The Role of Nutrition in Cognitive Development

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ABSTRACT

Nutrients are critical for optimal brain development and function. Although maintenance of adequate intake of all nutrients throughout life is important for brain health and function, certain nutrients have a more profound effect on brain development than others. The timing of nutrient supplementation or deprivation also has an important effect on brain development and function. Nutrient intakes may vary widely; yet, for certain nutrients, there must be a steady flow across the blood-brain barrier to maintain brain development and functional homeostasis. A host of transporters and regulators ensure that the brain receives neither too much nor too little of each nutrient.

This chapter reviews the evidence for the role of nutrition in brain development, concentrating specifically on nutrients that are important in the development of cognitive function. A short review of nutrient categories is followed by a section on how individual nutrients directly and indirectly affect developing brain structure and function. A detailed analysis of the nutrients that most profoundly affect brain development ensues, with emphasis on the importance of the timing of nutrient deprivation or supplementation.

Nutrient categories

MACRONUTRIENTS: Protein, fat, and carbohydrates are considered the three macronutrients. Protein is typically used by the body for somatic (tissue) protein and serum protein synthesis. Proteins also include all enzymes found within organs. Energy in the form of fat or carbohydrates is the metabolic fuel on which the body depends. The body preferentially uses carbohydrates (typically glucose) as the substrate for cellular metabolism to generate adenosine triphosphate (ATP). Neuronal metabolism is particularly dependent on glucose availability and is very sensitive to periods of carbohydrate deprivation (Volpe, 1995). The body maintains a small storage pool of carbohydrates in the form of glycogen that supplies glucose equivalents for a short period of time when glucose supply is limited. Hypoglycemia (low blood sugar concentration) has a particularly profound negative effect on the developing hippocampus (Kim, Yu, Fredholm, and Rivkees, 2005; Yamada et al., 2004). Fat, with its higher caloric value, provides energy for storage (as adipose tissue), but can also be utilized more slowly than glucose to provide energy to the entire body, including the brain (e.g., as ketone bodies). Certain fats and lipoproteins are important for normal neuronal cell membrane integrity and myelination. For example, cholesterol, phosphatidyl choline, and certain fatty acids are essential for cell membrane synthesis and integrity. Linolenic acid, linoleic acid, arachidonic acid, and docosohexaenoic acid are essential for normal brain membrane formation and myelination. During starvation or periods of illness, protein can also be used as an energy substrate. When protein is utilized in such a manner, it is not available for structural tissue (including brain) synthesis.

There is an extensive literature in both humans and animal models on the isolated and combined adverse effects of protein and energy malnutrition on the developing brain (Pollitt, 1996; Pollitt and Gorman, 1994; Pollitt, Watkins, and Husaini, 1997; Pollitt et al., 1993, 1995; Winick and Nobel, 1966; Winick and Rosso, 1969a,b). Pollitt and Gorman (1994) have pointed out that other nutrient deficiencies usually coexist with protein-energy malnutrition (PEM) in free-living populations.
MICRONUTRIENTS: Minerals, trace elements and vitamins are collectively grouped as micronutrients.

MINERALS The major minerals of the body are sodium, potassium (with their usual accompanying dietary anion, chloride), calcium, and phosphorus. Minerals are not classically considered essential for brain development, but deficiencies in these nutrients will lead to abnormal brain function, mostly through altering neuronal electrical function.

TRACE ELEMENTS This class of nutrients contains elements that are required in trace quantities by the body and are used, for the most part, in intermediary cellular metabolism. Members of this category include magnesium, manganese, iodine, zinc, copper, molybdenum, cobalt, selenium, fluoride, and iron. As with the major minerals, these elements are not classically considered to be uniquely important for normal brain development except as their deficiencies affect cellular (including neuronal) function. Some elements in this group, however, are exceptional in their particularly profound effect on cognitive development: iron, iodine, and zinc. Iron is required for enzymes that regulate central nervous system cell division (ribonucleotide reductase), monoamine synthesis (e.g., tyrosine hydroxylase), myelination (delta-9 desaturase), and oxidative metabolism (cytochromes). The effects of iron deficiency on the growing and mature brain are well documented. Iodine is essential for normal thyroid hormone synthesis. Brain development is severely compromised by hypothyroidism (cretinism) with particularly profound cognitive effects (Hetzel and Mano, 1989; Kretchmer, Beard, and Carlson, 1996). Similarly, zinc through its role in nucleic acid synthesis plays significant role in neurodevelopment. Both neuroanatomic and neurochemical changes have been described in zinc deficiency. Other than the extensive literature on these trace elements, little developmental work has been performed to assess the roles of the remaining micronutrients on cognitive development.

VITAMINS Vitamins are categorized as water- and fat-soluble. They generally are cofactors in intermediary metabolism, although some, like vitamin A, bind promoter regions of genes which regulate cell differentiation and neuronal growth (Mangelsdorf, 1994). As with the trace elements, vitamin deficiencies can potentially affect total body metabolism and consequently brain growth and development. Nevertheless, certain vitamins [e.g., vitamin A, folic acid, pyridoxine (B6)] appear to be more critical during certain periods of CNS development and their deficiencies present a greater risk to neurodevelopment (for review, see Pollitt, 1996). Folic acid deficiency during early pregnancy has been closely linked, both epidemiologically and in animal models, to neural tube defects such as meningomyelocele and encephalocele (Copp and Bernfield, 1994). Vitamin A deficiency is an important neuroteratogenic risk factor during the periconceptional period, but is also associated with retinal and neuronal degeneration in the postnatal period. Pyridoxine is critical for NMDA receptor synthesis and function (Guilarte, 1993).

The role of nutrition within the context of cognitive development

It is critical to appreciate that insufficient nutrition does not determine poor cognitive outcome. Likewise, adequate nutrient delivery alone does not ensure normal brain growth and development. Although adequate nutrition is essential for normal development, the
role of nutrition in cognitive development must be considered with regard to other biological and environmental factors (Figure 1). The effect of poor nutrition on development may be influenced by environmental factors. For instance, cognitive effects of nutritional deficiencies (as measured by the mental development index of Bayley Scales) are more severe for children living in homes where there is less stimulation compared to homes with higher levels of stimulation (Grantham-McGregor, Lira, Ashworth, Morris, and Assuncao, 1998).

Just like nutrient deficiency does not determine cognitive development, simply providing adequate nutrition may not support normal brain growth and development. Along with adequate nutrition, inborn errors of metabolism, growth factors, and stress need to be considered. An example of an inborn error of metabolism is phenylketonuria (PKU). Individuals with PKU lack the enzyme phenylalanine hydroxylase which converts phenylalanine to tyrosine, and therefore, phenylalanine accumulates. If not treated by limiting phenylalanine in the diet, brain development is altered, and individuals develop mental retardation.

GROWTH FACTORS It is important to recognize that nutritional status is not determined simply by nutrient availability. Once nutrients are ingested, they must be absorbed and translated into useful metabolic products that promote growth and development. This occurs through growth factors and anabolic hormones that translate potential nutritional value into tissue synthesis and function. Nutrients for the body are analogous to fuel for a car. Growth factors act as the transmission that “puts the car into drive” and makes it progress forward.

Growth factors (and therefore nutrient handling) are profoundly affected by the organism’s physiologic state. For example, starvation has a different effect than illness on somatic and cerebral metabolism even though both are characterized by low nutrient intakes. Typically, during starvation the body lowers its metabolic set point, thereby requiring fewer calories for maintenance of vital functions. Although insulin levels are low, counter-regulatory hormone concentrations that promote tissue breakdown (cortisol and glucagon) are not typically elevated. Provision of protein and energy at a level slightly higher than that needed for maintenance will result in some, albeit suboptimal, growth. In the young child, the fascinating phenomenon of “head-sparing” occurs, where somatic growth will suffer at the expense of brain growth during periods of marginal malnutrition. The mechanism of this regional growth effect is unknown. In contrast, illness activates cortisol and glucagon secretion to provide a ready source of glucose, and the body is relatively insulin resistant. Thus, brain growth is severely impaired during illness whereas it is spared during simple starvation.

