Malnutrition and the Central Nervous System

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The formation and differentiation of cerebral structures during and after intrauterine life is a very complicated process, depending on a series of metabolic changes that are influenced by fixed and variable factors. Among the former, genetically determined enzymatic induction and chronologically defined times of activity condition a series of changes that cover different stages, with accretion and chemical substitution of different compounds in the tissues. This process of chemical maturation occurs with variable velocity and timing in different animal species. Among the variable factors, nutrition and the environment play the most important role.

The question of the influence of nutrition, particularly nutritional deprivation, on brain development in early life and its later consequences on mental function has motivated a large number of reports in the past 20 years. Better knowledge of the role played by the child's social environment, degree of stimulation, and the mutual interactions with nutrition has necessitated a revision of the problem. During the evolutional process of brain maturation, there are some "vulnerable" periods, in which biochemical changes take place rapidly. These periods are chronologically different in each animal species. Nutritional deprivation can interfere with the regulating mechanisms, producing structural and metabolic distortions of the developing brain. An attempt to clarify the interrelations between malnutrition and the developing nervous system can be effected according to Dyson and Jones (3) by studying the repercussions of malnutrition on brain structure, function, and behavior.

BRAIN STRUCTURE

Encephalic Growth

The brain weight in all species, when plotted against age, seems to grow through a sigmoid curve (1). During the second part of human intrauterine life, both cerebrum and cerebellum show an exponential increase in weight, though while the cerebellum multiplies its weight almost 12 times between 20 and 40 weeks' gestation, the forebrain does so only five times in the same period. After birth, the growth pro-
cess slows progressively in both organs, especially after 3 months in the cerebellum and 6 months in the cerebrum. When the weight data are plotted on a semilogarithmic scale (logarithms of weight against gestational age), the direct gradient of the regression line obtained reflects the more abrupt growth of the cerebellum, with a gradient of logarithmic growth approximately 1.5 times greater than that of the forebrain (2). Reduction of brain weight has been reported in different species affected by malnutrition (6–8). Brown (3) found that the brain weight was significantly reduced from normal in children who died from severe malnutrition. In the autopsy series of Naeye et al. (4), the weight of the brain of low birth weight newborns from underweight mothers appeared to be relatively spared in comparison with the weight of other organs. The brain/body weight ratio is slightly raised in malnourished infants, which supposes a certain degree of brain sparing. There is a positive relationship between the occipitofrontal circumference and the cranial volume, with an extremely close correlation between the intracranial volume and brain size (5). Winick and Rosso (6) showed a correlation between head circumference and brain weight during the first year of life. Induced malnutrition in infant rhesus monkeys produces effects on head circumference (7). During severe malnutrition, reduced head circumference has been widely reported (8–11). Nutritional rehabilitation can produce catch-up of the head circumference, although this catch-up is not complete (12). The reduction in head circumference and brain weight is proportional to the degree of malnutrition (13). One should bear in mind that the less mature the brain, the greater the water content (14). The presence of brain edema, generally a complication of anoxia, can produce up to a 10% increase in brain water content (15). Other factors such as variations in the subdural space, scalp edema, and scalp thickness (16) can constitute sources of error when the head circumference is measured.

MORPHOLOGIC STUDIES

Structural changes depend on the duration and intensity of the nutritional insult as well as the stage of brain development at which the insult occurs. The brain is more affected by a nutritional insult when it happens during the growth spurt, which is when growth occurs at an accelerated rate. Histologic studies in animals show that undernutrition impairs the elaboration of neuro-processes (17). In rats, early malnutrition produces growth distortion in the cerebral cortex, with retarded cell division, impaired cellular differentiation and retarded synaptic development (17). Decreased cortical thickness, reduced number of dendritic spines, decreased dendritic length, and decreased synapse/neuron ratios and cellular deficit at the glial level have also been described (6,18–20). Malnutrition per se does not produce a destructive lesion. On the other hand, the intensity of the distortions will depend on the stage of development during which the nutritional insults take place. Malnutrition in rats occurring after their brain growth spurt has little effect on brain weight and brain cell number (21). In relation to the stage of development, the total number of neurons is not decreased, but the number of glial cells is reduced. The findings of Dobbing et
al. (22) and Cragg (23) demonstrate that postnatal malnutrition in rats does not affect the cells existing before birth, but it slows and distorts the normal process of cellular differentiation. Studies in rats with stereologic methods show a reduction of the number of synapses per neuron in the cortex (24). One should bear in mind when extrapolating experimental studies with rats to humans that the brain growth spurt in rats is fundamentally postnatal, and in humans it is perinatal. Synaptic number, which is influenced by environmental factors, decreases with sensory deprivation and increases with extra stimulation (25). By stimulating undernourished animals, it is possible to prevent expected deficits (26). Stimulation seems to increase the branching and length of the dendritic processes of the cortical pyramidal cells in rats (27). Greater vulnerability is observed in the cerebellum in relation to the other brain regions (22). Unde nourished rats show a reduction in the total number of dendritic segments, decrease in the length of distal segments, reduction of the cerebellar granule cell population, and a decrease in size of the Purkinje cell dendritic trees (28).

