The role of nutrition in the development of normal cognition

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ABSTRACT The goal of this section of the meeting was to review the relation between nutrition and cognition. The topics selected for discussion included generalized malnutrition, iodine deficiency, iron deficiency, iron metabolism, and the relation of fatty acids to the development of the nervous system. Each subject is immense and demands a detailed exposition, but can be treated here only in brief form. However, these short essays should give some insight into the status of our current knowledge. Am J Clin Nutr 1996;63:997S–1001S.

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GENERALIZED MALNUTRITION AND IODINE DEFICIENCY

We live in an era of multiple worldwide famines; these include famines in Somalia, Zaire, Liberia, parts of India, and other locales. In South America it is estimated that 16 million children suffer from malnutrition, and of these 16 million many will die and still more will be left with severely diminished cognitive ability (1). Diminished cognitive ability is not caused solely by malnutrition, but rather by the environment of poverty, infection, psychologic depression, and lack of stimulation.

In Chile, Mexico, and Guatemala, major social-intervention programs have been pursued successfully (2–4). Both the Mexican and the Chilean projects concluded that removing a child from a deprived situation and bringing the youngster into a stimulating environment where there is an opportunity for exploration have positive effects on eventual intellectual performance. These results differ from the conclusion that the cognitive disability encountered in malfed children can be ameliorated merely by the provision of food.

Pollitt et al (5), who worked with the nutrition unit in Guatemala, suggested that normal physical growth and physical activity are dependent on good nutrition. The model proposed by Pollitt et al was expanded by Wachs (6), but it was emphasized that environmental support and stimulation can result in an improvement in the cognitive state of malfed children.

Generalized malnutrition is primarily an issue of a shortage of meganutrients, but it is also often associated with a deficiency of specific micronutrients. The three micronutrients iron, vitamin A, and iodine are the most critical in global importance. It is on these substances that the wellness of billions of children depends. There are 20 million people whose brain damage could have been prevented by the provision of adequate amounts of iodine to the mother before conception and during pregnancy. The efficacy of this treatment was firmly established by Matovinovic (7) and Marine through their extensive work in Michigan and Ohio. There are one billion people in the world still at risk for iodine deficiency, regardless that this deficiency can be readily prevented. As an indication of failure, there are 200 million people with goiter, a condition prevalent in Africa and in certain parts of China and Vietnam (8).

In developing countries the number of people at risk for overt cretinism due to iodine deficiency is ~20 million, and 3 million people suffer from overt, absolute mental retardation. These data do not explain the full magnitude of the problem. Iodine deficiency disorders are now encountered mostly in the developing world, primarily in mountainous areas or where the soil has been depleted by erosion.

Endemic cretinism occurs in two forms: a hypothyroid or myxedematous type and a neurologic type (9). Classical myxedematous cretinism, often found in China and Zaire, involves dwarfism, and all the symptomatology of hypothyroidism. It is significant that these regions are also known to be deficient in selenium. The relation between selenium and iodine could be important in the synthesis of seleno-enzymes not only in the thyroid, but also in the liver. The neurologic type of cretinism is observed in Ecuador and is associated with deaf-mutism, spastic diplegia, mental retardation, crossed eyes, and decreased visual acuity. These types of cretinism result from iodine intakes < 25 μg/d, contrasting with the normal intake of 80–150 μg/d. Intake of iodine by women before conception or during pregnancy is the most important factor in the prevention


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of endemic cretinism. The effect of iodine deficiency on the infant is probably sustained during the first or second trimester.

In New Guinea, where there is a predominance of neurologic cretinism, mental retardation ranges from ≈80% to 100%. This is a disturbing statistic, because a little iodine could have prevented all these afflictions. Most people receive iodine in salt, but iodine can also be taken in bread and oil. A dose of iodized oil can last 3–4 y. In Papua New Guinea, a group of pregnant women received iodinated oil and of 593 births one child was afflicted with cretinism (10). Another group of women received only saline and they gave birth to 26 children afflicted with cretinism. All mothers were injected before conception, ensuring the effectiveness of the iodinated oil. The World Health Organization recommends that iodine be given to women before they give birth and the best form is the injectable iodized oil.

We have vast knowledge of the geographic distribution of iodine deficiency and the capacity to screen populations for a lack of the micronutrient. The costs of iodine supplementation are minimal. The problem lies with the various bureaucracies and their unwillingness to take the responsibility for ensuring that all people are iodine sufficient. Although malnutrition is clearly in the province of the biological sciences, economic and managerial analysis could and should be applied. With cooperation, cretinism can be eliminated as a major cause of mental retardation.

