INTRODUCTION

Low agricultural productivity clubbed with a poor distribution of food available and poor environmental condition have combined to make malnutrition a major public health problem in the developing countries.

Protein energy malnutrition is widely prevalent among the children of the developing countries (Bengoa, 1970; Enwonwu and Sreebny, 1970). Chronic protein undernutrition affect approximately 40% of the human population world wide (Stern et al, 1983). In India alone, approximately 35% of all children between 1 and 5 years of age are classified as moderately or severely undernourished.

The possible effects of pre and postweaning malnutrition on the growth and development of brain are gaining increased attention. There are ample reports which indicate that malnutrition per se alters the central nervous system by limiting its metabolic, structural and functional capabilities and performance (Barnes, 1971; Rajalakshmi and Ramakrishnan, 1972; Gabr, 1981).

Adequate nutrition is recognised to be necessary for structural development of the brain in early life. Several experiments have been conducted im the past two decades to find out the effect of undernutrition in early life. Most of these studies have been concerned with parameters which reflect the structural development such as brain weight, DNA, RNA protein and cholesterol. The studies concerning with protein deficiency in early life are few in number, that too those in the emphasis on enzyme systems involved in early metabolism are still much limited. Same is true for the deficiency of individual enzymes.

In the subsequent pages of this chapter an attempt has been made to present in brief the data available on morphological development of the brain, its vulnerability to nutritional insults both in experimental animal and actual case studies on human population.

Structural development of brain

The key role of the CNS in the orchestration of growth, metabolism, regulation and function of the living organism is very well known. The anatomical and metabolic heterogenity of the brain is still not clearly

TABLE-1 : Age related changes in the composition of different tissues in the rat.

Age (Days)	Composition of the whole organ (% of adult value)							
	Fresh weight		DNA		Protein		Lipid	
	0	20	0	20	0	20	0	20
Brain	14	74	31	91	11	76	4.5	41
Spinal cord	6.8	34	28	76	5.6	35	1.1	23
Heart	3.8	18	10	45	1.7	15	-	-
Liver	7	23	10	35	4.3	20	3.4	27
Intestine	4.2	42	-	-	3.5	45	6.2	40
Bone	9.9	16	-	-	0.84	18	55	66

Cf : Rajalakshmi, 1981

understood. The growth of the different anatomical structures, the development of different metabolic patterns and the spacing of the behavioral patterns have been known to be sequential processes. The complexity of the relationship between the anatomical and metabolic compartments of the brain are often changing until the matured adult stage is reached. This change is the result of many growth processes reaching their optimum activity and falling away at different times during the development of the brain.

In view of the fact, that brain plays such a vital role in the living system, it is not surprising that its development is initiated earlier than many other organs (Ritcher, 1964; Winick et al, 1972). This is well illustrated in Table-1. In most of the mammals rapid growth of the brain occurs prior to general body growth and human brain attains 75% of its adult weight by 2½ years of age (Ritcher, 1964).

The brain consists of many anatomical, morphological and functional compartments. The pattern of growth and maturation varies from region to region.

The regional variation of different areas of brain is reflected in rates of blood flow, oxygen consumption (Sokoloff, 1961; McIlwain, 1971) glycolytic rate (Sokoloff et al, 1977) and the rate of synthesis of amino acids from glucose and its quantitative distribution (Peter et al, 1973).

DNA per gram wet weight of any region or whole brain, is a convenient index to express the cell population. The cell size is indicated by the ratio of protein : DNA and RNA : DNA (Davison and Dobbing, 1968). The DNA content of the brain increases to optimal level in about 3 weeks postnatally in rat (Wimick, 1968) and one year in man (Altman, 1969). The completion of high rate of DNA synthesis takes place first in the stem, followed by cerebellum and then in the cortex (Fish and Wimick, 1969a). The peak levels of DNA in the cortex reach at 16 days in mice (Himmich, 1962), at 7 days in guinea pig (Dobbing and Sands, 1970) and during 6-8 months in man (Wimick, 1970c). The rate of DNA synthesis in different areas of the brain is different, and this constitutes much to the spatial heterogenity (Fish and Wimick, 1969a).

In rat brain, approximately 10% of the DNA is present at birth (Chase et al, 1969; Winick, 1970a). A major share of DNA in rat brain is synthesized during the first 14 days and is completed by the time of weaning (Miller, 1969). This is in agreement with the findings that brain weight increases 4-fold by 20 postnatal days and then grows at a slower rate (Bass et al, 1970a).

Neuronal multiplication starts in the third trimester of pregnancy in human and is complete by birth, whereas glial multiplication starts after birth (Angevine and Sidman, 1961; Altman and Das,1966). Even the type of cell dividing differ in different areas. Thus in cerebrum only glia multiplies postnatally, while in cerebellum both neurons and glia multiplies till 10 days after birth in the rat (Alica et al, 1974). This may be further supported by the fact that the maturation of different regions differ from each other. Thus at birth 90% of cells of the whole brain are accounted by cerebrum, whereas in adult brain more than 50% of cells are derived from cerebellum. In cerebrum most of the cells are found before birth with the exception of microneurones.However,in cerebellum

with the exception of purkinje cells, most of the neurones are formed after birth. Thus development of cerebellum is delayed beyond cerebrum (Balazs, 1971).

The growth of developing brain occurs in two phases. The initial phase is characterised by neuronal multiplication which takes place between 20-25 weeks of gestation in man and in late pregnancy in rat (Dobbing and Sands, 1973; Gross and Warshaw, 1974). The second phase which is termed as "brain growth spurt", takes place in postnatal period in rat and lasts 24 days. The first-half of brain "growth spurt" is associated with glial cell multiplication and the second half, in rapid phase of myelination and striking growth in dendritic arborization and establishment of synaptic connections (Gross and Warshaw, 1974). As in humans, the adult number of neurons are present in rat by birth (Miller, 1970; Gambetti et al, 1972). However, the much important functional development, such as dendritic arborization and synaptic contacts are achieved postnatally (Gambetti et al, 1972).

The adult number of neurones are virtually achieved before growth spurt begins. This occurs at 42 days of gestation in guinea pig, two postnatal days in rat and 25 weeks of gestation in human; and cell division after birth being mostly glial, is in parallel with development of dendritic arborization (Dobbing, 1970) and establishment of syna ptic contacts (Miller, 1970). In this respect human brain resembles that of the rat, in functional development such as dendritic arborization and synaptic connectivity takes place after birth (Rapport and Ritz, 1972; Dobbing and Sands, 1973; Pallis, 1974; Nowak and Munro, 1977). Rat brain witnesses a dramatic developmental changes; structural and functional during the first three weeks of postnatal life. That is represented by morphological changes such as neuronal maturation, synaptogenesis and dendritic arborization, followed by appearance of EEG activity (Bass et al, 1969; Bass et al, 1970; Schiebel and Schiebel, 1971).

A major share of human brain growth takes place in the postnatal age, which is the most vulnerable period of human brain development, a period in which children in developing countries are much

exposed to malnutrition (Nutr. Rev., 1975). Since brain exhibits diversity in the developmental profile of different regions (Fish and Winick, 1969; Dobbing and Sands, 1973), the effect of undernutrition probably may differ in different regions depending on the events taking place in each region at the time of malnutrition (Siassi and Siassi, 1973). Thus in rat brain (Chase et al, 1969; Culley and Ghosh, 1973; Dobbing and Sands, 1973; Smart et al, 1973; Nutr. Rev., 1974) as well as in human brain (Nutr. Rev., 1973; Sarma and Rao, 1974) cerebellum is the region which is most affected by postnatal malnutrition.

Biochemical Development

Brain of most mammals at birth is functionally, structurally and biochemically immature (Bass et al, 1969). The structural and functional changes taking place during the development of the brain are associated with several changes in chemical composition and metabolism. A remarkable changes in the metabolic pattern of rat brain is observed during its crucial postnatal development coinciding with the structural and functional changes that take place at that time (Bass et al, 1970a; Miller, 1970; Winick, 1970a Cocks et al, 1971;

Johnson, 1972). During the period of maturation there is transition from low to a high metabolic rate, with concomitant increase in oxygen consumption, (Wilber and Patel, 1974) as well as an increase in ADP/O ratio, which indicates a highly efficient oxidative phosphorylation (Milstein et al, 1968). Oxygen consumption of cerebral tissue is quite low at birth and is only 50% of that consumed by adult brain (Cocks et al, 1971; Wilbur and Patel, 1974). The greater demand for oxygen by cerebral tissue with age is supported by the fact that number of mitochondria as well as rate of oxidative metabolism increases with age (Samson et al, 1960; Thurston and McDongal, 1969).

The important events in the process of biochemical maturation of the brain also takes place during the first three weeks of life in rat. Thus myelination (; Davison and Dobbing, 1968; Winick, 1970a Gross and Warshaw, 1974) as well as DNA synthesis which marks cellular multiplication take place during this time (Winick and Noble, 1965, 1966; Bass et al, 1970a. There is a switching over from an anaerobic to a predominantly aerobic metabolism

(Adlard and Dobbing, 197a; McIlwain and Bachelard, 1971; Wilbur and Patel, 1974). Simultaneously rat brain exhibits a decreased capacity to utilize non-carbohydrate for energy and develop dependency on glucose for energy purpose (Bachelard and McIlwain, 1970; Cocks and Balazs, 1970; Balazs and Patel, 1973). This is further supported by an increased activity of enzymes of carbohydrate metabolism during this period (Schwark et al, 1972a; Wilson, 1972; Holtzman and Moore, 1973). This high rate of energy utilization on maturation is closely related to neuronal activity, and neuronal activity per impulse may be greater in adult than in neonatal brain (Swaiman et al, 1963). This biochemical behavior in energy metabolism is closely linked with the rapid development of the brain (Patel and Balazs, 1970; Cocks et al, 1971; Johnson, 1972; Balazs and Patel, 1973).

Metabolism of brain is characterized by high rate of incorporation of glucose carbon into free amino acids (Gaitonde and Ritcher, 1966). The conversion of glucose carbon to amino acids in brain is considered to be an index of maturity of brain (Cocks et al, 1971). However, this pattern of glucose metabolism characteristic of mature rat brain is absent in the newborn

(Gaitonde and Ritcher, 1966; Miller, 1969). It develops sharply at the critical period of 10-15 days of age, during which cortex becomes functionally mature. However, upto 10 days of age only 10% of ^{14}C from U-^{14}C glucose is incorporated into amino acids (Patel, 1974a). There is a three fold increase in the incorporation of glucose carbon into amino acids between 10-19 days of age in rat brain, compared to immature brain (Patel and Balazs, 1970; Cocks et al, 1971; Gaitonde and Roisinkelly, 1972). The values characteristic of adult rate of conversion of about 40% is reached by 20-30 days of age (Patel, 1974a). The increased conversion of glucose carbon to amino acids with maturation is thought to be due to the development of the enzymes of glycolysis and oxidation of glucose during this period of brain development (Gaitonde and Ritcher, 1966).

In adult rat brain a major portion of the U-^{14}C glucose is converted mainly to glutamate, aspartate, glutamine and GABA (Gaitonde et al, 1965). This may be supprted by the finding, that a rapid rise in the concentration of

these amino acids, with maturation of the brain (Oja, 1968; Miller, 1969). These amino acids, especially glutamate and GABA are found to function as neurotransmitters in the brain. The biochemical maturation of energy metabolism in brain is associated with an increase in glutamate pool, (Patel and Balazs, 1970) and is found to be associated with the rapid development of neuronal processes during the time (Johnson, 1972; Cocks and Balazs, 1974). The increase in the concentration of these amino acids, with maturation of the brain is attributed to the functional development of the brain (Oja, 1968; Johnson, 1972). This is associated with the establishment of the GABA shunt, (Vanderberg et al, 1970) and the emergence of adult pattern of EEG (Caley and Maxwell, 1971). Lead poisoning is found to cause a significant retardation in the conversion of glucose carbon to amino acids in the brain of rat during suckling period (Patel et al, 1974).