The brain is dependent on a host of growth factors for normal neurogenesis, synaptogenesis, dendritic arborization, and myelination. A complete review of these factors and their functions is beyond the scope of this chapter (for review, see Pleasure and Pleasure, 2003). By “growth factors” in this context, we mean small proteins that enhance proliferation of target cells either by encouraging cell division or preventing cell death. The brain contains growth factors that are found throughout the body, including insulin-like growth factor-I (IGF-I), epidermal growth factor (EGF), and fibroblast growth factor (FGF), as well as some that are specific to brain [e.g., brain-derived neurotrophic factor (BDNF) or glial growth factor (GGF)].
The expression and function of these growth factors are influenced by nutritional status. Malnutrition during fetal life (i.e., intrauterine growth restriction) down-regulates IGF-I and IGF-I binding protein expression (Nishijima, 1986). IGF-I has a mitogenic and posttranscriptional effect on oligodendrocytes, stimulates neurite outgrowth, and promotes neuronal differentiation (Fellows, 1987). Reduction in IGF-I levels can thus influence myelin production (McMorris and Dubois-Dalcq, 1988; Saneto et al., 1988), as well as neuronal number and complexity. The reduction in IGF-I concentrations noted in growth-restricted fetuses may account for the high rate of microcephaly seen in this population.

A study of transgenic mice underscores the importance of the interaction between IGF-I and malnutrition as they influence brain growth (Lee et al., 1999). Whole brain and regional brain growth were assessed in well-nourished and malnourished suckling transgenic mice that overexpress IGF-I. Transgenic overexpression of IGF-I in well-nourished mice increased whole brain weight by 20% over well-nourished controls, predominantly due to increased myelination, a modest increase in DNA content, and increased neuronal survival due to decreased apoptosis. Whereas generalized malnutrition reduced brain weight by 10% in control mice, the IGF-I overexpressing mice had brain weights comparable to well-nourished controls, implying sparing of undernutrition effects by the IGF-I. More importantly, the malnutrition in the control group and the ameliorating effect of IGF-I in the transgenic group were regional. The hippocampus and cerebellum were more affected by malnutrition than the cortex, diencephalon, or brainstem. The brain-sparing effects of IGF-I overexpression were more prominent in the undernourished hippocampus, cortex, and diencephalon, but were not seen in the cerebellum. This regionalization of brain effects from malnutrition may be related to the metabolic demand of the areas at this time of development as well as variations in the expression of IGF-I. A similar effect in terms of iron accretion has been described in young rats (Erikson et al., 1997; deUngria et al., 2000).

STRESS AND INFLAMMATION Stress, specifically activation of the hypothalamic-pituitary-adrenal (HPA) axis or administration of glucocorticoids (GCs), may alter brain growth, targeting cognitive structures such as the hippocampus, despite adequate nutrition. For instance, neonatal exposure to dexamethasone, a pharmaceutical synthetic GC, has been reported to have short-term alterations on hippocampal synaptic plasticity and memory performance in rats (Lin, Huang, and Hsu, 2006), and basal levels of the GC cortisol is inversely related to memory performance in infancy (Gunnar and Nelson, 1994).

GCs are catabolic hormones that counteract anabolic hormones such as growth hormones and insulin. GCs both act as insulin antagonists in carbohydrate and lipid metabolism and act to increase the activity of counter-regulatory hormones of insulin (e.g., glucagon) and therefore, may affect the hippocampus by inhibiting glucose metabolism (Byrne, 2001; de Leon et al., 1997; Endo, Nishimura, Kobayashi, and Kimura, 1997; Heffelfinger and Newcomer, 2001). GCs may also affect brain development by inhibiting glucose transport into neurons (Horner, Packan, and Sapolsky, 1990). Furthermore, stress is related to insulin resistance and metabolic syndrome (Byrne, 2001), and may have long term effects on glucose metabolism. Therefore, despite
adequate energy intake, in the presence of GCs energy metabolism may be inadequate to support CNS and/or hippocampal functioning.

GCs, in addition to their role in glucose metabolism, may also affect brain development by regulating growth factors. There is evidence that cortisol (the chief GC in humans) due to stress during late gestation may alter IGF and IGFBP-1, thereby restricting growth (Cianfarani et al., 1998). In newborns, cortisol is inversely related to IGF-I in cord blood (Cianfarani et al., 1998). Cell proliferation and differentiation are also dependent on GCs through their role in IGF gene expression (Fowden and Hill, 2001). For example in osteoblasts (bone cells), GCs inhibit transcription of IGF-I (Delany and Canalis, 1995; Swolin, Brantsing, Matejka, and Ohlsson, 1996), and it is likely that such a relationship exists in neurons.

Stress and activation of catabolic hormones such as GCs may reduce glucose availability, induce insulin resistance, and likely decrease brain growth factors, resulting in altered brain growth.

Inflammation and infection, specifically the role of cytokines, are also important to consider in metabolism and cognitive development. Cytokines are small molecular weight proteins which initiate tissue breakdown and are released in response to cortisol activation by either non-infectious or infectious agents. The predominant cytokines released are TNF-alpha (tumor necrosis factor) which promotes tissue breakdown to provide substrates for glucose production and IL-6 (intraleukin-6) which induces the liver to use amino acids for defense proteins rather than for tissue accretion. Thus, chronic cytokine activation by stress results in less available amino acids for protein synthesis, including that needed for brain structure. The roles of both stress and inflammation in the impact of nutrition on cognition are largely theoretical, but warrant future attention.

Selected nutrients and their effect on brain development

Table 1 categorizes the components of human nutrition and their likely relationships to central nervous system development and function. All nutrients are needed for normal somatic development, but some play a greater role in neurodevelopment than others. The following sections present the evidence for the nutrients that are most important to the developing cognitive systems of the brain.

PROTEIN-ENERGY STATUS The effect of protein-energy nutritional status on brain growth and neurodevelopment is one of the most extensively studied subjects in nutrition. The importance of providing protein and energy to developing and mature brains has been assessed almost exclusively through studies of protein-energy insufficiency (as opposed to evaluating whether there is a beneficial effect of supplementing a replete organism). Even large-scale epidemiological studies demonstrating beneficial effects of protein and energy supplementation have been conducted in populations where protein-energy malnutrition (PEM) is endemic (Gorman, 1995). Pollitt and Gorman (1994) suggest that chronic energy rather than protein deficiency is responsible for most of the neurobehavioral changes associated with PEM. Animal models, however, strongly implicate independent roles for protein and energy in brain structural changes.

PEM can occur throughout the lifespan from fetal life through adulthood. The likely neuropathology underlying the significant changes in brain development or function seen with PEM has been elucidated using animal models.
Effects of prenatal PEM As with most nutritional deficiencies, the most significant neurodevelopmental effects appear to occur when severe PEM is imposed on a rapidly growing brain. The brain grows most rapidly during fetal and early postnatal life. Restriction of macronutrients during fetal life results in deceleration of growth and bears the term “intrauterine growth restriction” (IUGR). Maternal hypertension during gestation accounts for 75% of all cases of IUGR, although maternal malnutrition, intrauterine infections and chromosomal anomalies can alter fetal growth as well (Low and Galbraith, 1974). In the latter two instances, the adverse neurodevelopmental outcome associated with small brain size is not due to PEM but to the underlying pathology of the precipitating condition (e.g., viral invasion of CNS cells). In the case of maternal hypertension, high blood pressure causes atheromatous (plaque-like) changes in the vessels of the placenta, which in turn restricts blood and nutrient flow to a smaller, more calcified placenta (DeWolf, Robertson, and Brosen, 1975). Evidence of PEM resides in the smaller weight, length, and fat and muscle content of the growth-restricted fetus and newborn. Brain growth is compromised if the hypertensive insult is early (second trimester), prolonged, or severe.

The neurodevelopmental effects of restricted fetal nutritional delivery and delayed brain growth have been a subject of extensive clinical and laboratory investigation. Most larger trials measured relatively neurologically nonspecific outcomes such as intelligence quotient (Strauss and Dietz, 1998). Smaller studies have looked more specifically at what areas of the brain may be preferentially affected by fetal PEM. These studies demonstrate a fivefold higher prevalence of mild neurodevelopmental abnormalities at 2 years of age (Spinillo et al., 1993), weak novelty preference on visual recognition memory tasks (Gottleib, Biasini, and Bray, 1988), and reduced verbal ability (Pollitt and Gorman, 1994) in the IUGR infants compared with appropriate-sized controls. It is important to recognize that these effects may be due to PEM alone (based on animal models), but may also be due to other micronutrient deficiencies (iron, zinc, selenium) or chronic intrauterine hypoxia. A significant postnatal confounder has been the consistent finding that fetal growth restriction occurs more frequently in women of lower socioeconomic status who receive less prenatal care and in whom there is an increased incidence of smoking (Strauss and Dietz, 1998).

