FETAL MALNUTRITION, BRAIN GROWTH AND MENTAL DEVELOPMENT

by

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INTRODUCTION

In the United States during 1972, there were 3,258,411 live births and 41,380 fetal deaths (1). Usher (2) concluded that 30% of the fetal deaths that he reviewed could be attributed to malnutrition of the fetus. Using that figure, 12,414 of the fetal deaths in 1972 could be ascribed to fetal malnutrition. Gruenwald (3), Urrusti et al. (4) and Scott and Usher (5) estimated that 33, 40 and 50% of low-birth weight infants are not "premature" but have suffered from fetal malnutrition or fetal growth retardation. Using an average figure of 41%, 205,736 of the 501,795 low-birth weight infants presumably were infants with fetal malnutrition. Therefore the estimated total incidence in the United States of babies either dying in utero from, or born with, fetal malnutrition would be approximately 218,150 infants per year.

In the past, any infant who weighed 2500 g or less was defined as premature. However, this definition did not take into consideration gestational age of the infant. Recently, "premature" infants have been divided into two groups: a) the true premature who is the normal size for his gestational age but is born too soon, and b) the small-for-date or small-for-gestational age infant who is full-term but has not grown properly in utero.

Small-for-date infants have been further divided into those with "intrinsic" growth failure and those with "extrinsic" growth failure (figure 1). Intrinsic growth failure results from congential malformations, inborn errors of metabolism and other genetic diseases. Whatever caused the growth failure is intrinsic to the fetus and does not involve

the placenta (6). Extrinsic growth failure is caused by abnormalities in the maternal and fetal environment.

Two types of extrinsic growth failure have been described (6). Type 1 generally is caused by maternal vascular disease. There is asymmetrical growth failure in the fetus. The brain seems to be of normal size and weight, but the liver is reduced in size and depleted in glycogen. Type 2 is caused by maternal malnutrition. Fetal growth failure is symmetrical in all organs. The brain and liver are reduced in size in proportion to body size.

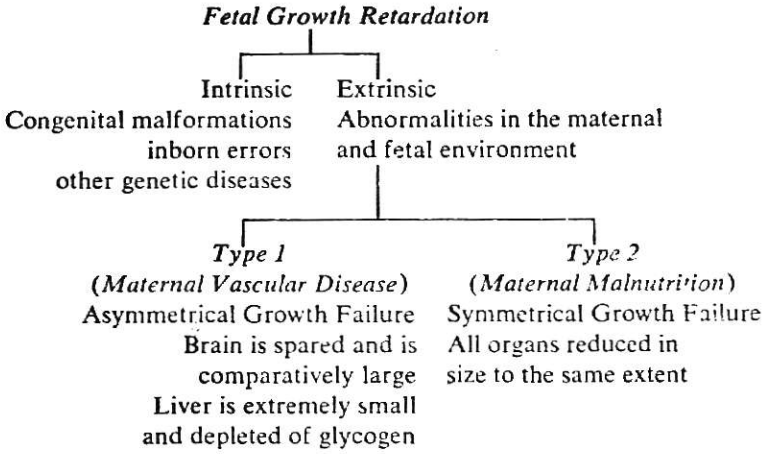

Fig. 1 Classification of fetal growth retardation (6).

Winick (6) stated that Type 1 fetal growth failure characterizes the vast majority of small-for-gestational age infants in developed societies; while Type 2 is the more prevalent form in developing countries and probably within the poorer segments of the United States. The purpose of this paper was to review current research concerning the relationship of maternal malnutrition to cellular brain growth and mental development of the offspring. The paper is divided into three main sections: normal growth and development of the brain, influence of malnutrition on brain development, and relationship of fetal malnutrition and mental development.

NORMAL DEVELOPMENT OF THE NERVOUS SYSTEM

Structural Development of the Nervous System

The human nervous system develops from the neural plate, a thickened area of embryonic ectoderm which appears during the third week of gestation. This plate becomes infolded to form a neural groove and neural folds. The neural folds fuse to form the neural tube which differentiates into the central nervous system, consisting of the brain and spinal cord. During the fourth week, the neural tube grows rapidly and forms the three primary brain vesicles: the forebrain, the midbrain and the hindbrain. The development of the adult shape of the brain is accomplished very early although the brain is still very immature. The forebrain gives rise to the cerebrum; the midbrain becomes the adult midbrain; and the hindbrain gives rise to the pons, cerebellum and medulla oblongata. The walls of the neural tube become thickened by proliferation of neuroepithelial cells which give rise to all nerve and macrogilial cells in the central nervous system. The neural crest cells differentiate into the posterior root ganglia, the sensory ganglia of the cranial nerves, autonomic ganglia and the Schwann cells. During this early period of organogenesis, the central nervous system is acquiring its general adult shape through a process of differential growth accomplished by cell division and migration within the tissue. The basic stages of nervous system development are essentially the same in all mammals (7,8,9).

Principles of Cellular Growth

Enlargement of any organ during the growing period may result from an increase in the number of cells (hyperplasia), an increase in the size of

already existing cells (hypertrophy) or the simultaneous occurrence of both. The total number of cells of an organ can be calculated by determining the total organ DNA (deoxyribonecleic acid) content and dividing by the DNA content per diploid nucleus (10). The DNA content per diploid nucleus is a constant which has been determined for several species. All diploid cells in the rat contain 6.2 pg DNA; while in the human all diploid cells contain 6.0 pg DNA. The average weight and protein and lipid content per cell can be determined by analyzing the total amount of each of these components and dividing by the number of cells. The result can be expressed chemically as weight/DNA, protein/DNA, RNA (ribonucleic acid)/DNA or lipid/DNA ratio. An increase in total organ DNA content represents an increase in the number of cells (hyperplasia). Increases in the weight/DNA or protein/DNA ratio represent an increase in cell size (hypertrophy) (11,12).

Figure 2 diagrams the three phases of organ growth. In the first phase, there is rapid cell division (hyperplasia alone), but cell size remains constant. Weight, protein and DNA all increase proportionally. In the second phase, both cell number and cell size increase as DNA and protein content rise. However, the rate of DNA synthesis begins to decrease (cell division) while protein synthesis continues at the same rate. Thus, during this second phase there is an increase in the protein/DNA ratio (cell size). In the third phase, increase in cell size results as a consequence of a further reduction or stoppage in DNA synthesis and a continued accumulation of protein. Growth finally ceases when protein synthesis and degration come into equilibrium (6).

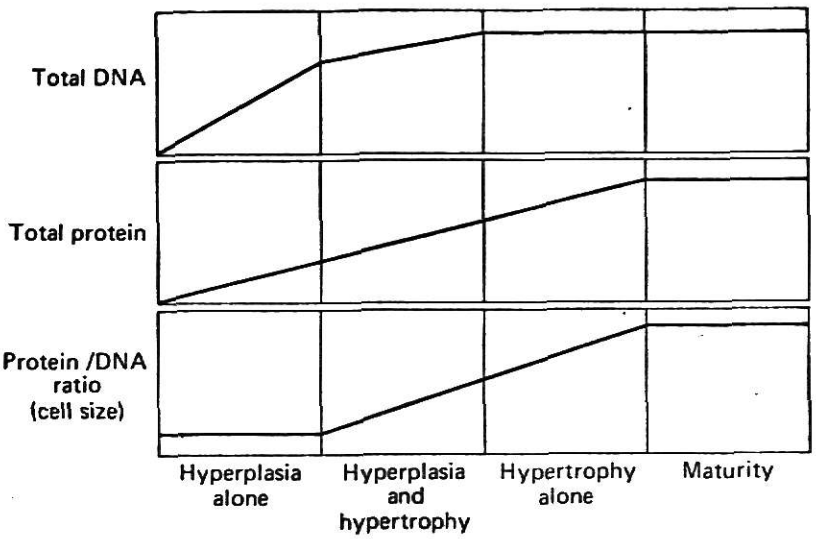

Fig. 2 Periods of cellular growth. Plotted above are the relationships between DNA and protein during the three phases of organ growth. It will be observed that DNA content crests and levels off well before organ size, as determined by protein accretion and weight gain, reaches its maximum (6).