NEUROCHEMICAL STUDIES IN ANIMALS

In early malnutrition, a deficit in myelin has been demonstrated in rats (29,30). This deficit has been attributed by Wiggins et al. (31) to a delay in the maturation of the oligodendroglial cells, and a reduction in their number (32). Sato et al. (33) consider that in neonatal rat malnutrition, there is a defect in the transport of de novo synthesized sulfatides into myelin and a problem in the assembly of these lipids into the myelin membrane. The study of Fishman et al. (34) shows that undernutrition in animals decreases myelination, but that the chemical composition of the myelin remains normal. However, other studies (29,31) have shown qualitative changes in myelin composition in nutritionally deprived animals. In malnourished mice, Yusuf et al. (35) found a quantitative decrease in myelin with a higher proportion of phospholipids and cholesterol relative to the galactolipid fractions when compared with normal controls. The synthesis of sulfatides used as a biochemical marker for myelin formation is decreased in nutritionally deprived suckling rats (36). Thus, it has been shown that experimental malnutrition can affect some aspects of myelin development during the entire period of myelination.

NEUROCHEMICAL STUDIES IN HUMANS

Chemical markers permit the establishment of correlations between values of a chemical parameter and certain structural components of the brain. During development, neuronal and glial proliferation have been correlated with the DNA quantification, neuronal differentiation with ganglioside content, and myelination with glycolipids. Reduced brain DNA in small-for-dates and malnourished infants has been widely reported (6,37,38). Although the DNA content of the brain can be cor-
related with the number of brain cells, in which case a reduction in the DNA values means a reduction of the number of brain cells, a certain reduction in the brain cellular content occurs in a large number of normally functioning brains. This reduction may be at the expense of glial cells, depending on the period during which the nutritional insult is produced.

The exact knowledge of normal chemical brain maturation allows a comparison of values obtained from nonmalnourished controls with malnourished children who died during the period of myelination. The study of a series of brains from newborn infants of different gestational ages has allowed us to follow the biochemical changes that occur during the early stages of maturation. The concentration of neutral glycosphingolipids, sulfatides, and sphingomyelin in homogenates of whole brain from 34 newborns, ranging in age from 22 to 45 weeks and born of well-nourished mothers, was determined (39). Up to 29 to 31 weeks' gestation there was little change, but after 32 weeks' gestation, a significant and progressive increase in the concentration of these substances occurred. The fatty acids of ethanolamine phosphoglycerides (EPG) and choline phosphoglycerides (CPG) were also studied (40).

Phospholipids are general components of the cellular and subcellular membranes (41) and are found in raised concentration in synaptosomal membranes. Long chain polyunsaturated essential fatty acids control the fluidity of membranes and in this way also control the activity of the enzymes that form part of these membranes. There are several studies of the fatty acid composition of the human brain (42-47). During intrauterine life, accretion of fatty acids depends on placental synthesis and transfer processes (48). Studies (40,46) have shown that fatty acids of the n3 family normally increase during maturation, while the n6 fatty acid family does not change significantly. There is also an increase in the 22:4n6/22:5n6 ratio throughout maturation. This increase adopts a parabolic profile. The 20:4n6 fatty acids decrease in EPG and increase in CPG as a result of activation or inhibition, respectively, of their elongation to higher members of the series as the maturation process continues. The brain of the younger gestational age infant has a higher content of 22:5n6. Its precursor, 22:4n6, moves in the opposite direction. With increasing gestational age, there is a slowing down of the 22:4n6 desaturation. There is a progressive increase in the ratio n3/n6, almost exclusively due to a rise in 22:6n3. This increase is parabolic rather than linear. There is competition between the n3 and n6 families of fatty acids. This competition is particularly marked when involving fatty acids of the same chain length. In accordance with the competitive theory, a greater n3/n6 ratio will cause a relative inhibition of the 22:4n6—22:5n6 desaturation reaction, giving rise to a higher 22:4n6/22:5n6 ratio. This is a very important point, because the enrichment of 22:6n3 in synaptic membranes suggests an important role of this fatty acid in neurotransmission. Its concentration in retinal rod outer segments has been linked to the movement of rhodopsin in the photoreceptive process (49).