The newborn rat brain is metabolically homogenous, and the heterogenity develops soon after birth. Manifestation of metabolic compartments appear with maturation of brain. The homogenous metabolic nature of immature brain changes as a result of

expansion of neuronal processes, whose metabolic pattern is qualitatively and quantitatively different from that of immature brain. Glial cells are less specialised and can utilise a wide range of substrates. The manifestation of metabolic compartment is related to maturational changes in glial-neuronal relation (Patel and Balazs, 1970).

Carbohydrate and other fuels of the brain (Metabolism of Brain) :

In contrast to most other tissues, adult brain is exclusively dependent on glucose as the substrate for its energy metabolism. Brain utilizes oxygen and glucose at very rapid rates, and is absolutely dependent on an uninterrupted oxidative metabolism, for the maintenance of its structural and functional integrity (Chandrasekharan et al, 1973; Kaur et al, 1983; Garris et al, 1984; Bryan et al, 1986).

Although brain weighs only 2% of the total body weight, it accounts for 20% of the basal metabolic rate. It also accounts for 15% of the cardiac output and 20% of the total body glucose utilization (Bachelard and McIlwain, 1970; Sokoloff, 1981a).

TABLE-2 : Rate of cerebral energy utilization with development in rat brain.

Age	Energy utilization ATP utilization nmole/kg brain/min
Fetus	1.57
1 day	1.33
7 day	2.58
Adult	26.58

Duffey et al. (1975)

No doubt, that brain possesses a tremendously high metabolic rate which is as high as 20 times the average body as a whole (Sokoloff, 1960; Balazs, 1970). Perhaps brain is the most vulnerable organ to systemic hypoglycemia (Bachelard, 1978). Though mature brain shows a selective dependance on glucose as the sole source of energy, it supplies only 50% of the energy need of immature brain (Peter et al,1973; Morris et al, 1974).

The rate of cerebral glucose utilization increases as the brain matures. Thus the adult brain utilizes 10 times more glucose than the immature brain (Growdown et al, 1971; Moore et al, 1971). The increased utilization of glucose by mature brain perhaps may be due to a remarkably high metabolic rate and high rate of phosphorylation (Thurston and McDongal, 1969; Devivo et al, 1973). It may be due to, an increased demand for energy associated with maturation as depicted in Table-2.

Cerebral glucose consumption varies markedly depending on the functional status. Thus a drastic reduction is reported in depressed activity associated

with anethesia, while the glucose consumption is increased many fold when the metabolic demand increases in conditions such as seizures (Seisjo, 1978).

Though glucose is the sole substrate for brain in adult age, immature brain can utilize substrate other than glucose (Cocks et al, 1971; Moore et al, 1973a). As a matter of fact, 40% of cerebral oxygen consumption is accounted for oxidation of substrates other than glucose in the newborn (Levitsky, 1973).

There exists a close coupling between energy production and functional events in the brain (Sokoloff, 1981). A diminition in the cerebral metabolic rate for glucose is reported in elderly human (Deshmukh, et al 1980) as well as in experimental animals (Sokoloff et al, 1977; Smith et al, 1980; London et al, 1981). The sensory, auditory and visual systems are particularly affected. These changes may be related to specific functional disturbances that develop in old age (Sokoloff, 1983).

The greater utilization of glucose and increased rate of synthesis and utilization of ATP by adult brain is due to its relatively high blood flow and

glucose flux as compared to the newborn. Newborn rat brain has a high "Kh" (Km for glucose phosphorylation) and possesses only 40% of the mitochondrial protein of that of adult (Moore et al, 1971). A lower glucose flux is also observed by Balazs et al. (1971) in immature brain. These factors may explain the relatively low glucose utilization by immature brain.

Transport of glucose is one of the key regulatory points in brain glycolysis (McIlwain and Bachelard, 1971a). Endothelial cells in the cerebral capillaries are responsible for blood brain barrier in the adults (Qwastel, 1972; Bachelard, 1978). Entry of glucose into the brain is a saturable carrier mediated mechanism, (Growdon et al, 1971; Moore et al, 1971), which shows stereospecificity (Cremer et al, 1979). Two distinct types of glucose transport have been demonstrated in cerebral tissues; a high Km (6 mm) and a low Km (0.25 mm) shown in synaptosomes. It is believed that the rate limiting stage in glucose transport may be the high Km uptake process by the glial cells (Bachelard, 1978).

However, the local rates of glucose consumption in brain, fall into two distinct distribution - one for grey matter and the other for white matter. In the

conscious rats, the consumption in grey matter vary widely, the highest values being in structures related to auditory function e.g., medial geniculate body, inferior collis and auditory cortex. The values in white matter are uniform (Sokoloff et al, 1977; Sokoloff, 1983).

Surprisingly, even under normal physiological conditions, brain possesses only 15-20% of the plasma glucose level (King et al, 1967). It is of interest that the rate of glucose influx into cerebral regions varies substantially from structure to structure, and is closely matched to the metabolic need of each region. Significant additional quantities of glucose can be delivered to various cerebral regions without the necessity of altering the circulating glucose concentration (Hawkins et al, 1983).

Glucose utilization by brain increased almost 3-fold between 10th and 20th postnatal days. Under hypercapnic conditions, glucose utilization is decreased by 50% in rat brain. Common conditions that produce hypercapnia that affect developing human brain are "Asphyxia neonatrum" and abuse of respiratory depressent

TABLE-3 : Rate of cerebral glucose utilization in different species.

	Glucose utilization (umoles/g/min)	
	In vitro	In vivo
Man	0.12	0.28
Monkey	0.15	0.29
Dog	0.39	0.34
Cat	0.40	0.39
Rat	0.50	0.96

Norberg and Seisjo (1974)

drugs, such as opiates and barbiturates by pregnant women (Miller and Corddry, 1981). LSD - a potent psychotomimetic drug, causes dose dependent reduction in the glucose utilization by rat brain. Acute morphine administration depresses glucose utilization in many areas of brain (Sokoloff, 1983).

The rate of cerebral glucose utilization shows species variation as in Table-3 (Growdin et al, 1971; Norberg and Seisjo, 1974). Thus cerebral glucose consumption of small laboratory animal, is remarkably higher than that of humans. The high rate of glucose and oxygen consumption by rat brain compared to that of human, may indicate a higher rate of oxidative metabolism in the former.

Brain is capable of utilizing mono sugars other than glucose (Ketty, 1957; McIlwain and Bachelard, 1971b). Nevertheless, glucose is the single most nutrient which support brain function in normal conditions. This is evident, as severe depression in blood sugar may manifest impaired mental and cerebral function

(Peter et al, 1973). It may cause permanent brain damage especially in the newborn period (Zuppinger et al, 1981). Incidentally , hypoglycemia is found to be the chief causative factor of death (Mukherjee, 1975) or survival with microcephaly and mental retardation in protein calorie malnutrition (Slone et al, 1961; Anderson et al, 1966). Besides a high proportion of patients with hypoglycemia show low IQ (Ingram et al, 1967; Bell et al, 1970). Kwashiorkor and marasmus are frequently accompanied by hypoglycemia (Alleyene et al, 1972; Mann et al, 1975) and is possible that this is the cause of death in severe cases (Oxman et al, 1968; Mukherjee, 1975). Hypoglycemia is a significant contributor to perinatal mortality and morbidity. Premature infants and those of low birth weight for gestational age, are particularly vulnerable to hypoglycemia. Human infants presumably tolerate blood glucose level as low as 1 mM (Hernandez et al, 1980). Hypoglycemia induced in experimental animals not only imprint a lasting effect on brain function, but affect many of the biochemical parameters (Anderson et al, 1967). It is evident by the diminished brain weight and cellularity, decreased protein content and reduced rate of synthesis of myelin lipids (Chase et al, 1973).

reduced in synaptosomes isolated from brain of pups whose mothers were fed a low protein diet during gestation and lactation (Kissane and Hawrylewicz,1973). Severe hypoglycemia is associated with coma and loss of spontaneous EEG activity, with gross derangement of cerebral energy state. During hypoglycemia cerebral oxygen consumption ($CMRO_2$) is not reduced to the same extent as cerebral metabolic rate for glucose, (CMRgl) indicating endogenous substrates are being consumed. Although the mechanism involved is not known, it is tempting to suggest that the derangement of cerebral energy state or oxidative breakdown of cellular membrane structure is responsible (Agardh et al, 1982).

Clinical, electrophysiological and morphological studies suggest that changes accompanying hypoglycemia are the route of regionally selective alterations of CNS function. Neuropathological changes in humans and animals dying from hypoglycemia, demonstrate that earliest damage strikes neurones of the cerebral, cortex, while that of the brain stem, being less vulnerable (Butterworth et al, 1982). Hypoglycemia does not have a uniform effect on brain glucose and energy metabolism and cerebellum

seems to be relatively protected. The functional and the neuropathological effects of hypoglycemia are not general, but regionally selective. Clinically this selective vulnerability is indicated by the fact that hypoglycemia dispenses higher integrative processes of brain before more fundamental functions are disrupted. Hypoglycemia in human and experimental animals produce damages in certain regions like cerebral cortex and basal ganglia while sparing others like brain stem, cerebellum and spinal cord. Regional metabolic difference exists, which apparently enables the cerebellum to continue oxidative metabolism and to preserve its high energy phosphate reserves. This may be because, it can extract glucose more efficiently than other regions even in severe hypoglycemic conditions (Ratcheson et al, 1981).

However, there is much dispute regarding the hypoglycemic effect on brain function. Thus Griffiths and Gillman (1971); Schulman et al. (1974) state that hypoglycemia neither impairs mental performance nor cerebral metabolic rate since brain is capable of utilizing substrates other than glucose, and thus preserve its vital function unimpaired. This is further supported by the finding that human brain utilizes

glutamate, lactate and pyruvate during insulin hypoglycemia (Rafelson, 1970) and animal brain too is capable of utilizing substrate other than glucose in such an emergency (Mann et al, 1973). Owing to its high energy reserves and low metabolic rate (Mayman et al, 1970) immature brain resists hypoglycemia and ischemia effectively.

Glutamate is found to be utilized by brain in seizure and in hypoglycemia as a source of energy(McKhan & Tower, 1959; Schulman et al, 1974). Human brain is found to take up glutamate, during insulin hypoglycemia (Rafelson, 1970). Thus glutamate may be considered as an alternate substrate for brain (Balazs and Hasl[illegible], 1[illegible]b) which may provide substrate for the smooth operation of TCA cycle in critical conditions (Johnson, 1972). Perhaps this may be the reason for the decrease in cerebral glutamate content in neonatal undernutrition when other energy reserves are unaltered (Hollowach and Prensky, 1971).

There is a close relationship between changes in local functional activity and glucose utilization (Sokoloff, 1983). Thus in visual system of the rat, the rate of glucose utilization is directly proportional

to the intensity of light and linearly related to the frequency of photoflashes (Sokoloff, 1981). This is more evident in the apparent difference in the rate of glucose utilization by grey and white matter of the brain. It is presumed that there is an increased demand for energy for performing intellectual work (Von Muralt, 1976). The functional activity of brain is related to the activity of (Na^+-K^+)-ATPase which is involved in the maintenance and restoration of neuronal membrane potential. It seems that even pure mental events alter regional energy metabolism in the human brain in specific pattern. Large parts of metabolic events in human brain are coupled to the maintaince and restoration of ionic gradients across neuronal membrane (Yarowsky and Ingawar, 1981).

