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The Relationship of Nutrition To Brain Development and Behavior

A position paper of the Food and Nutrition Board

prepared by

the Subcommittee on Nutrition, Brain Development, and Behavior
of the Committee on International Nutrition Programs

NATIONAL ACADEMY OF SCIENCES
NATIONAL RESEARCH COUNCIL

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NOTICE

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THE RELATIONSHIP OF NUTRITION TO BRAIN DEVELOPMENT AND BEHAVIOR

Introduction

The physical, chemical, and physiological development of the brain and consequent behavior in all species of higher animals evolve from the continuous interaction of genetic and numerous environmental factors. Among the latter are nutritional, disease, psychological, learning, and cultural variables. Of these, nutrition is concerned directly with providing energy and nutrients needed for cellular structures and various metabolic systems. Indirectly, food may serve as a stimulus for behavior as well as providing a basis for social interaction.

In most instances, the specific effects of sub-optimal nutrition on brain development in man are inseparable from those of other environmental factors. Adequate nutrition generally is part of a good environment; malnutrition occurs primarily within poor environments in which many other forces may also limit the individual's development. In any event, malnutrition is detrimental in both good and poor environments but not necessarily equivalently so.

In some instances--such as when nutrients are imperfectly utilized owing to inborn errors of metabolism, or when nutrients are lacking, as in specific nutrient deficiencies--malnutrition, *per se*, clearly alters the central nervous system by acutely or chronically limiting its metabolic, structural, and functionsl capabilities and performance. In other circumstances, malnutrition, reflected in chronic limitation of amounts of food consume , may result in general stunting of growth accompanied by reduced brain size, decreased brain cell number, and immature or incomplete biochemical organization of the brain.

Unified Concept of Factors Affecting Brain and Behavior

A concept unifying these many interrelationships is expressed in Figure 1. The diet provides the nutrients for the metabolism of brain cells. The quality (nutritional content, wholesomeness) and quantity of the diet depend not only upon the availability of foods, but also upon such other factors as appetite appeal, local custom, and purchasing power that may control food use. Furthermore, the individual's health (metabolic disease, dental status, infection, parasitic infestation) may modify nutritional requirements as well as alter the ingestion, digestion, assimilation, and utilization of foods.

The environment, in addition to influencing the composition and acceptability of the diet, has other important effects on the brain. External stimulation from the environment directly affects the neurophysiological activity of the brain. The diagram in Figure 1 shows how these diverse factors are interrelated and interdependent.

The many elements incorporated into this simplistic model may, in fact, occur in a wide variety of combinations. Their cumulative impact on brain and behavior is not simply additive but the interrelationships are multiplicative. Furthermore, there are certain critical or time limited periods in an individual's lifetime when the central nervous system is especially vulnerable, thus, the effect of a specific variable is dependent on the age when it occurs as well as the degree of severity of deprivation and its duration.

Gestation provides one example of such a critical period. Fetal development is controlled not only by genetic contributions from both parents but also directly by maternal physical and nutritional status. It is during gestation that neuronal growth is maximal. If the fetus is malnourished, resulting in low birth weight for age at delivery, or delivered prematurely because of maternal disability, his brain growth may be directly affected. Similarly, impaired fetal development may increase the vulnerability of the newborn infant to subsequent poor nutrition and environmental stress. Compared to a child normal at birth, the underdeveloped newborn would grow less well, would be likely to have more illnesses, and probably would have limitations in brain development and behavior.

Possible Modes of Interference with Learning and Behavior by Malnutrition

Nutritional and environmental factors may affect the central nervous system's capability and performance in a variety of ways. First, abnormalities of morphologic, biochemical, and/or physiological characteristics may so alter normal brain function as to reduce learning abilities. Secondly, the developmental process may be impaired by decreased exposure and responsiveness to environmental stimuli during critical periods when essential dequences of experience must be acquired to provide for continued orderly development. Third, the learning process may be disrupted by adverse changes in personality, emotionality, and behavior of the child. These changes may interfere with the interpersonal relationships that are necessary for learning experience. Furthermore, malnutrition among the persons in social contact with the child may militate against their providing adequate learning experience.

Fundamental Mechanisms Affected by Malnutrition

The fundamental mechanisms involved in these complex phenomena are just beginning to be understood. Extensive research in man and in animals during the last decade has provided a wealth of information documenting the changes that occur and indicating the likelihood of others. For the most part, these studies either measure the consequences of naturally occurring malnutrition in human beings or have been designed to manipulate a wide variety of states of nutrition and environmental deprivation and enrichment in experimental animals. The two major categories of change that have been considered have been anatomical and biochemical.