Fatty acid patterns in EPG and CPG of the brain and cerebellum in small-for-dates and malnourished newborns who died during the first months of life did not change. In liver and red cell lipid stroma, changes in the pattern of phosphoglyceride fatty acids are dependent on fatty acid dietary composition (50,51). The brain
appears to show strong resistance to modification of its fatty acid composition. In the case of malnourished newborns with normal brain phosphoglyceride fatty acid values, the degree of fatty acid deficiency was not sufficient to produce changes in the brain in spite of the fact that the newborn is sensitive to fatty acid deficiency (52). A deficiency in essential fatty acids disturbs brain maturation during the period in which its needs are particularly important (53). Clinical deficiency of the n3 family has been demonstrated in depleted rats, which failed to learn a two-choice discrimination problem (54), and in depleted newborn monkeys (55), which showed visual impairment with lower visual acuity thresholds. Chemical deficiencies have only been suspected in man (56). Until now, a deficiency concerning the omega-3 family in neural tissues has been demonstrated in rat (57) and in monkey (58).

We have recently studied the fatty acid composition in EPG and CPG of the human retina (59) in a series of eyes from newborns of different gestational ages and children who died from non-nutritionally related diseases. The fatty acid values were compared with the values obtained in the retina of three children who died of malnutrition. Two of these cases showed a very significant increase of 22:5n6 in EPG and CPG. One child who died at the age of 4 months showed a significant decrease in the content of 22:6n3 and a decrease of the index 22:6n3/20:4n6. Two children also had an increase of the content of 20:3n9 in EPG. These findings show that an n3 deficiency can be biochemically demonstrated in the human retina.

In a study by Chase et al. (37) in six small-for-gestational-age and 10 appropriate-for-gestational-age infants, the cerebellum was significantly affected during intrauterine development in the small-for-date infants, 35% of whom showed a decrease in the DNA content and 19% a decrease in the cerebral and brainstem fractions. Cerbroside-sulfatide content was significantly reduced in the small-for-date infants' brains, while the content of phospholipids, cholesterol, and gangliosides was not decreased. Galactolipid-sulfatransferase activity in the small-for-date brains was reduced. These findings suggest a decreased myelin content in the brain of small-for-date infants. Sarma and Rao (38) demonstrated a reduction in the DNA content of the cerebrum in small-for-date infants, while the values in other regions of the brain were no different from control values. No decrease was observed in the total content or concentration of glycolipids. In contrast, the cholesterol values were notably decreased in the brain.

We also studied the plasmalogen and ganglioside content of the cerebrum and cerebellum during development as markers of synaptogenesis and myelination, respectively, in order to establish the time at which their rates of accretion increased. In the forebrain, the concentration of these lipids accelerated significantly during the 32nd week of gestation. Lipid accretion was not constant but varied from one lipid to another. Plasmalogens were the lipids that accumulated at the fastest rate. Ganglioside concentration leveled off at 2 months postnatally, with the plasmalogen concentration reaching a plateau between the 4th and 6th week. In the cerebellum, the concentration of gangliosides was clearly lower than in the forebrain until 1 year of age, with the maximal rate of increase occurring between the last weeks of gestation and the second postnatal month. The plasmalogen concentration was somewhat
higher in the cerebellum than in the forebrain, but the concentration profile was similar to that followed by the gangliosides. In clear contrast to the concentration profiles in the cerebrum, both lipids apparently continue to increase in the cerebellum up to the 2nd postnatal year (60). Plasmalogens seem to be specially affected in marasmic infants (61), a finding consistent with the high speed of accretion of these myelin lipids in the human forebrain (60). Plasmalogens were decreased by 60 to 80% of normal values in the forebrain of seven marasmic children studied. Plasmalogen concentrations were decreased in the cerebellum in all but one of these marasmic infants, to about 80% of normal.

In this group, four infants who were undernourished after term had a decreased concentration of cerebral galactolipids. Cerebellar galactolipids, however, were normal in all prenatally and postnatally malnourished infants (61). These data show that myelogenesis is particularly affected by nutritional deprivation. Well-nourished infants who become marasmic a short time after birth show a significant decrease in the concentration of myelin lipids in the forebrain. These findings support the idea that during the perinatal period, the forebrain is more vulnerable than the cerebellum to nutritional deprivation. Ganglioside concentration was decreased, but to a lesser extent than the plasmalogen concentration, especially in the forebrain. There may be a biological sparing mechanism for the more important structures such as the synaptic and dendritic membranes. In fact, in marasmic children with a decreased forebrain and cerebellum weight, the index \( \frac{\text{brain weight}}{\text{body weight}} \times 100 \) of both organs demonstrated a significant degree of protection. The study of Fox et al. (62), isolating myelin from the white matter of severely undernourished infants, demonstrated an abnormal lipid composition of the myelin isolated from the brain and a reduction in cerebrosides and plasmalogens in the white matter. One might deduce from this that malnutrition causes a decreased accretion of normal myelin. Fishman et al. (63) found that the lipid composition of cerebral myelin at birth was quite similar to that of more mature myelin, with a slight decrease in phospholipids with age. Poduslo and Jang (64) reported only small lipid changes in human myelin from 1 month to 1 year of age. Data from our laboratory (65) have shown that the more myelin-specific constituents, such as galactolipids and 2', 3'-cyclic nucleotide 3'-phosphohydrolase, are present in approximately the same concentration in myelin from immature as from mature cerebrum, while phospholipids tend to decrease slightly. A severely marasmic infant who died at 9 months of age with a body weight at death of 2.2 kg had a reduction in brain weight of about 50% and a decrease in cerebral myelin to half normal levels (66). However, the quality of myelin was basically preserved, showing a high level of galactolipids and myelin basic protein. Thus, during nutritional deprivation, there is a decrease in the quantity, but not the quality, of myelin synthesized.

