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# PSYCHOLOGICAL AND CENTRAL NERVOUS SYSTEM CONSEQUENCES OF PROTEIN-CALORIE MALNUTRITION: A REVIEW OF RESEARCH FINDINGS AND SOME IMPLICATIONS

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*The effects of malnutrition on psychological development and on structural and biochemical changes in the central nervous system are reviewed in both animals and humans. The evidence to date suggests that malnutrition has deleterious consequences for the developing organism and that the effects are most pronounced if not irreversible when nutritional insult is suffered during the period of rapid brain growth. Theoretical and methodological problems in the study of the relation between malnutrition and mental development are also discussed. The need for investigating the specific psychological and cognitive processes affected by malnutrition is pointed out and several research paradigms emphasizing the use of psycho-physiological techniques are suggested as a means of elucidating the relation between brain and behavior in the context of the problem of malnutrition and mental development.*

*Este trabajo revisa estudios sobre los efectos de la desnutrición en el desarrollo psicológico y en los cambios estructurales y bioquímicos en el sistema nervioso central. Los datos hasta el momento sugieren que la desnutrición tiene efectos negativos en organismos en vías de desarrollo y que los efectos son más pronunciados, si no irreversibles, cuando la insuficiencia nutricional ocurre durante el período de rápido crecimiento del cerebro. También se discuten los problemas teóricos y metodológicos en el estudio de la relación entre la desnutrición y el desarrollo mental. Se enfatiza la necesidad de investigar los procesos psicológicos y cognoscitivos específicamente afectados por la desnutrición y se presentan varios paradigmas investigativos que utilizan técnicas psicofisiológicas como medios de aclarar la relación entre el cerebro y el comportamiento dentro del contexto del problema de la desnutrición y el desarrollo mental.*

Before the effects of protein-calorie malnutrition (PCM) can be discussed, several theoretical and methodological issues must be considered. Clinical medicine has defined two syndromes of malnutrition: marasmus and kwashiorkor. These conditions are usually recognized during late breast feeding or early post weaning (Eichorn, 1968) with kwashiorkor appearing later in time (McCance, 1968). The condition of marasmus is a result of undernutrition, with a deficiency of all food, particularly carbohydrate calories and protein. The clinical signs of

marasmus include a decline in the growth rate with physical stunting, mental and emotional impairment, and severe diarrhea which creates fluid and electrolyte disturbances (Brock, 1960). Typically, the infant receives an abundant supply of carbohydrate calories but little or no protein, and since hunger requires calories, but not necessarily protein, kwashiorkor is the state of the majority of the underprivileged world. In fact, in tropical areas, where children are weaned largely or wholly on starchy paps without an adequate supply of animal or vegetable protein, the disease is almost a matter of degree (Brock, 1960). Symptoms of kwashiorkor include retarded growth and development, mental apathy, edema, hypoalbuminemia, fatty infiltration of the liver, atrophy of the pancreas, and diarrhea.

However, the two diseases are often difficult to distinguish. Biochemically, the two factors of calorie and protein deificiency are interrelated and this prompted the World Health Organization (W.H.O.) Expert Committee (1962) to propose the term protein-calorie malnutrition to cover the whole spectrum. According to the W.H.O. (Platt & Heard, 1965, p. 571), "The utilization of dietary protein is reduced as the proportion of protein to the total calorie content of the diet is increased, and if the energy content of the food eaten fails to satisfy the consumer's needs, the protein value of the diet for the consumer is reduced, the reduction being proportionately much more than the extent of calorie restriction". In other words, if the caloric intake is inadequate, the protein content of the diet is burned for energy purposes and consequently the efficiency of utilization of protein for nitrogen nabolism is decreased. Experimentally, Platt, Pampiglione and Stewart (1965) have shown that a restriction of calorie intake by 30% of requirements lessens the protein value of a diet by about 60% of the value obtained when the same diet is fed in adequate amounts.