Brain Growth In the rat, brain growth from conception to 13 postnatal days is exclusively by hyperplasia. Between 13 and 17 days it is by hyperplasia and hypertrophy and after 17 days by hypertrophy alone (11).

The basic stages of brain development are essentially the same in all mammals (9). There is a similar embryological period followed by a period of rapid neuronal cell division. Next the oligodendroglial cells multiply and synthesize myelin. The last stage is the intricate process of dendritic growth and branching and the establishment of synaptic connections. All species go through this same developmental sequence. The anatomical regions that compose the brain are similar in chemical composition and in metabolic and electrophysiological properties from one species to another (13).

The major difference (apart from the degree of complexity of the final product) is the variance in timing of these growth stages according

to species. The event of birth apparently has no significance to the structure and function of the nervous system. Rodents, rats and mice are born before the growth spurt; guinea-pigs have almost completed this stage at birth. From the point of view of growth spurt, animals can be arbitrarily divided into 'prenatal', perinatal' and 'postnatal' brain developers. Figure 3 is an attempt to classify certain animals in this manner. The shape of each curve is without significance since it is affected by the adjustments which had to be made to the time scale in order to fit several species into the same illustration. The main fact which emerges is that the timing of the brain growth spurt in relation to birth varies according to species. Therefore, such expressions as 'fetal brain' or 'neo-natal brain' or 'post-natal brain' are quite meaningless unless the species and its growth characteristics are known (9).

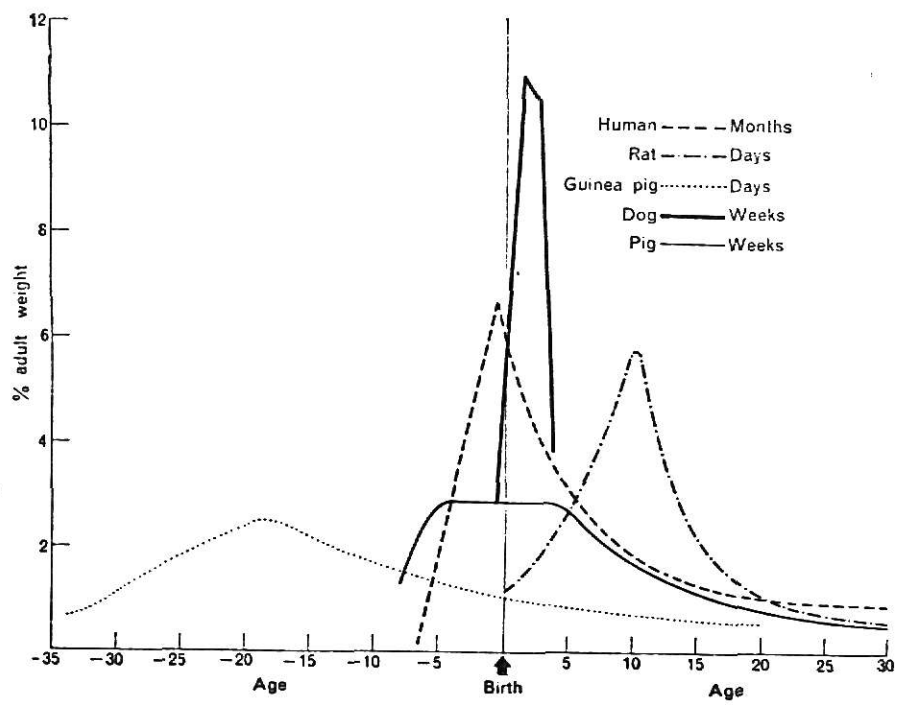

Fig. 3 Rate curves of brain growth in relation to birth in different species. Values are calculated at different time intervals for each species (9).

Weight and DNA, RNA and Protein Content of Whole Brain

The weight, and DNA, RNA and protein content of the whole rat brain have been studied (14). The weight of the whole brain increased linearly between 6 and 21 days of age. Whole brain protein content increased sharply from 49 mg at 6 days to 218 mg at 21 days (figure 4). Whole brain RNA increased from 2.18 mg to 4.91 mg and then tapered off. The whole brain DNA content increased threefold between 6 and 17 days but increased very little thereafter.

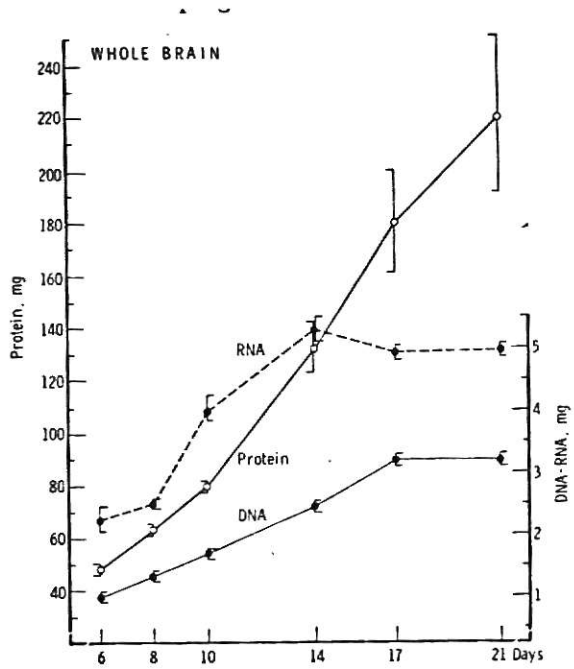

Fig. 4 DNA, RNA and protein content of whole rat brain in the developing rat. Each point represents a minimum of three animals. The ranges are indicated (14).

In the human, whole brain weight, protein and RNA increased linearly between 13 weeks gestation and 13 months of age after birth (16,17). At 13 weeks of gestation, the average brain weight was 5 g; at 13 months after birth, it reached 970 g (figure 5). During this same growth period, total brain protein increased from 193 mg to 54 g. Total RNA content increased

