Recent Evidence from Human and Animal Studies Regarding Iron Status and Infant Development¹⁻³

John Beard*  

Department of Nutritional Sciences, Pennsylvania State University, University Park, PA 16802

Abstract  

Infants are at risk for iron deficiency as breast milk or formula is replaced by semisolid foods during weaning. The scope of this article is to briefly review new findings on developmental iron deficiency and the persistence of deficiency effects into adulthood. A lack of sufficient iron intake may significantly delay the development of the central nervous system because of alterations in morphology, neurochemistry, and bioenergics. Depending on the stage of development at the time of iron deficiency, there may be an opportunity to reverse adverse effects, but the success of repletion efforts may be time dependent. The program project on "Brain and Behavior in Early Iron Deficiency" (B. Lozoff, P.I.) undertook preclinical and clinical studies to identify the regions of the brain and behaviors affected, and perhaps irreversibly altered, by early-life iron deficiency. Multiple outcomes are being measured in humans, nonhuman primates, and rodents. Data in monkeys show significant effects on neurodevelopment with dietary iron deficiency. Findings in human infants are consistent with altered myelination and changes in monoamine functioning. Rodent studies show that effects of iron deficiency during gestation and lactation persist despite restoration of iron status at weaning. These cross-species studies indicate a vulnerable period in early development that may result in long-lasting damage.  


The importance of iron status in infant development  

New insights are emerging from recent and ongoing investigations into the role of iron in neurocognitive and neurobehavioral development. The scope of this article is to briefly review what is known about the human biology of developmental iron deficiency and the persistence of deficiency effects and to discuss existing animal models and other datasets that provide us some biological underpinnings with regard to the human situation. For >30 y, it has been known that iron requirements are most likely to exceed iron intake at 2 time periods in the life cycle: 6–18 mo of postnatal life and then, for girls, during adolescence (Fig. 1) (1). An especially challenging situation develops when young women become pregnant because they still have high needs for iron for adolescent growth. The iron reserves of the teenage mother are likely insufficient to meet iron needs for maternal blood volume expansion and for fetal growth and development (2).

In the late 1990s, the American Academy of Pediatrics updated and synthesized its 1976 and 1989 recommendations for iron content of infant formula for full-term infants and recommended that iron-fortified formulas contain between 4.0–12 mg/L (3). According to data from the first NHANES (1971–1975) and from nearly all preceding studies of the U.S. population, the prevalence of iron deficiency in 6- to 18-mo-old infants historically exceeded 30%. The third NHANES survey (1988–1994) and datasets of other surveys conducted after the implementation of routine iron fortification of formula and some other strategies report a substantial decline in iron deficiency in this age group.

The increased provision of iron in the diet in combination with emerging data on absorption of iron in infants suggest that further refinement of iron dosages may be possible. Stable isotope absorption data now demonstrate that the human infant has a developmental increase in iron absorption within 2 to 6 mo of life (4). It is reasonable to expect that as we gain more insights into the developmental staging of the regulation of iron absorption, we may identify the optimal iron dosage in the diet for human infants in the years to come.
absorption, it will be possible to further refine dietary intakes most compatible with optimal iron status.

**Biological basis for functional deficits.** The biological basis for the deficits in neurocognitive and neurobehavioral development caused by iron deficiency is unknown, but the potential mechanisms were reviewed by Beard and Connor (5) as well as by Lozoff et al. (6). Accumulating evidence leads us to suspect possible alterations in 3 primary regions. The structures of the brain are abnormal because iron deficiency either in utero or in early postnatal life alters neurogenesis and differentiation of certain brain cells and brain regions (7). One critical cell type is the oligodendrocyte, which is responsible for making myelin. These cells are particularly sensitive to iron deprivation, which results in altered composition and amount of myelin in white matter (8,9). These alterations appear to be persistent and do not return to normal levels later in life. Observations discussed later in this article regarding alterations in startle responses, evoked potentials, and motor function in human infants and in monkeys may all be partially explained on the basis of a biological impact on myelogenesis.