Epidemiological studies show that poor prenatal head growth presages poor developmental outcome (Gottleib, Biasini, and Bray, 1988; Harvey et al., 1982; Low et al., 1982; Strauss and Dietz, 1998; Winer and Tejani, 1994). Employing a clever study design, Strauss and Dietz (1998) matched term IUGR infants to sibling controls who were of appropriate weight for term gestation, thus controlling for genetic and postnatal environment; they showed a significant decrement in broad measures such as WISC IQ and Bender-Gestalt scores at 7 years only if head growth had been compromised in the fetal period, but found no effect if intrauterine head growth had been spared.

The biochemical and neuroanatomic bases of neurodevelopmental impairment from early PEM can be found in human autopsy studies and in investigations using animal models. The human studies show significant reductions in brain DNA, RNA, and protein content (Winick and Nobel, 1966; Winick and Rosso, 1969a,b). IUGR infants have lower brain cell number, smaller cell size, and smaller head circumferences. Certain areas (e.g., the cerebellum, cerebral cortex, hippocampus) demonstrate more profound
effects than others, suggesting that the developing brain in some way prioritizes protein and energy during deficiency states.

Animal models of IUGR support the human findings of lighter brain weights, reduced neuronal DNA and RNA contents, as well as reductions in mRNAs for neuronal and glial structural proteins, synapse number, synaptic structures, and neurotransmitter peptide production. (Bass, Netsky, and Young, 1970; Cragg, 1972; Jones and Dyson, 1976; Wiggins, Fuller and Enna, 1984). Fatty acid profiles are profoundly altered, with subsequent reductions in myelination, brain lipid composition, and learning ability in fat-restricted rats (Yamamoto et al., 1987). Malnutrition also downregulates CNS growth factors critical for normal brain development (Nishijima, 1986). The study by Lee and colleagues (1999) in transgenic mice emphasizes the importance of maintaining IGF-I levels during periods of malnutrition in order to spare regions of the brain important for cognition.

It will be important in future research in IUGR infants to link specific regional neuropathologic or neurochemical findings (elucidated from controlled animal models of PEM) with deficits in behaviors known to be based in those regions. Thus, one should be able to relate the reduction in visual recognition memory processing in IUGR infants (Gottleib, Biasini, and Bray, 1988) to either reduced hippocampal volume or metabolism on MRI/NMR spectroscopy. Several studies have begun to examine such relationships between brain and behavior in IUGR infants. For instance, IUGR infants, when compared with matched-for-gestational-age controls, had reduced cerebral cortical gray matter, and this reduction in gray matter was correlated with attention interaction capacity (as measured by the APIB) (Tolsa et al., 2004). Another recent study (L. S. Black, deRegnier, Long, Georgieff, and Nelson, 2004) assessed electrophysiological correlates to recognition memory processing using event-related potentials (ERP); IUGR newborns, compared with matched-for-age controls, had ERP patterns indicative of accelerated maturation of auditory recognition memory. Continuation of such lines of research will be principle to clarify the relationship between specific aspects of brain development and cognition in IUGR infants.

Effects of postnatal PEM The postnatal brain grows rapidly during the first six postnatal months and then slows considerably during the last six months of the first year. Important regional changes that occur during this year include myelination of motor tract fibers, rapid cerebellar development, and establishment of hippocampal-prefrontal connections.

Similar to intrauterine malnutrition, extrauterine malnutrition bodes poorly for the developing brain. Preterm infants or those with severe illnesses during the neonatal period are particularly vulnerable. The protein and energy needs of these infants are high, and it is often difficult to meet the nutritional requirement of these infants due to their illnesses. Preterm infants whose head circumference (which reflects brain growth during typical development) fails to catch-up to the gestation-specific norm within 4 weeks have suboptimal head growth and lower developmental quotient at 12 months corrected age (Georgieff et al., 1985). In preterm infant with IUGR, these adverse effects are seen after only 2 weeks of poor postnatal head growth. Similarly, a recent prospective study found that IUGR infants had lower IQs and performed worse on measures of frontal lobe functioning at age 9 years compared with carefully matched controls (Geva, Eshel, Leitner, Valevski, and Harel, 2006). These findings were attenuated by postnatal catch-up
growth, such that IUGR children with incomplete catch-up growth had more cognitive
difficulties than those with complete catch-up growth.

Once infants are weaned from human milk or formula, their risk of PEM increases
because they are now dependent on the same foods as their adult food providers. A child
growing up in an area of the world where PEM is endemic will be placed at a risk
equivalent to or greater than the adult population of that area. The effects of PEM have
been extensively studied in children from age 6 months through the early teenage years in
these endemic areas. Although the studies show mixed results owing to differences in
degree, timing, type, and duration of malnutrition, it is safe to state that PEM of sufficient
degree and duration at a critical time during a growing child’s life will affect cognitive
abilities. In some cases, the negative effect on the brain is reversible with nutritional
rehabilitation, while in other cases the effects appear more “permanent”. However, as
discussed below, the assignment of nutritional causality to poorer cognitive outcomes in
free-living societies has been very difficult, given concurrent confounding variables such
as maternal mental health, maternal socioeconomic status, lack of infant mental
stimulation, and malnutrition-induced lack of infant motivation (Stein and Susser, 1985).

Until the mid-1990s, studies assessing the role of postnatal malnutrition in
cognitive development were dominated by two important theoretical concepts. The first
centered on the idea of “critical periods.” Winick and Noble’s histopathologic studies
introduced the idea that PEM during the period of rapid brain growth in the perinatal
period would cause more significant and hence more permanent perturbations in brain
structure and, ultimately, function (Winick and Noble, 1966). The vulnerable period was
subsequently extended until at least 3 years of age as it became apparent that
synaptogenesis, dendritic pruning, programmed cell death, and myelogenesist continued
well into the postnatal period. Dobbings’ work codified the concept of vulnerable or
critical periods in the field of nutritional neuroscience (Dobbing, 1990). Based on these
developmental neuroanatomic considerations, it was logical to expect that field studies of
PEM in 6-month-old to 3-year-old children should demonstrate significant cognitive
effects.

The other important theoretical concept centered on the role of covariates such as
maternal mental status, maternal – child interactions, and infant motivation in
determining the cognitive abilities of the malnourished infant (Lozoff et al., 1998; Pollitt
and Gorman, 1994). Theoretically, these covariates could be highly dependent on either
maternal or infant nutritional status, or they could be completely separate issues. Another
example concerns the effects of individual differences in infant motivation. An infant
could perform poorly on a set of cognitive measures as a function of what is perceived by
the investigator as “reduced motivation.” Reduced motivation could be due to depression,
decreased energy due to marginal malnutrition, or poor maternal – child stimulation
based on the mother’s (and not the infant’s) nutritional status. Lozoff has published a
diagram of these complex interactions with respect to iron deficiency (Lozoff et al., 1998;
Georgieff and Lozoff, in press), but the tenets are clearly applicable to PEM as well.
Finally, some of the impairments in developmental tests could be due to the effect of
malnutrition on the musculoskeletal system. As an example, preterm infants with
bronchopulmonary dysplasia, a condition that is associated with malnutrition (deRegnier,
Guilbert, Mills, and Georgieff, 1996) perform poorly on developmental tests, such as the
PDI component of BSID during infancy and toddlerhood (Raman, Georgieff, and Rao,
With nutritional rehabilitation and improvement in physical growth, these impairments also tend to improve.

Prior to the mid-1990s, studies in humans that attempted to associate mild to moderate PEM with poorer cognitive outcome were so hopelessly flawed that researchers in the field would reach diametrically opposite conclusions about the studies (see Stein and Susser, 1985). It may not be ethically possible to separate all of the nonnutritional confounding variables in a free-living human society, but studies published by Pollitt’s group in the mid-1990s have given credence to the hypothesis that nutritional factors (specifically, PEM) do influence postnatal cognitive development (Pollitt and Gorman, 1994; Pollitt et al., 1995; Pollitt, Watkins, and Husaini, 1997).