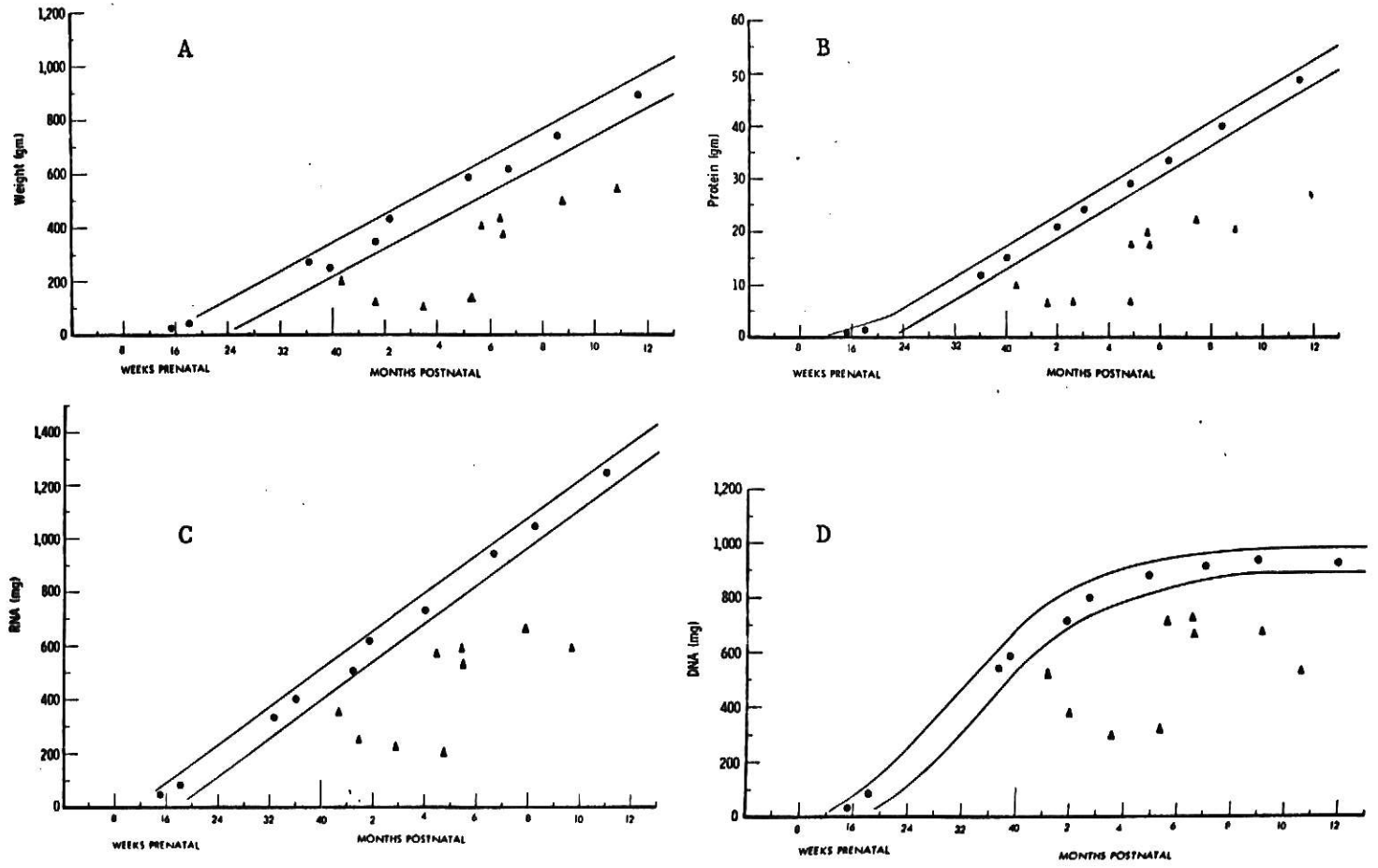

Fig. 5 Cellular growth in the brains of normal and malnourished children. Lines indicate normal range for U.S. population. o indicates normal Chilean children. Δ indicates Chilean children who died of severe malnutrition during first year of life. A. Total brain weight. B. Total protein content. C. Total RNA content. D. Total DNA content (14,15,17).

from 18 mg to 138 g. In contrast, the DNA content rose linearly from 25 mg at 13 weeks of gestation to 600 mg at birth and thereafter the slope of increase began to level off until a maximum was reached at about 5 months of age.

Winick's (15,16) data suggested that cell division in the human brain stops at 5 months of age. Dobbing and Sands (18,19) found that cell division continues into the second year of life. They showed that there are two spurts of DNA synthesis which occur normally during the development of the human brain (figures 6 and 7). The first growth spurt (primarily neuronal division) starts at about 10 to 18 weeks of gestation. The second spurt (oliogodendroglial multiplication) begins in mid-pregnancy and continues into the second postnatal year. According to their findings, 5/6 of the human brain growth spurt is postnatal.

Weight and DNA, RNA and Protein Content of Brain Regions

Not only do cellular growth rates vary among species, but individual brain regions in the same species undergo different patterns of growth. Rat In the rat, weight of the cerebrum, brainstem and hippocampus increased twofold between 6 and 21 days postnatally. During the same period, the weight of the cerebellum increased 6-fold. The weight of the cerebrum increased in a curvilinear fashion, while that of the cerebellum increased only slightly between 10 and 17 days. Weight in the brainstem increased slowly between 6 and 14 days and increased more rapidly thereafter (14).

DNA content of the cerebellum increased 8.5 times (figure 8) between 6 and 17 days. Cell division in the cerebrum progressed more slowly than in the cerebellum but continued for a longer period of time. DNA content

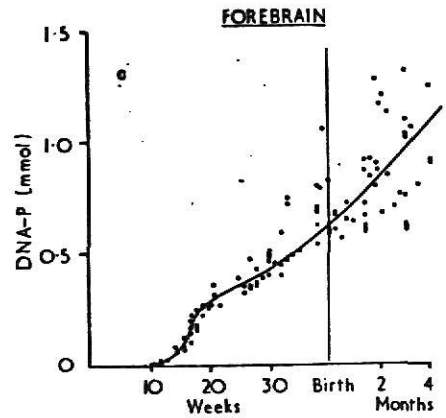

Fig. 6 The increase of whole brain DNA in developing human brain (18,19).

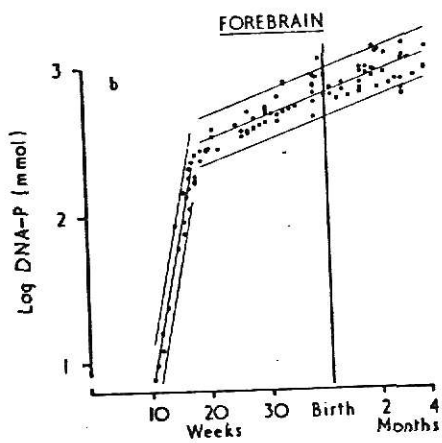

Fig. 7 A semilogarithmic plot of the data appearing in figure 6 to show the comparatively sharp separation of the two phases at 18 gestational weeks. Regression lines with 95% confidence limits are added (19).

of the cerebellum increased linearly from 0.428 mg to 1.01 mg between 6 and 21 days. DNA in the hippocampus did not increase except between days 14 and 17. This was believed to be due to a migration of cells from the lateral ventricle rather than cell division in the hippocampus (12). Most cell division in the brain stem occurred between 6 and 14 days when DNA content increased 65 percent. No further increase was seen after 14 days (12,14,16).

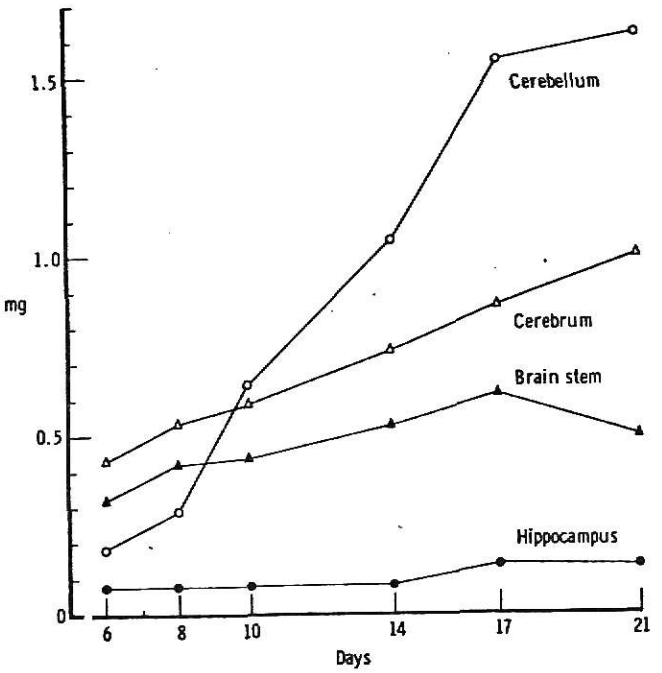

Fig. 8 Total DNA content in various regions of rat brain (16).

Cerebellar RNA increased almost fourfold between 6 and 14 days. Little increase was seen thereafter. Cerebrum RNA increased slowly from 1.09 mg to 2.36 mg between 6 and 21 days. In the hippocampus RNA increased until 14 days and then leveled off. Brain stem RNA increased sharply between 6 and 14 days and then tapered off (14).