The second biological dimension suspected of being altered by iron deficiency is neurochemistry, specifically the monoaminergic pathways (10–12). In both animal models and cell culture experiments there is a reproducible finding that dopamine and norepinephrine metabolism are altered by iron deficiency. Iron deficiency appears to alter the synthesis and catabolism of the monoamines. The evidence in human infants and in primate infants is limited. In the latter case, cerebrospinal fluid measurements in iron-deficient infant rhesus monkeys show alterations in norepinephrine levels (13). Voorhess et al. (14) showed 2 decades ago that urine of iron-deficient infants was particularly high in norepinephrine, which returned to normal with the restoration of iron adequacy. A number of the cognitive and behavioral tasks discussed in the following sections rely on adequate functioning of the nigrostriatal dopaminergic and mesolimbic pathways as well as the noradrenergic projected fields in the midbrain (6).

The third biological dimension currently being investigated is the effect of iron deficiency on bioenergetics. The capacity to utilize specialized nuclear magnetic resonance technology to measure the ability of the brain to produce high-energy phosphate compounds and the metabolism of substrates has been directed to studies of metabolism in the hippocampus of iron-deficient rodent brain tissue. De Deungria et al. demonstrated that the metabolic activity of cytochrome oxidase is reduced in prenatal iron deficiency, and as a result the processes for generating and utilizing metabolic energy in the hippocampus are altered (15).

These 3 aspects of brain biology affected by iron deficiency are likely not mutually exclusive events and are interactive in terms of their impact on neural functioning and development. In the sections that follow, we examine the recent information available from human, monkey, and rodent studies. These studies have attempted to examine the connection between the aforementioned biological alterations and developmental delays and abnormalities when iron deficiency is present in early life.

**Human studies of developmental iron deficiency**

Data are accumulating from an increasing number of controlled clinical intervention human trials of iron deficiency in the first year of life and the consequences of such deficiency. These trials have been reviewed recently by Lozoff and Georgieff (16) and Lozoff et al. (6). Many human infancy studies used the Bayley Scales of Infant Development (BSID)4 as the primary dependent variable. This index includes some scales that are motor oriented and others that are more cognitively oriented. Among the trials and follow-up studies, some important observations were made. Nine studies showed significant developmental delays that were irreversible with iron therapy. That is, with subsequent iron therapy, the functional alterations did not return to normal levels before the end of the study. Some of these studies utilized other adjunct scales in addition to the BSID, and these other tasks were abnormal as well. In a study conducted in Chile, the auditory evoked potentials showed apparent irreversible changes in central conduction time (CCT) in children who were treated for iron deficiency anemia in infancy and reexamined 3 to 4 y later (17). Additional studies measured academic achievement, motor and spatial tasks, verbal tasks, anxiety, and/or mood at extended follow-up to the original intervention (6,18,19).

Research is being conducted to document the more specific alterations in functioning that occur when infants have limited iron status in the first several years of life. This work has a focus on specific domains of functioning and attempts to relate the cognitive and behavioral dimensions of the alterations to biological processes that are sensitive to iron deficiency.

**Iron deficiency screening and prevention in Chilean infants.** Lozoff et al. (19) conducted a primary intervention trial in infants in Chile from 1991 to 1996. This large trial included nearly 1700 full-term apparently healthy infants having birth weights of 3 kg or greater. After infants were screened for anemia at 6 mo of age and found to be free of iron deficiency anemia (fingerstick hemoglobin > 103 g/L and normal ferritin levels), they were randomly assigned to a high-iron, a low-iron, or a no-added-iron intervention. The design of the trial was to examine the efficacy of the prevention of the development of iron deficiency with iron treatment. Infants who were anemic underwent further testing for iron deficiency and were treated if iron deficient. Those infants who had not received added iron were substantially different in their behavior and interaction with their environment from those who had been highly supplemented. Furthermore, Lozoff et al. (19) reported the novel observation of more tremulousness in infants who did not receive iron. At present, the prevention study participants are now

---

4 Abbreviations used: BSID, Bayley Scales of Infant Development; CCT, central conduction time; CNPase, 2',3'-cyclic nucleotide 3'-phosphohydrolase; QTL, quantitative trait loci.
10 y old, affording an opportunity to measure catch-up or repair long after iron status was normalized.

