Discussion on Iron

Discussion of Session V was focused on two important aspects of iron nutrition that have a significant impact on current efforts to reduce the worldwide prevalence of iron deficiency. The first presentation by Dr. Hurrell dealt with the effects of inflammation on iron absorption, and the second by Dr. Brittenham with safety issues and the putative risks of supplementation in regions where malaria is endemic.

The currently available strategies for alleviating nutritional iron deficiency are dietary diversification, supplementation, food fortification and biofortification. Fortification of staple foods and/or condiments is currently regarded as the best long-term approach to reaching all segments of the population. However, there are several obstacles to ensuring adequate absorption. The choice of iron compound, the food matrix and interactions with other nutrients are all important, but physiological control is the major determinant of absorption [1].

Hepcidin is the systemic regulator of iron absorption. Plasma levels rise in concert with increasing iron stores. Hepcidin binds to ferroportin, the only known cellular iron exporter on the surface membrane of intestinal mucosal cells and macrophages, causing it to be internalized and degraded, thereby inhibiting iron absorption and its release from stores.

Hepcidin is also a type II acute-phase reactant. Iron absorption is therefore decreased in infectious and inflammatory disorders adding another level of complexity to the correction of iron deficiency in regions where malaria and other infectious disorders are prevalent. Dr. Hurrell presented experimental evidence from studies employing stable isotopes demonstrating increased concentrations of inflammatory cytokines, C-reactive protein and hepcidin, and significantly decreased iron absorption in children with febrile malaria and women with afebrile malarial parasitemia. Dr. Sall asked whether minor infections such as skin infections and rhinitis that are common in Senegal have the same effect. In reply, Dr. Hurrell indicated that there is as yet no information on iron absorption in the presence of other infections, but that his group’s studies suggest that there is some degree of inhibition of absorption in regions with widespread infection. In response to a question from Dr. Rosenberg, Dr. Hurrell said that there is,
however, no direct evidence of reduced efficacy of fortification in regions where malaria is endemic. Salt fortified with ferric pyrophosphate was equally efficacious in Morocco (no malaria) and Ivory Coast (prevalent malaria). However, the studies compared different groups of children. More research is needed to clarify this issue. Efficacy should be compared in children drawn from the same population who are either healthy or infected. Dr. Hurrell also mentioned that based on their observations, the incorporation of iron into hemoglobin is not affected by infection.

The optimal approach to nutritional iron deficiency in the presence of infection was discussed briefly. Clinicians have traditionally withheld iron supplements until the infectious process has been controlled because the iron is unlikely to be absorbed and could be harmful. It may increase the virulence of pathogens. Iron requirements are reduced during episodes of infection because erythropoiesis is suppressed. Iron is redistributed from the functional compartment to stores. This iron is readily mobilized once normal erythropoiesis is restored. The effect of recurrent periods of infection on the iron status of iron-sufficient individuals may consequently be relatively limited. The impact is likely to be greater in those who are iron deficient because their ability to restore optimal iron balance is limited by infection. Individualized supplementation in the intervals between episodes of infection is unlikely to be feasible. Moreover, the intake of staple foods or condiments fortified with iron cannot easily be adjusted for recurrent infections. The best approach may be the use of highly bioavailable iron compounds that allow rapid upregulation of iron absorption during the intervals between episodes of infection.

Dr. Hurrell’s presentation describing the putative relationship between obesity and iron absorption generated a lot of discussion. Dr. Bhatia pointed out that the correlation between body mass index and iron absorption in the Thai women reported by Zimmermann et al. [2] is not very strong. This was, however, a retrospective analysis using data from an earlier study. The women were only mildly overweight with an average body mass index of 27.