In these studies, long-term cognitive effects of early supplemental feeding in children 0-7 years of age were examined in four Guatemalan villages from 1969 to 1977. Seventy percent of the children were followed up in 1988 at ages 11-26 years. The villages were in an area marked by mild to moderate PEM. Participants in two of the villages received a high-calorie/high-protein supplement that was administered to the mothers, infants and young children. Participants in the other two villages received a supplement with 40% fewer calories and 20% less protein. Test scores on knowledge, numeracy, reading, processing time, and vocabulary at follow-up (adolescence) were significantly higher in the group receiving more robust protein-energy supplementation. Within that group, no effect of socioeconomic status was observed. Interestingly, the group that received less supplementation not only had lower scores on cognitive tasks, but demonstrated a profound socioeconomic effect as well. This result suggests that marginal nutritional status may potentiate the effects of other neurologic risk factors. A similar effect has been described in animal models of iron deficiency (Rao et al., 1999).

Pollitt and colleagues (1995) very carefully considered potential alternative explanations (including differences between the villages, intervening factors between the initial intervention and the follow-up 10 years later, compliance with the dietary supplements, and the 30% dropout rate at follow-up), and concluded that none accounted for the observed differences in cognition. They do not claim that the study provided definitive proof of the effect of early mild PEM on later cognitive ability, but felt that the evidence is compelling enough to justify nutritional intervention as sound public health policy (Pollitt and Gorman, 1994).

From a mechanistic standpoint, it would be most useful for researchers studying postnatal PEM to assess whether the neurodevelopmental abnormalities that are observed fit the expected pattern of vulnerable brain areas and processes predicted from human and animal histopathologic, neurochemical, or neurophysiologic models. Although it is laudable to demonstrate effects of mild PEM on relatively broad cognitive function, it would be interesting to know whether neurologic circuits involved in the behaviors where differences are observed between groups are particularly at risk specifically for protein or energy malnutrition. For example, the reduced speed of processing could be easily explained by nutritionally induced hypomyelination. Alternatively, the same finding at the behavioral level could be due to reduced motivation to perform the task and may be related to damage or dysfunction of limbic structures such as the amygdala. If no data support amygdaloid vulnerability to PEM, the latter may be more effectively ruled out. Newer tools that assess the structure and functions underlying certain cognitive
capabilities (e.g., fMRI, event-related potential) now allow for more precise delineation of cause and effect of nutritional deficiencies such as early PEM).

Effects of specific macronutrients Infants in the United States and Canada are typically fed either human milk or infant formula derived from cow’s milk or soy plant products during this time. The significant, positive relationship between breastfeeding and cognitive development is intriguing, since it is unclear whether the positive effect is related to nutritional factor(s) present in human milk but not in formula, to positive maternal-infant interactions (including the propensity of higher-IQ mothers to choose breastfeeding), or both.

There is good reason to believe that multiple factors found in breast milk promote normal CNS development and that deficiencies of these nutrients in cow’s milk or soy-based formulas are responsible for slower rates of cognitive development (Lucas, 1997; Morrow-Tlucak, Haude and Ernhart, 1988; Wang and Wu, 1996). These factors include compounds such as nucleotides (DeLucchi, Pita, and Faus, 1987) oligosaccharides and long-chain polyunsaturated fatty acids (LCPUFA) (Innis, 1992) that are simply not synthesized by cows and soy bean plants. Because of their potential neurologic effects, within the past few years, LCPUFAs have been added to some cow’s milk and soy-based formulas. Other neurotrophic compounds (e.g., growth factors) have not been added because they are destroyed in formula processing or storage (MacLean and Benson, 1989).

The oligosaccharides and lactose that are present in human milk may play a significant role in brain development. Oligosaccharides are present only in the milks of humans and elephants, both species with a highly developed central nervous system which develops predominantly after birth (Kunz, Rudolf, Baier, Klein, and Strobe, 2000). Galactose- and sialic acid-containing oligosaccharides appear be important for myelination, synaptogenesis and learning (Kunz et al., 2000; Wang and Brand-Miller, 2003; Wang, McVeagh, Petocz, and Brand-Miller, 2003). Oral and parenteral supplementation of sialic acid results in greater accumulation of sialic acid containing glycolipid and glycoprotein in the cerebrum and cerebellum in rats (Carlson and House, 1986). The role of oligosaccharide supplementation has yet to be studied in human infants.

Long-chain poly-unsaturated acids (LCPUFA) are one type of macronutrient that have been given specific attention in neurodevelopment. LCPUFAs include docosohexaenoic acid (DHA; 22:6n-3) and arachidonic acid (AA; 20:4n-6). Both are transported by the placenta to the fetus (Carlson, 1997), and both accumulate in the CNS during the third trimester (Clandinin et al., 1980). These compounds are provided transplacentally by the mother during the last trimester. Accordingly, preterm infants are at greater risk of deficiency due to shortened nutrient placental transfer during late gestation. Furthermore, DHA and AA can be synthesized form the precursors alpha-linolenic acid and linoleic acid respectively; however, this synthetic pathway is immature in neonates, with limited synthetic capacity as early as 33 weeks gestation. However, full synthetic capacity is not thought to develop until 2 months post-term.

LCPUFAs potentially affect neurodevelopment because they are essential in all cell membranes. They are involved in intercellular communication, signal transduction
Evidence from animal studies shows that gestational DHA is necessary for normal brain development. Gestational DHA deficiency decreases neurogenesis in the rat brain (Coti Bertrand, O’Kusky, and Innis, 2006) and affects dopaminergic function (Levant, Radel, and Carlson, 2004). There is evidence that prenatal LCPUFA supplementation affects cognitive development in humans. In a double-blinded randomized supplementation study, children born to mother’s supplemented with DHA during pregnancy and three months of lactation performed better on cognitive tasks (mental processing composite of the K-ABC) at 4 years of age. Furthermore, the extent of DHA supplementation was correlated with the children’s scores (Helland, Smith, Saarem, Saugstad, and Drevon, 2003). In another maternal supplementation study, maternal DHA levels at birth were found to be correlated with the children’s performance on attentional tasks at 1 year and 2 years of age (J. Colombo et al., 2004).

LCPUFAs continue to accumulate during the first 18 months postnatally (Clandinin et al., 1980); however, postnatal supplementation of LCPUFA seems to have different effects in preterm and term infants. Randomized trials of LCPUFA supplementation in preterm infants show transiently improved visual acuity, faster processing time on electroretinogram, better visual recognition memory, and higher scores on the Mental Developmental Index of the Bayley Scales of Infant Development at 12 months of age (Birch et al., 1992; Carlson, Werkman, and Tolley, 1996). The retinal results with respect to rod electroretinogram threshold at 36 weeks gestation and visual acuity by forced-choice preferential looking and by visual evoked potential in preterm infants fed supplemented formula approach the findings in breastfed infants, and are significantly better than those of infants fed unsupplemented formula (Uauy-Dagach and Mena, 1995). Nevertheless, most of the effects appear transient. Furthermore, the transience of the findings is not due to withdrawal of the supplementation with subsequent lack of synthesis by the infants, since the trials typically lasted well beyond the age (6 months) when infants can synthesize LCPUFAs de novo. Term infants supplemented with LCPUFAs do not demonstrate nearly the beneficial effect that preterm infants show, perhaps because of an increased capacity to synthesize de novo AA and DHA at an earlier postnatal age (Jensen et al., 1997).

In spite of the mixed long-term results, the data are quite convincing that LCPUFAs (administered without the remainder of trophic factors and nutrients found in breast milk) independently alter neurologic function and perhaps development, and these findings provide clear evidence that nutrients can affect brain development and function. Although they appear to be supplementation studies, they are better considered studies of correction of deficiencies of essential nutrients in nonhuman milk formulas.

Nucleotides are nitrogenous compounds derived from the combination of a nucleic acid base (adenine, guanine, cytosine, thymine, or uracil) with a phosphorylated pentose sugar. Nucleotides and their precursors (nucleosides and nucleic acids) are critical for DNA and RNA synthesis. Thus, a steady intracellular pool of nucleotides is required to ensure cell division and protein synthesis. This de novo synthetic pathway is immature in all newborns, but particularly in premature infants, raising the still unresolved issue of whether dietary nucleotides are semi-essential in the newborn period. Nucleotide supplementation of infant formula has been postulated to have an impact on
the developing brain by increasing the levels of LCPUFAs such as arachidonic and docosohexaenoic acid (DeLucchi, Pita, and Faus, 1987; Gil et al., 1986).