Brain is potentially a major site of ketone body utilization in newborn animal and during infancy (Smith et al, 1969; Itoh and Quastel, 1970; Page et al 1971). This holds true in case of human infants also (Persson et al, 1972; Sokoloff, 1973). Ketone body utilization during infancy is due to ketosis of nutritional origin. Maternal milk is quite rich in fat (50% fat on dry weight basis in rat) which leads to ketotic state (Page et al, 1971; Gottestein, 1972).

Besides, the activity of enzymes of ketone body utilization are also high at this time (Page et al, 1971). In human also blood levels of ketone bodies are high during the first week of life (Wiener, 1971).

The ability to use ketone bodies varies in different species. Rats can derive 5-20% of the total brain energy requirement from ketone bodies. Human on the other hand may depend on ketone bodies for about 60% of the energy requirement after prolonged fasting (Hawkins and Mans, 1983). There is circumstantial evidence that ketone bodies can be almost the sole substrate for cerebral metabolism in the human (Cahill and Aolki, 1980).

Although ketone bodies can partially replace glucose as an alternate substrate in starvation and diabetes, it cannot completely replace glucose as a substrate (Sokoloff, et al, 1977b). Though, apparently hyperketonemia does not interfere with cerebral uptake and phosphorylation of glucose, it reduces the fraction of glucose that is fully oxidised (Corddry et al, 1982). Moreover the absolute contribution of ketone bodies as a fuel for brain is much less. There was no correlation between the energy requirement of various structures and

fraction of energy they could derive from ketone bodies (Hawkins et al, 1986).

Glycolysis

Apart from being the sole source of energy for the brain, glucose also serves as the precursor for the synthesis of a number of amino acids and a variety of transmitter substances like acetylcholine, glutamate, glycine and GABA. Owing to the operation of blood-brain barrier, cerebral tissue depends on glucose for the synthesis of macromolecules like nucleic acids, protein and lipids which are vital for cerebral growth and function (Glazer and Webber, 1971).

Warburg and his associates were the pioneers to demonstrate glycolytic activity of brain as back as 1924. This finding was later confirmed in vivo by Holmes and Holmes (1925). Under normal conditions cerebral tissue converts 13-15% glucose which it consumes to lactate, 2% to pyruvate and remaining 85% is oxidized through Kreb's cycle (Quastel, 1972; McIlwain and Bachelard, 1971b).

Studies by Geiger (1962) revealed that carbon 3 and 4 of glucose contributes 1/3rd of respired CO_2 by way of pyruvate, and 2/3rd come by means of TCA cycle (Carbons 1,2,5 and 6). However, radioactive studies indicate that $^{14}CO_2$ in the expired air from $^{14}C_6$ glucose is about thrice the yield from (1-^{14}C)-glucose, which conclusively show that carbon atom other than C-1 of glucose are rapidly oxidised in brain tissue (Guerra et al, 1967). Radioactive studies using specifically labelled glucose 1-^{14}C, 6-^{14}C and $^{14}C_6$ indicate that C-1 of glucose is mainly metabolised through Hexose monophosphate shunt in brain (Hostetler et al, 1970).

Though glycolysis is not the sole pathway of glucose metabolism in cerebral tissue, it is the major pathway of glucose utilization. Approximately 85% of glucose is utilized by this pathway (Balazs, 1970; Kaufmann, 1972; Wilson, 1972). Glycolysis is found to be more important in immature brain, where it plays a more critical role as source of energy in early stages of development (Quastel, 1972; Thurston and McDougal, 1969). On the contrary in liver of newborn animals, glycolytic activity falls due to decrease in activity of the key enzymes,

such as hexokinase, phosphofructokinase and pyruvate kinase (Kato and Lowry, 1973).

Although the metabolic pattern of glucose is similar in different areas of the brain (Chain et al, 1962); there is wide difference in the metabolic rate (CMRgl) in different areas of brain (Sokoloff et al, 1977a; Kao-Jen and Wilson, 1980; Hawkins et al, 1985; Bryan et al, 1986). However, cerebral gray matter posses greater glycolytic and respiratory activity than white matter. The high rate of metabolism in gray matter depends on metabolic turnover in synaptosomes and dendrites. Low rate of glycolysis in white matter probably may be due to relatively small content of neuronal cytoplasm (Nixon, 1970).

The availability of substrate or regulation of the catalytic activities of rate limiting enzymes or both, are probably the major factor which contribute to the regulation of glycolytic flux in brain. The reaction catalysed by hexokinase, phosphofructokinase, glyceraldehyde-3-phosphate dehydrogenase and pyruvate kinase as well as glucose entry appears to be far from equilibrium (Scrutton and Utter, 1968; McIlwain and Bachelard, 1971b). Phosphorylation of glucose itsle may constitute a regulatory factor which take place at a much slower pace (3-5%)

at which hexokinase is capable of catalysing (McIlwain and Bachelard, 1971a; Turek et al, 1986).

Hexokinase catalyses the initial step in the metabolism of glucose and represents a major regulatory role in cerebral energy metabolism (Mooler and Wilson, 1983; Synder and Wilson, 1983). It is well established that the rate of glucose consumption varies markedly depending on functional status, with depressed activity resulting from anesthesia being accompanied by an approximately 50% reduction in glucose consumption, whereas at the other extreme generalised seizures may increase utilization by 6-7 fold (Siesjo, 1978).

A close correlation between glucose influx and rate of glucose utilization has been observed. This would imply a link between the kinetics of glucose transport across capillary endothelial cells and the kinetics of hexokinase activity with the brain cells (Cremer et al, 1981).

The increase in particulate bound hexokinase takes place in cerebrum earlier to cerebellum which is an indication of the earlier maturation of cerebrum. However, the postnatal increase in latent hexokinase in cerebellum reflects synaptogenesis during this period which initiates

at 12-14 days in rat brain (Kellog, et al 1974). There is striking heterogenity in rates of energy metabolism for brain regions (Hawkins et al, 1985). As a corollary the levels of hexokinase in various regions of the brain are found to be correlated with the rate of energy metabolism i.e. more metabolically active regions having greater need for hexokinase activity (Kaojen and Wilson, 1980; Simurda and Wilson, 1980).

The lack of coordination of hexokinase activity with that of the other glycolytic enzymes may reflect the multiple role of hexokinase as the common initiating reaction for glycolysis, hexosemonophosphate shunt and glycogen formation (Wilson, 1972).

The level of glucose-6-phosphate is of critical importance since it is at the cross-road to various metabolic pathways. Glucose-6-phosphate is utilized by three different enzymes, viz., glucose-1-phosphate mutase; G6Pdehydrogenase and G6Pisomerase belonging to three different pathways. Hence the flux of glucose through each pathway is decided by the activity of the respective enzyme. Thus the activity of G6P dehydrogenase is more in neonatal brain than in adult brain and consequently hexosemonophosphate shunt is more active in neonatal brain

than in adult brain. But as the brain matures the activity of G6P isomerase increases and more and more glucose will be metabolized through glycolytic pathway (McIlwain and Bachelard, 1971). Thus in adult brain conversion of glucose-6-phosphate to fructose--6-phosphate is 10-24 times higher than the first stage of hexosemonophosphate shunt and 2 to 5 fold greater than the maximal conversion to glucose-1-phosphate (Bradford, 1968; Bradford, 1969).

Although hexosemonophosphate shunt constitutes only 5-8% of the total metabolic flux of glucose in adult brain, it is quite essential for the normal functioning of the brain (Hostetlet et al, 1970; Baquer et al, 1977). Radioactive studies using glucose specifically labelled at 1-^{14}C, 6-^{14}C and $^{14}C_6$ indicate that C-1 of glucose is mainly metabolised through hexosemonophosphate shunt (Hosletler et al, 1970).

Hexosemonophosphate shunt plays a key role in providing pentose sugars which are essential pre-requisite for the synthesis of nucleotides. NADPH generated by this pathway is essential for numerous metabolic reactions, such as synthesis of lipids, maintenance of sulphydryl groups (-SH groups) and hydroxylation reactions

([redacted]; Appel and Parrot, 1970; Baquer et al 1973). The production of hydrogen peroxide by monoamine oxidase contributes a considerable threat to the functional integrity of the cell by oxidising the essential sulphydryl group of the cellular membranes and of glutathione. Pentosephosphate pathway may function as an ultimate donor of hydrogen either for regeneration of membrane bound or other sulfhydryl groups, or in "mopping up" of free radicals to prevent lipid peroxidation (Baquer et al, 1977). Armstrong et al.(1974) have showed that products of peroxidative damage to lipids and proteins accumulate in brain with age and at an accelerated rate in some diseases and this accumulation was associated with massive neuronal death.

One of the salient feature of hexosemonophosphate shunt is its remarkable activity in synaptosomes (Appel and Parrot, 1970), Synaptosomes isolated from rat cerebral cortex converted (1-^{14}C) glucose into $^{14}CO_2$ more rapidly than (6-^{14}C) glucose which clearly indicates the predominance of this pathway in synaptosomes (Appel and Parrot, 1970; Kaufmann, 1972). It is believed that in synaptic endings hexosemonophosphate shunt may be responsible for the protection of membrane sulfhydryl groups and overall integrity and reactivity of synaptic plasma membrane.

Since synaptic endings are involved in storage and release of transmitter substances, an active hexosemonophosphate shunt is likely to have a direct or indirect effect on metabolism of transmitter substances (Appel and Parrot, 1970). One of the most potential limiting factor for the operation of hexosemonophosphate shunt in adult brain is the availability of the coenzyme NADP (Guerra et al, 1967; Quastel, 1972; McIlwain and Bachelard, 1971b) as well as the ratio of NADP/NADPH (Vallejo and Sebastian, 1971).

Phosphofructokinase is found to be one of the key regulatory enzymes of brain glycolysis (Uyeda and Luby, 1972; Schwark et al, 1972a; Dwyer and Wasterlain, 1985). Brain phosphofructokinase activity expressed in terms of tissue weight is relatively constant from 5 days before birth to 8 days postnatal. A 110% increase in activity occurs between 12 and 21 days of age when adult level reaches. This rapid rise in phosphofructokinase activity takes place immediately after the maximum rate of DNA deposition in rat brain. Since neuronal multiplication is virtually complete by birth, the increased activity after 12 days of age may be within glial cells. However, the response of the enzyme to ATP and citrate do not

change markedly during brain development. Hence the control of glycolytic rate via phosphofructokinase is exercised in the same way throughout development in spite of postnatal changes from anaerobic to aerobic metabolism. Thus the maturation of phosphofructokinase takes place at the time of maximum brain growth - a period when brain may be most vulnerable to nutritional deprivation (Adlard and Dobbing, 1971a.).

A depression of cerebral phosphofructokinase activity is observed in alloxan diabetes which is primarily due to an extraordinarily high level of phosphocreatine in the diabetic condition. Phosphocreatine is a potent inhibitor of phosphofructokinase (Thurston et al, 1975). This may probably be supported by the finding that cerebral glucose utilization is decreased in diabetic ketoacidosis owing to inhibition of phosphofructokinase.(Rurderman et al, 1974). Glycolytic flux is primarily controlled at the level of phosphofructokinase in tissues where glycolysis is the major route of metabolism. The increased flux observed in anaerobic to aerobic transition probably results from decreased level of ATP and increased levels of ADP and AMP which cause activation of phosphofructokinase (Scrutton & Utter, 1968).

The total activity of glycolytic pathway is apparently quite high in brain than in liver. This is probably due to the activities of the key enzymes of glycolysis. The activity of hexokinase, phosphofructokinase and pyruvate kinase are much higher in brain than in liver. The activity of hexokinase is 20 times higher in brain than in liver (Krebs and Woodward, 1965).

