Discussion on Folate and Vitamin $B_{12}$ Importance in Cognitive Development

Dr. Troen has provided a contemporary insight into the ways in which folic acid and vitamin $B_{12}$, their interactions and deficiencies might impact upon cognitive and brain development in the child and even at the other extremity of the life cycle, older age. We need to remember that when we speak about folic acid, we need to add our specificity, especially when we refer to the possibility of adverse effects. Folic acid is a synthetic form of folate. The synthesis was accomplished in the late 1940s. The synthetic form of the folic monoglutamate is not the same as folate in foods which tend to be reduced and tend also to be in the conjugated form of polyglutamates. As we think about the effects of folic acid administered as a supplement before or during pregnancy, we need to speak in terms of whether there are special effects of synthetic folic acid, which has to traverse a somewhat different metabolic pathway than so-called ‘natural’ folate. That distinction is probably going to turn out to be important as we explore further the matter of epigenetics and the way in which folic acid or other methyl donors may be influencing gene and gene expression. Also the pathways leading to methylation of the DNA genome are going to be a very interesting approach to epigenetic regulation.

Regarding brain development, as with physical growth and development, deficiency of almost any essential vitamin and mineral (as we have heard with iodine and iron and other B vitamins, thiamine, niacin and vitamin $B_6$) can affect brain development and cause disease. The complex relationship between nutritional status of micronutrients and brain development is before us. The special consideration that was emphasized by Dr. Troen is the interaction of the last two of the discovered vitamins. I remind you that the last two vitamins that were discovered in the 1940s and 1950s were folic acid (which became vitamin $B_9$) and vitamin $B_{12}$. (It turned out that vitamin $B_{10}$ and $B_{11}$ were both forms of folic acid.) But the history is entrained in a very important way so that before we had the identification of vitamin $B_{12}$, while we already had synthetic folic acid, folic acid was used in the treatment of pernicious anemia even before it was known that pernicious anemia was vitamin $B_{12}$ deficiency conditioned
by an absorption defect of intrinsic factor. The result was that many patients were reported to have a worsening of their neurologic problems when they were treated with high doses of folic acid before we learned that vitamin B\textsubscript{12} was the therapeutic need. These observations had a large impact on the later definition of the safe upper level of folic acid, which was defined in the DRI (Dietary Reference Intake) report for the US Institute of Medicine in terms of what would happen if you gave large doses of synthetic folic acid in the presence of limiting vitamin B\textsubscript{12} status. That continues to be a challenge for us now, and it reemphasizes the importance of updating our information about what should be the safe levels of folic acid supplementation using synthetic folic acid. I am not talking about any adverse effect of folate as food folate. Perhaps in the next version of the DRIs we are going to have to look at a much more complex interaction using some of the kinds of methodologic evaluations that Dr. Troen presented (including epigenetic gene expression) to arrive at an understanding of not only how folate and B\textsubscript{12} influence brain development and cognitive development but perhaps how their interaction might be important in the generation and maintenance of health.

When Dr. Troen was asked whether he thinks that the closure of the developing neural tube in the presence of perhaps adequate amounts of folic acid is a good model for us to be thinking about the effect of folic acid on brain development, he replied that we still don’t understand the mechanism despite the powerful effect of folic acid supplementation. There are clear trophic effects of this metabolic pathway on different aspects of brain development at different critical windows. Perhaps the problem we have with fortification is that we undertook the public health initiative to prevent neural tube defects without full knowledge of observations in populations that are exposed with respect to a whole range of other important health outcomes and risks.

Dr. Haschke added two questions related to epigenetic phenomena which Dr. Troen described, the first one is the Indian study on maternal B\textsubscript{12} and cognitive function at 9 years of age. We must be very careful because this is a highly selective population in terms of nutrition. The low vitamin B\textsubscript{12} cohort is probably a vegetarian cohort, and it might be that the children have also very low B\textsubscript{12} intake as children from parents who are vegetarians. And the second phenomenon described is the periconceptional folic acid supplementation. The study by Steeger seems to show lower birthweight if the mothers are supplemented. This was not the primary outcome of the study, and the sample size is much too small to really show differences in birthweight. You need at least 80–100 per group to rule out the type 2 error. If folic acid when given perinatally results in lower birthweight, this potentially important finding has to be confirmed in adequate studies.

Dr. Troen added that we don’t know that the Steeger’s study demonstrates that there is an effect of periconceptional folic acid on birthweight. We are looking at one gene. His point was that by virtue of our standard practice we can
show a measurable effect on a measurable biological change that has a known consequence in terms of expression of the gene product and downstream effect. But that's one gene out of our entire genome, the entire genome is exposed, the whole panel of imprinted genes is exposed, we don't know what this does overall. So, he was not unduly concerned, and he doesn't think that we have reduced birthweight across the folic acid-fortified population.

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