

## Editorial

Already Joseph Glanvill (1636–1680), an English writer, philosopher and clergyman, stated that ‘Iron seems a simple metal but in its nature are many mysteries and men who bend to them their minds shall, in arriving days, gather therefrom great profit, not to themselves alone but to all mankind’. Indeed, we have learned that iron is essential to virtually all living organisms. The most important biological characteristic of iron is its capacity to oscillate between the divalent and trivalent status, ferrous ( $\text{Fe}^{2+}$ ) and ferric ( $\text{Fe}^{3+}$ ) iron, thereby donating or accepting 1 electron. It is most likely this ability to transfer electrons together with its abundance in nature that made evolution select iron as a prosthetic group of a number of iron-dependent proteins with key functions in a remarkable array of metabolic processes. Besides its role in hemoglobin and oxygen transportation to the tissues, iron is critical for normal brain development including myelination and transmitter function, for a functional immune system, ATP production, protein and DNA synthesis, and thereby tissue regeneration.

Due to the rapid growth during infancy, iron requirements in late infancy are higher than during any other period in life, and iron deficiency (ID) is in fact the most common nutritional deficiency in children worldwide with a high prevalence in both low- and high-income countries. It is estimated that close to 50% of preschool children are anemic globally, and most of these children are anemic due to ID. Although ID is most prevalent during periods of rapid body growth, i.e. from 6 to 24 months of age and again at puberty, the prevalence rates in developing countries are often generally high throughout childhood.

Thus, it is quite clear that prevention of ID is an important task as well as treatment of already established deficiency, particularly if it is pronounced enough to cause iron deficiency anemia (IDA). Iron is, however, a double-edged sword because of the ability of ferrous iron to reduce oxygen intermediate species to harmful free radicals. Due to this and the low solubility of ferric iron at physiological pH, all organisms have binding molecules, or chelators, in order to transport and store iron and to control its reactivity. The concentrations of these are often used to assess iron status. During recent years, it has become increasingly evident that for many nutrients more is not necessarily better, and this is particularly true for iron. A challenging task is to define those individuals who are at risk of developing ID and those who have already established deficiency as well as to design proper preventive strategies and treatment protocols for those target groups or individuals. Much new information has been obtained during the last decade on the requirements, metabolism, physiological and neurodevelopmental effects of iron as well as of ID and the effects of various preventive strategies. Because of this and the lessons learned that this might be a more difficult challenge than previously thought, this issue of the *Annales Nestlé* is dedicated to the topic of ‘Iron in Infancy and Childhood’.

*Bo Lönnerdal* from the Department of Nutrition, University of California, Davis, Calif., USA, and *Olle Hernell* from the Department of Clinical Sciences/Pediatrics, University of Umeå, Sweden, introduce the readers to the dynamics of iron status during infancy in term and preterm infants as well as the molecular mechanisms of iron

absorption and its regulation. They raise the question if the conventional definitions of ID (typically defined as s-ferritin concentration <12 ug/l) and anemia (typically defined as hemoglobin concentration <110 g/l) are appropriate for infants, or if these definitions may in fact overestimate the prevalence of both ID and IDA. New cutoff values are suggested for these and other useful indicators of ID such as s-transferrin receptors, s-zinc protoporphyrin and mean cell volume. They also question whether definitions should be different for boys and girls based on a Swedish-Honduran study showing lower hemoglobin, mean cell volume and s-ferritin and higher s-transferrin receptor and s-zinc protoporphyrin concentrations in boys than in girls at 4, 6 and 9 months of age. At 9 months of age, boys were also at a greater risk of being classified with IDA than girls. To what extent these observations reflect normal physiological differences in these indicators between genders already at this age, or reflect higher incidence of ID in boys, needs to be studied. Another point raised is if iron homeostasis may not be fully developed at birth. Whereas 9-month-old infants appear to be able to downregulate iron absorption when they are iron replete, 6-month-old infants cannot do this. Iron may be provided to infants as drops or in iron-fortified products. There is evidence to suggest that the forms provided may be metabolized differently and excess iron in drops may cause adverse effects, possibly due to the limited ability to regulate iron absorption in young infants.