Ratio of aldolase/DNA is found to increase as brain matures in rat. This is indicative of an increase in activity per brain during maturation due to cumulative effect of both increased activity per cell and an increase in number of cells (Swaiman et al, 1970). A major share of aldolase activity in cerebral tissue is associated with particulate fraction (Clarke and Masters, 1973). Aldolase is found to be the enzyme of lowest maximal catalytic capacity in glycolytic sequence of nervous tissue (Clarke and Masters, 1973). Lowest catalytic activity is one of the characteristic feature of all rate limiting enzyme (Stifel et al, 1972). Hence, aldolase may function as a rate limiting enzyme in cerebral glycolysis.

Pyruvate kinase is one of the key regulatory enzymes of cerebral glycolysis (Balazs, 1970; McIlwain and Bachelard, 1971b).

Apart from its role in glycolysis, the enzyme may affect ionic transport. Pyruvate kinase is also involved in lipid synthesis and in metabolism of nucleic acids. However, at equilibrium the reaction strongly shifts in the direction of ATP and pyruvate formation. But the reaction in brain is not in equilibrium in terms of observed tissue levels of substrate. Hence it is postulated that phosphoenolpyruvate, the compound with highest known "free energy" may be available for several energy requiring processes (Tamir et al, 1972).

Similar to other enzymes in the glycolytic pathway in brain, pyruvate kinase also increases with maturation (Schwark et al, 1972a). Fetal human brain pyruvate kinase activity is less than 10% of the adult value. Fetal brain pyruvate kinase and hexokinase are more vulnerable to inhibition in phenyl-ketonemia. This may have a role in brain damage observed in phenylketotic patients. Decrease in pyruvate kinase activity leads to decline in ATP generation and other nucleotide triphosphates (Webber, 1969). Decreased pyruvate kinase activity in cerebral tissue results in decreased rate of glycolysis, leading to reduced rate of energy production, curtail synthesis of lipids, which are required for the development of brain (Tamir et al, 1972).

Lactate dehydrogenase is also found to increase in activity in rat brain (Swaiman et al, 1970) and in mouse cerebral cortex (Leverde and Lehrer, 1973) and almost doubles in activity as the brain matures (Khulman, 1960). In rat brain during development lactate dehydrogenase activity is found to be related to the differentiation of glia and deposition of myelin in addition to general glycolytic metabolism. However, in adult brain this special function is found to be disappeared (Robinson and Phillips, 1964).

Adlard and Dobbing (1971) showed that the distribution of isozymes of lactate dehydrogenase changes in parallel with the metabolic changes of differentiation. This is supported by the fact that in adulthood the ratio of two isozymes of LDH changes in all tissues. The ratio of HLDH/MLDH increases in adulthood. This is due to the lowering activity of MLDH. Lower levels of M-LDH in old age may make the tissue more oxygen dependent (Singh and Kanungo, 1968). Tolerance to anoxia by newborn rat brain probably may be due to the absence of H-LDH which is inhibited by excess pyruvate. During postnatal maturation this enzyme is found to be increased when neurogenesis depends on aerobic glycolysis (Bonavita, 1964).

TRICARBOXYLIC ACID CYCLE :

Metabolism of pyruvate in brain takes place by two ways. It undergoes oxidative decarboxylation to form acetyl CoA. The other pathway being its entry into tricarboxylic acid cycle by CO_2 fixation to form oxaloacetate (Flock et al, 1966; Wilbur and Patel, 1974).

Although a larger share of pyruvate is metabolised to acetyl CoA by means of pyruvate dehydrogenase (Quastel, 1969; Patel and Grover, 1973; Wilbur and Patel, 1974), about 10% of the total flux of pyruvate in brain is accounted by CO_2 fixation by pyruvate carboxylase (Cheng et al, 1971; Balazs et al, 1973; Patel and Grover, 1973; Wilbur and Patel, 1974). Thus among the various acetyl donors for the synthesis of acetyl CoA in brain, pyruvate is the most important (Heinrich et al, 1973). It is observed that 2.5 moles of oxygen are taken up for each mole of pyruvate oxidised in brain in vivo under normal conditions. In adult rat brain pyruvate accounts for nearly all the oxygen uptake (Reynolds and Blass, 1976).

The rate of oxidation of pyruvate to CO_2 in rat brain via pyruvate dehydrogenase increases with maturation. The ability of newborn to oxidise (1-^{14}C) pyruvate to

$^{14}CO_2$ is low, and increases four fold during 10-25 days of postnatal life (Wilbur and Patel, 1974). Approximately 70% of the glucose phosphorylated yields CO_2 by way of pyruvate dehydrogenase, pointing to the fact that a constant fraction of about 30% of all the glucose utilized at every stage of development is retained in the form of nonoxidised product such as lactate (Hothersall et al, 1979).

The conversion of pyruvate to acetyl CoA by means of pyruvate dehydrogenase is a rate limiting step in the operation of TCA cycle in brain (Quastel, 1972). Pyruvate dehydrogenase is not uniformly distributed in mammalian brain (Reynolds and Blass, 1976). The localization of pyruvate dehydrogenase in brain mitochondria (Quastel, 1972; Wilbur and Patel, 1974) may be important from the point of view of supplying acetyl CoA for the smooth operation of TCA cycle.

The existence of pyruvate dehydrogenase in two forms, an active dephosphorylated and an inactive phosphorylated form, may be another regulatory factor of cerebral oxidative metabolism (Quastel, 1972; Nicklas et al, 1971; Wilbur and Patel, 1974). The overall activity of the enzyme depends on the relative activities of the

inactivating ATP dependent kinase and the activating phosphatase (Nicklas et al 1971; Jope and Blass, 1975). Besides the ratios of cellular acetyl CoA/CoA and NAD/NADH in brain are also important regulatory factors of pyruvate dehydrogenase activity (Nicklas et al 1971).

Pyruvate dehydrogenase starts to increase at about 15 days of age. The ability of rat brain mitochondria to oxidise pyruvate follows a similar developmental pattern to that of pyruvate dehydrogenase. It is noteworthy that until 15 days after birth almost 100% of the total pyruvate dehydrogenase present is in the active form. After this period, as the total pyruvate dehydrogenase activity increases, the active form declines to about 70% of the total which is the value found in mature brain. The reason for the limited utilization of glucose during suckling period perhaps may be due to the late development of pyruvate dehydrogenase (Land et al, 1977). Regulation of pyruvate dehydrogenase is of special interest. There is relatively little excess of pyruvate dehydrogenase activity available compared with pyruvate flux in the brain.

The properties of pyruvate dehydrogenase isolated from brain, heart, kidney and liver are very similar and all undergo phosphorylation and dephosphorylation.

The regulation of pyruvate dehydrogenase activity in brain differs from that in other tissues, in that, pyruvate dehydrogenase activity did not change during starvation with presumed ketosis (90 hr starvation). However, several agents which have been reported to reduce carbohydrate utilization by brain did not alter the proportion of pyruvate dehydrogenase in the active form. Small variations in the flux of pyruvate may occur without changes in the phosphorylation state of enzyme, while metabolic alterations, severe enough to alter the energy state of the brain did alter the proportion of pyruvate dehydrogenase in the active form (Jope and Blass, 1976).

Pyruvate dehydrogenase catalyses the flux generating steps of the Kreb's cycle. The total activity of pyruvate dehydrogenase in brain is considerably lower than that of any other glycolytic enzyme (Hawkins and Mans, 1983). The enzyme plays a pivotal role in brain metabolism. It is regulated by a variety of allostoric factors. It is conceivable that modulation of pyruvate dehydrogenase activity could influence synaptic physiologgy via fluctuations in the synthesis of

acetyl CoA; the precursor for acetyl choline. However, it should be noted that under normal conditions, brain metabolism is almost totally dependent on glucose and pyruvate dehydrogenase activity in brain appears to be only marginally sufficient to maintain normal pyruvate flux through oxidative pathway (Browning et al, 1981; Reding et al, 1982).

The direct inhibition of pyruvate dehydrogenase complex by keto acids is the important cause of brain damage in phenylketonuria and Maple syrup urine disease (Blass and Lewis, 1973). In patients with partial deficiency of pyruvate dehydrogenase, cerebral ataxia has been most prominent (Reynolds and Blass, 1976).

Walsch and his associates (1964) were the first to demonstrate CO_2 fixation in brain. Mitochondrial pyruvate carboxylation by pyruvate carboxylase is the major site for CO_2 fixation in brain (Patel, 1973; 1974a. Although only 10% of the total pyruvate flux is accounted by this pathway, it plays a key role in transporting acetyl equivalents in the form of citrate across inner mitochondrial membrane for the biosynthetic process in cytosol (Patel and Tilghman, 1973) as well as synthesis of dicarboxylic acids such as glutamate and aspartate for providing C-4 acids for synthetic purposes (Tilghman and Patel, 1972; Wilbur and Patel, 1974).

AcetylCoA is found to be in a crucial turning point in brain metabolism. It is the substrate for enzymes of three different pathways. Citrate synthase for maintaining TCA cycle, choline acetylase for synthesis of acetylcholine and for free fatty acid synthesis (McIlwain, 1971). Though the flux of pyruvate to acetylcholine is less than 1% of that to CO_2 in brain, pyruvate utilization can limit acetylcholine synthesis in brain (Gibson and Blass, 1976; Ksiezak and Gibson, 1981).

The activity of citrate synthase and aconitase are very low at birth. The activity of citrate synthase develop significantly in the 3rd postnatal week and reaches adult value. Acetivity of aconitase rapidly develops during 10-25 days reaching adult value (Wilbur and Patel, 1974).

In cytosol citrate is metabolized by aconitase to isocitrate which is decarboxylated to α-ketoglutarate by NADP isocitrate dehydrogenase. Isocitrate occupies a central position in intermediary metabolism and is the substrate for a variety of synthetic and energy yielding pathways. Thus probably NADP-isocitrate dehydrogenase may serve as an important link between TCA cycle intermediates and amino acid metabolism in cytosol which is particularly active in immature brain (Leverde and Lehrer, 1973).

NADP isocitrate dehydrogenase is mainly localised in the cytoplasm. However, less than 10% of the activity is observed in mitochondrial fraction also. The localization of NADP-isocitrate dehydrogenase suggests that this enzyme is associated with a pathway which directs TCA cycle intermediates into amino acids in cytosol. This may be possible since in developing mice cerebellum peak isocitrate dehydrogenase activity reaches at birth or earlier, a time when turnover of protein is maximal in brain (Loverde and Leher, 1973). The intracellular localization of mitochondrial NADP-isocitrate dehydrogenase is more like that of glutamate dehydrogenase than that of NAD-isocitrate dehydrogenase. The NADP-isocitrate dehydrogenase have a specific function in TCA cycle involved in the synthesis of small glutamate pool. Hence the high activity of NADP-isocitrate dehydrogenase in growing brain may indicate a large flow of metabolites through this pathway in the direction of α-ketoglutarate in growing brain as compared to adult brain.

Among the NADPH generating system in brain i.e. G6P dehydrogenase, 6PG dehydrogenase and NADP-isocitrate dehydrogenase, only cytosolic NADP-isocitrate dehydrogenase showed a positive correlation with acetyl CoA carboxylase and fatty acid synthase during development (Baquer et al, 1973). Interestingly, both NADP-isocitrate

dehydrogenase and NADP-malate dehydrogenase (malic enzyme) are localized in both cytosol and mitochondria and both these enzymes are involved in CO_2 fixation in brain. However, under physiological conditions both these enzymes do not contribute much to CO_2 fixation (Patel, 1974a). Under physiological condition equilibria of both NADP-isocitrate dehydrogenase and NADP malate dehydrogenase favour decarboxylation (Patel, 1973; Renefrankel, 1973).