IRON  Iron is the second most commonly studied nutrient in relation to brain development, after protein-energy. Iron deficiency is common worldwide; 30% of the developing world’s population and 11% of U.S. toddlers are iron-deficient due to a low-iron diet combined (especially in the developing world) with a high rate of intestinal blood loss. Iron deficiency is the world’s most common nutritional cause of anemia.

It is not unreasonable to study the relationship of iron to neurodevelopment and neurologic function, given the role of iron in many brain cellular metabolic processes (Camack, Wrigglesworth, and Baum, 1990; Larkin and Rao, 1990; Thelander, 1990; Youdim, Ben-Sachar, and Yehuda, 1989). Iron-containing enzymes and hemeproteins are involved in numerous neurodevelopmental processes including myelination, energy metabolism, dendritogenesis, synaptogenesis, and monoamine metabolism (Rao, Tkac, Townsend, Gruetter, and Georgieff, 2003). As with PEM, a convincing relationship can be drawn between this nutrient and brain development based on deficiency states.

There are three time periods when children are at particular risk for iron deficiency: the fetal/neonatal period, infancy and early toddlerhood (6-24 months of age), and following the onset of menarche in girls (Bruner et al., 1996). Brain growth and development is relatively rapid during two of these periods, while it is nearly complete during the third. This distinction allows for studying the comparative effects of a single nutrient deficiency on a growing versus a mature brain. Because of its intricate involvement in cell cycle kinetics and myelination (Larkin and Rao, 1990; Thelander, 1990), one would expect profound neuroanatomic changes in a brain that is still growing, but perhaps no structural effect in a relatively mature brain. Teenage iron deficiency would not be expected to affect myelination since it is largely completed by that time; however, iron deficiency prior to 3 years of age would likely result in profound and possibly permanent myelin changes (Algarin, Peirano, Garrido, Pizarro, and Lozoff, 2003). Furthermore, areas that are growing particularly rapidly might be expected to be most affected. Since the brain does not develop homogenously (i.e., not all parts mature simultaneously), iron deficiency during one growth period (e.g., fetal life) may result in very different neuroanatomic and neurobehavioral deficits than iron deficiency during another growth period (e.g., infancy). Iron also has important effects on neurochemistry and neurometabolism through its effects on monoamine metabolism and oxidative phosphorylation (Cammack, Wrigglesworth, and Baum, 1990; Youdim, Ben-Sachar, and Yehuda, 1989). Iron deficiency may affect these chemical and metabolic aspects of brain function similarly in developing and mature brains. Therefore, neurotransmitters, such as dopamine and glutamate (Rao et al., 2003) would be vulnerable to iron deficiency at any age.

Iron deficiency most commonly occurs during infancy, between 6 and 24 months of age, due to low dietary iron intake (through consumption of either low-iron formula or cow’s milk and delayed introduction of iron-containing solid foods). It is not surprising that this age group has been more extensively studied than any other iron-deficient group, and animal models have focused on ID during this time. Dietary iron deficiency has been induced in rats from weaning (21 days) to 35 days of age in order to model iron deficiency of human infancy.
Multiple well-controlled clinical studies in this age group demonstrate significant decrements in motor and mental achievement (Lozoff, 1990; Lozoff et al., 1982, 1987; Nokes, van den Bosch, and Bundy, 1998; Walter, Kowalskys, and Stekel, 1983). While the motor findings are less robust and generally reversible with iron therapy, the significant cognitive deficits that have been documented are more resistant to reversal, and in some studies are very long-term (Lozoff, 1990). The cognitive deficits include a 10- to 12-point reduction in the Mental Developmental Index of the Bayley Scales of Infant Development, significantly associated with the degree of anemia (Lozoff, 1990). These cognitive deficits appear to be irreversible with treatment. The findings are not thought to be due to anemia itself, since rapid correction of the anemia does not affect the neurodevelopmental test scores.

The apparent permanence of these neurobehavioral findings has three important implications. First, there appears to be a differential regional effect of iron on the growing brain, perhaps mediated by differences in regional blood-brain iron transport regulation. This regionalization concept is supported by the nonhomogenous (e.g., cognitive greater than motor) deficits induced by iron deficiency. Second, iron deficiency during this period of brain development likely changes neuroanatomy since the deficits remain extant over much longer periods of time than would be expected for neurochemical or neurophysiological alterations. Third, and perhaps of greatest concern, the results demonstrate that certain brain lesions induced by nutritional deficiencies are beyond the reach of CNS reparative or compensatory processes which may be termed “plasticity”.

The presence of iron in the brain is critical for myelination (Larkin, Jarratt, and Rao, 1986). Iron deficiency in immature animal models results in a predictable loss of enzyme activity and in hypomyelination (Larkin and Rao, 1990). In animal models, early ID affects myelin lipid synthesis and permanently alters brain lipid composition despite repletion (Kwik-Uribe, Gietzen, German, Golub, and Keen, 2000; Ortiz et al., 2004; Rao et al., 2003). If the same process occurs in infants, one could predict a specific neuroanatomic effect (potentially visible with high-resolution magnetic resonance imaging) or a neurophysiologic effect (potentially detected by electrophysiologic assessment). Although the former has not been assessed, Roncagliolo and colleagues (1998) have reported delayed latencies on auditory brainstem-evoked responses in iron-deficient 6-month-old infants. They attributed this delay to the effects of iron deficiency-induced hypomyelination. These effects appear to be long-lasting despite iron treatment. At ages 3 and 4, delayed latencies in auditory brainstem responses and visual evoked potentials have been observed in children with iron deficiency anemia despite treatment during infancy (Algarin et al., 2003).

Iron also has important effects on neurochemistry and neumometabolism through its effects on monoamine metabolism and oxidative phosphorylation (Cammack, Wrigglesworth, and Baum, 1990; Youdim, Ben-Sachar, and Yehuda, 1989). Monoamine metabolism involves iron dependent enzymes (tyrosine hydroxylase and tryptophan hydroxylase), and animal studies which model ID in infancy show long-term monoamine alterations (Beard and Connor, 2003; B Lozoff et al., 2006). For instance extracellular dopamine and epinephrine increase, while monoamine transporters and dopamine receptors D1 and D2 decrease, and such alterations occur without reductions in brain iron concentrations (Beard and Connor, 2003; Beard et al., 2006). Decreased exploration and
increased hesitancy have been observed as a result of early ID in rodents, likely due to altered dopaminergic function (Felt and Lozoff, 1996; Pinero, Jones, and Beard, 2001). There is evidence for similar behaviors in infants with ID anemia. They were observed to be more wary and hesitant, easily tired, less playful, and make less attempts at test items (Lozoff et al., 1998). Accordingly, reduced activity and inhibited exploration may lead to hampered cognitive abilities.

The selectivity of iron deficiency for certain areas of the brain can be similarly assessed. Striatal development is also rapid during late gestation and early infancy and is altered by ID during this time. The striatum contains high concentrations of both iron and dopamine (Beard and Connor, 2003), and striatally-mediated behaviors in the rodent are affected by ID (Felt et al, in press). There is evidence that striatal development is altered by ID during infancy and has long-term cognitive effects. Children with severe ID during infancy performed worse on tasks that rely on striatal-frontal connections. For instance, at 11-14 years of age, children who had severe, chronic ID during infancy had poorer performance on tasks of spatial memory and selective attention compared with children without severe ID during infancy (Lozoff, Jimenez, Hagen, Mollen, and Wolf, 2000). Furthermore, at the age of 19, poor performance on tasks of executive function, primarily those of inhibition and planning, was associated with ID during infancy (Burden, Koss and Lozoff, 2004).