Methodological problems in dealing with the effects of PCM are complex. Of particular salience is the difficulty of separating socioeconomic from strictly nutritional variables. For example, Cravioto and Delicardie (1968) have underscored the fact that nutritional risk is associated with the underprivileged segments of society, that is, poorer housing, little education, a high incidence of infectious diseases, greater attachment to outmoded patterns of child care, obsolete concepts of the causes of health and disease, and lack of modern technology. Klein (1969), in discussing the relationship of nutrition to intellectual development pointed out that mental and social development are multidetermined processes, malnutrition being but one of a variety of adverse conditions which affect a child's intellective-social development. Other factors include the nutritional status of the mother, absence of prenatal care, birth injury, disease, and the complex psychological and social deprivations inherent in the miserable conditions in which malnutrition abounds. Klein suggested that an adequate operational definition of malnutrition requires knowledge of the mother's nutritional status during pregnancy as well as measures of the child's nutritional status from birth onwards.

The importance of the nutritional status of the mother has been demonstrated both in human and animal research. Sontang and Wines (1947) divided 205 mothers into five groups, the protein content of the diets of the mothers ranging from greater than 85 grams per day to less than 45 grams per day. They found a relationship between protein intake and length and weight of the infant, although protein content was not related to ossification. The effect of maternal undernutrition resulting in lowered birth weight was also found by Smith (1947) but birth weight improved with dietary improvement. Lastly, Burke, Harding, and

Stuart (1943) reported that birth weight, birth length, and pediatric ratings during the first two weeks of life were related to the protein content of the mother's diet during pregnancy. Furthermore, increases in length, weight, and improved pediatric ratings were observed with each additional increment in the mother's diet, irrespective of the height of the mother.

In rats, protein deficiency had been shown to result in a reduction in the number of eggs ovulated, the number of eggs implanted, and in the number of fetuses alive at 13-15 days (Gupta & Lacy, 1967; Gupta & Christie, 1968; and Hsueth, Agustin, & Chow, 1967). Growth retardation was also observed by Bert (1967), Hsueth et al. (1967), and Gupta and Lacy (1967). In addition, the necessity of protein in early development was shown by Bert (1967) by studying the relationship of dietary protein to maintenance of pregnancy in rats at two stages of gestation; after mating (day zero) and after implatation of the blastocyst (day five). Fanally, the two studies by Gupta (Gupta & Lacy, 1969; and Gupta & Christie, 1968) showed that the development and differentiation of the placenta was affected by protein restriction as the elaboration and penetration of the placental capilaries was poor when compared with controls.

Often, however, the history of malnutrition extends beyond one generation and the possibility of concomitant effects of malnutrition over several generations must be considered. This effect was demonstrated in a study by Cowley and Griesel (1963) who found retardation of growth of the emergence of certain early response patterns in PCM rats. Specifically, the eyes and the external ear flaps opened at a later age in the second filial generation of the PCM rats, and they responded to auditory stimuli at a later age than did the normally fed controls. The authors concluded that PCM produces, concurrently with anatomical retardation, a retardation in the functioning of the receptors. Later, the authors found that the PCM rats scored a greater number of errors on the Hebb-Williams maze than the controls when both groups reached maturity.

## EFFECTS ON PSYCHOLOGICAL DEVELOPMENT

### Human studies

The effect of PCM on intellectual development is an area of concern to many. The most frequent questions raised are: Does nutritional insult produce intellectual retardation? If so, are the effects reversible?

Stoch and Smith, in three articles (1963, 1967, 1968) reported the results of an eleven year study on the effects of undernutrition on intellectual development, comparing 20 grossly undernourished infants with a control group from the same socioeconomic background. The controls were hardly well nourished, but were adequately nourished in comparison to the experimental group. Four tests were administered at two year intervals; the Gesell Norms, Merril-Palmer Test, National Bureau Tests and the New South African Individual Scale. Intelligence estimates (e.g. IQ) from the Gesell, Merrill-Palmer, and National Bureau Tests showed a consistent difference of about twenty points between the two groups, whereas the New South African Individual Scale showed a group difference of about 15.5 points. However, on the latter test, at the end of eleven years, 60% of the undernourished group fell below the level of the lowest child in the control group and only one child from the undernourished group exceeded the mean (barely) of the control group. Furthermore, an analysis of the non

-verbal subscales of the New South African Individual Scale showed a deficit in the visual-motor ability and pattern perceptions of the undernourished children. Stoch and Smith (1967) noted that this pattern was similar to that found in cases in which brain damage had occurred and speculated that severe undernutrition may cause organic brain damage. They also suggested another hypothesis; the inactivity and lack of energy associated with PCM results in a decrease in receptiveness to external stimuli and may impair learning of perceptual patterns during the sensory-motor period of development.