Protein content of the rat cerebellum increased threefold between 6 and 14 days. Cerebral protein content continued to increase linearly

during the entire reference period. The exact rate of increase in protein in the hippocampus was unclear. It appears that there was a slow steady doubling between 6 and 17 days. In the brain stem, protein content increased 6-fold with the most rapid growth occurring after 10 days (14).

Human Patterns of cellular growth are not as well defined in the human brain regions as they are in the rat. Available data are based on relatively small numbers of human samples. Howard et al. (20) determined the cerebral and cerebellar weight and DNA and RNA content of 28 human fetuses following surgical interruption of pregnancy. Cerebral weight increased from 0.446 g to 178.09 g between 10 and 31 gestational weeks. The increases in DNA of cerebrum and cerebellum are plotted on logarithmic scales against gestational age in figures 9 and 10. The increase of the logarithm of cerebral DNA with respect to age is linear between 10 and 13 weeks, indicating an exponential rate of increase during this period. Thereafter the rate of increase declines, and the plot on an arithmetic scale is linear between 14 and 30 weeks.

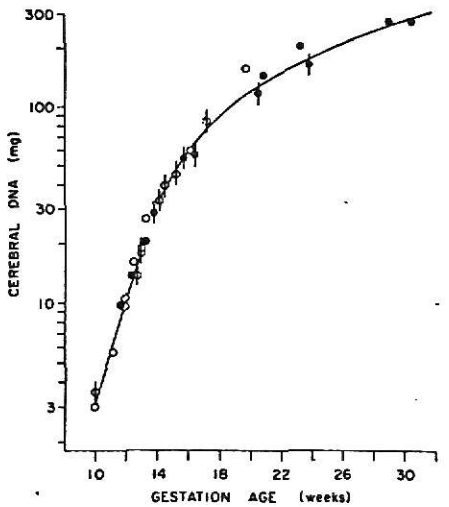

Fig. 9 The increase of total cerebral DNA during development of the human fetus. DNA in mg on a logarithmic scale. Each circle represents one brain. Solid circles, specimens from Uppsala; open circles, from Baltimore (20).

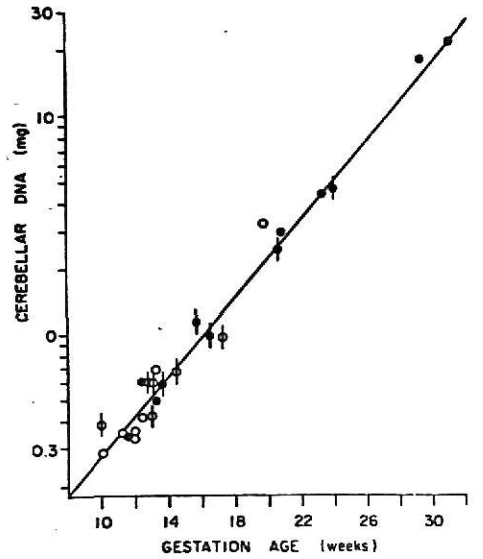

Fig. 10 The increase in total cerebellar DNA during development of the human fetus. Symbols as in figure 9 (20).

The cerebellar RNA/DNA ratio increased rapidly between 12 and 14 weeks. It continued to increase thereafter but at a slower rate (20). The slower rate of DNA increase in the cerebrum between 14 and 31 weeks suggests that cell division in some areas of the cerebrum may be terminated earlier than in the cerebellum.

Winick et al. (21) studied the cerebral and cerebellar DNA content of 12 normal children who died of accidents, poisonings or sudden death. Their data indicate that there was a progressive increase in wet weight, dry weight, total protein content and total RNA content in the cerebrum, cerebellum and brain stem during the first 2 years of life. In the cerebellum there was a 7-fold increase in wet weight, a 12-fold increase in dry weight and protein, and a 10-fold increase in RNA content between birth and 2 years. In the cerebrum, wet weight increased 3-fold, dry weight 4.5-fold, protein 9-fold and RNA 4-fold. Brain stem demonstrated a 3.6-fold rise in wet weight, a 4.5-fold rise in dry weight, an 8-fold rise in protein and a 5-fold increase in RNA content. These increases were

approximately linear in all three regions from birth to 2 years. Thus cerebrum increased in total mass and dry mass at one-half the rate of cerebellum. However, DNA content of cerebellum increased 4-fold during the first 8 to 10 months and only 0.2-fold thereafter (figure 11).

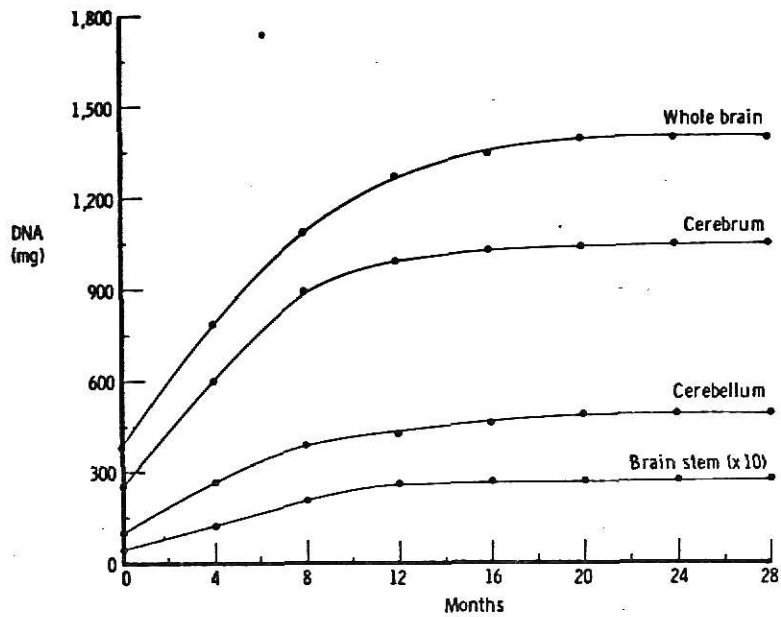

Fig. 11 DNA content in various regions of human brain during normal growth (6,21).

Cerebrum showed a 3-fold increase in cell number between birth and 6 to 8 months. Thereafter there was very little increase. Brain stem increased 2-fold to about 10 months and very little thereafter. Thus cell division proceeds at an only slightly faster rate in human cerebellum than in cerebrum (21).

Myelination

Myelination is accompanied by a progressive increase in brain function. It is always preceded by the proliferation of oligodendroglial cells. This is followed by glial cells surrounding the nerve axon in a

spiral fashion. When this "wrapping" process is completed, a progressive deposition of lipids begins within the myelin sheath. Myelin is a complex lipid made up of several components. The largest lipid component is cholesterol, but significant amounts of ethanolamine phosphatide, galactolipids, cerebrosides and cerebroside sulfates are also present (6,9).

There are at present no satisfactory morphological methods for measuring rate or degree of myelination. Analysis of component lipids or total lipids is used as a chemical index of myelination since there is very little myelin turnover within the brain (15,16). Most investigators have found a marked increase in total lipid content and concentration during early development in human, rat, dog and rabbit brain (22). Cholesterol, sphingomyelin, cerebrosides and sulfatides show a significant increase with age (23-25). Serial analysis of lipids in human brains indicated that the lipid/DNA ratio (the amount of lipid per cell) rose shortly after birth until at least 2 years of age (figure 12). This increase was reflected in a rise in both cholesterol/DNA ratio and phospholipid/DNA ratio. Postnatal lipid synthesis proceeded at a more rapid rate than DNA synthesis as a result of rapid myelination and the decrease in cell division (6,17).