The second group of developing humans at risk for iron deficiency is late gestation fetuses and newborns. Infants born to mothers with iron deficiency, gestational conditions such as diabetes mellitus, IUGR and maternal smoking are at risk of fetal and neonatal iron deficiency. The adverse effects of fetal and neonatal iron deficiency have been studied in infants of mothers with diabetes mellitus during pregnancy and infants who suffered IUGR. Each group has a 50% prevalence of low iron stores at birth, 25% of which are at a risk for brain iron deficiency. Autopsy studies have documented up to a 40% decrease in brain iron in the most severely affected infants. Both groups of infants are at increased risk for neurobehavioral abnormalities. Animal models of perinatal iron deficiency support the concept of regional loss of iron-dependent brain metabolic function, with the hippocampus and its prefrontal projections demonstrating particular vulnerability (deUngria et al., 2000). Regions that are developing rapidly during a state of ID are likely to be most affected. During late fetal and neonatal development, the hippocampus is developing rapidly, and animal models show alterations in hippocampal neurochemistry, structure and electrophysiology (Jorgenson, Sun, O'Connor, and Georgieff, 2005; Rao et al., 2003; Jorgenson, Wobken, and Georgieff, 2003). Poor performance on hippocampal-mediated memory performance (e.g., spatial memory tasks) is associated with ID in the rodent model of early ID (Felt and Lozoff, 1996). Thus, a putative link between perinatal iron deficiency and newborn and long-term neurobehavioral sequelae can be proposed. Unfortunately, like all other clinical population studies, each group has other significant neurologic risk factors (e.g., hypoglycemia, hypoxia, PEM) that may affect long-term outcome and confound any attempt at causally relating perinatal iron deficiency with neurobehavioral deficits. However, in a study of infants born to mothers with diabetes mellitus, those with iron deficiency at birth showed delays in auditory recognition memory when tested at birth compared with iron sufficient infants of diabetic mothers (Siddappa et al., 2004). This
finding suggests that the effects in recognition memory are due to iron rather than to other risk factors associated with gestational diabetes.

The neurobehavioral study of iron-deficient teenage girls provides an interesting contrast to iron-deficient infants since the brain is neuroanatomically relatively mature and myelination is complete at this age. Iron supplementation of young women with iron deficiency anemia improves memory and learning but has no effect on attention (Groner et al., 1986). These findings can be contrasted with the long-term (and perhaps permanent) deficits found in toddlers who became iron-deficient and were subsequently treated. The reversibility of the neurobehavioral deficits with iron therapy in the teenage population argue for an effect of iron on neurochemistry (e.g., dopamine) or neurophysiology (oxidative metabolism) as opposed to potential structural changes in neuroanatomy that may have occurred in the toddlers.

ZINC A strong case can be made for the essentiality of zinc for normal brain development and function. Zinc deficiency affects neuroanatomy, neurochemistry, and neurophysiology through a variety of mechanisms. The global effects of zinc are in part due to the essential role that zinc plays in basic protein biochemistry and in cell replication. Zinc has a direct effect on brain growth and morphology through its role in enzymes that mediate protein and nucleic acid synthesis (Sandstead, 1985; Terhune and Sandstead, 1972). Profound zinc deficiency in the growing animal results in decreased brain DNA, RNA, and protein content (Duncan and Hurley, 1978; Sandstead, 1985). Zinc has an indirect effect on brain growth because its presence is needed for normal insulin-like growth factor-I (IGF-I) activity (McNall, Etherton, and Fosmire, 1995). Zinc influences brain neurochemistry (and presumably function) by inhibiting binding of opioids to μ receptors and of magnesium to μ and δ receptors in the cerebral cortex (Tejwani and Hanissian, 1990). Zinc also inhibits γ-aminobutyric acid (GABA) stimulated chloride influx into hippocampal neurons (Li, Rosenberg, and Chiu, 1994). Zinc is released into the interneuronal space from presynaptic boutons (Frederickson and Danscher, 1990). Zinc’s effect on brain neurophysiology is evident in abnormal electroencephalographic tracings found in zinc-deficient rats (Hesse, 1979).

The cerebellum, limbic system, and cerebral cortex are particularly rich in zinc and demonstrate the most profound effects of zinc deprivation (Frederickson and Danscher, 1990). These effects include truncated dendritic arborization and reduced regional brain mass in rats. As with iron deficiency, the neuroanatomic sequelae of zinc deficiency in young rats persist into adulthood with attendant persistent behavioral sequelae (Frederickson and Danscher, 1990). Two-year-old rhesus monkeys fed a zinc-deficient diet have reduced spontaneous motor activity and poorer short-term memory compared with the pre-deficiency baseline period (Golub et al., 1994). Similar results have been found in mice and rats.

Zinc is essential for growth, as it is involved in cell replication and nucleic acid and protein synthesis. Accordingly, zinc is especially critical for infants, children, adolescents, and pregnant women (FAO/WHO, 2004). It is likely that during times of rapid growth and/or rapid brain growth, individuals might be vulnerable to zinc deficiency. The rate of inadequate dietary intakes of zinc in infants and toddlers in developing countries suggest that the rate of zinc deficiency is fairly high (FAO/WHO, 2004). Furthermore, inadequate dietary zinc intakes among middle-class and upper-class
infants and toddlers in the United States also suggest that the rate of zinc deficiency is common among American children (Skinner et al., 1997), and according to the latest national nutrition survey (NHANES III), young children ages 1-3 and adolescent females are at risk for inadequate zinc intakes (Briefel et al., 2000).

Despite the evidence in animal models, zinc supplementation trials in children have yielded inconsistent results. During infancy, there is some implication that zinc supplementation improves motor development and promotes activity in the most severe cases of zinc deficiency (for review, see Black, 2003). However, other findings show zinc deficiency in humans results in significant changes in neuropsychological performance on tests that tap the anatomical areas shown to be vulnerable in the animal models (Sandstead et al., 1998). Six- to nine-year-old first-graders with low zinc status were assessed biochemically and neuropsychologically before and after treatment. The tasks included design matching to assess visual perception, delayed design matching to assess short-term visual memory, a spatial orientation memory test, and Pollitt’s oddity task to assess concept formation and abstract reasoning. Zinc supplementation for 10 weeks resulted in significantly better zinc status and improvement in these particular neuropsychological assessments.

IODINE There is overwhelming evidence that iodine sufficiency is critical for normal early CNS development. An analysis of available epidemiological studies has helped elucidate the effect of severity, timing, and duration of iodine deficiency on brain development and neurologic outcome. Iodine deficiency can range from severe to mild based on the availability of iodine in the food supply (Hetzel and Mano, 1989). Endemic areas of severe dietary iodine deficiency include parts of China, Zaire, Iran, and India (Hetzel and Mano, 1989; Kretchmer, Beard, and Carlson, 1996), with 35% of world’s population having insufficient iodine intake (de Benoist, Andersson, Egli, Takkouche, and Allen, 2004). Classic older studies from these areas helped characterize the syndrome of endemic cretinism that, in its severest neurologic manifestation, includes mental retardation, spastic diplegia, and deaf-mutism. More recently, investigators have concentrated on describing the neuropsychological and motor effects of moderate or mild iodine deficiency and the effect of iodine prophylaxis or treatment in high-risk groups (Aghini-Lombardi et al., 1995; Azizi et al., 1993). A clear dose-response effect can be appreciated across the studies, with moderate iodine deficiency resulting in reduced verbal IQ and subset coding ability on the Wechsler Intelligence Scale for Children-Revised (WISC-R) as well as motor impairments on simple reaction time tests in children of elementary school age (Fenzi, Giusti, and Aghini-Lombardi, 1990). Mild iodine deficiency results in reduced motor ability without any apparent effect on cognition when children of the same age were assessed with the same tools (Azizi et al., 1993). It is unclear whether the latter group had early cognitive findings that were “reversed” with postnatal iodine treatment or whether they were never affected in the first place.

As with any nutrient deficiency, timing and duration are of critical importance. Cretinism results from severe iodine deficiency during early pregnancy, rather than late pregnancy. Moreover, developmental delays associated with prenatal iodine deficiency appear to be specific to deficiency during the first two trimesters, but not the third (Cao et al., 1994; O'Donnell et al., 2002). Interventional studies with iodine treatment clearly demonstrate that prophylaxis is effective. Iodine-deficient women living in endemic areas
who were injected with iodinated oil prior to pregnancy did not produce infants with cretinism (Hetzel, 1987). In a Chinese population at risk for iodine deficiency, iodine supplementation before the third trimester predicted higher Bayley scores at age 2 (Cao et al., 1994) and higher psychomotor test scores around the age of 6 (O'Donnell et al., 2002) compared with those who received supplementation during the third trimester or postnataally. In animal models, treatment later in pregnancy had a much less dramatic effect, and postnatal treatment of humans and animals appeared to have little effect. These observations lend credence to the hypothesis that the critical window for brain responsiveness to iodine is during early fetal life. Nevertheless, it should be noted that children and adolescents living in areas of endemic iodine deficiency will demonstrate alterations in psychomotor development with reduced IQ, even with normal physical growth (an indicator of less severe iodine deficiency) (Azizi et al., 1993). Although very few studies have been performed that assess the effect of repletion of iodine status on cognitive performance in children with mild to moderate iodine deficiency, a recent randomized, placebo-controlled, double-blind intervention, found that iodide supplementation improved performance on cognitive tasks of information processing and problem solving in children between the ages of 9 and 10. (Zimmerman et al., 2006).