In a study in Guatemala (Klein, Gilbert, Canosa & DeLeon, 1969), PCM and control groups were selected on the basis of the height for age ratios. This is a comparison of expected height with actual height and yields a good estimate of a child's nutritional history. The test battery in this study consisted of 15 tests organized into the following categories; tests of memory, perception, language, learning, curiosity and exploratory behavior, resistance to distraction, and a task requiring the control of a motor response. It was found that the group differences involved tasks requiring attention or concentration rather than particular cognitive abilities or capacities. For example, in one test, two conditions were used, fast tapping and slow tapping. No differences were found in the slow tapping condition, but in the fast tapping condition, the controls performed signifantly better than the PCM group. Klein et al. suggested a hypothesis similar to that of Stoch and Smith -- that due to lower energy levels, children suffering from PCM do not develop the set to invest sustained attentional involvement in difficult cognitive tasks.

Kugelmass, Poull and Samuel (1944) compared mentally retarded with normal but PCM children and mentally retarded with normal control children. The Binet was administered after nutritional rehabilitation to the normal children in the first group. The results showed a mean rise in the Binet score of 10 points for the retarded children of group one and 18 points for the previously PCM children whereas in the second group no changes were found.

The Binet was also used in a study of 14 severely malnourished infants in Chile (Monckenberg, 1968) who were treated, released, and given supplements of milk. By three to six years of age the clinical signs of PCM had disappeared. However, the average IQ, (Binet) was 62 with 76 as the highest score. The Gesell was also administered, and while this test is only valid up to 42 months of age, only one child was able to reach the limits in all four areas. The author concluded that "brain damage in infancy is permanent at least up to the sixth year of life, despite improving nutritional conditions" (p. 272).

Cravioto and Robles have reported two studies (1963, 1965) conducted in Mexico in which 30 children suffering from severe PCM were rehabilitated. The Gesell was administered to the three age groups: lees than six months, between six and thirty months, and after thirty months. At the end of one year the results showed a reduction in all developmental spheres on the Gesell. As recovery from PCM occurred performance improved with language the slowest to recover. However, the rate of recovery was a function of the chronological age at admittance in the youngest age group, the deficits remained constant during the entire observation period.

The intersensory development of school age children was investigated in two studies by Cravioto and Delicardie (1968). In the first study, a geometric form presented to one sensory modality was compared with forms presented in another modality thereby comparing visual-haptic, visual-kinesthetic and haptic -kinesthetic systems. They found that the PCM children misjudged identical

forms presented across two modalities more than the control children. The same results were found for the number of errors in judging non-identical forms and was most notable in the youngest group (age six). In the second study, the PCM children performed poorer than the controls on a visual-auditory task involving the identification of a visual dot pattern corresponding to the pattern of a rhythmic auditory stimulus.

The results of Soviet research with children on the effects of nutritional insult were reported by Brozek (1962). The capacity to elaborate new conditioned reflexes was first affected by malnutrition, but even previously established reflex responses were depressed or abolished. In the course of dietary rehabilitation the recovery of the reflexes which had been affected was slow and reflected the slow normalization of the metabolic processes basic to the function of the cerebral cortex. Thus, it was concluded that cortical disturbances, as measured by conditioned reflex activity, were traced to dietary deficiency. Cravioto and Delicardie (1966) have pointed out the importance of conditioning studies for nutritional research, for conditioning demands the integration of two stimuli, each of which belongs to a different sensory modality. If interrelationships among sensory modalities are inadequate, conditioning may be delayed or pairing stimuli may not produce conditioned responses.

With the exception of a few clinical electroencephalographic (EEG) tracings of malnourished children, psychophysiological measures have not been used with human subjects to study the effects of nutritional insult. In a study mentioned previouslys. Stoch and Smith (1968) found a great deal of EEG instability under experimentally induced stress in the PCM children. Of the 20 children examined, 12 had poorly formed low voltage alpha waves with poor responses to eye openings while the opposite was found in the controls. In addition, the mean alpha index was lower in the PCM children. Two abnormal EEG's were found in the PCM group; one showed a primary epileptic dysrhythmia, the other a slow wave focus.

Engel (1956) reported EEG's of 25 children, aged eight months to five years, who were suffering from kwashiorkor. The brain wave tracings were abnormal with activity below the usual range of frequency considering each age group. In seven children who did not survive, the EEG was taken before a comotose state developed and showed a preponderance of 1-3 cycles per second slow waves but absence of a dominant basic occipital frequency with a range from 1-6 cycles per second. Most of the children, however, showed a recovery in their tracings with nutritional rehabilitation, with the exception of two cases whose EEG's never returned to normal.