Anatomically, various indices of the brain structure,including brain weight, cell number, cell size, cellular organization, and myelin formation, have been found to be decreased by moderate to severe malnutrition occurring early in development. With malnutrition beginning at birth, the rat brain grows poorly with a reduced rate of cell division in all dividing cells. The most marked effects are seen in areas where cell division is most rapid. In man, severe malnutrition in the first year of life also reduces cell number in whole brain with the effects most evident in cerebrum and cerebellum.

There are now ample data demonstrating that severe general malnutrition during early postnatal life will affect brain structure and disrupt normal chemical development. Numerous biochemical features have been found to be reduced or altered by early malnutrition. This has been shown by measurements of RNA, DNA, proteins, glycosides, lipids, activity of a variety of enzymes, and neurotransmitters.

Myelination of the brain in the rat, pig, and man is also significantly affected by severe early malnutrition with reduction in cholesterol, phospholipid, and ganglioside content. Activity of certain enzymes involved in myelin synthesis is reduced with diminution in the rate of myelin formation. In rats, many of these changes are not reversible if the rehabilitation is begun after the age when normal myelination occurs.

There is evidence in experimental animals and man suggesting that in the prenatal period there are at least two types of intrauterine malnutrition. The first type ensues from a poor maternal diet before and/or during pregnancy which results in a reduction of the number of brain cells in the fetal brain (rats, guinea pigs) and in an increased effect of subsequent postnatal malnutrition (rat) on later brain growth. The second type of intrauterine malnutrition results from placental insufficiency. Although having a lesser effect on the developing brain than does maternal dietary inadequacy, placental insufficiency may nevertheless produce changes in the activity of certain enzymes (rat) and in the DNA, RNA, and protein content of the cerebellum (primate). Further information is necessary to elucidate the mechanisms involved in these changes, the precise conditions necessary to produce them, and their physiological significance.

Environmental Enrichment and Deprivation

Studies of developing organisms have shown that rearing adequately nourished animals under environmental enrichment or isolation significantly influences the ultimate structure, and function, of the brain. In enriched environments, experimental animals have been found to have significant increases in brain weight and nucleic acid content, dendritic arborization, myelination, acetylcholinesterase content, etc. In contrast, isolation has been shown to have a profound and opposite effect on these indices of development.

The conceptual scheme illustrated in Figure 1 diagrams the pathways that account for the similatiries between nutritional and environmental deprivation and between nutritional and environmental enrichment. The neurohumoral systems of the body react to conditions of stimulation and stress, mediating alterations in the metabolism of nutrients in brain cells that result in the changes observed. With malnutrition, the nutrient supply available to the brain cells is reduced, producing metabolic abnormalities and decreases in neurochemical activity as well as potentially deranging the neuroendocrine systems that transmit the effects of stress and stimuli to the brain.

Electrophysiological Measurements in Malnutrition

The electrophysiological activity of the nervous system serves to integrate its metabolic and neurochemical processes into functional and performance capabilities. A number of techniques of measurements of electrophysiological activity such as electroencephalogram (EEG), evoked response, electroretinogram, and nerve conduction velocity, have been used in the study of malnourished subjects.

In man and in lower animals, the normal EEG patterns and their developmental sequence have been shown to become abnormal in chronic and acute states of malnutrition suggesting alterations in normal cellular electrical activity. The abnormal electroencephalographic tracings seen in malnourished subjects generally improve toward normal with adequate nutritional therapy. These evaluations have routinely been made by visual inspection of the EEG tracings without the benefit of contemporary quantitative analysis, which might be more informative. Furthermore, no long-term follow-up recordings have been compared with EEG's of normal control subjects.

Effect of Malnutrition on Human Behavioral Development

Early severe malnutrition requiring hospitalization and rehabilitation is consistently associated with deficits in physical and psychological development during early life. Studies of the familial characteristics of severely malnourished children have also revealed significant social-familial pathology among those sampled. Similarly, follow-up studies in which children who were malnourished and rehabilitated early in life were tested at school ages have generally indicated that the previously malnourished children did more poorly than unrelated well-nourished controls. Some studies also have utilized well-nourished siblings to control for genetic and family factors. Again the malnourished child did poorly. However, the data are not consistent. Some studies suggest that the previously malnourished children showed little or no deficit in performance after several years of schooling; in other studies, such children appear to remain seriously retarded in test performance. Here again social-familial factors are seen to play an important role.