The developmental profile of NADP-isocitrate dehydrogenase is distinctly different from other enzymes of TCA cycle in brain. It starts increasing at the time of birth and continues till 14th day of age and then decreases rapidly till weaning when it reaches the adult value (Robins and Lowe, 1961).

Since NADP-isocitrate dehydrogenase is markedly more active per unit weight of fresh tissue than G6P dehydrogenase, it may represent a major source of NADPH in both myelinated and unmyelinated areas of CNS in human (Chabas et al, 1979).

However, unlike NADP-isocitrate dehydrogenase, NAD-isocitrate dehydrogenase is mainly localized in mitochondria of brain (Vignais and Vignais, 1961; Murthy

and Rapport, 1963; Leverde and Lehrer, 1973). In adult brain NAD-isocitrate dehydrogenase predominates over NADP-isocitrate dehydrogenase (Leverde and Lehrer, 1973). During maturation of rat brain, a six fold increase in NAD-isocitrate dehydrogenase activity per unit weight of protein is observed (Swaiman et al, 1970).

Similar to other enzymes of TCA cycle in brain, succinate dehydrogenase also showed an increase with maturation of the brain (Adlard and Dobbing, 1970; Swaiman et al, 1970). The developmental increase in succinate dehydrogenase is found to be at a critical period in guineapig brain. The sharp increase in succinate dehydrogenase activity in guineapig cerebral cortex coincides with marked structural changes in the neurone, including the dendritic arborization and establishment of electrical activity of brain (Ritcher, 1967).

Metabolism of brain is characterized by high rate of incorporation of glucose carbon into free amino acids. Brain differs in this respect from other organs. More than 70% of glucose carbon is converted to amino acids in brain while in liver it accounts only 8-11% of the total glucose utilized (Gaitonde and Ritcher, 1966). Besides in brain glutamate is the chief amino acid derived from

glucose while in liver alanine is the amino acid which is principally derived from glucose (Gaitonde, 1965; Flock, et al, 1966). The normal increase in cerebral glutamate in rats during the first week of life is associated with growth of anatomical structures which are rich in glutamate (Thurston et al, 1971). This may be further supported by the fact that there is an enlargement of glutamate pool of brain parallel to the increased utilization of glucose as brain matures (Roach et al, 1974). The high glutamate content in brain in the early period of brain growth may be justified as glutamate is as effective as glucose in increasing oxygen uptake by brain slices of rats below 10 days of age (Swaiman and Cohen, 1964). Glutamate is found to be utilized by brain in seizures and in hypoglycemic conditions as source of energy (McKhann and Tower, 1959; Schulman et al, 1974). Human brain too, takes up glutamate during insulin hypoglycemia (Rafelson, 1970). Thus glutamate may be considered as an alternate substrate for brain (Balazs and Haslam, 1965), which may provide substrate for the smooth operation of TCA cycle in such emergency conditions (Johnson, 1972).

Vulnerability of Developing Brain

Animal studies

(a) Protein Calorie restriction :-

Brain has a favoured and dominating position among all other organs of the body. It is well protected by the full enclosure of the solid skull and is safeguarded by very refined mechanism of regulation of blood circulation and its oxygen supply. It is also protected by a nutritional device known as "brain sparing" against starvation (Von Muralt, 1976), Brain is apparently endowed with a much larger supply of neurones than needed as loss of neuronal cell is irrepairable. It is significant even glial cells do not increase in number in the adult animal although they are replaceable. This may be related to the need to maintain stable glial neuronal inter-relationships.

The chemical stability of the nervous system is further guarded by the operation of the blood brain barrier. Though brain is a highly vascularised tissue, the entry of substances from the blood to brain is restricted by the operation of this barrier (Ehrlich, 1895). The composition of extracellular fluid surrounding neuronal

cell is further safeguarded by the cerebrospinal fluid which diffuses with it as well as glial cells. The composition of cerebrospinal fluid is itself carefully regulated by the choroid plexus which not only abstracts substances from the blood but also secretes unwanted substances into the same. Thus CSF is not just an ultrafiltrate but its composition is maintained in the face of marked changes in the blood. For instance, the potassium concentration of CSF shows practically no change either with hypokalemia or hyperkalemia (Rajalakshmi, 1981).

The maturation of brain is also associated with the increased efficiency of the mechanism which enable the maintenance of the structural and functional integrity of the brain. These include the development of the blood brain barrier (Purdy and Bondy, 1976) and metabolic compartmentation (Berl, 1965; Patel and Balazs, 1970; Vanden Berg *et al* 1970).

It may be obvious that the rapid maturation of the brain in early life and its high metabolic activity throughout life demands an adequate supply of nutrients. Though due recognition was given first to the role of heredity and then to psychological environment in the

development of learning and intellegence, the role of nutrition in the development of brain was not given its due share.

The environmental stimulation is sensed by nervous system only in terms of modulation of complex pattern of physiochemical processes. The efficiency of transmission of impulses depends on among other things on factors such as myelination, dendritic arborisation and synaptic connections which are largely completed in early life. But even after the apparent completion of structural development, glial and neuronal cell division, the brain has a high rate of metabolism as evidenced by high rate of oxygen consumption (Gaitonde and Ritcher, 1956; Ketty, 1957).

Adult nervous system is known to be very resistant to undernutrition (Karlson and Srewnerholm, 1978). It is well established that severe undernourishment of adult animals, leads to reduction in body weight. Although most body organs are equally affected by this deprivation, the conservation of brain tissue mass even during starvation is striking. Consequently all other body organs evidence marked weight loss before there is significant decline in brain weight (Dyson and Jones, 1976).

As a matter of fact, in earlier periods brain was thought to be a static organ, which may resist any sort of nutritional deficiencies once it is matured. This was because earlier studies on starvation and protein deprivation in adult animals showed no change in the composition of the brain in either condition (, ; , Mandel et al, 1950; Lehr and Gayet, 1963). The age of the animal as well as the short term nature of the studies lead to erroneous conclusion about susceptibility of the brain to undernutrition and protein deficiency. This view has now been modified as a result of information accumulated following extensive studies on laboratory animals. Animal experiments have shown that malnutrition imposed during critical phase of growth of CNS can adversely affect its growth and development (ICMR Bulletin, 1975).

Although brain enjoys a high degree of ontogenic and metabolic priority when supply reach the bottom of the barrel, it has to share the deficits with other organs. It is hardly likely that the development of nervous system in early life and its subsequent functioning will be unaffected by a dearth of nutrients.

Different species are born at different stages of maturity. This can be expressed as different timings of brain growth spurt in relation to birth. Thus rat is characterized as postnatal (Dobbing and Sands, 1970); guineapig as perinatal (Dobbing and Sands, 1973), brain developer. However, studies by Dobbing and Sands (1973) revealed that 80% of human brain growth spurt is postnatal and in this respect resembles rat much more closely. Thus if nerve nets and associated synaptic connections in the cerebral cortex are regarded as the main anatomical requirement for higher functions of the brain, it is clear that the anatomical substrate for higher function has not yet developed in the human infant at the time of birth (Ritcher, 1964). The crucial events in the development of brain such as dendritic arborization and synaptic connections are prominently postnatal in both human and rat brain and hence are equally susceptible to the hazards of immediate postnatal malnutrition (Balazs, 1972; Rapport and Fritz, 1972; Dobbing and Sands, 1973; Pallis [illegible], 1974; Nowak and Munro, 1977). However, objections has been raised from various quarters against rat as an experimental model and extrapolating the results to human conditions. This has been due to difference in the developmental profile of rat brain from that of human (Dyson and

Jones, 1976a as well as that of increased demand of protein for the growing rat in comparison to that of child (Waterlow and Payne, 1975; Cheek et al, 1976). However, research in animals has provided certain insights into disturbances in growth, strucutre, composition and metabolism of nervous tissue that could not have been acquired in any other way (Dodge et al, 1975). Most of the information in literature regarding malnutrition relates to the rat. The sequence of brain development in other species including man follows similar pattern, but with an altered schedule that is especially relevant to the impact of malnutrition (Nowak and Munro, 1977).

Preweaning undernutrition :

The time of maximum velocity of brain growth in rat is distinctly postnatal (Novak and Munro, 1977). Undernutrition in early life produces neurological (Morand et al, 1982; Hawrylewicz et al, 1983) as well as behavioral alterations (Chamove, 1980) in rats.
The preweaning period witnesses structural and morphological changes such as neuronal maturation, synaptogenesis followed by appearance of EEG activity (Bass et al, 1970b; Scheibel and Scheibel, 1971). Thus the newborn and immediate postnatal period of life in mammals are characterized by high anabolic tendency never equal in

life and is most vulnerable period of development (Miller, 1970; Czajkamarian et al, 1973). Surprisingly at this time of birth the mammal is suddenly transformed from an environment in which relatively little regulation and adaptation are required to one in which these functions are the essence of survival (Winick, 1970a).

Although the ill effects of malnutrition during preweaning period is due to calorie restriction, evidence show that both protein and calorie are the most limiting nutrients in such studies. Weight gain of rat changes almost directly with protein intake. The requirement of protein for neonatal rat is equivalent approximately 5 mg N/day/g body weight or approximately 30g protein/day/kg body weight i.e. a value 15 times that of adult (Miller, 1970). This is true in case of humans too. It is suggested that 1.27g protein/kg body weight is sufficient for a one year old child. While adult requires only 0.57g protein/kg body weight, i.e. about half of that of one year old child. This is because adult has a lower requirement of maintenance, due to decrease in the rate of most of the metabolic reactions, e.g. basal oxygen uptake, rate of total protein turnover, and rate of albumin synthesis (Waterlow and Payne, 1975).

Similarly the energy requirement of brain also is three times greater in infant than in adult. The infant brain a major consumer of glucose, is also relatively larger (Kerr and Stevens et al, 1978). The neonate is considerably more vulnerable to malnutrition. For many tissues the time of cell division constitutes "vulnerable period" during which nutritional deficiency leads to permanently reduced cell number and thus organ size. Thus, in rat, prenatal malnutrition affects the neuron population whereas early postnatal malnutrition affects glial cells (Novak and Munro, 1977). The impact of malnutrition on cell population is most severe in the cerebellum which is consistent with the particularly rapid growth of the region during suckling period (Chase et al, 1969). In contrast to cerebrum, neurogenesis occurs postnatally in cerebellum. Dobbing et al. (1971) have reported marked deficit in neurones in cerebellum during postnatal undernutrition.

Preweaning undernutrition may cause structural, neuro-chemical, developmental and behavioral alterations in animals (Balazs et al, 1979; Villecas et al, 1981; Vendite et al, 1985). Preweaning undernutrition has been associated with a reduction in brain weight (Swaiman et al, 1971; Sobotka et al, 1974; Dyson and Jones,

1976b. However, the reduction in brain weight (10-15%) was much less in comparison to that of body weight (50-70%) (Dobbing, 1968b).

The reduction in brain weight is associated with reduction in cell number (Sugita, 1918) as well as DNA content (Winick and Noble, 1966; Dobbing, 1968a & b; Swaiman et al, 1971; Enowunu and Glover, 1973). In brain, myelin which make up almost half of the dry weight of brain is produced by oligodendroglia. Presumably glial cell multiplication is retarded in undernutrition as substantial deficit is observed in myelin in early undernutrition. It is possible that myelinated axons decrease their speed of conductance when myelin is deficient. This could account for functional deficit.

Another possible role of glial cell in brain involves cellular nutrition. The histological arrangement of neurons and glia in mammalian nervous system also suggested such functions for glial cells. In mammals, neurons are rarely in direct contact with blood capillaries but rather separated from blood vessels by glial cells. This interposed arrangement between neurones and their blood supply has frequently suggested a nutritive or regulatory function for glia (Shoemaker and Bloom,1977).