There is reason to believe that late-onset iodine deficiency (hypothyroidism) affects brain function, but not anatomy. Smith and Ain (1995), using $^{31}$P magnetic resonance spectroscopy, demonstrated reduced oxidative metabolism in the hypothyroid brain (Pleasure and Pleasure, 2003) that was reversible with thyroid replacement therapy.

**SELENIUM** Selenium is a micronutrient whose role in brain development is only now being elucidated. Selenium deficiency is seen in geographical regions where there are low selenium levels in the soil. Food crops and pasture grasses grown in these soils will have lower selenium content; therefore, populations who depend on local food crops and animal products are at risk for selenium deficiency. The highest rates of selenium deficiency are in communities living in several regions throughout China with low soil content (FAO/WHO, 2004). Several other regions with low soil content (e.g., Finland, New Zealand, United Kingdom) have reduced the rates of selenium deficiency due to importation of crops and animal products raised in high content regions. Finally, another population at relatively high risk of selenium deficiency is preterm infants because of their lower body stores and generally poorer antioxidant status.

Although direct evidence of selenium’s effect on cognitive development in humans is lacking, its role in brain thyroid and iodine metabolism, as well as its interaction with other micronutrients (e.g., iron, copper, zinc, lead) that affect brain development, is important to note. Selenium is required for the synthesis of proteins (selenoproteins) that are involved in thyroid metabolism. Thus, as with iodine, selenium deficiency can lead to hypothyroidism and cretinism. Studies linking selenium status with behavioral development in animal models have been published (Mitchell et al., 1998; Watanabe and Satoh, 1994). Thus, it is likely that research on the role of this nutrient in human brain development will be forthcoming.

**CHOLINE** Developing fetuses and postnatally breastfed infants may be at risk for choline deficiency if the mother has poor choline body stores and/or poor dietary choline intake. Formula-fed infants may also be at risk for choline deficiency depending on the
formula used as the choline concentrations range between 50% to 140% that found in human milk. Human milk is also abundant in several choline-containing compounds, and formulas do not contain the same composition of these compounds as human milk (Blusztajn, 1998; Meck and Williams, 1999). Additionally, during the early postnatal period, there is a brief spike in choline concentrations in human milk which is not mirrored in infant formulas (Meck and Williams, 1999).

Choline serves several metabolic functions essential for neurodevelopment. The majority of choline in the body is present in two phospholipids that are essential for both plasma membrane and myelin synthesis (Blusztajn, 1998; Colombo, Garcia-Rodenas, Guesry, and Rey, 2003). Choline is also involved in cholinergic neurotransmission, as it is the precursor for acetylcholine, serves as a methyl source in single-carbon metabolism of protein synthesis and transmethylation reactions (Blusztajn, 1998), and is involved in transmembrane signaling during neurogenesis and synaptogenesis (Meck and Williams, 1999). During fetal development, choline is essential for stem cell proliferation and apoptosis (Blusztajn, 1998).

Choline has permanent effects on rodent memory and attention development. Prenatal choline supplementation results in better spatial memory performance in the adult rat compared with control rats and impairs memory performance in prenatally choline deficient rats. (Meck and Williams, 1999). Prenatal choline deficiency is associated with long-term effects on attention which may be related to the long-term effects on memory. Gestationally deficient rats perform poorly on attention tasks compared with controls and choline supplemented rats, showing difficulty selectively attending to stimuli and showing an increased rate of age-related decline in attention (Meck and Williams, 2003).

Several mechanism for the effects of choline supplementation on memory development have been identified (Meck and Williams, 2003). Prenatal choline deficiency increases the rate of apoptosis in the hippocampus, thus potentially altering hippocampal structure and function (Holmes-McNary, Loy, Mar, Albright, and Zeisel, 1997). Another potential mechanism involves adaptations in cholinergic transmission (Meck and Williams, 2003); prenatal choline has long-term effects on cholinergic transmission, altering hippocampal acetylcholine function despite repletion (Blusztajn, Cermak, Holler, and Jackson, 1998). Yet another mechanism linking choline to memory is through hippocampal long term potentiation LTP; the stimulus threshold for LTP is inversely related to prenatal choline status (Pyapali, Turner, Williams, Meck, and Swartzwelder, 1998).

Because choline supplementation of older animals does not seem to improve memory as it does following supplementation during fetal development, it is likely that choline during early development alters the developmental trajectory of neural circuits that support memory, leading to long-term alterations in memory and attention (Meck and Williams, 2003).

Despite the mounting evidence from animal research for the role of choline in neurodevelopment and memory and attention performance, questions still exist whether these findings translate to humans. However the evidence from animal models highly supports the hypothesis that dietary choline during pregnancy and the early postnatal period is necessary for normal cognitive development.

*The role of timing in nutrient deprivation and subsequent repletion*
A common theme in the discussion of each of the nutrients has been the roles of timing, duration, and severity of nutrient administration or deficiency.

Clear evidence exists that brain growth and development is not an even process and that various “circuits” come on line at different times between conception and adolescence. Nutrient requirements are increased during a period of rapid growth for any organ, including the brain. Human and animal model experiments also support the concept that nutritional deprivations during a period of rapid growth result in more profound structural, chemical, and physiological changes than if the same degree of deprivation is imposed during a more quiescent period. What remains of great interest is whether these early changes are reversible.

Reversibility (or amenability to nutritional rehabilitation) can be looked at in two ways—through a large-scale population-based approach, as Pollitt has done (Pollitt and Gorman, 1994), and through further understanding of the critical nutrients required for normal ontogeny of brain development. Both approaches beg the question of “plasticity” within the developing system. Pollitt’s studies clearly demonstrate that developmental benefits of nutrient supplementation are a function of the timing of that intervention (Pollitt et al., 1993). The earlier the timing, the greater the benefits. Yet, it is difficult to argue that the “critical window” is ever “closed” during childhood. Studies of children suffering from prenatal malnutrition (IUGR; Morgane et al., 1993; Strauss and Dietz, 1998) or postnatal malnutrition (Pollitt et al., 1993) clearly demonstrate recoverability of function well beyond the period of rapid brain growth.

A similar effect is seen in the growth and development of preterm infants. Greater than 50% of preterm infants become microcephalic during their hospital stay due to inadequate nutrient delivery, severe illness resulting in catabolism, and a very rapid expected rate of brain growth (Georgieff et al., 1985). Although nutritional management of preterm infants has improved substantially during the years (Georgieff et al., 1989), preterm infants leave the NICU with significant postnatal growth restriction and altered body composition which remain extant until more than 1 year of life. Catch-up growth and development has been described well into the teenage years. The developmental outcome of these infants far exceeds the expectations based on the number of neurologic risk factors (including malnutrition) they encounter. A reasonable hypothesis is that the expected developmental sequelae of this “extrauterine growth restriction” is reversed postnatally with catch-up growth. Although it would be preferable never to have had a nutritional deficit in the first place, it is clear that recovery is entirely possible and, in fact, likely. Consequently, periods of rapid growth may not only confer a risk factor when nutrients are deprived, but may also offer a window of opportunity for rapid and complete repair when nutrients are subsequently provided. Pollitt (1996) notes that there is evidence for recovery following PEM in all age groups, including fetuses who receive adequate postnatal nutrition (IUGR), infants malnourished before 2 years of age who were not supplemented until after 3 years, and infants malnourished postnatally but also treated before 2 years of age.

A review of the nutrients that affect brain growth and development reveals striking differences with respect to vulnerability and timing. Deficiencies of certain nutrients, such as selenium, folate and vitamin A, exert their effects in a very narrow post-conceptional window. Later supplementation of these nutrients will do little to alter damage that occurred in the first 12 weeks post-conception. These nutrients play
important roles in neuronal differentiation, cell division, protein synthesis, and neuronal migration. Other nutrients (e.g., protein, energy, iron, zinc, iodine) play a role throughout development. Deficiencies of these nutrients at different ages result in variable neuroanatomic, neurochemical, and neurobehavioral effects. These differences may be regionalized within the brain, with certain areas being spared at one age and not at another (deUngria et al., 2000; Erikson et al., 1997). In humans, nutrient deficiencies tend to cluster and are frequently prolonged, thus exposing vulnerable brain regions to multiple nutrient deficiencies over time. Only through careful modeling of each nutrient’s effect on brain development combined with utilization of nutrient-specific assessments (e.g., if hypomyelination is a distinguishing hallmark of iron deficiency, the effect in a population could be studied electrophysiologically) (Roncagliolo et al., 1998) will it become possible to unravel the precise effects of nutrient deficiencies at the various stages of neurodevelopment.