At present, it is impossible to say whether malnutrition, *per se*, contributes more or less to the depressed cognitive development of previously malnourished children than do unfortunate social and environmental conditions. No investigation has completely addressed the question of the relative importance of malnutrition versus social environmental factors in cognitive development; the findings have consistently been that both are significant.

Nevertheless, in spite of many serious methodological shortcomings in the studies that have been made, the weight of evidence seems to indicate that early and severe malnutrition is an important factor in later intellectual development, above and beyond the effects of social-familial influences.

The effects of mild to moderate protein-calorie malnutrition, or chronic sub-nutrition, on later intellectual development is less clear. Here again, social-familial factors are seen to play an important role. Studies that have attempted to assess the relative contribution of moderate malnutrition (or undernutrition) and social factors to later intellectual performance have frequently found that malnutrition does play a role apart from factors related to social status. This is a tentative conclusion, however, and confirmation awaits more systematic research.

In addition to such problems of generalized undernutrition are those associated with specific nutrient insufficiencies; anemia is a case in point. Although the data are not entirely clear, the existant studies suggest that anemia in the preschool years adversely affects motivation and ability to concentrate for extended periods of time. The mechanisms moderating these behavioral changes are by no means clear. More research is obviously important.

The Effect of Hunger on Intellectual (School ?) Performance

It is surprising that little or no objective, soundly planned research concerning hunger and the behavior of children has been reported. In this context, it is pertinent to note that hunger differs from malnutrition in important ways. Hunger occurs when an individual has insufficient food intake to provide a general sense of wellbeing and to meet immediate energy needs. Although it has both physiologic and psychologic components, hunger does not permanently alter neurological structures. One difficulty in systematically studying hunger is that the more frequently used nutritional standards may not describe or quantify hunger. Furthermore, the outcome variables most probably lie in general behavior patterns rather than in the standard measurements of intelligence (IQ). However, disruption of behavior patterns in learning situations ultimately probably would adversely affect IQ test performance.

One way to assess the impact of hunger on child development is to examine behavior and learning in preschool and school settings. In all such settings, undernourished or hungry children have been reported to exhibit behavioral alterations--including apathy, lethargy, inability to pay attention, and perhaps over-concern about food--so that responses to educational stimulation do not occur. Hyperactivity or hyperirritability may also accompany hunger and contribute to poor learning ability.

Learning is recognized as progressing in stages, each of which becomes a foundation for the next developmental period. By not responding to early stimulation, a hungry or malnourished child gradually would become less able to benefit from later experiences. Thus he would fail to learn, not because the genetic potential or neurological structures were absent, but because he lacked the experiential foundation. The potential importance of these possibilities are readily apparent.

There is an extensive feeding program for school children in the United States and there are plans to include both breakfast and lunch in many areas and to extend the program to preschool children. These programs are predicated in part on the assumption that they will facilitate learning. And yet, the impact of hunger on school performance has not been documented nor have the comparative results of breakfast, snack, or lunch programs been demonstrated in learning and behavior in school settings.

More careful studies on the physiologic and psychologic aspects of hunger and school performance clearly are needed to provide information to assist in designing the most effective school feeding programs for educational gain.

Behavioral Studies with Experimental Animal Models of Severe Protein-Calorie Malnutrition During Early Life

Studies on experimental animals have contributed a great deal to our knowledge of the interrelationships between nutrition, brain development, and behavior. Rats, mice, pigs, and monkeys have been used most extensively--each species providing clues that have made it possible somewhat realistically to translate findings from the experimental model to man. Even though final conclusions regarding nutritional effects in man must come from studies in man himself, the use of experimental models facilitates the control of nutritional and environmental variables far beyond that which can be achieved in man. Furthermore, the animal model permits a relatively rapid accumulation of knowledge from which specific concepts can be selected for verification in human beings, thus simplifying the experimental design and improving the chances of successful studies in man.

The infant animal subjected to protein-calorie malnutrition exhibits the same characteristics of apathy to its surroundings as those seen in the malnourished infant human being. Even more striking than apathy in the experimental animal is the actual avoidance of a new object introduced into a familiar environment. Because of the potential importance of avoidance behavior to learning and intellectual development, this phenomenon should be examined in studies with malnourished infants.

There is a striking similarity in the behavioral characteristics seen in the experimental animal following rehabilitation from early severe malnutrition and the abnormal behavior of the animal that has recovered from a period of environmental isolation during infancy. When nutrition and environment exposure have been restricted for short periods after birth and the animals are then permitted to grow to adult size under normal conditions, early isolation has exaggerated the behavioral effects of early malnutrition. Conversely, early environmental enrichment greatly decreased the abnormal behavior expected to result from early malnutrition. Preliminary studies in malnourished children suggest that both nutritional supplementation and educational stimulation may be required to overcome the effects of severe deprivation in early life.