Although counts provide information about the general state of tissue development, the functional significance of altered cell number remain obscure. The total number of neurones in the brain is believed to be far excess of that necessary for normal function. In man even in the presence of quite significant amount of cortical tissue destruction, it may be difficult to detect changes in behavior (Dyson and Jones, 1976a).

Undernutrition in the preweaning period not only reduces the cell number in different regions but also changes the morphological feature of the cell (Sugita, 1918). Decrease in proportion of neuropil to neurone, as well as the number of axons associated with a neuron (Bass et al, 1970a Cragg, 1972b Clark et al, 1973) and density of pre- and postsynaptic ending have been observed in cerebral and cerebellar cortex (Harnes and Altman, 1973; Pysh and Perkins, 1975). Distortion of both axons and dendrites with cerebellar region has been observed (Griffin and Woodword, 1976).

Autoradiographic studies suggest a late maturation of external granular layer and reduced mitotic rate in cerebral cortex (Lewis et al, 1975). The short axonal neurones of the sixth layer of cerebral cortex which are

believed to be involved in the establishment of both intralaminar and interlaminar connections and in conveying information related to learning are found to be reduced by undernutrition (Escobar, 1974). Dyson and Jones (1976b) have reported a deficit in synapse per unit area in the cortex of the undernourished rats. Neonatal undernutrition effects predominantly the axon extension and dendritic arborization (Santos and Tasso, 1980).

Investigations over recent years have increased our understanding of synaptic organisation at an ultra-structural level. As synapse is the critical point of contact between connecting nerve cells, these investigations on adult developing tissues are of crucial importance. Maximal neuronal proliferation in rat cerebral cortex takes place between birth and twenty five days of age. This involves axonal and dendritic growth as well as formation of synapses. The increased neuronal packaging observed in malnourished animals suggest this has not taken place. There is both a decrease in synaptic numbers and fewer synapses per neuron in postnatal undernutrition (Cragg, 1972b, Hogan et al, 1973). A large number of macromolecular changes have been found to be associated with learning and experience. It is the synapse which plays an integral part in brain function (Dyson and

Jones, 1976a). Various studies strongly indicate a delay in synaptic development in undernourished rats. This may perhaps be true in case of delayed maturation of mental development observed in low birth weight children (Williams and Davies, 1974).

Though proliferation of neurons are spared in postnatal malnutrition, a reduction in neuronal density (Dobbing et al, 1971), decrease in dendritic processes (Salas et al, 1974) and synapses per neuron (Cragg, 1972b; Shoemaker, 1972; Gambetti et al, 1972a; Hogman et al, 1973) have been reported.

Electron microscopic studies carried out by Jones and Dyson (1976b) indicate that the thickness of pre and postsynaptic dendrites were affected in the twenty day old undernourished rat. The deficits may be quite large as evidenced by a 30% deficit in the maximum presynaptic thickness. Further analysis of this presynaptic index demonstrates that the highest of the dense projections are significantly affected, being 24% less in undernourished junctions.

Dense projections are thought to be intimately related to the synaptic vesicles of the presynaptic terminal ([illegible]; Gray and Willis, 1970; Jones and Bradford, 1971).

If this is the case, the projections are probably involved in the accumulation and release of neurotransmitters at the presynaptic membrane. A delay in their proper formation during brain development would be anticipated to delay the onset of neurological functions. This may not be unreasonable in view of the delay in appearance of reflexes (Simson et al, 1969; Smart and Dobbing, 1971a,b) reported in undernourished conditions.

The adverse effects of nutritional stress during suckling period on the maturation of neurones (Cragg, 1972b; Gambetti et al, 1974; Burns et al, 1975; Shoemaker and Bloom, 1976) glia (Siassi and Siassi, 1973; Krigman and Hogan, 1976) and myelin formation (Bass et al, 1970b; Stewart et al, 1974; Krigman and Hogan, 1976; Griffin et al, 1977) are well documented. The structural changes have been found to be associated with chemical changes as expected. Preweaning undernutrition has been associated with a reduction in brain weight (Chase et al, 1969; Swaiman et al, 1971; Sobotka et al, 1974; Dyson and Jones, 1976b). A reduction in cell number was reported by Winick and Noble (1965), Shoemaker and Bloom (1977). A decrease was found in DNA

content (Winick and Noble, 1966; Dobbing, 1968a,b; Guthrie and Brown, 1968; Swaiman et al, 1970; Enwonwu and Glover, 1973; Sobotka et al, 1974).

Preweaning undernutrition was found to affect the lipid composition of the brain. Thus different lipids like cholesterol, phospholipids and cerebrosides were reduced during preweaning undernutrition (Rajalakshmi and Nakhasi, 1974; Krigman and Hogan, 1976; Reddy et al, 1982). Neonatal undernutrition is found to reduce the concentration of polyphosphoinositides in the brain. They are found to be play an important role in the structural development of neurones, glia, and myelin (Uma and Ramakrishnan, 1980). Thus the decreased myelination found in histological studies (Bass et al, 1970b) is consistent with decrease in lipids, particularly cholesterol (Dobbing, 1963; Dickerson and Jarvis, 1970). Most of the investigators have reported reduction in phospholipids (Dobbing, 1968b; Geison and Waisman, 1970; Rajalakshmi et al, 1974d). A reduction in galactolipids, particularly cerebrosides which are considered as an index of myelination has been found in a number of studies (Burton et al, 1966; Rajalakshmi and Nakhasi, 1976). A decrease in myelin yield associated with relatively greater deficits in myelin phospholipids and galactolipids, have been found by different authors (Nakhasi et al, 1975; Krigman & Hogan, 1976).

The structural, developmental and neurochemical changes observed in preweaning undernutrition (Balazs et al, 1979; Winick, 1979; Villescas et al, 1981) may be expected to be associated with metabolic changes. Indeed it is so. Early malnutrition was found to alter the pathway of cerebral glucose metabolism (Winick,1970; Chase et al, 1976). Brain is unique in the operation of GABA shunt and glutamate and GABA are important neurotransmitters. Activity of glutamate dehydrogenase (GDH) and glutamate decarboxylase (GAD) the enzymes associated with the metabolism of these two neurotransmitters are found to be decreased in neonatal undernutrition (Rajalakshmi et al, 1974; Chase et al, 1976). It is interesting to note in this connection that the development of metabolic compartmentation of glutamate is delayed in undernourished animals (Roach et al, 1974; Patel, et al, 1975). Since acetylcholine is a major neurotransmitter, a number of studies have been carried out on the metabolism of acetylcholine. Decrease in the activity of acetylcholine esterase was found with undernutrition in a number of studies (Sereni et al, 1966; Adlard and Dobbing, 1971). It is of interest to note that acetylcholine metabolism is closely linked to pyruvate oxidation.

Undernutrition during suckling has also been found to result in decreased activities of several brain enzymes

namely succinate dehydrogenase, aldolase (Adlard and Dobbing, 1971a, 1971b). Reduced activity of (Na^+K^+)-ATPase in isolated synaptosomes from cerebral and cerebellar cortices have been observed (Simon and Johnson, 1976).

Mitochondria isolated from brain of undernourished rats were found to take up lesser oxygen compared to control (Muzzo et al, 1969). Similarly oxygen consumption of cortical tissues from undernourished rats were low (Mysliveck et al, 1968). This could be due to a decreased glycolytic activity of the brain due to undernutrition (Dyson and Jones, 1976a). A deficit in the incorporation of glucose to amino acids in brain has been reported. At 21 days 31% of acid soluble ^{14}C was combined in amino acids in controls in contrast to 18% in undernourished. The conversion of glucose into amino acids in brain is considered as an index of maturity (Cocks et al, 1971). As mentioned earlier, the rise in the rate of conversion of glucose carbon to amino acids with maturation is associated with the increased flux through glycolysis and Kreb's cycle during this period (Miller, 1967). There was a depression in the overall utilization of glucose. The incorporation of ^{14}C into lipids was approximately halved in undernourished animals. Thus maturation of glucose metabolism was retarded in brain of

undernourished animals (Balazs and Patel, 1973). At 21 days the rate of glucose oxidised through Kreb's cycle is much less in brain of undernourished animals (Balazs and Patel, 1973).

However, the effect of preweaning undernutrition on cerebral metabolic pathways was not uniform. Undernutrition did not interefere with certain maturational processes in the brain. Thus the development of GABA nerve terminal compartment was not affected by undernutrition during suckling period. The GABA compartment also develops simultaneously with glucose metabolism (Balazs and Patel, 1973).

Undernutrition has been found to be associated with a delay in maturation of the evoked cortical response (Mysliveek et al, 1968) an observation consistent with the deficits in neuronal maturation and myelination. The most conspicuous effect of undernutrition during the neonatal period is a retardation of reflex behavior and neuromotor development. These findings first made by Lat et al.(1960); Cowley and Griesed (1963) have now been confirmed by many investigators (Altman et al, 1971; Smart and Dobbing, 1971; Rajalakshmi, 1975).

Postweaning undernutrition

In contrast to malnutrition produced by reduced milk supply during the suckling period malnutrition imposed on experimental animals after weaning usually represents a reduction in the intake of either of protein or of energy and protein. The former is analogue to human kwashiorkor and latter represents marasmus. Most of the studies attempt to model kwashiorkor and many of the biochemical features of this deficiency state have been successfully produced in the rat (Krish et al, 1968; Enwonwu and Sreebny, 1970; Anthony and Edozien, 1975).

In contrast to malnutrition in suckling period, postweaning protein or calorie deficiency has no effect on brain DNA, though reduced weight, protein and RNA have been registered (Winick and Noble, 1966; Ahmad and Rahman, 1975). These deficits are reversible with adequate nutrition (Winick and Noble, 1966). Since all the tissues of the body show considerable increase in cell number during suckling period, it is not surprising that malnutrition at this time severely reduced whole body and organ DNA content at weaning (Winick and Noble, 1965; 1966).

The brain of adult rat is preferentially protected from the effects of malnutrition as evidenced by the fact that even prolonged malnutrition of mature rat has no significant effect on brain weight, protein or nucleic acid levels (Lehr and Gayet, 1963; Mandel and Mark, 1965). Platt et al. (1964) reported reduced brain weight and various histological and morphological anomalies in dogs as a result of protein deficiency after weaning.

There is good evidence to show that early malnutrition results in reduced brain growth in man (Winick and Rosso, 1969). There was less DNA and proportionately decreased RNA; protein and weight in human infants who died of marasmus in the first year of life. Cell number in all brain regions was reduced by early malnutrition (Winick, 1970). In contrast children who died during their second year, particularly those with kwashiorkor showed little deficit in brain DNA, whereas dry weight/DNA, protein/DNA and lipids/DNA were severely reduced (Winick, 1970a). There is an extensive microneuron proliferation (Gramule, Stellate and braket cells) postnatally in man and would therefore be susceptible to nutritional factors affecting cellular growth (Nowak and Munro, 1977).

Protein deficiency in the immediate postweaning period was found to affect adversely the glutamate metabolism of brain (Rajalakshmi et al, 1969; 1974c). Feeding restricted amount of an adequate diet affected brain enzymes only if animals had been malnourished during suckling period (Rajalakshmi et al, 1974a). Permeability of brain to certain metabolites may be allowed on the basis of altered integrity of cell membrane observed by histologic examination of protein deficient animals (Platt et al, 1964). Rajalakshmi et al. (1971) have reported that brain tissue slices of low protein fed animals use glutamate more efficiently than those of high protein animals, whereas reverse is true in the case of homogenates.