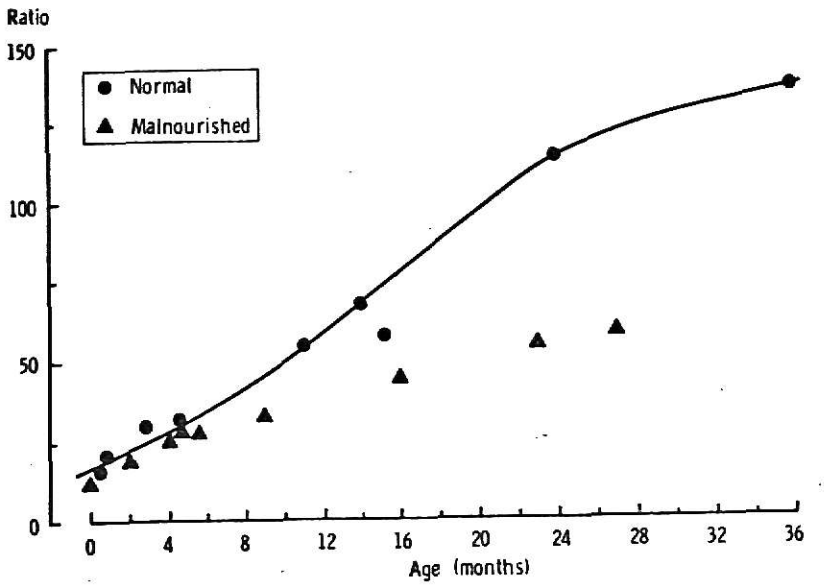

Fig. 12 Lipid/DNA ratio in normal and malnourished children at different ages (17).

MALNUTRITION AND DEVELOPMENT OF THE NERVOUS SYSTEM

Malnutrition and Cellular Growth of the Brain

Early organ growth of all nonregenerating tissues is due primarily to cell division and an increase in the number of cells. Later organ growth is due to hypertrophy with existing cells becoming larger. Winick (12,26) studied the effect of malnutrition on the stages of cellular growth in the rat. Three groups of rats were exposed to 21 days of caloric restriction at varying time intervals. The first group was malnourished from birth to 21 days, a period when all organs are growing by hyperplasia. This group showed a proportional reduction in brain weight, protein and DNA. Since the protein/DNA ratio was normal, the decrease was in the number of cells not in cell size. When refed, these animals remained with a deficit number of cells. In the second group, undernourished from 22 to 43 days of life, there was a decrease in the number of cells in all organs except the brain and lungs. These organs reached their normal cell number prior to 22 days. In the brain and lungs, cell size was reduced. When refed, the brain and lungs recovered, but the remainder of the organs were left with a deficit number of cells. In the last group, undernourished from 65 to 86 days, the normal number of cells had been reached in all body organs prior to undernourishment. This group suffered only a decrease in cell size. Cell size returned to normal in all organs upon refeeding.

Thus if malnutrition or undernutrition is imposed during the prolific phase of growth, the rate of cell division is slowed, and the ultimate number of cells is reduced. Winick's studies (12,26) indicate that the number of cells present in any organ at maturity is only

partially under genetic control. Environmental variables, such as nutrition, during the rapid phase of cellular growth affect the ultimate number of cells by altering the rate at which cell division occurs during the time prescribed by the genetic make-up of the animal. Malnutrition slows the rate of cell division, but cells continue to divide for the same period of time in the malnourished animal as in the normal animal (6).

Since fetal growth is characteristically of the prolific type, it should be particularly vulnerable to malnutrition. However, the fetus is isolated from the environment by the mother and placenta. Animal and human studies were examined to determine whether the mother or placenta provide any fetal protection (27).

Malnutrition and Brain Development in the Rat

Animal models can be useful to isolate the effects of nutrition alone on brain development. Care must be taken when extrapolating results of animal studies to humans. In studies on brain development, stages of development must be compared. Dobbing (13) hypothesized that the rat brain at birth is equivalent in developmental stage to the human fetal brain of 18 weeks gestation; the human brain at birth is developmentally equivalent to a rat brain of 5 to 7 days. The exact comparison of human and rat developmental stages has not been unanimously agreed upon; therefore, both pre- and postnatal studies of the rat were reviewed.

Body Weight Many investigators studied the effect of maternal malnutrition on the body weight of offspring. Chow and associates (28,29) reported that reduction in dietary intake by as little as 25% of the control resulted in growth stunting of the progenies. Other researchers investigated the effect of maternal protein restriction on birth weight of

offspring (30-32). Varying levels of protein restriction also resulted in decreased birth weight in offspring. Other workers (33,34) found that diets deficient in one essential amino acid retarded the growth of offspring when compared to controls.

Malnutrition and undernutrition for varying periods postnatally in the rat, pig and dog resulted in a decrease in body weight (35-38). Even after ad libitum refeeding, the animals never reached the body weight of controls.

Weight and DNA, RNA and Lipid Content of Whole Brain Many studies have been done on maternal dietary restrictions during gestation in rats. Some workers (39-42) found a reduction in total brain weight, total cell number and total protein content of the whole brain. Others (40-45) found that the cerebrum showed a greater reduction in DNA (cell number) and protein content than other regions in the rat brain.

Postnatal undernutrition in the rat may be a more accurate model for human fetal malnutrition. Culley and Lineberger (36) studied the effect of undernutrition in the rat from 5 until 11, 17 and 60 days of age on various brain parameters (table 1). Whole brain weights were significantly less in all rats on restricted diets when compared to controls. Brains from rats on the restricted feeding regimen until 11, 17 and 60 days each contained significantly less DNA and RNA than controls of the same age ($P < 0.01$). The amount of DNA in rats restricted until 17 and 60 days was not increased by ad libitum feeding until 110 days of age even though there was a greater than 50% increase in brain weight. If ad libitum feeding was begun at 11 days of age (prior to the time the brain stops accumulating DNA), some of the deficit in DNA was overcome.

TABLE 1

Effect of feed restriction on the composition of rat brain (36)

Regimen [1]	A11	A17	A60	A110	R11	R11A110	R17	R17A110	R60	R60A110
No. of rats	12	10	12	12	10	10	10	10	12	12
Body wt, g	23 ± 2	37 ± 3	247 ± 25	428 ± 54	13 ± 1	392 ± 48	16 ± 1	321 ± 45	24 ± 1	289 ± 40
Brain wt, mg	1021 ± 41	1390 ± 57	1823 ± 37	2083 ± 105	801 ± 32	1841 ± 98	1010 ± 36	1708 ± 87	1102 ± 53	1672 ± 72
DNA, mg /brain	1.77 ± 0.10 [2]	2.46 ± 0.09	2.56 ± 0.08	2.52 ± 0.11	1.35 ± 0.07	2.29 ± 0.11	2.09 ± 0.09	2.15 ± 0.09	2.12 ± 0.09	2.07 ± 0.12
DNA, % [3]	0.173 ± 0.011	0.177 ± 0.008	0.140 ± 0.005	0.121 ± 0.007	0.169 ± 0.005	0.124 ± 0.006	0.207 ± 0.010	0.126 ± 0.006	0.192 ± 0.009	0.124 ± 0.007
RNA, %	0.259 ± 0.011	0.274 ± 0.013	0.180 ± 0.008	0.162 ± 0.010	0.281 ± 0.015	0.157 ± 0.008	0.321 ± 0.019	0.163 ± 0.008	0.230 ± 0.012	0.159 ± 0.009
Lipid, %	5.8 ± 0.2	7.0 ± 0.3	10.6 ± 0.3	11.8 ± 0.3	5.3 ± 0.2	11.2 ± 0.4	6.2 ± 0.2	10.7 ± 0.3	9.4 ± 0.3	10.5 ± 0.4
Protein N, %	1.12 ± 0.06	1.30 ± 0.08	1.74 ± 0.07	1.85 ± 0.09	1.14 ± 0.07	1.87 ± 0.07	1.26 ± 0.06	1.84 ± 0.07	1.69 ± 0.08	1.82 ± 0.09

[1] A11, A17, A60 and A110 indicate animals fed ad libitum from birth until killed at 11, 17, 60 and 110 days, respectively; R11, R17 and R60 indicate animals fed limited amounts from 5 days of age until killed at 11, 17 and 60 days respectively; R11A110, R17A110 and R60A110 indicate animals fed limited amounts (similar to R11, R17 and R60) from 5 days of age until 11, 17 and 60 days of age, respectively, and then fed ad libitum until 110 days of age.

