnose anemias *before* assigning treatments...." If their conclusion were given credence, the burden of the human and financial costs incurred would literally put a halt to international anemia intervention programs, which are already going at an unacceptably slow pace. Since 1990, when the World Health Assembly on Children proclaimed that the prevalence of anemia should be lower by the year 2000, it has actually increased (8). Instead of the retrogressive measures suggested by Solomons and Schümann, we believe that there are several innovative interventions on the horizon for anemic infants in malaria-endemic settings, including the Malaria Intermittent Treatment that is being seriously considered by the World Health Organization (9) and the use of sprinkles containing several micronutrients.

Finally, Solomons and Schümann were confused about the description of side effects and adherence to treatment. We originally wrote that "starting 2 wk after baseline and then every 2 wk for the duration of the study, mothers were asked about compliance with treatment over the preceding 7 d, and fieldworkers checked supplies of drops and sachets." We used all of the data from the 4 monitoring visits, and thus the denominator represents the combined data.

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Erratum

Friedl KE, Westphal KA, Marchitelli LJ, Patton JF, Chumlea WC, Guo SS. Evaluation of anthropometric equations to assess body-composition changes in young women. *Am J Clin Nutr* 2001;73:268–75.

It is incorrectly reported in the Abstract that the women gained 2.5 kg fat-free mass, rather than the 2.0 kg correctly reported in Table 2 and discussed in the text. In Table 3, the equation of Jackson et al (23) is incomplete, and the coefficients provided are wrong. Readers are unable to calculate a meaningful value from this equation and cannot determine which equation from the cited paper was used. Friedl et al actually used the first of the 18 equations published in Jackson et al's article (see below), and this was their intention. Friedl et al have verified that the calculations were done correctly in the master data set and that their analyses were appropriately based on these calculations. The correct equation is

$$\begin{aligned} \text{Body density} = & 1.0970 - 0.00046971(\text{sum of 7 skinfold thicknesses}) \\ & + 0.00000056(\text{sum of 7 skinfold thicknesses})^2 - 0.00012828(\text{age}) \end{aligned}$$

Friedl et al regret the inconvenience that these errors may have caused their readership.

Erratum

Persky VW, Turyk ME, Wang L, et al. Effect of soy protein on endogenous hormones in postmenopausal women. *Am J Clin Nutr* 2002;75:145–53.

In Table 2, the units for plasma isoflavone concentrations should be nmol/L instead of $\mu\text{mol/L}$.