Some of the Chilean infants with iron-deficiency anemia at 6 mo of age did not enter the prevention trial. Instead, they, together with a new comparison group of nonanemic infants, were invited to participate in neurophysiology studies (20). Both groups were treated orally with 15 mg elemental iron (as ferrous sulfate) daily for 1 y. Auditory brainstem responses (noninvasive) were tested at 6, 12, and 18 mo. Response to the intervention was tested in 85% of infants at 12 mo of age and in 71% of infants at 18 mo of age. The CCT was considered to be the most important of these response measures because it is affected by the status of nerve myelination. The maturation of the CCT at 3 different ages is shown in Figure 2. The nerve conduction times were significantly longer for infants who had been iron-deficient at 6 mo of age compared with nonanemic infants despite intervention with iron therapy and normal values for iron biochemical tests at 12 and 18 mo of age. One interpretation of these data is that a threshold of iron sufficiency must be met some time in the first 6 mo of life; infants who do not achieve that level of iron sufficiency may have significant delays in the development of the central nervous system.

In a follow-up study at 4 y of age, CCT measures in the children who were treated for early iron deficiency had still not matured to the level of the comparison group (17). In extrapolations from these data, CCT maturation was not projected to normalize before 6 y of age. These children were growing normally, so it is unlikely other nutrient deficiencies may have been present and undetected. The possibility does exist, however, that other nutrient deficiencies may have been present at 6 mo of age and were causally related to this persistent change in CCT.

Program project on developmental consequences of iron-deficiency anemia. New basic science findings led a group of researchers to propose the program project “Brain and Behavior in Early Iron Deficiency” to NIH in 2000. The overall purposes of the program-project grant when it was funded were to understand how iron deficiency alters brain and behavior in early development and to identify interventions that will correct or prevent ill effects in the short and long term. These goals were based on significant holes in the scientific literature regarding timing and severity of iron deficiency, the causal linkages between brain biology and behavioral outcomes, and conflicting results regarding the benefits of iron therapy. The authors recognized that some of the past field trials were possibly subject to confounding factors, both nutritional and nonnutritional. Some of these might have included micronutrient and macronutrient limitations in some of the trials in Latin America and Asia as well as differences in social and economic variables that were not controlled for in the original analysis (21).

As soon as the National Institute of Child Health and Human Development funded the program project in 2001, one team began screening full-term African American infants in inner-city Detroit for possible participation. Infants were screened on a wide variety of iron status biomarkers and categorized as iron-deficient anemic, marginal iron deficient, iron deficient but not anemic, and iron sufficient (B. Lozoff, unpublished data). The overall motor findings have been published in abstract form (22). The motor assessment consisted of Peabody Developmental Motor Scales, the Infant Neurological International Battery, the motor-quality factor of the BSID, and a sequential/bimanual coordination toy retrieval task. There is a significant positive linear relation among iron and developmental milestones, the Peabody Fine Motor test, and the toy retrieval task. The iron-deficient infants scored significantly lower than infants with normal iron status after adjusting for age. Other studies of motor control also show altered movement. A number of alterations in cognition and motor development are consistent with the concept of effects of iron deficiency on myelination and striatal maturation. We interpret the data as suggesting that some structures and developmental dimensions are affected, but not all. This is not to suggest that other brain regions and processes are not adversely affected by iron deficiency in infancy. Indeed, it is interesting to return to the concept that iron-deficient infants consistently show altered affect and engagement with their environment. It has been hypothesized that as an organism becomes nutritionally stressed, it draws within its resources and disengages from the environment because the nutritional cost of engagement is too taxing. Such behavior may be protective for survival in the short term, but for the developing infant, nutritional deficiency (i.e., iron deficiency) and a state of functional isolation may stymie central nervous system development because the brain at this stage is highly plastic and responsive to environmental stimulation.