[2] Mean ± SD for five or six samples (two brains per sample).

[3] Percentage of the component in brain.

The brains of rats restricted from 5 until 11, 17 and 60 days contained significantly lower percentages, as well as total amounts, of lipid than the brains of animals fed ad libitum the entire period. After ad libitum refeeding of restricted rats until 110 days of age, the percentage and total amount of brain lipid remained significantly lower ($P < 0.01$) than noted for the control brains (36). The timing and duration of underfeeding and refeeding affected the subsequent weight and DNA, RNA and lipid content of the brain.

DNA, RNA and Protein of Brain Regions Fish and Winick (46) studied the effect of malnutrition on regional growth of the developing rat brain. There was a 35% deficit in cerebellar DNA content of malnourished animals by 6 days. This deficit remained relatively constant throughout the rest of development (figure 13). The cells in the cerebrum divide more slowly than in the cerebellum. The effects of malnutrition on cell number (DNA content) were not seen until 14 days (80% of normal). These effects became more severe as the animal aged. There was no significant difference between the DNA content of the hippocampus of the control and malnourished animals between 6 and 14 days. However, at 17 days, when the DNA content normally rises, a 20% deficit was observed in the malnourished animals.

There was a 50% reduction in total protein by 21 days in the malnourished animals when compared to the controls. Very little difference in protein content in the hippocampus was seen between the two groups. These data demonstrate that the effect of malnutrition is proportional to the rate and type of growth in the region studied. Cell division was curtailed earliest and most severely in those parts where cells were rapidly dividing (46). In summary, maternal restriction of calories, protein or both resulted in a decrease in birth weight, brain

weight and brain DNA and RNA content in the offspring. Malnutrition affected cell number in the cerebrum more than in other areas. Thus it appears that in the rat the maternal-placental barrier is not effective in protecting fetal brain from cellular effects caused by maternal food restriction. Postnatal malnutrition or undernutrition of rats resulted in a decrease in body weight, brain weight and DNA content of the brain. Some of the deficits could be regained if refeeding was begun before cell division stopped. Postnatally, the cerebellum suffered a greater reduction in cell number as a result of malnutrition than did the cerebrum and hippocampus.

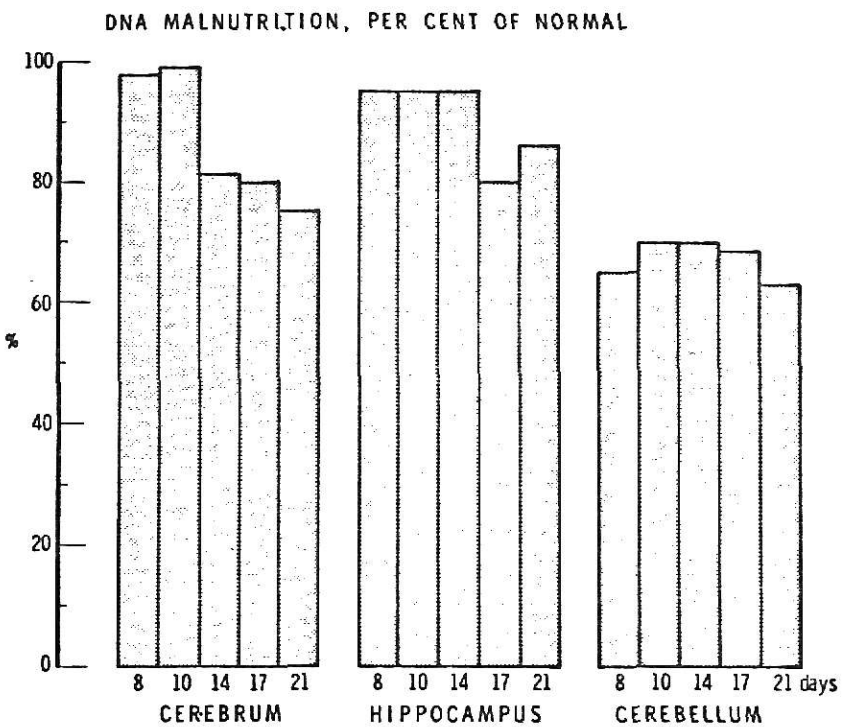

Fig. 13 Effect of malnutrition on regional growth of the rat brain (46).

Malnutrition and Brain Development in Humans

Birth Weight The number of human studies involving malnutrition during pregnancy and its effect on fetal development have been limited. Most have dealt with relationships between maternal nutrition and pregnancy outcome in terms of pregnancy complications, fetal and neonatal mortality and birth weight.

Antonov (47) evaluated the effects of an 18 month period of relative starvation during the seige of Leningrad (August, 1941 to January, 1943) on the outcome of pregnancy by studying birth records during this time period. Beginning in 1942, the average birth weight was 500 to 600 g below normal. The rate of prematurity (infants less than 2500 g) was 41.2% of all births. Many of these premature infants might be classified now as small-for-gestational age rather than premature. There was also a doubling of the stillbirth rate and a considerable increase in neonatal mortality.

Smith (48) studied the effects of a shorter period of maternal undernutrition in Holland between September, 1944 and May, 1945. The study differed from the one in Leningrad in that the populace had been fairly well nourished up to September, 1944, and the period of severe undernutrition was brief. During the time encompassed by the study, daily nutritional intake averaged below 1000 calories and 40 g protein. Average birth weights declined 240 g in infants whose mothers had been undernourished during the last trimester of pregnancy. The number of stillbirths and neonatal deaths did not increase.

The influence of nutrition during pregnancy upon the condition of the infant at birth was studied by Burke et al. (49). The diets of 216 women were rated as excellent, good, fair or poor. According to their standards,

forty percent of the women were malnourished. A statistically significant relationship between maternal diet and the condition of the infant at birth was found. All stillborns, all infants (except one) who died within a few days of birth, most infants who had marked congenital defects, all premature and all functionally immature infants were born to mothers whose diets were rated fair or poor.

Chase (50) reported a 39% reduction in the mean birth weight of four full term small-for-gestational age infants dying at or near birth. Naeye (51) found birth weight of 11 fetuses 36 to 41 weeks gestational age to be 54% of the control values. Naeye et al. (52) identified undernutrition as the cause of low birth weight (13 to 17% less than control) in a group of 83 infants born to poor urban mothers in the United States.

Brain Weight The results of the few studies to determine the brain weights of small-for-gestational age infants do not agree. Chase et al. (50) found a 23% reduction in the brain weight of four full-term small-for-gestational age infants. Naeye (51) reported an 18% reduction in brain weight of 11 fetuses. The decrease in brain weight may not have been due entirely to maternal malnutrition since 5 of the 11 cases showed some signs of placental abnormality. In a second study, done by Naeye and associates (52), no significant difference in brain weights between low-birth weight and normal-weight infants was reported. Sparing of the brain is generally seen in cases of intrauterine growth failure due to placental insufficiency which restricts the flow of nutrients to the growing fetus. There was no evidence of uterine or placental disorders in the 83 cases studied.