Nelson (1959) and Nelson and Dean (1959) compiled EEG's of 47 children suffering from kwashiorkor, ranging in age from 12 to 36 months. The authors reported that 36% of the PCM group had abnormal electrical activity originating in the temporal or post temporal areas and that the spindle activity found in the controls during sleep was low in the PCM group. In these children rehabilitation was also successful in improving brain wave activity.

### Animal studies

Research dealing with the effects of PCM on animal behavior falls into three categories, the first of which parallels the work with humans showing the clinical symptoms of marasmus and kwashiorkor. These studies will not be reviewed except to point out that the clinical signs of malnutrition found in humans have been

replicated experimentally in the laboratory with monkeys (Ramalingaswami, 1968), rats (Bernes, Reid, Pond & Moore, 1968), pigs (Barnes et al., 1968; Platt, Pampiglione & Steward, 1965), and dogs (Stewart & Platt, 1968; and Platt, 1968). The other two categories of animal studies, wich are discussed below, are the effects of PCM on learning and brain wave activity.

In one study, rats deprived of protein were found to perform poorly on a visual discrimination task when compared with controls (Rajalakshmi, Govindarajan & Ramakrishnan, 1965). A study by Cowley (1963) showed no differences between PCM rats and controls on the Hebb-Williams test of animal inteligence.

Barnes et al. (1968) conducted a series of studies on the effects of PCM on learning in both rats and pigs who had been subjected to nutritional deprivation during the time of "natural" breast feeding. This means a period of time following parturition roughly equal to that of gestation. Dietary restriction in rats was accomplished by forcing lactating females to nurse unusually large groups of pups, a procedure widely used in nutritional research with rats. One year old rats were tested in a standard Skinner box and when shaping procedures were used to elaborate the bar pressing response, no differences were found between the experimental and control groups. Without the use of shaping only the male controls performed better than the PCM group. Elsewhere, Barnes et al. (1968) reported that malnourished rats performed poorer than controls on an exploratory task, and on learning a discrimination test in a Y shaped water maze.

Barnes et al. (1968) constructed a modified Skinner box to establish a bar pressing response in pigs weaned on a restricted diet. Shaping was not used and the controls learned the response faster than the experimental group. Barnes et al. (1968) also reported two conditioning studies with pigs on a restricted protein diet. In the first test a classical conditioning paradigm was used with a change in light intensity serving as the conditioned stimulus (CS) and an electrical shock as the unconditioned stimulus (UCS). No differences were found in the rate of acquisition of conditioning, although extinction was slower in the PCM group than in the controls. In fact, after 30 trials, five of the PCM pigs did not extinguish the response. The second test was avoidance conditioning in a shuttle box. The PCM showed poorer performace than the controls; they made fewer avoidance and more non-escape responses than controls.

The extensive work in the Soviet Union on conditioning and its relation to nutrition has been reviewed by Brozek (1962). According to Brozek, the Soviet orientation in nutrition derives from the Pavlovian notion that conditioned responses represent sensitive indicators of the functional status of the central nervous system (CNS) and that they can disclose CNS changes, one of which can be nutritional. Furthermore. Pavlov suggested that changes in "cortical dynamics" (inferred from conditioned reflexes) take place prior to the development of clinical symptoms and can thus serve as easy and sensitive indicators of the changing neurophysiological status of the organism.

Makarychev (Brozek, 1962) found that protein deficiency in an other wise normal diet can alter the general cortical activity level and the relations between the fundamental Pavlovian processes of exitation and inhibition in the cerebral cortex. Makarychev further suggested that an organism's response to protein deficiency depends upon that individual's type of nervous system. Rozental (Brozek, 1962) was unable to establish a conditioned salivary reflex to the sound of a metronome over 348 trials in a malnourished dog, while Frolov (Brozek, 1962) found that the sequence of the disappearance of conditioned salivary

reflexes follows, in reverse, the order in which they were established. The higher, most complex forms of conditioned reflexes were the first to suffer as the inner inhibitory processes weakened. For example, a conditioned response had been established to a light stimulus but when a second light stimulus was presented, the subjects could not make the discrimination. Makarychev and Sergeeva (Brozek, 1962) found that high protein increased cortical excitability in both dogs and rats. The low protein group was slow in elaborating conditioned responses and their sensitivity to unconditioned stimuli was decreased.