**NEUROTRANSMITTERS AND MALNUTRITION**

Nutritional deprivation during development can induce changes in brain function involving neurotransmitter synthesis. The correct coordinated development of neu-
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 neurotransmitter systems is dependent in part on the availability of the plasma precur- sors, essential for neurotransmitter synthesis, as well as for appropriate activity of the converting enzyme, the neurotransmitter uptake sites, and the receptors. Alter- ations in normal function can affect synthesis, storage, or release of neurotransmit- ters. Choline availability to the brain influences the rate of synthesis and release of acetylcholine by the cholinergic neurons. Availability of tyrosine affects the func- tion of the catecholamine system, while serotonin synthesis is dependent on the con- centration of plasma tryptophan.

Plasma concentration of the precursor depends on food intake. A delayed de- velopment of anticholinesterase activity until weaning has been reported in mal- nourished rats (67). This activity is lower than in controls matched for age. However, when controls are matched for body weight, the deprived rats demon- strate increased enzyme activity (68). The administration of choline increases blood choline, brain choline, and brain acetylcholine levels in rats. Undernutrition in ani- mals reduces activity of the cholinergic system in the developing brain and produces changes in certain brain functions involving monoamine transmitter systems. Mal- nutrition in pups produces an increase in the concentration of noradrenaline in the prefrontal cortex (69). Food intake influences the plasma concentration of amino acids and can affect the synthesis of serotonin. Alterations in sleep patterns can oc- cur as a result of changes in the synthesis of serotonin and transmission to the brain. Newborn infants receiving a formula supplemented with tryptophan enter into active sleep earlier than those who receive a formula without supplementation (70). The central noradrenergic systems are involved in brain functions such as long-term memory (71), learning acquisition (72), and sleepwalking behavior (73). Effects of malnutrition on the development of neurotransmitter systems may be studied quanti- tatively, knowing the concentration of the precursors and the activity of the enzymes involved in the process of synthesis.

NEUROLOGIC FINDINGS RELATED TO MALNUTRITION

In the acute phase of malnutrition, a pattern of apathy, irritability, poor motiva- tion, and environmental unresponsiveness is present. Marasmic infants have re- duced muscle tone and abnormal feeding behavior. In addition, they spend most of their time sleeping. They frequently present stereotyped head and hand movements. Dissociation of motor development, described as delayed sitting and standing and hypotonia of the lower limbs with normal development of the head and arms, has been reported (74). Poor reaction to any stimulus, a monotonous wailing cry, and a reluctance to follow moving objects are frequently present. The apathy of the mal- nourished child includes a reduction in his capacity to respond to a stimulus. At the same time, the mother, faced with the reaction of a malnourished child, may change her attitude toward that child, with the result that there is a reduction in interaction between mother and child. As in experimental animals (75), malnutrition in early life functionally isolates the developing infant from his immediate environment. Af- ter nutritional rehabilitation, development will depend on the intensity and duration
of the previous episode of malnutrition, the persistence of an inadequate food intake, and the influence of the social environment, particularly the degree of stimulation. Early malnutrition seems to have a greater effect than malnutrition at an older age (76). Malnutrition reduces the child's activity level, thus limiting his ability to utilize and respond to his own environment (77). Echoencephalographic studies (78) have shown a transient increase in the size of the lateral ventricles in kwashiorkor. Different degrees of brain transillumination have also been reported (79). Motor nerve conduction velocity is reduced to a moderate degree (80–82) in protein-energy malnutrition (PEM) and returns to normal after recovery. Waking EEG rhythms (83–85) and evoked auditory potentials (86) show reversible alterations. In infants malnourished for more than 4 months from birth, there is an increased number of sinus pauses occurring during quiet sleep (87). Some spectrographic investigations of crying in infants with marasmus demonstrate alterations similar to those observed in children with brain damage (88). In children with kwashiorkor, crying analysis was normal. Lester (89), studying the crying of malnourished infants with a real-time spectrum analyzer, found a higher pitch, lower amplitude, longer duration, and longer latency to the next signal in malnourished as compared with well-nourished infants.