DNA, Protein and Lipid Content of Human Brain Studies on alterations in human brain biochemistry following intrauterine growth retardation are

rare. Chase et al. (50) found that the mean cerebrum-brain stem weight of four small-for-gestational age infants was 23% lower ($P < 0.02$) and cerebrum weights were 36% lower ($P < 0.01$) than those of the control group. Total DNA was 19% lower ($P < 0.02$) in the cerebrum-brain stem fractions and 35% ($P < 0.02$) in the cerebellum fractions in the small-for-gestational age infants compared to seven average-for-gestational age infants. Total protein was not significantly reduced in the small-for-gestational age cerebellum or cerebrum-brain stem fractions. The cholesterol content was lower ($P < 0.05$) in brains of the four term small-for-gestational age infants than those of the control infants. The total lipid, phospholipid, and lipid N-acetyl-neuraminic acid (NANA) contents of the brains from the two groups were not statistically different. The cerebroside and sulfatide fractions from each brain were analyzed together, and were lower ($P < 0.01$) in total content or concentrations in the brains of the small-for-gestational age infants.

In summary maternal malnutrition even during short periods is associated with an increase in low-birth weights and fetal complications. The number of studies on human brain parameters affected by malnutrition is limited. However, the limited information available appears to indicate that there is some reduction in parameters of brain biochemistry and cell number as a result of maternal malnutrition.

Children who have died of marasmus or kwashiorkor have been studied. Brain cell numbers in children dying from these diseases seem to follow patterns that have been observed in rats. Prenatal malnutrition in the rat reduces the number of brain cells at birth by 15 percent. Postnatal malnutrition from birth to 21 days also reduced the number of brain cells by about 15% at weaning. However, prenatal and postnatal malnutrition

produce a reduction of 60% in the number of brain cells (figure 14) 12,16,53).

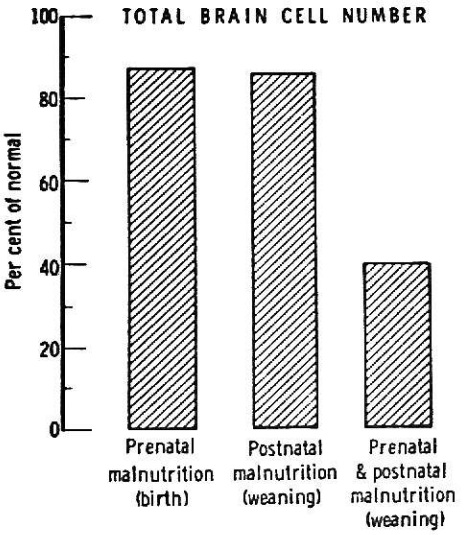

Fig. 14 Comparison of caloric restriction after birth, protein restriction during gestation and "combined" prenatal and postnatal restriction in the rat (12,16,53).

These same three patterns emerge in infants who have died of severe postnatal malnutrition. Full-term infants who died of severe food deprivation (marasmus) during the first year of life had 15 to 20% reduction in total brain cell number (figure 15). Infants weighing 2000 g or less at birth who died of marasmus during the first year of life showed a 60% reduction in total brain cell number. It is possible that the infants were malnourished in utero (small-for-gestational age infants) and represent a human counterpart of the animal model deprived from conception to 21 days of life. Brains of older children (presumably well-nourished during the first year of life) who died of kwashiorkor at 2 or 3 years of age do not show any reduction in cell number. Thus the limited data in humans agree with data in rats (53,54).

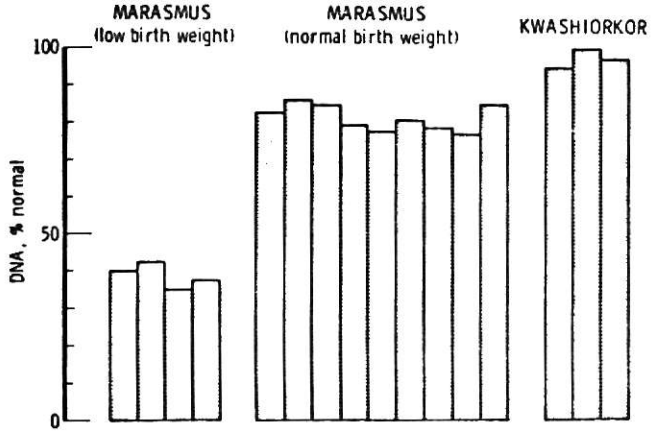

Fig. 15 Total DNA content in brains of children who died of malnutrition (12,16,54).

What implication does this have for the small-for-gestational age infant who suffers from intrauterine growth retardation as a result of maternal malnutrition? In theory, part of the brain cell deficit incurred in utero could be made up if rehabilitation was started immediately after birth. Although research indicated that malnutrition during periods of rapid cell division reduces the ultimate number of cells, does a reduction in cell number inhibit mental development or performance? This topic will be discussed in the last section.

MALNUTRITION AND MENTAL DEVELOPMENT

Adult intellectual capacity is the result of continuous interaction of genetic and environmental factors. One of the many environmental factors is nutrition. Needless to say, it is very difficult to isolate the influence of nutrition or diet on mental development or behavior. Diet provides the nutrients for the metabolism of brain cells. Environment influences what food is available. External stimulation affects the neurophysical activity of the brain. Figure 16 diagrams how these factors are interrelated and interdependent (55).

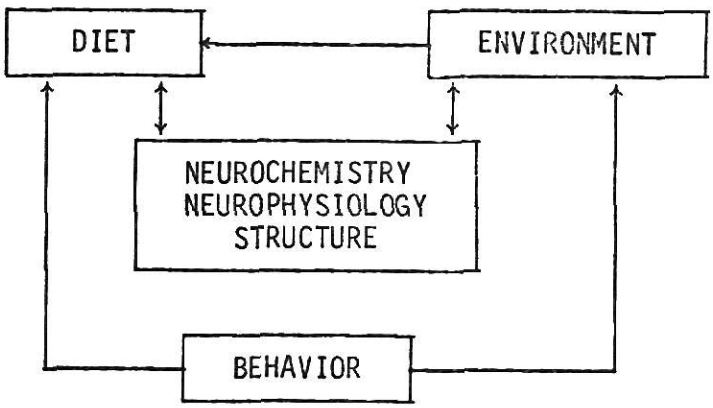

Fig. 16 Interrelationships and interdependence of factors affecting mental development (55).

Hopefully, it becomes evident why determining a cause and effect relationship between malnutrition, brain development and mental performance has not been easy. Given the animal and limited human research evidence that malnutrition during the rapid cell division stage can alter the ultimate number of brain cells, does it necessarily follow that decreased brain cell number leads to decreased mental ability? It appears that much of the research which has been done has made this assumption. Perhaps

performance is not related to the number of neurons. It is known that total absolute brain weight is unrelated to intellectual performance (man 1300 g, elephant 5000 g, whale 7000 g). There is similar lack of significance to be attached to brain weight as a percentage of body weight (man 2.5%, mouse 2.5%, dolphin 2.6%, squirrel monkey 8.3%, brontosaurrus 0.0001%) (9). In an effort to find a cause and effect relationship between malnutrition and impaired mental performance, much research has been done with animal models. Ethical restrictions do not allow manipulation of human maternal diets. It was also assumed that all variables except nutrition could be controlled in an animal experiment. Results of some of the animal experiments are reviewed in the following section.

Malnutrition and Behavior in Rats

Caldwell and Churchill (56) restricted protein intake of mother rats from mid-gestation to parturition. Offspring were tested at 30 to 35 days of age in the Lashley III water maze and at 50 to 55 days of age on the pole-jump-avoidance learning task. The control diet subjects were significantly faster in traversing the water maze than the protein restricted animals on the first day of testing only ($P < 0.025$). The protein-deprived animals might be regarded as "slow learners" when compared to the performance of controls. The performance of the control animals on the pole-jump-avoidance learning conditioning task was significantly superior to the experimental animals ($P < 0.01$).