As mentioned before, EEG tracings have been made on animals suffering from malnutrition. Platt et al. (1965) found in pigs that PCM resulted in a marked decrease in the fast components of the EEG, the dominant frequencies being 4-15 cycles per second instead of the normal 20-40 cycles per second. Similarly, Stewart and Platt (1968) reported EEG deviations in PCM dogs which took the form of a paucity of normal rhythmic activity, an excess of irregular slow activity of large amplitude and frequent multifocal discharges. When the PCM animals were transferred to a high protein diet their physical appearance improved but the EEG changed only slightly. The same study also reported EEG findings in pigs which took the form of an increase and irregularity of slow waves and a decrease in the fast components. Lastly, Stewart (1968) reported the EEG from a PCM dog which consisted of a series of irregular waves of large amplitude with multifocal spikes and sharp waves. Interestingly, the author noted the similarity between the dog EEG and the EEG of PCM children presented by Nelson (1959).

## EFFECTS ON THE CNS

Historically, research on the effects of nutritional insult on the CNS began with measures of brain weight and head circumference (Platt & Wheeler, 1967; Dobbing, 1968, 1970). As Platt and Wheeler (1967) point out, it has been known for more than a century that the brain of the human and animal adult is highly resistant to inanition and that during deprivation the brain does not share the loss in body weight. There are, however, two qualifications necessary to bring this history up to date.

First, while research has shown that the brain is spared during various forms of malnutrition, it is also known that this is only the case for the fully developed brain (Platt & Wheeler, 1967; Dobbing, 1968, 1970). As will be shown later, when nutritional insult occurs early in life serious CNS consequences are imminent. Recently, Dobbing (1968, 1970) has formulated a vulnerable periods hypothesis which has received theoretical as well as experimental support, and states that "Processes of development in the brain are likely to be more vulnerable to restriction and other stress at the time of their fastest rate" (1970, p. 249). This vulnerability will vary within the general growth spurt, which is a period of rapid growth which occurs in all mammalian species before that of the whole body. The hypothesis further states that the nearer the time of the peak growth rate, the less will be the stress needed to produce a given effect, and the adult brain will be affected minimally, if at all, by acute stress.

This hypothesis has several implications for experimental research. It is known, for example, that all mammalian species pass through a similar sequence of developmental processes; early organogenesis is almost identical. However, one important species difference is the relation of fastest period of brain growth to

birth. Thus growth would have to be retarded at distinctly different times in relation to birth in different species, if the same developmental processes were to be similarly affected. In humans, the brain growth spurt occurs during the last trimester of pregnancy and the first several months of extrauterine life. By the end of the second year, the human brain is virtually complete; the adult number of neuronal cell numbers have been reached and the myelin sheaths have formed and reached metabolic stability (Dobbing, 1970; Stoch & Smith, 1967). The rat is a particularly attractive experimental subject because the growth spurt in this species is entirely postnatal and occurs within the first 21 days of life.

The other problem with the early historical notion of the resistance of the brain to inanition is the techniques of measurement used. As Dobbing (1968) has noted, brain weight or head circumference *per se* are not valid measures. For one thing, the brain weight must be considered in relation to the weight of the body --a small brain will carry no handicap for an animal with a correspondingly small body. In addition the brain: body ratio changes with normal development. In rats, the ratio falls during development as the age and body weight increase and in premature babies, the brain: body ratio is higher than in full term babies.

Recently, some rather sophisticated techniques have been developed to detect possible CNS damage due to malnutrition. They involve an analysis of the deoxyribonucleic acid (DNA) content of the brain and an estimate of the degree of myelination of nerve axons. However, before these techniques are outlined, an understanding of the process and function of myelination is desirable.

The process of myelination has been neatly outlined by O'Brien (1970). Myelin is a sheathlike structure which surrounds axons much like insulation around a wire, and like insulation, is thought to prevent short circuiting of electrical impulses from one axon to another. Myelin is formed in the peripheral nervous system by the spiral wrapping of the external membrane of the Schwann cell and in the CNS by the encasement of the oligodendrocyte around the nerve axon. The dry weight of myelin is composed of 75-80% lipids and the rest protein.