THE EFFECTS OF EARLY CHILDHOOD MALNUTRITION ON LATER INTELLECTUAL AND MOTOR DEVELOPMENT

The question of later intellectual and motor development in infants previously affected by early childhood malnutrition of varying degrees is widely debated as a result of the enormous difficulty in strictly separating purely nutritional factors from all the other socioeconomic-cultural factors that have an important influence on development. Can malnutrition itself lead to a permanent physical and/or behavioral deficit? Winick (90) has discussed this question recently. A comparison of different studies demonstrates results that are sometimes contradictory.

Hoorweg and Stanfield (91) compared 60 children between 11 and 17 years of age in Kampala, who had PEM between 8 and 27 months of age, with 20 controls. Environmental variables were also studied. They concluded that PEM exerts a permanent effect on intellectual ability and motor development. However, in all processes, there are several variables involved. A school-age group of 37 children who had presented with kwashiorkor between 6 and 30 months of age and their siblings as controls were studied by Birch et al. (92). The administration of the full-scale WISC IQ to the previously malnourished group resulted in IQ scores of 68.5, with the controls scoring 81.5. Verbal and performance differences were present. In all cases, it should be pointed out that long periods of hospital admission can contribute to the malnourished child's state of depression. A group of 14 children with marasmus between 1 and 5 months studied by Monckeberg et al. (93) showed significant and permanent language retardation at 3 to 6 years of age. These workers compared two groups of children to determine whether chronic, but not severe, undernutrition
modified behavior and mental capacity in preschool children. Delayed psychomotor development was observed in the lower socioeconomic group, with the degree of retardation being directly related to the amounts of animal protein consumed. Cabak and Najdanvic (94) studied children of 7 to 14 years of age who had been malnourished between 4 and 24 months of age. When they were examined, the degree of somatic development was normal. However, the IQs were less than in the normal control group. An objection can be made to this study, in that the social backgrounds of the families were very different.

Evans et al. (95) compared 14 previously malnourished children with a mean age of 8.9 years with well-nourished sibling controls. There was no significant difference between test and control groups on nonverbal IQ. It has been said that positive nutritional factors contribute to the elevation of verbal intelligence (96) and that environmental stimulation leads to an elevation in the nonverbal scores (97) in malnourished children. Champakam et al. (98) have shown that in children of 8 to 11 years, who had become malnourished during some period in the first 3 years of life, cognitive function is affected. Stoch and Smythe (8) studied 20 children between 15 and 18 years of age who had been affected by severe undernutrition in early life. They noted a marked visual/motor perception disturbance in 17 of the 20 children. In addition, the authors considered that there was evidence of irreversible intellectual impairment.

Nineteen children who had been malnourished during the first year of life were compared by Chase and Martin (99) with a group of normal children 3 to 4 years after the episode of malnutrition. On follow-up, the children had a lower development quotient, particularly those who had been malnourished for the longest time. Language development was severely affected. A group of infants who were undernourished at less than 6 months of age, studied by Cravioto and Robles (100) 3 to 4 months after the acute episode of malnutrition, had lower scores in adaptive behavior. Cravioto (101), who studied the motor skills of children after severe malnutrition, found that coordination, agility, strength, and balance were severely affected, while suppleness was not. Liang et al. (102) in Indonesia studied 107 children from 12 to 15 years of age from low social class families, 46 of whom had previously been malnourished. The lowest IQ values were found in those previously malnourished. The presence of minor neurologic signs, evidenced by impaired performance of seven repetitive motor tasks, has been reported by Galler et al. (103) in children between 5 and 11 years, who had previously been marasmic. Later studies in the same population at age 9 to 15 years showed a significant correlation between such minor neurologic signs at early age and later impaired performance on the Purdue pegboard test. The administration of the Purdue test to children with antecedent kwashiorkor during the first years of life showed similar or greater deficits than the children with histories of marasmus. Galler and colleagues (104) arrived at the conclusion that malnutrition in early life plays the most important role in later deficiencies. The studies of Cravioto (101) and Galler et al. (103,104) are very important, because the authors have attempted to isolate malnutrition from other socioeconomic variables that could affect development. It has been shown in children with
pyloric stenosis and a brief period of undernutrition that a high degree of starvation decreases test scores, particularly for short-term memory and attention (105).

In other studies where there is no evidence of a strict relationship between malnutrition and impaired intellectual development, the role of the environment is stressed. Richardson et al. (106) reported on children who had previously been severely malnourished and were studied between 6 and 10 years of age. Those with antecedents of severe malnutrition who were tall and of good social background had IQs 11 points higher than those who did not have antecedents of malnutrition but who were short and from an unfavorable social background. The group who had previously been malnourished, were from an unfavorable social background, and were of short stature had IQs nine points lower than the nonmalnourished children.