Preclinical studies
Nonhuman primate studies of iron deficiency and neurodevelopment. The primate facility at the University of California, Davis, has the capacity to do studies that use entirely bottle-rearing procedures in which all neonate animals are bottle reared in the primate nursery. Using these facilities, Golub et al. (23) conducted a prospective intervention trial in which rhesus monkeys were deprived of iron during either prenatal or early postnatal brain development and compared with iron-sufficient monkeys during early development. All monkeys were iron replete at the time of testing, as reflected in hematological measures. Both prenatal and early postnatal iron deprivation led to abnormal behavioral effects at 4 mo of age. Spontaneous motor activity and inhibitory response to novel environments were reduced for monkeys deprived of iron in utero. Healthy full-term newborn monkeys that were fed an iron-deficient infant formula demonstrated poorer performance on object concept tasks than infants that were iron sufficient, and had differences in emotionality.

Golub et al. (23) also measured the auditory brainstem startle response in a fashion similar to that conducted in the Chilean infants (20). Her team tested iron-sufficient and iron-deficient infant monkeys at 1, 4, and 8 mo of age. The monkeys fed iron-deficient diets in the early postnatal phase of brain development...
had a longer peak latency of waveforms than controls at 8 mo
(P = 0.03) but not at the earlier time points. This pattern of
longer latency to maximum response is similar to the observa-
tions in human infants who had been iron-deficient at 6 mo of
age (20). A strong consistency across species is also observed
when the rodent literature is examined. We recently noted that
iron-deficient rats also have a significantly prolonged latency to
maximum acoustic startle that is affected by the diurnal cycle
(12,24). Alterations in 24-h patterns of response have not been
conducted in the monkey studies, although Angulo-Barroso and
Lozoff (25) have noted that iron-deficient human infants have
altered movement patterns/activity at night compared with iron-
sufficient infants.

At the University of Wisconsin Primate Research Center in
Madison, newborn rhesus monkeys are raised with their mothers.
The natural prevalence of iron deficiency for infant monkeys in
the colony is ~30%, a proportion similar to what was measured in
U.S. human infants before fortification of infant formulas.
Lubach and Cee (26) have utilized this naturally occurring
prevalence of iron deficiency in the rhesus monkey to document
that infant monkeys become iron-depleted at 4 to 8 mo of post-
natal life but begin a positive iron balance after that and return
to normal blood ferritin concentrations at 10 mo of age. When iron-
deficient infant monkeys were examined, they showed impaired
object discrimination and reversal learning (13).

**Rodent studies of iron deficiency and neurodevelopment.**

The effects of iron status during the developmental period were
also studied in rat pups born to young dams provided with iron-
deficient or control diets from early gestation through weaning
(27,28). Iron deficiency in utero and during lactation were
sufficient to reduce pup performance on several developmental
measures, such as vibrissae-evoked forelimb placing. In this test,
the pup is placed close enough to a desk top that its whiskers
touch the hard surface. The neural connections to the vibrissae
are linked through the rat midbrain to the motor cortex, and
such whisker stimulus will characteristically elicit the response
of the rat’s paw reaching out toward the surface. In this way, the
rat’s whiskers are important to contributing cues to tell it where
it is in 3-dimensional space. Negative geotaxis is another test of
fundamental development milestones and is used to assess how
well the animal can right itself. Iron-deficient pups tested poorly
on both vibrissae placing and negative geotaxis, further sup-
porting the conclusion that iron deficiency leads to develop-
mental delays.

In the next phase of the investigation, the rat pups were
repleted at weaning with an iron-sufficient diet and then tested
for cognitive abilities in adulthood at 120 d of age using the Morris
Watermaze Swim Test (28). This test provides an opportunity to
examine functioning of vision, spatial memory, and the animal’s
search strategies. Rats that were iron-deficient during gestation
and lactation but then iron-sufficient into adulthood performed
significantly worse on this task than rats that had never been iron-
deficient. This task is a measure of cortical, hippocampal, and
striatal neural functioning and suggests persistent alterations in
neural functioning as a result of early-life iron deficiency. The once-
iron-deficient rats failed to generate alternative search strategies
when the submerged platform was moved to another location, an
observation consistent with inferior hippocampus and prefrontal
cortex development.