Future Directions

EPIGENETIC PROCESSES Epigenetic processes are those that alter the mammalian genome by covalently adding a methyl group to specific genomic sites (CpG sites – cytosine followed by guanosine). This methylation of DNA affects numerous events including DNA repair, gene stability, and gene transcription (Robertson and Jones, 2000). For example, addition of methyl within promoter regions inhibits genetic transcription.

Several nutrients, such as choline, folate, vitamin B12, methionine, and betaine are involved in the metabolic pathways which supply methyl groups for all methylation reactions (Mason, 2003), and reductions in dietary methyl sources can change genetic expression and subsequent phenotypes (Cooney, Dave, and Wolff, 2002; Waterland and Jirtle, 2003)

Choline is a key dietary source of methyl-groups, and there is a growing body of evidence for choline’s role in epigenetic processes and related brain development (Zeisel, 2004). Choline deficiency in human neuroblast cell cultures decreases methylation of the promoter region of a gene responsible for inhibition of cell proliferation. Hypomethylation of this gene’s promoter leads to its overexpression and subsequent reduction in cell proliferation (Niculescu, Yamamuro, and Zeisel, 2004). Choline has also been shown to alter expression of numerous genes of neuronal precursor cells, several which are known to be regulated by the methylation of promoter or intron regions (Niculescu, Craciunescu, and Zeisel, 2005).

Furthermore, epigenetic process (genomic methylation) is a mechanism by which early maternal care can affect offspring throughout life. In the rat, maternal care affects the development of the HPA system through epigenetic processes (Weaver et al., 2004). Although, nutrition has not been examined in the context of such epigenetic processes which link maternal behavior to offspring development, it will be interesting in future research to examine the potential role of nutrients required for methylation reactions in these and other epigenetic processes involved in neurodevelopment.

FETAL ORIGINS HYPOTHESIS According to the fetal origins hypothesis, organisms adapt to their in utero nutritional environment, and these adaptations have permanent effects on physiology and metabolism (Barker, 1997). The in utero environment acts as a
“forecast” of the nutritional environment into which the fetus will be born; therefore, structural, physiological, and metabolic adaptations occur during fetal development to prepare for this “forecasted” environment (Hales and Barker, 2001). For instance, newborns born small for gestational age (IUGR) may develop a thrifty phenotype. Fetal undernutrition leads to physiological and structural adaptations in various tissues and organs (such as pancreas, liver, and blood vessels) in preparation for a suboptimal nutrition postnatal environment. The initial findings have found associations between IUGR and coronary heart disease, type 2 diabetes, and hypertension; however, it will be important to consider brain development as well.

Physiological and metabolic adaptations to undernutrition involve regulatory hormones of fetal growth, including insulin and growth hormones (Hales and Barker, 2001). These adaptations may alter the availability and utilization of nutrients. Accordingly, depending on the early environment, differential programming would lead to different nutrient metabolism throughout life, and therefore, nutrient availability to the CNS. Thus, it will be important to consider the consequences of fetal programming of nutrient metabolism on brain development.

COMPLEMENTARY AND SUPPLEMENTARY MEASURES The apparent permanence of some cognitive impairments in nutrient deficiencies, suggests the need for additional measures that complement the specific nutrient supplementation. Nutritional and non-nutritional measures that influence disparate pathways of a specific neurological process appear attractive for this purpose. For example, simultaneous supplementation of LCPUFA may correct hypomyelination due to iron deficiency, since both nutrients are involved in fatty acid metabolism (Rioux, Lindmark, and Hernell, 2006). Similarly, environmental enrichment may have additive beneficial effects in nutritional deficiency conditions (Fig 1). However, a thorough understanding of their mechanistic aspects is necessary for these measures to be successful.
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GEORIEFF, M. K., J. S. HOFFMAN, G.R. PEREIRA, J. BERNBAUM, and M.


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<td>Protein-energy</td>
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<td>Weak verbal ability/reduced vocabulary</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decreased speed of processing</td>
<td></td>
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<tr>
<td>Iron</td>
<td>(1) ↓ Brain DNA, RNA protein content</td>
<td>Variable, based on age of insult</td>
</tr>
<tr>
<td></td>
<td>↓ Ribonucleotide reductase activity</td>
<td>(see text for details)</td>
</tr>
<tr>
<td></td>
<td>(2) ↓ Tyrosine hydroxylase activity</td>
<td>Hippocampus targeted at young ages</td>
</tr>
<tr>
<td></td>
<td>↓ Cytochrome c and c oxidase activity</td>
<td></td>
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<td></td>
<td>↓ Delta-9 desaturase activity</td>
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<tr>
<td></td>
<td>(3) ↓ Dopamine activity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓ Neuronal oxidative metabolism</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓ Myelination</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(4) ↓ Bayley MDI</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓ Bayley PDI</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓ Spontaneous movement</td>
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<tr>
<td></td>
<td>Delayed latency on evoked responses</td>
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<tr>
<td></td>
<td>↓ Spatial working memory</td>
<td></td>
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<td></td>
<td>↓ Memory and learning</td>
<td></td>
</tr>
<tr>
<td>Zinc</td>
<td>(1) ↓ DNA, RNA, and protein content</td>
<td>Cerebellum, limbic system, cerebral cortex</td>
</tr>
<tr>
<td></td>
<td>↓ Cell replication</td>
<td>Many effects are</td>
</tr>
<tr>
<td></td>
<td>(2) ↓ IGF-I activity</td>
<td>neurochemical/neurophysiological, given their reversibility</td>
</tr>
<tr>
<td></td>
<td>↓ Synaptic Zn release</td>
<td>with treatment</td>
</tr>
<tr>
<td></td>
<td>Altered neurotransmitter receptor binding</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(3) Truncated dendritic arborization</td>
<td></td>
</tr>
</tbody>
</table>
Reduced regional brain mass
↓ Inhibition of GABA
↓ Binding to receptors
(4) ↓ Spontaneous motor activity
↓ Short-term visual memory
↓ Concept formation and abstract reasoning

| Iodine\(^c\) | (1) ↓ Brain DNA, stable protein:DNA ratio
↓ Membrane signaling proteins
↓ mRNA for microtubule proteins
↓ Binding of gene promoter regions for stem cell differentiation
(2) Abnormal fatty acid synthesis
↓ Axonal and dendritic microtubule protein
↓ Neuronal oxidative metabolism
(3) ↓ Brain weight
↓ Dendritic arborization
Migration defects
↓ Neuropil
Hypomyelination
(4) ↓ Verbal IQ
↓ Subset coding ability (WISC-R)
Motor impairment (reaction time)
Spastic diplegia
Mental retardation |
| Selenium\(^f\) | (1) Down-regulation of myelin genes in oligodendrocytes
(2) Biochemical findings of hypothyroidism (see iodine deficiency)
(3) Increased dopamine turnover
Hypomyelination (↓ myelin basic protein)
(4) ↓ Thermoregulation
Impaired motor ability |
| Choline | (1) ↑ Apoptosis
↓ Transmethylation reactions
(2) ↓ decreased acetylcholine concentrations.
(4) Impaired memory & attention |

Table 1. Selected nutrient effects on cognitive development at the (1) molecular, (2) biochemical, (3) structural, and (4) behavioral level*
*The model portrayed is based on integrated human and animal behavioral, histological, and cell culture data.

† Iodine’s effect on the CNS is strictly through its role in thyroid hormone, not elemental iodine deficiency.
‡ Selenium’s primary effects are through interaction with iodine and thyroid status.
Genetic Factors

Nutrients

Environmental Enrichment

Developing Brain

Brain micro-architecture

Maternal-Infant bonding

Growth factors
Inborn Errors of Metabolism
Figure Legend
The role of nutrition in the developing brain. Genetic factors, nutrients and environmental factors play major roles in neurodevelopment. In addition to their direct involvements (thin arrows) in neurological processes such as myelination, cell proliferation, synaptogenesis and neurotransmission, these factors interact with each other (thick arrows) in shaping the developing brain. Curved arrows indicate interaction within a major group (e.g. nutrient-nutrient interaction).