Discussion on Vitamin $B_{12}$ and Folic Acid Fortification

Forty years after the discovery of vitamin $B_{12}$, there is still much work left to be done. This connects also with Dr. Troen's remarks on folic acid. The powerful effects of the randomized controlled trial that led to the decision in some countries to fortify flour with folic acid in order to prevent neural tube defects present additional challenges for interpretation. The message of those trials was not just that there needs to be better folic acid status in the preconceptional period in order to limit, even if not to altogether prevent, the incidence of neural tube defects. Another message of those trials is that we need to be much more concerned about the entire nutritional status of women in the periconceptional period. This isn't just about folic acid, nor is it even just about those other micronutrients which may be involved in prevention of neural tube defects. We have heard throughout these few days that the maternal nutritional status before as well as during pregnancy and even after pregnancy is a very important target with really substantial public health implications much beyond the prevention of neural tube defects. Perhaps this returns us to the observation that was made by Dr. Jooste. I will paraphrase his story about 'think globally and act locally' to say we need to think critically globally and act locally upon a much better nutritional database than we currently have. The notion to me of a flour fortification initiative that says that we need to use data from a limited number of countries to make public health decisions about fortification or even levels of fortification throughout the world, without knowing nearly enough about the status of either folate or $B_{12}$ or other factors, strikes me as not thinking critically globally. As Dr. Allen states, we have a need for a lot more information about $B_{12}$ status around the world, and about folate status around the world, not just to consider the incidence of neural tube defects.

When asked to comment further on what we know about the efficiency of absorption of either folate or $B_{12}$ from breast milk (since one mistake of the DRIs was to suggest that the absorption of breast milk folate was less efficient than the absorption of synthetic folic acid), Dr. Allen stated that it's clear that
early in infancy the mechanism of absorption is different from later in infancy. Vitamin B\textsubscript{12} is probably absorbed bound to haptocorrin early in infancy and then later there is enough intrinsic factor and peptic digestion for B\textsubscript{12} to be absorbed as free B\textsubscript{12}. B\textsubscript{12} is bound incredibly tightly to haptocorrin in milk, which is why the assay has been difficult. Interestingly, Dr. Lönnerdal showed that the haptocorrin reduces the growth of \textit{Escherichia coli} in the intestine, so that's another reason why it's also probably really important. She didn't know what percent is broken down and absorbed. Because the assays were wrong formerly, we underestimated requirements of those infants and breastfeeding women. The values are going to be double. There is a big study going on in Denmark where they don't have supplementation of women in pregnancy and lactation to get normal values for breast milk vitamin B\textsubscript{12}.

In response to Dr. Kalantari's comment that the B\textsubscript{12} content of breast milk is dependent on the daily diet of the mothers, Dr. Allen noted that one interesting thing about B\textsubscript{12} is that the efficiency of absorption falls off quickly with increasing doses, even in the usual range of intakes. For example, she has just done a study with eggs labeled with isotopic B\textsubscript{12}, and you get half the absorption from two eggs as you do from one egg. So, it appears not to make any difference whether you eat one or two eggs. Even in the low range of intake, if you give a dose in one bolus, then you have poor efficiency of absorption, and so that's what we are doing when we give these high-dose supplements to lactating women. That's why when treating B\textsubscript{12} deficiency, physicians give high doses, and that's because only 1\% of those high doses are absorbed compared to 50\% of really low doses. So, you really need a system with B\textsubscript{12}, where you are delivering it in small amounts during the day to have an effect. And then the other unknown is what comes from the mother's liver. Clearly, mother's status is related to infant's status and infant's liver content even 2 years after they were born. Perhaps some of the B\textsubscript{12} in breast milk comes from stores and not from current intake. We are not certain about that with practically any nutrient, how much comes currently from the mother's diet versus from stores that she already has. But she thinks the efficiency of absorption is the issue here.

Dr. Allen added one really important comment about folate and B\textsubscript{12} that the folate concentration in breast milk is not much affected by maternal status. What happens is that the mother gets more and more depleted as lactation goes on if she is not replacing it from the diet, and the breast milk levels change hardly at all, so you don't get infant depletion as a result of low breast milk levels of folate, nor does high folic acid intake affect breast milk levels very much.

Dr. Penny asked whether Dr. Allen could give some idea about how much animal source food is needed and for how long in terms of amount for women and for children.

Dr. Allen replied that in Kenya we fed sort of the RDA as animal source foods as milk or meat to schoolers of whom about 80\% were deficient or depleted. After a year, we had a substantial improvement, after 2 years the severe
deficiency went away, but we still had a lot of depletion and even deficient levels. In Guatemala, what I didn’t show were the results of this intervention study where we gave meat to these kids or the RDA as supplements, and that had absolutely no effect on their serum levels of B₁₂ over one meal a day feeding 70 g of beef or the equivalent of about a microgram of B₁₂. I don’t think it’s malabsorption because those that were drinking cow’s milk were doing just fine, and the cow’s milk had much higher levels of B₁₂ in it than we were giving. So, it’s hard to replete a B₁₂-deficient person once he/she is depleted, and we need to understand much more about that.

Irwin H. Rosenberg