**Neurobiological alterations**

**Genetic determination of iron-related neurobiology.** A
common assumption concerning nutrition is that humans of
similar sex, age, size, and baseline status will react equally to
nutrition adequacy (or lack thereof) in the environment. The role
of genetic variation in humans has not yet been strongly
considered. Several studies using inbred strains of mice explored
the genetic components of this variation in response to iron
depriation in the environment (29,30). In the case of recom-
binant mice, there are multiple strains that are hundreds of
generations old. Each strain is different from another strain in
genomic profile, but the mice within a strain are nearly exact
clonal replicates. These recombinant inbred strains of mice were
examined as adults after eating typical mouse chow, without
any dietary manipulation, from weaning until midadulthood.
We observed as much as a 3-fold variation in ventral midbrain
iron concentration despite the exact same environment of diet
and living conditions (30). More recently, we utilized quantita-
 tive trait loci (QTL) analysis to examine the genetic components
of iron, copper, and zinc trafficking in the brain (31). Because the
mouse genome is completely mapped, and the phenotypes are
known, ventral midbrain iron data and other related factors can
be entered into an online website (http://webqtl.org) to conduct
a large cluster QTL analysis to identify candidate genes that are
associated with concentrations of ventral midbrain iron or other
factors. This approach will be utilized in future investigations to
explore the genomic responses to early iron deficiency. A related
approach, microarray analysis, has already been utilized to de-
termine persistent changes in gene expression in the whole brain
of rats after a period of early-life iron deprivation (32). The
genes that remained different in adulthood were genes involved
in cell cycling and microstructure of cellular organelles. In com-
bination, the QTL and microarray approaches have suggested
candidate genes that may mediate some of the biological out-
comes previously discussed.

**Effect of iron deficiency on the biology of neurons.** There is
substantial, unequivocal evidence that nerve cells are structurally
different in iron-deficient animals (33). Iron deficiency
causes different responses in different regions of the brain (34).
Iron-deficient diets significantly reduce brain iron concentration
by 22–63% and increase transferrin concentration by 22–130%
(35). The corpus callosum, white matter of the cerebellum, and
lateral ventricles express the highest levels of transferrin mRNA,
whereas transferrin-receptor mRNA levels are lowest in these
regions compared with other regions but highest in cortex,
hippocampus, and the gray matter of the cerebellum. In response
to iron deficiency, transferrin receptor is reduced in the thala-
mus, CA1 and CA3 of hippocampus, cerebral cortex, and
dells of dentate gyrus (35,36). In the case of immature oligo-
dendrocytes, transferrin-receptor expression is reduced, which
decreases iron uptake (35,37). These cells also exhibit reduced
myelin production and are structurally distinct from control cells
(34).

**Myelination.** Iron deficiency in early life is associated with
hypomyelination of nerve cells. Despite iron repletion, the deficit
in myelination persists. Beard et al. (8) studied the effect of
preweaning (postnatal d 4–21) and postweaning (postnatal d 21–63)
iron deficiency on a marker of oligodendrocyte metabolic
activity: 2',3'-cyclic nucleotide 3'-phosphohydrolase (CNPase)
activity. Iron-deficient rats had significantly lower CNPase activity and myelin basic protein in the cerebrum and
hindbrain; the fatty acid composition of phospholipids in the
hindbrain was altered as well. Ortiz et al. (9) demonstrated that
limiting iron intake decreased myelin proteins and lipids (e.g.,
proteolipid protein), altering the composition of myelin in
rodent models. Thus, the absolute amount of myelin was altered
as well as the lipid and protein constituents of the myelin. Such compositional changes resulting from disrupted iron homeostasis in early stages of growth may contribute to the abnormal behavior that has been observed in developmental testing of auditory and visual evoked potentials.