The Dutch experience (107) during the period of hunger in World War II showed that pregnant women with a restricted energy intake had smaller infants. However, as shown 20 years later (108), there was no mental retardation associated with pregnancies occurring during the famine. These infants had had nutritional deprivation not directly associated with an adverse home environment. The longitudinal study of Sheffer et al. (109) deals with mental development in 17 Jamaican children, who had previously been malnourished. They were compared with 20 normal controls. The Caldwell Inventory of Home Stimulation was administered 24 months later. The scores were similar in both groups. The conclusions were that the mothers of the malnourished group were poor but had positive maternal child interactions and that the ecology of malnutrition differs in different cultures. The study of Hansen et al. (110) shows that a single episode of kwashiorkor in infants after the age of 10 months does not affect brain development in the long term if there is a positively reinforcing environment. In the study of Lloyd-Still et al. (111), socioeconomic factors were eliminated. Patients with cystic fibrosis who presented with malnutrition during infancy were compared with healthy siblings. Between 2 and 5 years after the episode of malnutrition, an intellectual deficit was observed. However, later on, there were no differences. In these cases, long periods of hospital admission and separation from the family can play a significant role in affecting infant development. The two studies with Korean children adopted in the United States (112,113) show that when their environment was changed at an early age, the previously undernourished deprived infant performed developmentally at a normal level.

CONCLUSION

Nutrition and the environment are two inseparable factors that continuously affect a child's development. For this reason, the answer to the question of whether an early nutritional insult to the brain constitutes an irreversible event affecting mental development is a difficult one to answer. In fact, there is no general answer applicable to all cases. The difference in the mother's educational background may also play an important role. In addition, it is difficult to establish the influence of mother–infant interaction. Generally, with the passing of time, the difference in per-
formance between previously malnourished patients and controls tends to disappear. Interaction effects between nutritional and social determinants of cognitive development may be different for boys and girls. It should be borne in mind that the scores of the tests administered to preschool children are often unsatisfactory predictors of later intelligence scores. In addition, some tests reflect the skills and concepts of a particular culture. Evans et al. (95) affirm that catch-up can occur at any time, an opinion not supported by Stoch and Smythe (8). The possibilities of catch-up depend in a great part on the mutual interactions between nutritional rehabilitation and the degree of stimulation. Long periods of malnutrition with a background of impaired socioeconomic support and a minimal degree of stimulation offer the worst prognosis. A combination of poor nutrition and a lack of environmental stimulation can interfere with normal cognitive development, leading to a definitive impairment of developmental status.

It appears that during the period of fastest brain growth, there is greater vulnerability to nutritional deprivation. Experiments with deprived animals and research on human malnutrition have both shown that nutritional deprivation can produce structural distortions in the brain and changes in the accretion rate and composition of neural lipids. It is important to stress that findings such as suboptimal head circumference, suboptimal brain growth, decreased number of cells, decreased DNA, and chemical alterations of neural lipids cannot be correlated directly with later behavior and the level of intelligence. Structural and chemical alterations cannot be extrapolated directly to brain function.

The animal model of malnutrition is far from being free of contaminating psychosocial variables. On the other hand, the human brain may be relatively protected against nutritional insults. Brain-sparing during nutritional deprivation involves a relative resistance to the macromolecular changes that appear in other nonspared tissues (114).

It should be noted that in the human, it is impossible to separate nutrition from other factors that can affect gross and fine motor skills, behavior, and final intelligence. Factors such as the availability of nutrients, dietary intake, infectious diseases, and general pre- and postnatal factors form a constellation with significant interactions. The intensity, timing, and duration of the nutritional deprivation; positive or negative environmental factors; the degree or lack of family stimulation; and the quality of nutritional rehabilitation and psychosocial support can lead either to a good or to a poor developmental outcome.

FUTURE RESEARCH

More neurochemical studies of synaptogenesis and myelination in humans will be necessary in order to define precisely the deviation from normal. Studies with nuclear magnetic resonance in malnourished children will allow the study in vivo of the alterations in the pattern of myelination and in some aspects of brain metabolism during nutritional deprivation. More knowledge of the requirement for and role of
the very long chain fatty acids in relation to brain maturation and the development of visual function will allow a better understanding of the problem of subclinical deficiencies, particularly during the neonatal period. More research concerning possible alterations in neurotransmitter synthesis in children with malnutrition will allow a better definition of the role of carbohydrate and protein in neurotransmitter synthesis.

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DISCUSSION

**Dr. Monckeberg:** Dr. Ballabriga spoke about the effects of malnutrition and environment on brain composition. The three questions I feel are most pertinent are the actual damage to the brain, whether the main factor is malnutrition or environment, and whether it is reversible.