In a similar study of maternal protein restriction, Zamenhof (41) reported abnormalities of gait and response to environmental stimuli in the offspring. A series of studies done by Simonson and associates (57-60) studied different aspects of rat behavior and development. In the

elevated multiple T maze, progeny of underfed mothers exhibited an increase in starting and running times and total errors when compared to the control group. The protein restricted animals showed delays in development, a decrease in exploratory activity and some neuromotor abnormalities.

Rats undernourished during the weaning period only, showed delayed eye opening, puberty, estrous cycle and exploratory behavior (61,62). In contrast, no lasting impairment in voluntary running, in learning a Lashley Type III maze, in visual discrimination in a water maze or in avoidance conditioning behavior was observed in other studies (63,64). However, striking behavior disturbances and increased learning errors were observed in animals malnourished from conception to weaning (64,65).

The assumed advantage of an animal model is that all variables except the one being studied can be controlled. In theory, it may seem possible to control the environment except for the nutritional variable, but in practice this has never been done. Producing malnutrition in neonatal rats has been done by allowing more than the normal size litter to nurse from one mother and by malnourishing the nursing mother. These simple manipulations change the amount and quality of mother-progeny interaction which may have a more pronounced effect on future behavior than the abnormalities caused by malnutrition. If an animal does not run a maze, does it mean that the animal is unable to learn or not motivated to learn? Perhaps all that can be concluded from the animal studies involving malnutrition and mental development is that in some cases the behavior or learning rate of the malnourished animal differs from the control (6).

Malnutrition and Mental Development in Humans

Many problems plague the accuracy of studies relating the effect of nutrition on mental development in humans. Besides the interaction of environmental factors previously mentioned, proper matching of controls and experimental groups and standardization of intelligence tests pose problems to the validity of human studies. It is also difficult to interpret the results of a developmental test given at 2 years of age or less in reference to adult mental performance or capacity. Despite these obstacles studies have been done and continue to be done in an effort to solve the mystery surrounding the relationship of nutrition and mental development.

Using the circumstances of the Dutch famine during World War II, Stein et al. (66) attempted to isolate the experience of famine from other elements of the social environment and relate maternal starvation during pregnancy to the mental status of the offspring in adult life. The famine affected the large cities of western Holland. The people in the rural towns were able to reach food-producing areas. These two areas constitute the experimental and control groups. The study population comprised 125,000 males born in the selected famine and control cities between January, 1944 and December, 1946 who were inducted by the military at about 19 years of age. This group represents approximately 98% of the surviving and resident males conceived or born during the famine. The military induction examination included clinical examination, psychological and educational tests. Two conclusions were drawn from this study: 1) Starvation during pregnancy had no detectable effects on the adult mental performance of surviving male offspring and 2) The association of social class with mental performance was strong. The authors cautioned

that this study examined the effects of a period of actue starvation in a group of previously well-nourished pregnant mothers. These results should not be generalized to the circumstances of chronic malnutrition in developing countries.

Osofsky (67) studied 118 women of low economic status who resided in an urban poverty area in the United States. During the last trimester of pregnancy these women had repeated nutritional evaluations. All the women were of low economic status and some of the mean values of nutrient intake fell below the RDA, but as a whole the women were not severely deprived at any time during the last trimester of pregnancy. The third day after birth, all infants were evaluated using the Brazelton Neonatal Behavioral Assessment Scale. A correlation analysis of the relationships between maternal nutrition and Brazelton Neonatal Behavioral Assessment measures revealed few significant relationships. Protein and total caloric intake related to a number of reflex measures. There was a positive relationship between protein intake and the total types of activity that the infant used in self-quieting ($P < 0.05$).

Drillien (69) compared the IQ's of small-for-gestational age infants and control infants when both were 10 to 12 years old. There was no difference in IQ between small-for-gestational age infants and control infants raised in upper class homes. A difference was noted in IQ's between small-for-gestational age infants and controls raised in average and poor homes.

Lechtig and associate (69-71) are conducting a long term maternal protein and calorie supplementation program in four Guatemalen villages. One group receives a caloric supplement and the other a calorie and protein supplement. Preliminary reports indicated that both supplements

(when a total of 40,000 calories was consumed) increased the birth weights of infants born to the mothers participating in the program. In addition, there was a higher proportion of children in the caloric supplemented group that had low psychological test performance. However, in both groups there was a higher proportion of children with low psychological test performance when the total caloric supplementation consumed by the mother during pregnancy was less than 40,000 calories.

The results of these few human studies seem to indicate that maternal malnutrition during pregnancy does not produce a permanent impairment in the mental performance of the adult offspring if the infant is properly nourished after birth. However, in a majority of present-day cases of maternal malnutrition during pregnancy the infant is not properly nourished after birth. If the cause of malnutrition during pregnancy was a lack of quality and/or quantity of necessary nutrients, the same deficiencies will probably also exist after birth. It then becomes necessary to identify high risk infants either in utero or immediately after birth in order to prevent further developmental impairment which may occur with continued postnatal malnutrition.

SUMMARY

About 15% of all successful pregnancies in the United States yield low-birth weight infants (less than 2500 g). It is estimated that in about one-third to one-half of these infants, low-birth weight is not due to prematurity, but is the result of fetal malnutrition.

Normal brain growth in all mammals proceeds through three stages characterized by stage 1, hyperplasia; stage 2, hyperplasia and hypertrophy; and stage 3, hypertrophy alone. Malnutrition or undernutrition during periods of rapid cell division decreases the rate of cell division thereby decreasing the ultimate number of brain cells.

In rats, maternal restriction of calories, protein or both resulted in a decrease in birth weight, brain weight, brain DNA and RNA content in the offspring. Postnatal malnutrition or undernutrition of rats resulted in a decrease in body weight, brain weight, and DNA content of the brain. Human maternal malnutrition during pregnancy is associated with low-birth weight. The relatively few human studies seem to indicate that there is some reduction in parameters of brain biochemistry and cell number as a result of maternal malnutrition during pregnancy.

Results of studies relating malnutrition in rats to abnormalities in behavior and learning ability disagree and have been difficult to interpret in terms of their implications for humans. The results of a few human studies seem to indicate that maternal malnutrition during pregnancy does not produce a permanent impairment in the mental performance of the adult offspring if the infant is properly nourished after birth.

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FETAL MALNUTRITION, BRAIN GROWTH AND MENTAL DEVELOPMENT

by

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About 15% of all successful pregnancies in the United States yield low-birth weight infants (less than 2500 g). It is estimated that in about one-third to one-half of these infants, low-birth weight is not due to prematurity, but is the result of fetal malnutrition. This paper reviewed normal growth and development of the brain, influence of malnutrition on brain development and relationship of fetal malnutrition and mental development.

Normal brain growth in all mammals proceeds through three stages characterized by stage 1, hyperplasia; stage 2, hyperplasia and hypertrophy; and stage 3, hypertrophy alone. Malnutrition or undernutrition during periods of rapid cell division decreases the rate of cell division thereby decreasing the ultimate number of brain cells.

In rats, maternal restriction of calories, protein or both resulted in a decrease in birth weight, brain weight, brain DNA and RNA content in the offspring. Postnatal malnutrition or undernutrition of rats resulted in a decrease in body weight, brain weight, and DNA content of the brain. Human maternal malnutrition during pregnancy is associated with low-birth weight. The relatively few human studies seem to indicate that there is some reduction in parameters of brain biochemistry and cell number as a result of maternal malnutrition during pregnancy.

Results of studies relating malnutrition in rats to abnormalities in behavior and learning ability disagree and have been difficult to interpret in terms of their implications for humans. The results of a few human studies seem to indicate that maternal malnutrition during pregnancy does not produce a permanent impairment in the mental performance of the adult offspring if the infant is properly nourished after birth.