**Hippocampal structure and function.** Jorgenson et al. (33) conducted immunohistochemical analyses of hippocampal CA1 dendritic structure and growth in iron-deficient rats compared with a control group at postnatal d 15 and again on postnatal d 65 after iron repletion. Microtubule-associated protein-2 was used as the index. On postnatal d 15, iron-deficient pups had truncated apical dendritic morphology that persisted into adulthood despite iron repletion. It appears that the number and length of dendrite arborization in rodents may be irreversibly changed by a short period of iron deficiency during the perinatal period. Jorgenson et al. (38) also measured long-term potentiation of CA1 hippocampal nerve fibers in iron-deficient rats compared with a control group at postnatal d 15 and 30 and again after iron repletion on postnatal d 65. This measure is a functional indicator of basal synaptic nerve transmission and reflects the electrical basis of memory. As the normal rat brain ages, it acquires a characteristic mature pattern of long-term potentiation. However, rats that were made iron-deficient during the fetal and early postnatal period exhibited delayed matura-
tion of electrophysiological processes beyond the period of deficiency (12% loss of long-term potentiation relative to control at d 65). These results further extend knowledge of how perinatal iron deficiency disrupts developmental processes in the hippocampal subarea CA1 and confirm that several abnormalities persist despite iron repletion. Such structural and electrophysiological abnormalities may contribute to the learning and memory deficits that result from iron deficiency during early development. Neurochemical studies using high-energy proton nuclear magnetic resonance show that energy metabolism in the hippocampus is also dramatically altered by early-life iron deficiency (7,39). Such evidence is suggestive that both structure and functionning of the hippocampus are altered by iron deficiency early in life.

**Monoamines.** The dopamine transporter is essential to maintain extracellular dopamine concentrations within desired limits. Mice without this transporter protein are extremely fragile to stressors, fail to respond well to pharmacologic agents, and lack synaptic efficacy. Erikson et al. (40) surmised that the dopamine transporter was functionally altered in postweaning iron deficiency in rats, that the attenuated effects varied by region, and that these effects were likely related to decreased density of the transporter. Depending on the stage of development at the time of iron deficiency, there may be an opportunity to reverse adverse effects, but the success of repletion efforts may also be time dependent. As part of our interest in the timing of iron repletion, we investigated whether in utero iron deficiency beginning on gestation d 5 could be reversed by repletion beginning on postnatal d 25 (27). Rat pups that were born to deficient dams were weaned to an iron-sufficient diet. Dopamine transporter abnormalities were not completely corrected within the period of iron repletion tested, although the iron concentrations in various regions of the brain were normalized with the iron intervention. Dopamine \(D_2R\) levels remained significantly depressed in terminal fields despite the normalization in brain iron concentration. These findings suggest that intervention at weaning is too late to correct some of the alterations in the dopaminergic systems. Further investigations are needed to better define the critical time frame for intervention.

This article has summarized some of the most recent work involving animal models and ongoing human studies of iron deficiency and early infant development. The scope is limited to those areas of neurodevelopment, cognition, and behavior that modern science would suggest as being sensitive to effects of early iron deficiency. There may well be other effects and persistent consequences that are as important as those discussed here. This brief update on what is emerging from a number of talented research groups is not exhaustive or inclusive of all the important studies going on around the world. Nonetheless, several important observations can be summarized.

Iron deficiency in early life, when examined across 3 species, results in particular changes in both biology and behavior. For example, data from human infants and from monkeys suggest that motor development and fine motor control are altered by early iron deficiency, and rodent data confirm that alterations in myelination of white matter tracks in the brain occur with early iron deficiency. There are alterations in startle response in all 3 species, which might be mediated by this poor myelination. The developmental delays seen in the rodents in terms of developmental milestones such as negative geotaxis may also be an aspect of the alterations in visual acuity and recognition seen in human infants and in infant monkeys.

The rodent studies and 1 monkey study with cerebrospinal fluid samples all document alterations in monoamine metabolism with iron deficiency. The observation from rodents that the striatal and prefrontal cortex regions of the brain are strongly affected by early iron deficiency provides some additional biological explanation for the decreased exploratory behavior characteristic of early iron deficiency. This is not to imply that only striatal or frontal cortex biology is changed. Indeed, the alterations in bioenergetics of the hippocampus and the decreased synaptic connections documented in the CA1 region are highly suggestive that hippocampus-striatum connections may be a key region affected by early iron deficiency.

The emerging information from the genomics and proteomics of early iron deficiency in the brain will further direct our investigations to better understand the influence of brief periods of iron deficiency on persistent effects on cognition and behavior. One might ask how much of the decreased CCT observed in once-iron-deficient children at the age of 5 y can be attributed to a failure in appropriate neurogenesis, myellogenesis, and neurochemistry in the first 6 mo of life. Within several years the genomics and proteomics of early iron deficiency will be characterized, leading to a clearer understanding of the biochemical processes that are altered by iron deficiency during late gestation and lactation.