Myelin speeds impulse conduction by reducing the mean capacity per unit length of the nerve fiber. Current flow in myelinated fibers is six times as fast as current flow in unmyelinated fiber of the same length and thickness. This is due to the property of the myelin sheath which causes the nerve impulse to jump from node to node on the axon which is faster than the continuous conduction of nerve impulses found in unmyelinated fibers (Butter, 1968). Furthermore, as O'Brien (1970) has pointed out, the nerve conduction in the peripheral nerves of humans is age dependent, the most rapid increase occurring in the first year of life when neonates have a mean nerve conduction velocity of 20 meters per second. This rate rises to 35 meters per second after the first year, and slows down after that reading 40 meters per second by 3-5 years of age, and 60 meters per second in the 20-60 year old adult. This increase in conduction from infancy to adulthood is due to the myelination process.

There is an interesting relationship between the time of onset of myelination of particular nerve fibers and the behavioral activity of the nerves. In general, tracts in the nervous system become myelinated at the time when they become functional. Although complex behavioral activity can occur before nerve pathways in the CNS have acquired a myelin sheath, the coordinated behavior of organisms improves dramatically when the major nerve pathways are myelinated. For example, the fetus receives tactile, proprioceptive, auditory and gustatory stimuli in utero; the nerves transmitting these stimuli are partially myelinated by

six months of gestation age. The optic and pain nerve tracts are not myelinated until birth and become rapidly myelinated when the neonate receives optic and pain stimuli, the latter occurring later than the former. In fact, myelination can be slowed by preventing the conduction of impulses in a nerve, as in the case of the myelination of the optic nerve which can be delayed by preventing the opening of an eyelid. This suggests that impulse conduction in a nerve may stimulate myelination, but it is not known how this process works.

The degree of myelination has been measured by estimating a characteristic myelin lipid in the tissue sample such as cholesterol. The lipid estimate is thought to yield an accurate measure of myelination because the proliferation of oligodendroglia in the CNS and the Schwann cells in the peripheral nervous system precedes the synthesis and deposition of lipids (Dobbing, 1968). Similarly, the estimation of tissue deoxynucleic and phosphorus content (DNA-P) was used as an index of glial multiplication (glial cell development follows the development of neuronal cells) by Dobbing (1968). Finally, the estimation of DNA tissue has been used as an index of the total number of brain cells, on the assumption that each cell, regardless of type, contains the same quantity of DNA (Dobbing, 1970; Zamenoff, Van Marthens & Margolis, 1968; and Winick & Noble, 1966).

### Human studies

Only three studies have been reported in which the human CNS has been examined following nutritional insult (Winick & Rosso, 1969; Jackson, 1925; and Fishmen, Prensky & Dodge, 1969). In one of these (Winick & Rosso, 1969) ten normal human brains were compared with the brains of nine children who suffered from malnutrition. Before death, the malnourished children were found to differ in height, weight and head circumference when compared with the controls. Stoch and Smith (1963) in their eleven year longitudinal study mentioned previously, also found head circumference to differentiate normals from controls. However, as noted (Dobbing, 1968) there is some doubt as to the validity of this measure. The results of the study by Winick and Rosso (1969) showed that all nine PCM children had reduced brain weights (another questionable measure) but also reduced quantities of protein, ribonucleic acid (RNA) and DNA, when compared with controls. In addition, the data indicated that the earlier the onset of malnutrition, the more marked the effect. Three children who weighed less than 2000 grams at birth, had a 60% reduction in brain DNA content. This retardation in brain growth was explained by the decreased number of brain cells indicated by the severe DNA reduction. The protein/DNA ratio remained unchanged suggesting that those cells present were intact. Thus, the authors concluded that cell division may have been affected by malnutrition.

Fishman and Prensky (1969) studied the brains of four malnourished and four normal children. They found that the three classes of lipids which are most closely linked to myelin membranes, proteolipids, cerebrosides and plasmalogens, were significantly reduced in the malnourished children. Finally, cell damage in the form of chromatolysis, increased sallitosis, ghost cells and gliosis were reported by Jackson (1925) in the brains of children suffering from inanition. Similar pathologies have been found in the brains of animals experimentally malnourished, and are reviewed below.