*Sally Grantham-McGregor and Helen Baker-Henningham* from the Tropical Medicine Research Institute, University of the West Indies, Mona, Jamaica, briefly explain why ID could affect neurodevelopment and cognition and then examine systematically and critically studies of ID and child cognitive and motor development and behavior for evidence of a causal link, thereby classifying the various studies based on how they were designed and the age of the children. It is noted that children with IDA generally come from poor socioeconomic backgrounds, which could account for some or all their deficits. On the other hand, it is clear that infants with diagnosed IDA have evidence of disturbed brain function. The authors rightfully point out that many trials aiming at treatment of ID lack statistical power due to small sample sizes, inclusion of children without ID in the sample, or due to iron treatment resulting in little or no differences in iron status between the placebo and the treated group(s). In children with IDA below 3 years of age, randomized trials indicate that iron supplementation is usually beneficial to motor development, but the effect on mental develop-

ment is inconsistent and more studies are needed. Iron supplementation also benefits cognitive function in school-aged children with IDA. Evidence for a threshold level of ID at which child development is affected seems inconsistent, but children with ID severe enough to result in IDA are most likely to benefit from iron supplementation.

*Maria Andersson and Richard F. Hurrell* from the Human Nutrition Laboratory, Institute of Food, Nutrition and Health, Swiss Federal Institute of Technology Zürich, Zürich, Switzerland, discuss in depth various strategies to prevent ID in infants and children. Generally accepted prevention measures for infants include iron supplementation of pregnant women, delayed cord clamping at delivery and exclusive breast-feeding for 4–6 months. That complementary foods given after the first 4–6 months are rich in iron is critical. Iron fortification of infant formulas, infant cereals, micronutrient powders for addition to home-prepared complementary foods, or provision of iron drops are the most effective prevention strategies. Early introduction of meat products and delayed introduction of cow's milk are also important. Effective strategies in older children include approaches to increase the iron content and bioavailability of the diet and consumption of iron-fortified foods. In areas of extensive ID, iron supplementation is often required, although iron fortification is the most cost-effective intervention strategy. However, only iron compounds of high bioavailability should be used. At home, iron fortification for infants and young children should be expanded in low-income countries. The authors suggest that all interventions to control pediatric ID should be integrated into larger national and global health programs for pregnant women and children, including health education, malaria prevention and deworming, and that the impact of ID prevention strategies on the prevalence of ID should be monitored by measuring iron status periodically in population-based cross-sectional studies.

Finally, *Klaus Schümann* from the Center for Nutrition and Food Research, Technische Universität München, Freising, Germany, and *Noel W. Solomons* from the Center for Studies of Sensory Impairment, Aging and Metabolism, Guatemala City, Guatemala, address the important issue of efficacy and safety of iron administration. Administration of iron is part of any strategy for preventing or reversing ID. Iron can be administered parenterally or, as mentioned, as fortified foods or oral supplements. Efficacy means the ability to reverse ID or increase iron stores. Once efficacy has been established, either via the enteral or parenteral route, the impact of an

intervention becomes the measure of effectiveness. Safety issues may appear at the point of administration, i.e. in the gut lumen, and as a consequence of excessive iron stores resulting from the interventions. Parenteral iron administration has not been widely used in children, but recent improvements in the pharmacology of parenteral iron compounds may change this, primarily for therapy in hospital settings, but even in public health. Oral supplementation in combination with folic acid (clinical setting) or multiple micronutrients (community level) is the cornerstone for treatment of IDA and for prophylaxis for the nonanemic population. Biofortification, i.e. enriching the iron content of crops during cultivation, is a novel approach to combat ID yet to be fully implemented or evaluated for children. Side effects and toxicity after oral iron intake are seen in the gut lumen. After oral and parenteral iron intake, the rise in circulating iron can increase the risk of complications from coexisting infections, notably with malaria, and when individual iron status is adequate. Growth impairment occurs with ex-

posure of iron-sufficient children to iron interventions, so that targeting of iron to ID individuals seems advisable. Numerous adverse consequences from accumulation of excessive total body iron stores show up as a consequence of iron-mediated oxidative stress.

Although the physiological role of iron and the importance of preventing and treating ID and IDA are old, much of the new knowledge gained has focused on infants and children and highlights that also with respect to iron infants and young children are different from adults. This is reflected by their requirements, development of iron status, iron homeostasis, strategies for prevention and not least by the risk of adverse effects of too much iron given to iron-replete individuals.

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