**Question and answer session**

**Q1:** I am concerned about infants on the other end of the spectrum, who are exposed to iron overload, or to a very high-iron environment, particularly in developing countries such as Mexico, who are weaned to fortified formulas in combination with other iron-containing products. What are the detrimental effects of too much iron? For example, does it promote deficiency of other nutrients?

**Dr. Beard:** I think this is an important question and one of actual concern. In both the 1993 and 1998 CDC recommendations for iron assessment in pregnancy and infancy and the Dietary Reference Intake committee's deliberations in 2003 in developing recommendations for iron intake took care to be precautionary about the use of iron drops for infants who were exclusively breast-feeding. The recommendation is that if the mother needed to use iron drops, to be very, very careful. Little...
information is available describing any neuropathologies related to early-life exposure to high amounts of iron. There are a couple of rodent studies, one of which a former student of mine reported. In this study, rat pups of iron-deficient lactating dams were iron repleted by cross-fostering them to other dams administered very high amounts of iron—300 ppm as opposed to 35 ppm. The breast milk from those dams was very high in iron, so the iron concentration of the pup brain rose rapidly in response. These animals were tested for behavior in early adulthood. Curiously, the repleted rats performed nearly as poorly as the animals that had not been rescued and were iron deficient. This is speculation on my part, but perhaps the push in early brain development is to acquire iron, and under the conditions created by this experiment, that natural process was not scaled back once the animal was repleted.

[Q2]: Preclinical studies can be very tightly controlled, but clinical studies of iron deficiency need to account for numerous potential confounders in terms of cognitive development, such as vitamin B-12 and iodine. Could you comment on this?

[Dr. Beard]: Yes, many studies have not controlled for confounding factors. Potential confounders are a concern to Dr. Lozoff’s original Costa Rican studies, in that participants may have had concurrent vitamin B-12 deficiency that may be causally related to the outcomes measured. Those individuals now are close to 30 y of age, and as adults they score differently on global scales as well as on more specific scales of attention and vigilance, memory, and different aspects of functioning than other members of those villages who were not iron deficient in early life. I think we can exclude the macronutrient deficiencies as confounders in those studies but certainly not all potential micronutrient deficiencies.

[Q3]: We presume, because infants have the highest concentration of ferritin in the entire lifespan after the absorption of the extra red cells, that they would be in a position to want to down-regulate if they could. Is there a differentiation between the infants to exclude the extra iron that they do not need, that is, down-regulation in the gut, and perhaps what you were alluding to, which is that it takes time to develop the selective competitive up-regulation to replete the iron that is needed? What is known about those phenomena?

[Dr. Beard]: Yes. A lot of the queries are for premature infants, and what do we do about iron biology in that situation, where they don’t have that. We have not specifically tested the ability to actively down-regulate in early infancy. However, there are 2 or 3 articles published now that are very carefully done regarding regulation of absorption. These data are convincing that regulation develops in the gut fairly early in postnatal life but may not be complete at 6 mo of age. The ability to down-regulate absorption when iron supplementation occurs was examined by Dr. Domellöf and colleagues in 2002.

[Q4]: What you described in the dyad of the iron-deficient mother and the deficient baby is wariness: they are not engaged with each other as a “frolicky” mom-and-kid relationship; they are both looking around elsewhere. In an evolution situation, that might seem to be adaptive under some scenarios. So can we look at scenarios in evolutionary life—tribal, cave life—where what the iron deficiency provokes in mom and infant is perhaps more adaptive to the circumstances than being on the Cancun beach.

[Dr. Beard]: This is an interesting question, but I don’t know that I have any great thoughts to share with you. It’s my thinking that we have bought into the notion that the greater the amount of environmental engagement and stimulation that occurs, the better—whatever “better” means—the better off the infant is, and this is clearly the functional isolation model by both the activity and actions of the mom as well as the actions and responsiveness of the infant. I think the outcome for the infant is not positive. But it might be adaptive.

**Literature Cited**