### Animal studies

Stewart and Platt (1968) compared normal with PCM pig brains and found that the myelin sheaths in the latter were less dense than in the normals. The large

motor nerve cells in the anterior horns of the spinal cords were consistently affected by a loss of chromatin. There were also changes in the higher levels of CNS in the forms of a loss of neurons of the cortices of the PCM pigs. In addition, these changes were modified by the time of onset of PCM; those animals malnourished from the 19th day of birth showed less severe changes than those given the same diets from the 14th day of life, and more severe changes than those malnourished from the 26th day of birth. The authors also noted that there was a great deal of diversity in the form and degree of change found throughout the CNS of the experimental animals. Within a single group of cells, some appeared normal and others showed pathological changes ranging from slight chromatolysis to satellitosis, ghost cells and severe alteration of the Nissl structure. The latter are particularly important for they are believed to be involved in the synthesis and utilization of protein (Platt, 1961). Degeneration of the Nissl granules following PCM in pigs was also reported by Platt (1961) and Stewart (1968).

Dobbing (1968) subjected pigs to PCM during the period of maximal brain growth and then rehabilitated the animals with a high protein diet. At three years of age the brains of the pigs were examined and were found to be smaller than those of normal pigs. More importantly, however, the concentration of cholesterol was 21% less than in the PCM animals than in the controls, given the difference in brain size. In addition, the concentration of DNA was 29% less in the experimental than in the control animals, and the author concluded that the smaller brains of the malnourished pigs were under-myelinated. In the same study, rats were also given a protein deficient diet and the same results were obtained; the concentration of cholesterol and DNA was significantly reduced in the PCM animals. Prolonging the malnutrition in rats until 23 weeks, long after the period of maximal brain growth, had no further effect. In this study, DNA-P and lipid concentration had been used as measures of the degree of myelination and the results from both rats and pigs suggested to the author that myelination may be especially vulnerable during the period of maximal brain growth.

Several studies have shown the importance of time of onset of PCM in determining ultimate brain size in the rat. Winick and Noble (1966) found that in rats malnourished at the time when brain cells are actively dividing, cell division is curtailed and the ultimate number of total brain cells is reduced. Another study also found a reduction in rat brain cells when cells were dividing and malnutrition occurred, and, in addition, found that this reduction will occur if the rats are malnourished from birth or if their mothers are malnourished during pregnancy (Zamenof, van Marthens & Margolis, 1968). It was also reported that protein synthesis in the rat brain was reduced when protein deficient diets were fed to the weanling rat. Protein synthesis was not affected, however, when adult rats were maintained on a protein deficient diet (Ogata, Kido, Furusawa & Satake, 1968). Lastly, Chase, Lindsley and O'Brien (1969) found a reduction in protein content and smaller cells in the cerebrums of malnourished rats.

The concentration of certain enzymes in the cerebrum as well as the amino acids of glutamic acid, gamma aminobutryic acid (GABA), aspartic acid, and alanine were found to be significantly lower in PCM rats (Rajalakshmi, Govindarajan & Ramakrishnan, 1965). Of particular interest in GABA and its precursor glutamic acid. The presence of GABA is unique to the brain; it has electrophysiological properties and is thought to serve as a modulator of dendritic activity. The same study, as reported earlier had also shown that these protein deficient

rats performed poorer on a visual discrimination learning task than did controls. Thus, this study demonstrated that a condition associated with a learning deficit is also associated with a deficit of GABA and of the enzyme involved in its formation.

## Conclusions

It seems logical to conclude from the preceding literature review that serious psychological and CNS impairment can result from malnutrition, and that such damage is most likely during the period of maximal development of the brain. Psychologically, I.Q., intersensory development, and the processes of inhibition and excitation seem to be affected in humans. Physiologically, there is evidence that the myelination process and cell number of the brain are impaired. There is, however, a large hiatus in our knowledge of the relation between the psychological and physiological consequences of nutritional insult. In fact, only a single study (Rajalakshmi, Govindarajan & Ramakrishnan, 1965) was reported in which learning was related to a metabolic change in the CNS.

It is also interesting to note the conspicuous absense of psychophysiological research in the study of the effects of PCM. The use of psychophysiological measures would seem to be an excellent starting point to investigate the relationship between psychological and physiological consequences of malnutrition. For example, several studies (Stoch & Smith, 1968; Engel, 1965; Nelson, 1959; and Nelson & Dean, 1959) reported EEG tracings of PCM children. This technique could be elaborated to monitor cortical activity during learning situations, particularly in infants, since this is the time of rapid brain growth in humans. Are there differences, for example, in the cortical activity of PCM infants as compared to normal infants during habituation or the number of trials to learn or extinguish a classically or operantly conditioned response? The use of classical conditioning in such a study could serve to test Pavlov's notion that the functional status of the CNS can be ascertained through the elaboration of conditioned responses (Brozek, 1962).