The postulated etiology of reduced iron absorption in obese individuals is increased hepcidin production caused by proinflammatory cytokines secreted by visceral fat. While accepting the evidence of poor iron status in obese children, Dr. Haschke questioned the pathogenetic relationship between obesity and impaired iron absorption at this age. He stated that the distribution of fat in children is different from that in adults. Children have less central obesity and visceral fat which is the site of cytokine production. However, the evidence presented by Dr. Hurrell strongly supports an inflammatory process as the link between overweight and reduced iron absorption. Iron intake did not seem to be an important factor. It was the same in overweight and normal-weight children in their Swiss study. Dr. Zimmermann pointed out that children as young as 6 years of age have increased IL-6 and C-reactive protein associated with obesity. This relationship has been observed in healthy children in Switzerland,
Italy and the United States. He went on to mention a soon to be published prospective study in South Africa which includes obese, normal-weight and stunted children. The observed odds ratio of remaining iron deficient after a period of supplementation among obese children is twice that of the other two groups.

Childhood obesity and its potential long-term consequences are the subject of intensive research at the present time. To some extent, the disagreement between the discussants may have been their failure to specify the age groups of the children that they were commenting on. There is a considerable body of evidence supporting an association between obesity and low-grade inflammation in children over the age of 3–6 years, the age group that Dr. Zimmermann was referring to. The situation may be more complex in younger children [3]. Finally, Dr. Zhou asked about the practical implications of the reduced iron absorption associated with obesity. In Dr. Hurrell’s opinion, it is too early to make specific recommendations. More research is needed to define the magnitude of the effect as well as the long-term consequences.

One aspect of the relationship between inflammatory and infectious disorders and iron absorption was not discussed. Some conditions affect the duodenal mucosa directly. Chronic Helicobacter infections may lead to achlorhydria and reduce iron absorption in older men and women [4]. Gluten enteropathy (celiac disease) may cause significant impairment of iron absorption. It is prevalent in several western societies. Finally, the possible role of tropical enteropathy and recurrent diarrhea deserves further study.

In reply to a question from Dr. Bhatia, Dr. Hurrell stated that it is difficult to document the impact of mass fortification in western countries. The practice was introduced without any prior efficacy or effectiveness studies. The evidence for an impact of fortification of infant foods on the prevalence of early childhood anemia is more convincing. Mass fortification is nevertheless generally considered to be a contributor to the very low prevalence of iron deficiency in the United States. At least 20% of the iron consumed is derived from fortification. On the other hand, the impact of current policies addressing mass fortification in the developing world may be considerably smaller. Dr. Hurrell described briefly an analysis carried out a few years ago to evaluate the potential impact of wheat flour fortification in 78 countries that have established national programs to fortify wheat flour with iron as well as other micronutrients [5]. The conclusion drawn from the analysis was that an impact on iron nutrition could be expected in only 6 countries. The primary reason for the anticipated lack of effectiveness is the widespread use of iron compounds that are not bioavailable, particularly hydrogen-reduced iron powders. They are favored by millers because of their low cost and lack of chemical reactivity. The workshop participants recommended that efforts be made to convince millers to use electrolytic iron or other more absorbable iron compounds instead of hydrogen-reduced iron powders.
There were two questions related to the risk of fortification. Dr. Ganguly asked about the effect on potentially pathogenic bacteria in the gastrointestinal tract. Dr. Hurrell replied that in their study in the Ivory Coast there was a fivefold increase in pathogenic enterobacteria and a decrease in lactobacilli among the children receiving biscuits fortified with electrolytic iron [6]. They also reported evidence of gut inflammation. However, more research is needed to establish the practical implications of this finding. Dr. Bhatia expressed his concern about iron overload in individuals who are iron sufficient and consuming a fortified diet. Dr. Hurrell replied that the risk for the general population is low. Individuals who are single trait carriers of the common form of hemochromatosis (HFE hemochromatosis) or the thalassemia syndromes do not accumulate excess iron. The problem is limited to the minority of individuals who are hemochromatosis homozygotes and those who have clinically evident thalassemia. The risk is further reduced in HFE hemochromatosis because of the low penetrance of the disorder.