**Dr. Tanner:** Since the data on brain lipids were derived from babies who were dead, can we be sure they are representative of a predeath physiologic status? Second, are we talking about small-for-gestational-age babies as though they were a good model for infants with malnutrition?

**Dr. Ballabriga:** The question regarding biochemical results in brain obtained after death is an important one. Manuela Martinez found that differences in the lipid composition of myelin attributable to differences in methods of isolation were minimal, except when the brain homogenate was very old (1). Storage in a frozen state seemed to have little influence on myelin lipids. An important factor is, however, the effect of the disease that has produced death. We have always used, as a control group for children who suffered from nutritional deficiencies, infants who had died during the first day of life without clinical nutritional deficiencies.

The brains of undernourished children studied in our laboratory show that plasmalogens were decreased in children over 32 weeks of gestational age, including small-for-dates, although two infants with intrauterine undernutrition whose gestational ages were below 32 weeks had a normal concentration of cerebral plasmalogens.

The problem is, of course, that we cannot be certain that there is a correlation between the structural or biochemical changes that are observed and later function, or when a structural
change becomes impossible to reverse. We may only hypothesize that it will depend on the intensity and duration of the insult as well as the eventual environment of the infant. There is no strict correlation between chemical alteration, weight of the brain, head circumference, and function, reconfirming the myriad of factors affecting developmental status.

Dr. Guesry: Have any studies looked at the relative importance of calories versus protein on the growth of the brain during the first 4 months of life?

Dr. Ballabriga: Changes induced by deficiencies in essential fatty acids affect the composition of the cell membranes. This is very important in relation to the brain. Surprisingly, however, the important role is not played by the father of the family, in this case, linoleic acid for the family of n6, or linolenic acid for the family of n3. Normally, these fatty acids are the result of the action of the Δ-desaturases in the liver for production of arachidonic and docosahexanoic acid. We do not know the degree of activity of these enzymes in the malnourished human liver, although in premature babies there is a definite lack of activity. For this reason, perhaps, in the rehabilitation of the infant, we should consider providing several fatty acids that are not normally included, such as 22:6o3.

Dr. Suskind: There are three points that should be addressed. First is the question of brain-sparing in malnourished infants. The literature indicates that the brain does not regenerate as fully as other organs in terms of function. Second, it appears, at least clinically, that the impact of malnutrition is significantly more severe when it occurs before the second year of life. Why is the older child protected in terms of development, when earlier there is such a devastating effect on total DNA content? Finally, since essential fatty acid deficiency could be a significant factor relative to the process of myelinization, what is the optimal type of nutritional support for the malnourished child during recovery?

Dr. Ballabriga: Malnutrition does not provoke destruction of the central nervous system, but only a distortion of its normal development. That is, if one has an acute episode of malnutrition, the histologic findings in the brain will not show destruction of the neurons. One will see, instead, distortions, for example, at the ends of the synapses, where there will be a decreased number of connections. Up to the second year of life, there will also be a reduction in the total number of glial cells. It is important to remember, however, that we are not able to correlate this distortion with final function, which is also dependent on the infant's environment and the production of neurotransmitters.

Dr. Brunser: I agree that the vulnerability of cells to malnutrition will be dependent on their mitotic rate at the time they are affected by nutritional deprivation. In the case of the central nervous system, we are referring to a tissue, the proliferative stage of which has been completed either before or shortly after birth. Postnatal malnutrition will, therefore, distort aspects such as differentiation and synaptic development, maturation of neuronal and plasma membrane composition, and myelin deposition.

Regarding the question of whether tissue taken after death is representational of living tissue, we should review what happens to tissue that is separated from its irrigation. The first factor to consider is time. Signs of damage begin to appear after about 3 min. Damage within the cell structure increases the longer the tissue is kept unfixed. Morphologically, however, some cell organelles or differentiations are more resistant to this type of damage: The mitochondria and the Golgi apparatus are still recognizable after long periods of anoxia, as is the endoplasmic reticulum, although it fragments into vesicles. The fact that it is possible to recognize these structures, however, does not mean that they are still functioning as if they were in the tissue in situ.

Severe alterations in the morphology of cells and tissues generally begin, however, immediately after death. Until the development of peroral devices for biopsy of the mucosa of the
small intestine, studies of the morphology of this organ were rare and often marred. In the question of tissues taken after death, if the aim is to gain information about the main components of the body, i.e., nitrogen, water, and sodium, cadavers yield valuable data. However, one must be aware of the limitations of studying tissues that have begun to disintegrate.