Another research possiblity is the presentation of a series of learning tasks of increasing complexity and again looking for EEG differences between PCM and control subjects. For example, one might begin with classical conditioning and then move to discrimination learning, reversal learning, or stereotype conditioning, hypothesizing that EEG differences might become more pronounced as the level of difficulty of the task increased (assuming, of course that all children are capable of the response. However, if they are not, i,e., if PCM children cannot perform complex learning tasks, such data would be salient in itself).

Lastly, what are the developmental differences between PCM and control children? Some of the research showed improvements in EEG activity after rehabilitation from malnutrition (Nelson, 1959, Nelson & Dean, 1959; and Engel, 1956). Does such improvement accompany improvement on learning tasks? One could sample PCM and control subjects over a range of ages from infancy through adolescence and investigate the relation between cortical and learning behavior.

It should also be pointed out that other measures besides EEG could be used to study the psychophysiological concomitants of malnutrition. Psychophysiological measures such as heart rate are mediated by the CNS and could provide valuable information concerning the role of the CNS in processing incoming

stimuli. Heart rate, for instance, had been widely used with normal children as a measure of the attentional or orienting response. Such studies could be replicated with malnourished children to determine if, as Klein et al. (1969) and Stoch and Smith (1967) suggested, children suffering from malnutrition are lacking attentional involvement with their environment. Interestingly, the mental apathy associated with kwashiorkor has resulted in the clinical dictum that "Once a child can be persuaded to smile, he is well on the way to recovery" (Clark, 1951, p. 229).

The notion of an attentional deficit associated with malnutrition also prompts some theoretical speculation concerning a possible relation between the psychological and physiological effects. An organism interacts with his environment through his nervous system, that is, environmental input is received by the receptors and then transmitted along the afferent pathways to the brain. If, as the research presented here suggests, nerve conduction is inhibited as a result of incomplete myelination of the nerve fibers, stimuli may not get to the brain as fast as they should for appropriate behavioral responses, or stimuli may get to the brain in a non-adaptive manner. In other words, malnutrition may be a physiologically mediated form of stimulus deprivation in which environmental input is simply not being received, or being improperly received by the cortex. And the consequences of stimulus deprivation, particularly in early development have been well documented (Eichorn, 1968; Kessen, Haith & Salapatek, 1970). For example, the study by Klein et al. (1969) found that the tests that discriminated PCM from control children were not tests differing in cognitive ability, but tests requiring the rapid processing of environmental input. The authors hypothesized an attentional deficit due to lower energy levels, however, it is also possible that incomplete myelination resulted in a defect in the ability to process stimuli rapidly. Additional support comes from the studies of Brozek (1962), in which the ability to elaborate conditioned reflexes and maintenance of established reflexes was affected by malnutrition, and Cravioto and Delicardie (1968) who reported defects in the intersensory development of children suffering from PCM.

A logical objection to this hypothesis is the possibility of cortical damage due to malnutrition which certainly has been suggested by the literature. That is, brain damage may act either in concert with or independently of nerve condition. However, one must keep in mind that a reduction in the number of brain cells *per se* does not necessarily imply a reduction in intellectual capacity. It is often said that only a small fraction of the adult brain is actually used, anyway, so a smaller brain may not necessarily be a handicap. Furthermore, the research by Winick and Rosso (1969) showed that although the number of brain cells were reduced as a result of malnutrition, the cells that were present were intact. Finally, the status of the brain may be irrelevant. Stimuli arrive at the brain via the nervous system and so it seems parsiomonious to examine their path at the port of entry. If the route to the brain is somehow impaired then the activity of the brain itself is secondary.

A test of this hypothesis would be extremely difficult and only indirect from a behavioral point of view. Research dealing with the ability to process stimuli, such as conditioning studies might prove useful. For example, if one could find normal EEG's in malnourished children but slower rates of habituation or conditionability, one might infer impairment of the different or efferent nerves. However, even such a finding would not be conclusive, for the relation between EEG activity and behavior is still nor clear. The need for research specifying the neuropsychology of behavior is obvious.

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