Acetylcholine is an important neurotransmitter of the CNS. It has a high turnover rate in the brain. Protein deficiency in the postweaning period is found to reduce acetylcholine content in the brain (Rajalakshmi et al, 1974b). Protein malnutrition is found to elevate concentration of histamine in brain of rats during postweaning period.(Enwonwu and Worthington, 1974; Enwonwu and Worthington, 1975). Many other neurotransmitters were adversely affected in protein malnutrition. This perhaps may under lie some of the behavioral abnormalities

noticed in protein malnutrition. Of particular significance are the histological and neurophysiological changes observed in primates subjected to malnutrition in the postweaning period. Squirrel, monkey subjected to severe protein deficiency for 15 weeks after weaning have been found to show morphological changes in the brain suggestive of abnormalities in ribosomal rosettes (reduced number and density), endoplasmic reticulum (paucity of dense granules) golgizone, dialated vesicles, and mitochondria (irregular shape in the dialated cristae) (Rajalakshmi, 1981).

Neurophysiological changes have been found in dogs, pigs and rats subjected to protein deficiency after weaning. The effects were much more adverse if they had also been born of and raised by malnourished mothers. The changes observed included motor incordination in pigs, spasmodic trembling of the head and forepaws and atoxic gait in dogs and disturbances of EEG pattern (Rajalakshmi, 1981). The morphological changes are found to be greater in spinal cord and medulla than in higher regions and included in the case of spinal cord, chromatolysis, foaming of the cytoplasm due to perhaps to vacuolation, an increase in oligodendroglia, increased number and thickness of astrocytic fibres and degeneration of Nissel granules (Platt et al, 1964).

The possibility of alteration in cell permeability in postweaning protein deficiency has been suggested (Rajalakshmi et al, 1971).

Human studies

A substantial section of the world's population is either undernourished or malnourished or both. Children in the postweaning period are the group most vulnerable to malnutrition, as the diets provided for them are often deficient in quantity and quality while their nutritional requirements are greater in relation to body weight. The major nutritional deficiency among those infants is energy rather than protein. The major differences between infants and adult is in the rate of energy utilization. It is three times greater in infant per unit body weight. The infant brain a major potential consumer of glucose is also relatively larger. It is therefore to be expected that energy reserves would be much more rapidly depleted in a fasting infant. Because of the large brain to body weight ratio human brain requires a much larger proportion of the whole body energy requirement than does the brain of any other species (Hawkins and Mans, 1983). Availability of energy is of prime importance in prevention and treatment of malnutrition (Kerr et al, 1978).

Malnutrition during infancy and childhood is classically described in terms of two syndromes, kwashiorkor - associated primarily with protein deficiency in the diet and marasmus which is an overall deficit of food intake notably energy.

Kwashiorkor occurs between the age of 1-3 years in children whose diet is grossly deficient in protein, usually as a result of being transformed from breastmilk to starchy diet. The child with kwashiorkor suffers from growth failure. The most striking biochemical abnormality is the reduced level of plasma albumin, but the fall in serum transferrin content is more sensitive index of severity.

In contrast to kwashiorkor, marasmus occurs most commonly in children under 1 year, where it is basically due to insufficient food. The main clinical features include marked growth failure, the child often being less than 60% of normal weight for age and having a reduced body w length. The clinical picture of severe muscle wasting is common. However, the serum protein levels are near normal and there is no edema (Nowak and Munro,1977).

Marasmus is found to be the commonest form of malnutrition. While kwashiorkor is typically precipitated by an acute infection such as measels, the onset of marasmus is quite early. It is known that kwashiorkor is more common in rural areas, while marasmus is more predominant in urban area. Marasmus getting more commoner because of increasing urbanization and decreasing breast feeding (Waterlow and Payne, 1975).

These children are usually adequately breast fed and grow well for the first 4-6 months; thereafter breastmilk does not provide adequate protein (Jelliffe, 1955; Scrimshaw and Behar, 1961). The most obvious manifestation of early undernutrition or malnutrition in these children, is a reduction in body size associated with varying deficits in many other parameters. Although weight is readily affected by short term nutritional insult, height seems to be affected adversely only by long term severe insult. Head circumference is reportedly affected by inadequate nutrition in early life and is considered to be an index of brain size (Stock and Smythe, 1963; O'Conell et al, 1965; Graham, 1968; Winick and Rosso, 1969; Rainbow, 1972; Engsner, 1974). Studies based on transillumination and electroencephalography suggest that brain of malnourished children may be even smaller

than is suggested by head circumference (Rozovski et al, 1971; Engsner and Vahlquist, 1975). Autopsy studies have confirmed the smaller brain size of malnourished children (Udani et al, 1962; Brown, 1965; Rosso et al, 1970; Chase et al, 1972; Marcordes et al, 1973). Since malnutrition has been found to be associated with both, a reduced brain size and mental retardation, it would be tempting to see an association between the two. However, no association between head size and intelligence has been found (Mann, 1984).

Protein energy malnutrition is frequently present from birth and in some developing countries it represents 30% of all live births. Calorie rather than protein is the limiting factor in diet of populations suffering from protein energy malnutrition (Behar, 1977). Human studies have shown that intrauterine and postnatal malnutrition during the first 18 months of life interferes with the brain cell division after which the cell size is primarily affected. Protein calorie malnutrition may lead to permanent molecular erros in brain membrane composition and thus affect biochemical maturity of brain (Ghosh et al, 1979).

Protein energy malnutrition in the preschool children is a major public health problem (Kamala, 1982).

It also exposes the child to an increased risk of mortality and slowing of growth (Ricour and Duhamal, 1983).

Severe protein energy malnutrition in children has been found to be associated with changes such as decrease in cell number based on estimation of DNA (Chase et al, 1972; Ganguly et al, 1972; Subba Rao and Sarma, 1972); decrease in brain RNA, protein and total lipids (Winick and Rosso, 1969; Ganguly et al, 1972; Subba Rao and Sarma, 1972) cerebrosides and sulfatides (Fishman et al, 1969; Mokashi et al, 1972) and gangliosides (Mokashi et al, 1972). Bachawat et al. (1972) reported deficits in the concentration of glycolipids in white matter in malnourished children. A reduced brain size is associated with a reduction in cell number as judged by DNA (Rosso et al, 1970; Chase et al, 1972; Ganguly et al, 1972).

It is believed that the most rapid period of brain development in human is between 5th month of gestation to the first six months of infancy. The nutritional status of the mother during pregnancy particularly during the second half may therefore be of crucial importance with respect to development of fetal brain. The diets of most pregnant women belonging to the poor

income group in our country are inadequate with respect to many nutrients. Synthesis of myelin in human brain starts around 30 weeks of gestation and at birth the rate of synthesis is very high. Nutritional status of the mother during pregnancy is believed to be one of the important factors which influences the birth weight of the infant. The incidence of small-for-date infants is several fold higher among the low-income group as compared to the well-to-do segments of our population. The brains of small-for-date infants were lighter in absolute terms, but when expressed in terms of unit weight they were heavier. However, there was no significant difference in the biochemical profiles of brain between the two groups. Hence intrauterine growth retardation of the type generally seen in infants born to undernourished mothers is not associated with demonstrable changes in the gross composition of brain. The motor and adaptive development also showed no difference between the two groups (ICMR Bulletin, 1975).

Brain growth in human is very rapid during the first year of life and almost complete by the end of second year. Undernutrition during this critical period might inhibit brain growth and that this could result in permanent reduction in brain size and impaired intellectual development (Stoch and Smythe, 1976).

However, the composition of brain of children (3-4 years) who died of kwashiorkor were found to be altered. Brain weight as percentage of body weight was found to be similar to that in normal children. Though the content of DNA was similar to control, RNA protein and lipids, particularly glycolipids and mucopoly-saccharide content were all significantly low. Thus postweaning malnutrition in humans alters the cell size and composition in the brain. Perhaps this may explain the poor mental performance shown by kwashiorkor children (ICMR Bulletin, 1975).

Though neuronal division is virtually complete by birth in human, the important functional developments such as dendritic arborization (Pallis, 1974) and development of synaptic connections are primarily postnatal (Rapport and Fritz, 1972; Dobbing and Sands, 1973). Hence the immediate postnatal period is the most vulnerable in human brain development. This is the period in which children in the developing countries are much exposed to malnutrition (Smart et al, 1974; Nutr. Rev. 1975) undernutrition in the first year is found to curtail brain cell number in humans (Rosso et al, 1970). In humans too, cerebellum is found to be more affected by malnutrition (Nutr. Rev., 1973; Sarma and Rao, 1974).

Immediate postnatal malnutrition is more crucial to brain development than that of maternal malnutrition (Smart et al, 1974).

Glycogen content of liver is the chief source of circulating glucose and deficiency of liver glycogen store is most common cause of infantile hypoglycemia. Liver of malnourished children is particularly low in glycogen (Anderson et al, 1966; Anderson et al, 1967; Bell et al, 1970). In fact carbohydrate metabolism is impaired in infantile malnutrition. Protein energy malnutrition is frequently accompanied by hypoglycemia and may be the probable cause of death in severe cases (Oxman et al, 1968). An impaired glycogenolysis of muscle at aldolase step is observed in kwashiorkor children (Baig and Edozien, 1965; Alleyene et al, 1971). It is worth to recall that early malnutrition in rat was found to alter the pathway of glucose metabolism in brain (Winick, 1970a). These defects in carbohydrate metabolism observed in malnutrition may be due to endocrine imbalance (Heard, 1966; Kamala et al, 1971). There is deficit of insulin, thyroid as well as growth hormone in animals and in humans in protein calorie malnutrition (Heard, 1966). The functional and morphological alteration in thyroid gland with consequent

defect in the synthesis of thyroxine (Kamala et al, 1971). Surprisingly a diminished oxygen uptake is also noticed in children who are malnourished. This probably may be due to decrease thyroid activity and an alteration in the mitochondrial structure (Monckeberg et al, 1964; Kamala, et al, 1971).

Protein calorie malnutrition in human changes the course of brain carbohydrate metabolism. The proportion of glucose undergoing oxidation is reduced and it is converted to long chain fatty acids in brain. In severe protein calorie malnutrition the cerebral oxygen consumption was significantly lower, while glucose consumption was higher than in normal children (Mehta et al, 1977).

Mental changes in children with kwashiorkor may be related to the significant reduction in the concentration of potassium in the brain (Garrow, 1967). It is relevant in this context to know that potassium exert profound influence on brain metabolism. The most important role of the cation is its regulatory effect in the conversion of pyruvate to acetylCoA (Kim, 1959).

Platt (1962) was the first to point out the impact of severe malnutrition on CNS function. He suggested that

the animal or child dying of severe protein malnutrition dies a "central nervous death". This conclusion was based on the observation of the cessation of electrical activity of the brain before that of the heart. The histopathological changes observed by Platt et al. (1964) in piglets were independently observed in severely undernourished children by Udani (1962).

EEG abnormalities similar to those observed in malnourished animals have been reported in malnourished children (Taori and Pereira, 1974; Coursen, 1974). Motor nerve conduction velocity is found to be affected more in kwashiorkor than in marasmus. Rhodes and Synder (1975) reported the aberrations of EEG patterns in malnourished children and the changes in response of the same to light flashes. Similar abnormalities have been reported in congenital mental retardation; mongolism, hypopituitarism hypothyroidisms and hypoxia in early life. Since some of these conditions are found to be associated with brain damage and mental retardation, a question arises about the significance of similar changes in malnourished children (Rajalakshmi, 1981).

The psychological changes in the malnourished children were recognised long before the anatomical and biochemical changes. Carothers (1953) stressed the

mental arrest of malnourished children in his report to WHO. Extreme apathy is a common feature of children suffering from kwashiorkor (Platt, 1961). A kwashiorkor child gives an appearance of total detachment with environment (Rajalakshmi and Ramakrishnan, 1972). Children experiencing early malnutrition perform very poor on tests measuring motor performance, adaptive behavior, language skills and personal development (Champakram et al, 1968; Monekberg, 1968; Cravioto,1979).