Dr. Ballabriga: Concerning the development of the central nervous system, we should also consider the possible existence of subclinical malnutrition involving fatty acids. Especially affecting newborns, this would not be apparent through clinical symptoms, but rather through subtle clinical influences on the composition of brain membranes that may play a role in final intellectual ability. Work in our laboratory has indicated that the two fatty acids that probably play an important role are 20:4n6 and 22:6n3. We have found a deficiency of the latter in the pattern of fatty acid phosphoglycerides in the retina of a marasmic child.

Dr. Jackson: Some of these problems would be overcome if we had peripheral markers for the central changes. One attempt, with respect to synaptogenesis, has been the work on N-acetyl neuraminic acid (NANA). Rat studies have suggested that the level of NANAs in blood might provide a valuable index of central function (2). While it has not been possible to demonstrate a similar pattern in malnourished children, this is an important area to explore (3).

In measuring desaturase activity, I wonder whether one might use stable isotopic markers and mass spectrometry to determine the rate of desaturation as an index of the child's ability to produce some of the more exotic fatty acids.

Dr. Ballabriga: The problem is the difference between rats and humans. It is difficult to assess the activity of the Δ-desaturases in the human liver in vivo. In addition, the timing of the development of the enzymatic system is not the same, and, of course, we cannot perform liver biopsies in normal newborns. If the infant is dead, we may be able to but with the recurrent problem of live versus dead tissue.

Dr. Truswell: Of the four main families of fatty acids, the omega-3 long chain polyunsaturated fatty acid forms an important proportion of brain lipids. Is there evidence of conversion, in infants, from omega-6 to omega-3, or do all the omega-3 fatty acids in the brain have to come by concentration from the very limited amount that is taken in orally? While some infants, via their mother's intake, receive omega-3 fatty acids in breast milk or, later, in solid foods, other children receive very little. How large a range in the omega-3/omega-6 ratio is compatible with full intellectual development? How critical is this proportion in normal children?

Dr. Ballabriga: It is difficult to know the relative proportions that must exist between the intake of omega-6 and omega-3. The Δ-desaturases are enzymes acting on two different substrates, preferably on the n3 family. Experiments by Bourre (4) in Paris show that the addition of 20:4n6 and 22:6n3 into the culture medium of nerve cells produces better function of the neurons expressed by an increase in the release of neuropeptides. It may be that the ideal proportion of n6 and n3 families in infant formulas, for example, may be that of the proportion found in breast milk.

Dr. Truswell: But that is variable.

Dr. Ballabriga: Its variability is dependent on the intake of the precursors. For instance, consuming a large quantity of linolenic acid does not necessarily mean increasing the concentration of the 22:6n3. That will be dependent on the activity of the enzymes involved.

Dr. Aggett: It is my understanding that varying the composition of the dietary intake of infants does lead to considerable change in the fatty acid composition of the erythrocyte membranes associated with different activation energies of membrane-bound enzymes such as acetylcholinesterase. Are you aware of any work that has been done to demonstrate that such phenomena may occur in the neural membranes of the brain?
Dr. Ballabriga: I am not certain that dietetic manipulation can change the brain composition. It would be very difficult. We know we can change the composition of subcutaneous fat or the phosphoglycerides of the aorta wall and of the liver. In order to study the effects of parenteral nutrition, newborns were fed high doses of linoleate. The brain showed an increase in the 18:2n6 values of choline phosphoglycerides, but there was no increase in the longer n6 fatty acids. This resulted in a reduction of the 18:2n6 elongation/desaturation and an increase in the ratio 18:2n6/18:1n9 in brain choline phosphoglycerides (5).

Dr. Aggett: My understanding is that when fatty acid intake is altered in animal models, there are changes in functional characteristics.

Dr. Suskind: What is the role of protein and other nutrient intake, such as iron, on neurotransmitter synthesis and behavior?

Dr. Ballabriga: We know very little about transmitter synthesis in malnourished children. Soto-Moyano et al. (7), however, have done some animal studies on the effect of early malnutrition on the noradrenergic system. I do not have any personal experience with regard to the role of iron on neurotransmitter synthesis or behavior.

Dr. Grantham-McGregor: There is little evidence linking function to biochemical or neuroanatomic changes in the brain. Nor are there consistent findings showing a difference in the long-term functioning of children malnourished before and after 6 months of age, up to 2 years. We assume the effect is greatest in the first 24 months, because that is when brain development is most rapid, but I do not believe we have evidence to support that statement.

I am also concerned that the parameters used to indicate brain-sparing are brain weight over body weight. Perhaps that indicates only that the body has lost weight in the form of adipose or muscle tissue, which the brain cannot do. We certainly do not have any indication that the brain is spared in the sense that it can develop new tissue. Use of such terms may lull us into a false sense of security in relation to the effect of malnutrition on brain function. In Jamaica, for example, we looked at the head sizes and heights of severely malnourished infants. We found head-age to be younger than height-age, which would not indicate brain-sparing.

REFERENCES