**IRON STATUS, BRAIN FUNCTION, AND COGNITIVE PERFORMANCE**

This brief review of a substantial field of knowledge focuses on the association of iron status, development, and cognitive function. The topic of iron deficiency and cognition has been the focus of several reviews (11–14). We refer to these articles where appropriate and to the original sources when they provide the best information. Iron is not only an essential element and important nutrient but also a potent toxin. Thus, an elegant system has evolved that regulates the delivery of iron to brain cells and has as its major known components transferrin and its receptor. Iron is an essential component of several general cellular functions as well as of functions more specific to neurologic activity such as the synthesis of dopamine, serotonin, catecholamine, and possibly γ-aminobutyric acid and melatonin formation (15–18). Iron uptake into the brain is maximal during the period of rapid brain growth, which coincides with the peak of myelogenesis (19, 20). However, iron uptake into the brain continues throughout life; this uptake is reportedly homogeneous and followed by a redistribution to the basal ganglia (21). Dallman et al (22, 23) showed two decades ago that young rats deprived of iron in early postnatal life had significantly lower (27%) whole-brain iron contents than did controls 28 d postnatally and were quite resistant to restoration of their normal complement of brain iron despite aggressive dietary repletion for 45 d (still 20% lower). The regional distribution of iron and the responsiveness of various brain regions to iron nutritional states in these conditions has not been documented and remains underexplored. The timing of this acquisition of iron by the brain is unknown and the developmental dependency of great concern.

Iron deficiency is the most common single-nutrient-deficiency disease in the world and is a major concern for ≈15% of the world’s population (24). The World Health Organization estimates that 1.3 billion people are anemic and iron deficiency is the causal agent in many cases. Perhaps as many as 40–45% of children are iron deficient and anemic. The true impact of childhood iron deficiency on cognitive development and functioning is undetermined. Recent reviews have covered the growing research area relating iron nutrition to cognition and behavior (11–14, 25, 26). The studies reviewed demonstrate a consistency in the observation that iron-deficient children have alterations in attention span, lower intelligence scores, and some degree of perceptual disturbance. Interestingly, no such database exists in the adult human literature other than that which we are in the process of generating in both adolescent mothers and in young college-age women through use of a computerized cognitive task. Although there are strong reasons to believe that the relation of iron to cognition is developmentally linked, others have shown alterations in brain functions in adults with variations in iron status. Studies in older children showed decreased attentiveness, narrow attention spans, and perceptual restriction (see references 11, 25, and 26 for reviews). Lozoff and Brittenham (26) observed a significant effect of anemia on affective behavior. Low affect in iron-deficient children was significantly related to poor performance on the Bayley Mental Developmental Index in the model proposed by these investigators. Lozoff’s Costa Rican studies and those of Walter (27) in Chile both noted a failure of active iron therapy to improve performance in many of the anemic children with despite prompt hematologic response and normalization. In addition, children with storage depletion but no anemia showed no measurable behavioral abnormalities. An important point, however, is that the cognitive domains tested by these achievement-oriented tests are far different from the developmental constructs applied to the infants. A sensible idea is that iron status affects a state variable like attention or arousal, which, in turn, alters performance (14, 25). Idjadiyntata and Pollitt (28) showed through use of a double-blind crossover design with the inclusion of a placebo-treated, iron-deficient group that cognitive deficits in iron deficiency could be reversed with iron supplementation. This finding, which needs to be verified in other populations, provides strong evidence that at older stages of development, cognitive deficits are seen to be reversible. Key unresolved questions concerning iron and cognitive performance are: 1) Are the effects of acute iron deficiency different from the effects of chronic iron deficiency? 2) Does the severity of iron deficiency have an effect? 3) Are there biological or psychosocial causal models that explain some of this relation?

**FATTY ACIDS AND NEURAL FUNCTION**

Several categories of neural function can be distinguished, including sensory, motivational-arousal, cognitive, motor, and social. Behavioral endpoints within each of these categories have been used to assess development in mammals under a variety of conditions including fatty acid deficiency. Wainwright (29) reviewed essential fatty acids and rodent behavior, beginning with the first study by Caldwell and Churchill (30) nearly 30 y ago. Her article includes an overview of the factors critical in studies of behavior and nutrition, issues addressed in detail by Burger et al (31). Both of these articles are excellent
introductions to the issues important for validly studying the effects of nutrition on behavior.

The diets fed in most rodent studies of deficiencies of essential fatty acids have contained insufficient amounts of both linoleic (18:3n-3) and linoleic acids (18:2n-6); ie, they were deficient in both n-6 and n-3 fatty acids. Fat-free diets and those prepared from coconut or palm-kernel oils are included in this category. As a result, it is not possible to determine from most of these studies if the behavioral effects were due to a deficiency of either or both of these families of fatty acids. In a handful of studies, however, changes in behavior can be attributed to n-6 deficiency because both groups were fed an n-3-deficient fat, and only one received sufficient linoleic acid (n-6). Fat sources that provide sufficient n-6, but not sufficient n-3 fatty acids, include corn, sunflower, and safflower oils. There is evidence that n-6 deficiency results in delayed reflex development, poorer discrimination learning, and shorter retention of memory of an aversive stimulus like a foot shock (32-34).