Animal studies have also shown that among the long lasting behavioral changes caused by early malnutrition is an elevated or exaggerated emotionality when the animal is exposed to an aversive, painful, or frightening situation. There is also evidence that motivation is altered by such rewards as food and water. These behavioral changes influence the performance of an animal in a learning test.

Some of the long lasting behavioral changes seen in the postnatally deprived rat also have been observed in rats that were nutritionally deprived during in utero development as a consequence of malnourishment in the pregnant dam. In order to separate prenatal from postnatal deprivations, pups from malnourished dams were foster-suckled by dams fed normally during their pregnancy. The results of these studies suggested that nutritional deprivations of the mother that exist prior to parturition can have long lasting behavioral effects on her progeny.

The combined effects of early malnutrition and early environmental enrichment on behavior in experimental animals suggest that abnormal behavior and ability to learn are not necessarily permanent consequences of malnutrition, but that variable degrees of improvement may be obtained by the appropriate application of environmental enrichment and nutritional rehabilitation.

Finally, early severe protein-calorie malnutrition has been shown in lower animals to result in a long lasting, possibly permanent retardation in the growth of various parts of the body including the brain. This stunting of growth, which reflects a decrease in the total number of cells formed in such tissues as the brain, may be related to an impaired function of that tissue. However, a causal relationship has not yet been established between the smaller brain of the previously malnourished animal and its behavioral development.

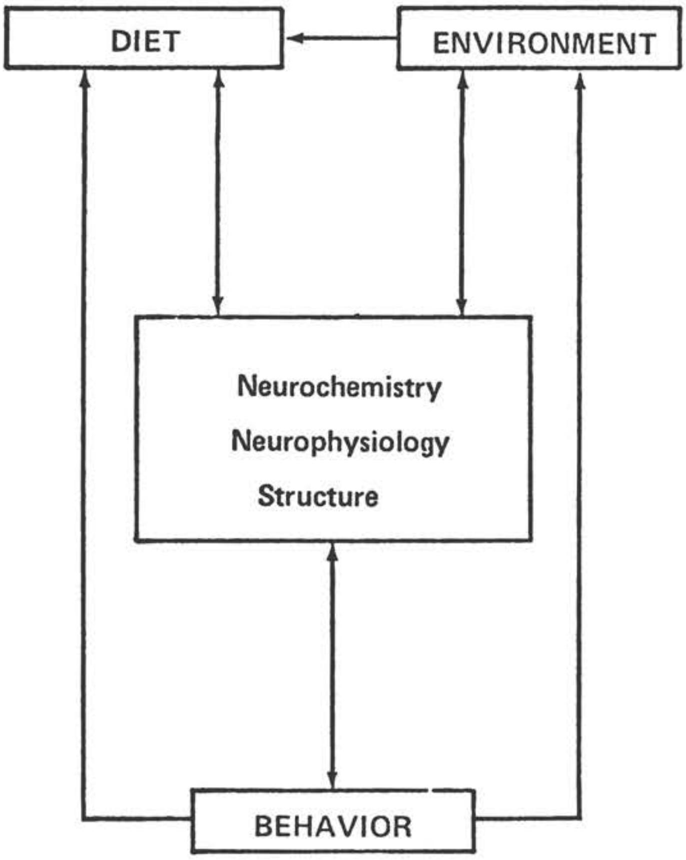
Projected Needs

Present evidence indicates that malnutrition, *per se*, and as an integral part of the environmental complex, may adversely affect brain development and behavior both directly and indirectly.

However, continued study in animals and man is needed to identify and document more clearly the interacting effects between nutrition and other environmental factors in terms of brain development and behavior. The subtleties of these interrelationships, their prevalence, and their consequences for the individual and for both national and international communities need to be defined. We must identify underlying mechanisms and improve means of treatment and prevention of their derangement. These tasks will require major and continuing commitments of money and people to basic research, development of more specific and sensitive testing techniques for both man and animals, and constant improvement in the design and conduct of studies at all levels.

Every effort must be made to disseminate information about what is already known in order to correct and prevent malnutrition even though solutions to these problems are not yet available. If effective measures to do this are not at hand, they should be developed and applied to their fullest extent using the most appropriate means available.

The effectiveness of these approaches, their further improvement, and continued success will depend on ongoing research. Close collaboration among resources from the scientific community, government, and industry will be essential to refine methodologies and to achieve the goals implied in the terms "good nutrition" and "optimal intellectual development."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