Dr. Brittenham introduced his presentation by describing the dilemma faced by nutritionists because of the observations reported from the iron, folic acid and zinc supplementation trial carried out in Pemba, Tanzania [7]. The results indicate that the risk for severe morbidity and mortality from malaria is increased in young children who are iron deficient. On the other hand, universal iron and folic acid supplementation raised the risk for severe morbidity and mortality in the population of children under the age of 3 years as a whole. The results of this trial were discussed in some depth. It was pointed out that earlier smaller studies raised concerns about the risk of iron supplementation in regions where malaria is endemic. However this very large, well-controlled trial is the first to provide a more definitive answer. It would be valuable to know whether we are dealing with a relatively minor although important factor that affects the whole population or a more powerful contributor in an as yet unidentified subgroup. Dr. Black stated that the data from the Pemba study do not provide the information that would be needed to address this issue. A redesigned trial with the statistical power to answer the question does not seem feasible at the present time. Dr. Brittenham said that alternative approaches that are focused on developing a better understanding of the underlying pathophysiological mechanisms are more likely to be fruitful. Such studies should include pregnant women.

Dr. Rosenberg suggested that folic acid supplementation could have played a role since it was always given with the iron, and the antimalarial drug being used at the time is an antifolate agent. Dr. Black discounted this possibility because responses in community and hospital-treated children did not differ. Furthermore, earlier studies tend to incriminate iron.

The putative risk of iron supplementation in the setting of other infectious diseases was discussed briefly. Dr. Brittenham stated that there is evidence implicating iron in HIV disease and tuberculosis, and that the observations made by Zimmermann et al. [6] suggest that it may well play a role in diarrheal
diseases. They reported that iron fortification favors the growth of potentially pathogenic gut bacteria associated with inflammation of the gastrointestinal tract in African children.

The postulated mechanisms for the adverse effects of iron supplements were discussed at some length. A pivotal role for non-transferrin-bound iron (NTBI) is favored at the present time. It could promote microbial virulence. Dr. Brittenham described recent unpublished observations that he and his colleagues have made that support this contention. When blood that has been stored for some time is transfused, the red cells are rapidly sequestered and processed in the spleen resulting in the release of NTBI. They transfused stored blood into healthy human volunteers. Blood samples from these volunteers contained NTBI. They allowed bacteria that cause infections in human beings to grow more readily, suggesting that NTBI may well increase the risk of severe morbidity and mortality from bacteremia.

The mechanisms that lead to increased morbidity in malaria may be different. Dr. Brittenham listed several possibilities in his presentation. One involves increased expression of endothelial adhesion molecules, which might lead to the sequestration of Plasmodium falciparum-infected erythrocytes in the microvasculature causing obstruction and severe clinical manifestations such as cerebral malaria. Dr. Brittenham pointed out that if this postulate proves to be correct, supplemental iron may not be a risk factor in vivax malaria since vascular adhesion does not occur. It might also provide an explanation for potentially disastrous consequences of P. falciparum malaria in pregnancy.

The concentration of NTBI is proportional to the serum iron level. The serum iron rises rapidly after a dose of supplemental iron. The height of the rise is determined by dose, the presence of absence of food and the iron status of the individual. The highest levels occur when supplemental iron is consumed in the fasting state. When taken with food, the increment is smaller. There is no measurable increase with fortification iron. It seems paradoxical that the highest peak serum iron levels are encountered in iron-deficient individuals who seem to benefit from iron supplements. One would anticipate the generation of more NTBI and increased risk in them. However, Dr. Solomons said that they have unpublished observations demonstrating that the areas under the curves for NTBI concentrations after a dose of supplemental iron are similar in iron-sufficient and iron-deficient volunteers. In addition, NTBI clearance may be accelerated in iron deficiency because of the increased demand for iron.

Several questions related to the best pragmatic approach to iron deficiency in individuals suffering from malaria or other infections. Dr. Brittenham recommended that the infection be treated before giving iron since there is usually no immediate urgency to correct iron deficiency. Dr. Solomons pointed out that although the correction of iron deficiency is not regarded as urgent in the clinical sense, periods of iron deficiency in early childhood may have long-term consequences for physical, cognitive and emotional development. Iron
deficiency should therefore be corrected as soon as possible. Dr. Brittenham concluded by saying that there are no simple, universally applicable answers to these questions. The guiding principle should be avoidance of the production of NTBI by using lower doses of iron over longer time periods. He also emphasized the importance of prevention in infancy and childhood. Enhancement of the mother’s iron status during pregnancy and the correction of iron deficiency in women before pregnancy are essential.

Sean Lynch

References