Behavioral effects specific for n-3 fatty acid deficiency have also been produced in rodents and in nonhuman primates. To create an n-3 deficiency, vegetable oils with very high ratios of linoleic (18:2n-6) to linolenic acid (18:3n-3), such as safflower, sunflower, or corn oil, are fed to animals during periods of rapid neural development. The behavior of these animals, who are deficient in n-3 but not n-6 fatty acids, is compared with that of controls fed adequate amounts of both n-6 and n-3 fatty acids. Fats that contain large amounts of both essential n-6 and n-3 fatty acids include soybean, perilla (sesame), and canola oils. Galli et al (35) showed a reciprocal relation between n-6 and n-3 fatty acids: n-3-deficient diets decrease the elongation-desaturation product of linolenic acid, docosahexaenoic acid (DHA, 22:6n-3), with a commensurate increase in docosapentaenoic acid (22:5n-6), an elongation-desaturation product of linoleic acid. Lamprey and Walker (36) were the first to report behavioral effects of an n-3-deficient diet. They found fewer correct responses with a black and white discrimination test involving a Y maze in rats fed an n-3-deficient diet (safflower oil) compared with an n-3-sufficient diet (soybean oil).

The relation between fatty acid composition and function in the visual system has been addressed in detail by Neuringer (37). Neuringer et al (38, 39) first showed that retinal responses to light or electroretinograms and visual acuity were abnormal in infant monkeys deprived of n-3 fatty acids. Clandinin et al (40) and Martinez (41) demonstrated the rapid accumulation of very-long-chain n-3 and n-6 fatty acids such as DHA and arachidonic acid (20:4n-6) in the human brain and retina beginning during the last intrauterine trimester. Sanders and Naismith (42) and our early work (43) suggested that infants fed vegetable oils compared with human milk, which contains DHA, had poorer DHA status. These observations together formed the basis for our hypothesis that DHA might be a conditionally essential nutrient for very-low-birth-weight infants who are born near the beginning of the last intrauterine trimester; ie, that diets containing linolenic acid alone might not provide for optimal neural and retinal accumulation of DHA.

Experimental formulas containing DHA were provided to preterm infants in three randomized trials to test the hypothesis that feeding DHA in addition to linolenic acid would enhance neurodevelopmental outcome. The endpoints determined in these studies included retinal responses to light, visual acuity, the number and duration of visual fixations during familiarization and visual recognition testing, and early cognitive measures such as the Bayley Mental Developmental Index. All three trials found higher early visual acuity in DHA-supplemented infants than in those fed a formula based on soybean oil. At 2 and 4 mo adjusted age, we found higher visual grating acuity (defined as the smallest spatial frequency that can be detected as a pattern by the infant through use of the Teller Acuity Card procedure) in healthy preterm infants fed soybean oil plus marine oil DHA compared with soybean oil alone, but the effect was transient (44-46). Birch et al (47) observed higher evoked-potential visual acuity in preterm infants fed soybean plus marine oil DHA compared with soybean oil–based formulas at 4 mo adjusted age, the only age tested. Only the group of infants randomly assigned to be fed an n-3-deficient formula had poorer electroretinogram responses (48).

Visual recognition memory (novelty preference) and the number and duration of visual fixations during habituation and novelty testing were determined at 6, 9, and 12 mo (Fagan Infantest, Infantest Corporation, Cleveland). The novelty preference data were published earlier in preliminary form (49). Infants supplemented with marine oil and those fed soybean oil had equivalent novelty preference, but the supplemented group had significantly more discrete looks (P < 0.02) and a significantly shorter look duration during novelty testing (P < 0.03) compared with that in control infants (50). These data are analogous to those of Reisbick et al (51), who reported longer visual fixations in n-3-deficient compared with n-3-fed rhesus monkeys. Because the duration of visual fixation is associated with speed of visual processing, the monkey and human infant studies suggest that speed of visual processing is enhanced by DHA status.

We also measured the 12-mo Bayley Mental and Psychomotor Developmental Indexes of preterm infants randomly assigned to be fed control or marine oil–supplemented formulas for up to 11 mo after delivery. Infants receiving DHA scored significantly better than control infants on the Bayley Mental Developmental Index; the groups were fed a nutrient-enriched formula designed for preterm infants with or without DHA for 5 mo (from 3 to 2 mo from expected term). In an earlier randomized trial, when both groups received a standard diet designed for term infants as a basis for nutrient intake after hospital discharge at ~1.8 kg, the DHA-supplemented and control infants performed similarly on the Bayley Mental Developmental Index. The preliminary data have been published (52).

Several neurobehavioral outcomes of preterm infants fed linolenic acid have been enhanced by the addition of DHA to the diet, but studies in preterm infants have used only a few of the possible neurodevelopmental endpoints that may be influenced by fatty acid status. These behaviors are likely to remain the basis for determining efficacy in future studies in infants. Such studies should also provide an opportunity to examine other behaviors that may be influenced by n-3 fatty acid status.
REFERENCES

25. Pollitt E, Metallinos-Katsaras E. Iron deficiency and behavior. Con-