A number of studies have suggested the poor psychological performance of the malnourished children (Stock and Smythe, 1963; Cobak and Najdamvic, 1965; Stoch and Smythe, 1967; Monekberg, 1968; Chase and Martin, 1970). Persistent effects of early malnutrition on psychological performance are found in some studies (Cravioto, 1966; Hertzig et al, 1972). The studies of Cravioto and Robels (1965); Stoch and Smythe (1963, 1965) suggested a correlation between the age at which the children were hospitalised and intellectual impairment. But such correlations were not found in the apparently more systematic studies of Hertzig et al. (1972). Low IQ have been reported in kwashiorkor (Udani et al, 1976).

Apart from nutritional studies, factors such as paucity of cultural environment, social and economic disadvantage, poor housing, poor maternal attention and child health are also bound to influence the intellectual development.

Some of the chemical changes found in animals have also been found in the brain of malnourished children. Deficits in lipids have been observed by number of investigators (Chase et al, 1972; Kokarady et al, 1972). Similar deficits have been found in plasmalogens (Fishman et al, 1969).

The impaired or delayed maturation of the malnourished brain is also evident from neurophysiological studies. EEG abnormalities similar to these found by Platt and his associates in malnourished pups have been found in malnourished children (Botha et al, 1968; Coursin, 1974; Taori and Pereira, 1974). Several studies pointed to the association of severe apathy (Platt et al, 1964; Kinsbourne, 1971) and mental retardation (Cravioto and Robels, 1963; Monekberg, 1968).

The maximum nutritional requirement of the fetus are however during the last trimester and poor maternal weight gain during this period is associated with poor placental development characterised by low placental weight and reduced protein content and cellularity and low birth weight (Qurreshi et al, 1973; Litching et al, 1975). Full term babies with birth weights less than 2 kg. account for 10-15% of total or more among the poor in India (Achar and Yamkauer, 1962; Ghosh et al., 1972). Since this period and early postnatal period are critical for the development of nervous system and are characterised by neuronal growth including axonal and dendritic growth, synaptic connectivity, glial proliferation, myelination, the growth and maturation of six layers of the cerebral cortex, the maturation of spinal cord and reflux activity and the emergence of a primitive EEG rhythm (Lindsley, 1974), there is a possibility that human brain too may be vulnerable to nutritional insults. Emperical evidence for this view was provided by several studies reporting the higher incidence of mental retardation in low birth weight babies (Jackson, 1968; Winick, 1968; Davies and Stewart, 1975). However, such small-for-dates are not found to differ from controls in several other studies (Chase and Martin, 1970; Rajalakshmi and Ramakrishnan, 1972). Similar observations

have been made on small babies born during World War II (Stein et al,1972). Low birth weight by itself may not be critical factor. Typically low birth weight baby is born in a house, where postnatal development is also at risk. This is more relevant in the context of rapid industrialization and the changes it brings in the life styles of the poor. One such changes being a decline in breast-feeding (Winick, 1976; Ghaffer, 1977). Thus, while the small birth weight per se may not bring any adverse effects, it predisposes the child needlessly to subsequent malnutrition and the consequences thereof.

Malnutrition during early life exposes the child unnecessarily to the possibility of impaired emotional and psychological development not to mention other features such as stunted growth, increased proneness to infections and poor motivation and a restriction of voluntry activity which may persist throughout life. The overall quality of the child's life is affected. It is indeed tragic that avoidable sequence of events occurs in an appreciable proportion of worlds population as 1-2% of the world's poor are affected. In absolute term they run into millions.

Vitamin A deficiency

The physiological role of vitamin A in normal vision is well-known. Besides it is essential for the normal growth and reproduction. The vitamin has important physiological role in the synthesis of steroid hormones, control of membrane permeability and in inducing protein synthesis in intestinal cells (Sundaresan, 1972; Goodman and Gillman, 1980).

One of the major physiological functions of the vitamin is to maintain structural and functional integrity of the cellular and subcellular membranes. (Dingles et al, 1962; Krause and Beamier, 1969; Mack et al, 1972; Ram and Misra, 1978). An increased cholesterol phospholipid molar ratio was observed in vitamin A deficiency in rat liver. The ratio has been implicated as governing factor in maintaining the integrity of biological membranes and influence their osmotic permeability. The vitamin has a strong affinity to membrane and may be acting as cross-linking agent between lipid and protein of the membrane (Adhikari et al, 1978). Vitamin A in the membrane can alter the surface charge of the membrane and change confirmation

of membrane bound enzymes. This in turn may affect transport of nutrients, ions and water through membrane and influence cellular metabolism (Mack et al, 1972; Porkovsky et al, 1972). The vitamin perhaps might be exerting a regulatory role on carbohydrate and lipid metabolism (Nobles and Phillips, 1969; Bhatt and Rama Rao, 1973). Deficiency of the vitamin is found to cause a decrease in liver glycogen in rat (Wolf et al, 1957) an impaired muscle glycogenolysis, low blood sugar in chicks and decreased mucopolysaccharide synthesis in rat colon (Wolf and Varandani, 1960).

It is posulated that the vitamin may be functioning as a coenzyme in many enzymatic reactions (Sundaresan, 1966; Goodman and Gillman, 1980). The functional and structural integrity of epithelial cells throughout the body is dependent upon an adequate supply of vitamin A. In presence of retinol basal epithelial cells are stimulated to produce mucus. In the absence of retinol, goblet mucus cells disappear and atrophy of epithelium occurs, followed by proliferation of basal cells at the expense of mucus cells. The suppression of normal secretions leads to irritation and infection (Goodman and Gillman, 1980).

Vitamin A deficiency is one of the major public health problems of the developing countries.(Nutr. Rev. 1985). Recent reports shows that around ten lakhs children develop xerophthalima in the world and of which 10-25% become permanently blind and many children die before they attain school age (Bauernfeind, 1983). Approximately twelve to fifteen thousand preschool age children lose their eye sight every year in India as a result of vitamin A deficiency (Srikantia, 1978). Human milk is considered to be the best mode of transport of vitamin A from the mother to the infant. Fetal liver stores of vitamin A is very poor. Human colostrum and milk are very good sources of vitamin A. Women from the poor socioeconomic group has low vitamin A in the milk (Davila et al, 1985). This may be a possible reason for the prevalence of vitamin A deficiency among the children from poor socioeconomic group.

A close interrelationship is observed between protein nutritional status and vitamin A metabolism. Protein deficiency is one of the contributing factor for the development of vitamin A deficiency (Srikantia, 1975, 1978). This is supported by the fact that a higher incidence of clinical symptoms of the vitamin deficiency is observed in children with protein energy malnutrition

(Pereira and Begum, 1974; Srikantia, 1975; Sivkumar and Reddy, 1978). Protein malnutrition thus might be influencing vitamin A metabolism (Zaklama, 1973; Smith et al, 1975; Srikantia, 1975).

Several studies have indicated a close relationship between vitamin A and protein metabolism. McLaren (1959) found that the onset of vitamin A deficiency could be delayed by reducing protein intake. It is a common observation that children suffering from kwashiorkor have a very low concentration of vitamin A in plasma. It is postulated that independently of both the dietary intake and liver stores of vitamin A, a functional deficiency of the vitamin occur in kwashiorkor and other forms of severe protein deficiency as a consequence of reduced proteins (Arroyave, 1969).

However, there are considerable number of opposing views. It is suggested that vitamin A absorption perse in kwashiorkor children is normal. Dietary inadequency is the primary reason for the prevalence of vitamin A deficiency in these children (Sivakumar and Reddy, 1978; Srikantia, 1978).

The diets which infants in poor income group receive when they are weaned are almost exclusively vegetable based and therefore contain B-carotene and little preformed vitamin A except for what is derived from breast milk. Diet survey in preschool children in India have shown that their dietary intake is much below the recommended allowance and most of which is derived from β carotene. The actual availability of β carotene present in these diets may be even less, since there is little or no fat in the diet and among factors that influence absorption of carotene, fat is an important one. All available evidence clearly shows that the dietary intake of vitamin A falls considerably short of recommended allowances and is the major aetiological factor in the development of vitamin A deficiency. (Srikantia, 1975). In some parts of Africa habitual diets contain red palm oil which is rich in B carotene. In such populations though protein energy malnutrition is widespread among children, occular signs of vitamin A deficiency are extremely rare even amongst serious cases of kwashiorkor (Scragg and Rubidge, 1960). It is observed that many children with protein energy malnutrition have associated infections and during episodes of infection, absorption of vitamin A is impaired (Srikantia, 1975). Perhaps this may be one of the factor for the low level of serum vitamin A in kwashiorkor.

It is found that corneal xerosis can be rapidly and completely reversed by administration of vitamin A alone without simultaneous administration of any other nutrient including protein. This may be indicative that in the development of even advanced stages of corneal involvement, the singlemost important factor is insufficiency of vitamin A. In Singapore and Indonesia where infants were being fed with skim milk preparations or condensed sweetened milk, severe eye lesions were reported without any sign of protein energy malnutrition (Srikantia, 1975).

It is known that vitamin A deficiency arrests growth and that growth increases the vitamin requirement. Vitamin A absorption and storage in protein deficiency also was observed. On a protein free diet it seems likely that decreased absorption of vitamin A in protein deficiency outweighs the reduced utilization due to low protein intake, the net result being a lowered liver storage of vitamin A on a protein free diet. In vitamin A deficiency total serum protein is decreased. There is a significant decrease in serum albumin (Vakil et al, 1964). Autopsy studies revealed that storage of vitamin A in children with protein energy malnutrition is much lower (Zakalamaz et al, 1972). Vitamin A deficiency is found

to decrease the protein synthesis. It is found that the vitamin deficiency affects protein synthesis at the translational level (De Lucca and Wolf, 1969).

Vitamin A is necessary for stabilisation of membrane by acting as cross-linking agent between lipid and protein. The amount of total lipids and lipid phosphorus per unit of mitochondrial protein was significantly decreased in vitamin A deficient rats. One reasonable mechanism is that vitamin A may be an integral structural component of the cellular and subcellular membrane. A shift in the relative concentration of vitamin A in the membranes may cause changes in permeability and stability (Mitchell et al, 1968).

In severe protein deficiency a liberal intake of vitamin A reduces the urinary excretion of nitrogen indicating probably a protection of the tissues from excessive catabolism. It may be suggestive that many proteins in the body are stabilised by vitamin A and deteriorate in its absence. This would be a good explanation for many of the gross manifestations of vitamin A deficiency (Arroyave, 1969). There is

evidence to indicate that the universal function of vitamin A may be related to the integrity of living membranes (Arroyave, 1969).

Metabolic requirement of vitamin A for growth and development of nervous system is quite critical with regard to the formation and closure of neural tube. Nerve lesions, increased CSF pressure and hydrocephalus are reported in experimental animals in its deficiency (Ritcher, 1965; Morton, 1965; Goodman and Gillman,1980). Action of vitamin A in growth of nervous tissue is believed to be related to thyroid hormone since in cretinous rat, development of cortical neuropil and maturation of behavior can be significantly improved by administration of large dose of vitamin A (Ritcher,1965).

Vitamin A has a remarkable contribution in the process of myelination and the deficiency of the vitamin during suckling period in rat delayed the process of myelination due to decreased sulphatide synthesis (Clauson, 1969). This is supported by the findings of Bhatt and Rama Rao (1978) who has reported degeneration of myelin during the suckling period in maternal vitamin A deficiency. Similarly a close relationship between the vitamin nutrition and myelin lipid formation during the

postnatal development is reported (Joshi et al, 1982). However, Mukherjee and Bachawat (1967) did not find any change in sulphate activating enzymes and thereby synthesis of PAPS in liver and brain in the vitamin deficiency in experimental animals.