CHAPTER IV

SUMMARY

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In previous studies in this laboratory on rats protein deficiency in the immediate postweaning period was found to be associated with decreased activities of brain glutamate dehydrogenase (GDH) and decarboxylase (GAD) (Rajalakshmi et al, 1965). Similar deficits were not observed with undernutrition suggesting the differential effects of protein and energy deprivation (Rajalakshmi et al, 1974). However, during the neonatal period when the biochemical maturation of the brain is still in progress, undernutrition may have more serious consequences. The present studies were undertaken to investigate this problem further and were concerned with the effects of neonatal undernutrition on growth and composition. The parameters studied were protein, DNA and activity of GDH and GAD. The specific aspects investigated were :

1. effects of a low plane of nutrition on the development of the progeny;
2. effects of neonatal undernutrition in relation to duration and severity;
3. reversibility of the effects of undernutrition during neonatal period;
4. effects of neonatal undernutrition on the susceptibility of animals to nutritional deficiencies during the postweaning period.

5. reversibility of the combined effects of neonatal and postweaning deficiencies; and
6. effects of neonatal undernutrition in different regions.

Prenatal undernutrition resulting from maternal protein deficiency during gestation was found to affect body and brain weight significantly but neither protein concentration nor activities of GDH or GAD were affected. However, in other studies in this department with similar body and brain weight deficits, activity of acetylcholine esterase was decreased and this was associated with a delayed appearance of reflex activities such as righting, negative geotaxis, and cliff avoidance which are found in normal animals within the first three days after birth. Thus the effects of prenatal deficiency may depend on the parameter investigated.

Neonatal undernutrition induced by increasing litter size was found to decrease the activities of GDH and GAD at weaning and the deficits were apparent during the second week of life when they were also the greatest. No deficits in enzyme activity were found at one week of age although significant deficits were found in body and brain weights.

The size of the deficits in enzyme activity was not found to increase with a more severe degree of undernutrition induced by feeding the mothers a low protein diet during gestation and

lactation. Similar observations have been made with regard to the effects of increasing severity of protein deficiency during the postweaning period. This might be because brain enzyme activities are maintained within relatively narrow range. In contrast, in other studies in this laboratory, the deficits in brain lipids were found to increase with more severe degrees of undernutrition (Rajalakshmi and Nakhasi, 1974). These findings suggest that the effects of deficiencies on metabolic activity may present a picture different from that on chemical composition although the two are interrelated. When undernutrition was restricted to different ages, the effects of the same were found to vary with the period of treatment and also with the age at which it was introduced. GDH was found to be more susceptible to undernutrition than GAD.

When rats undernourished from birth to 3 weeks were fed adequately for 6 weeks the activities on GDH and GAD were restored to normal levels although deficits in body and brain weights persisted to some extent. When neonatally undernourished rats were subjected to protein deficiency during postweaning period the deficits in GDH were not found to increase further, and in fact, appeared to decrease in the case of GAD although the body and brain weight deficits increased during this period. The interesting observation

was made that, although postweaning undernutrition had no effect on brain GDH in previous studies, a deficit was evident when it was preceded by neonatal undernutrition suggesting that the effects of nutritional deficiencies are influenced by the previous nutritional status of the animal. The combined effects of nutritional deficiencies during both the neonatal and postweaning periods on brain enzymes were also reversed by subsequent rehabilitation but deficits in body and brain weight were not completely bridged.

Studies on the effects of neonatal undernutrition on the cerebrum, cerebellum and brain stem showed greater deficits with regard to gross weight as well as DNA content in the cerebellum than in the cerebrum and brain stem. The latter two were similarly affected with regard to weight. The DNA content of the cerebrum was less affected and that of the stem not affected. The activity of GDH was affected at 2 and 3 weeks of age in the cerebrum and cerebellum and the deficits seemed to be greater in the latter. Again, stem was unaffected, GAD activity was affected in the cerebrum at 2 weeks of age whereas in the case of the cerebellum a deficit was evident only at 3 weeks. Again, the stem was found to be unaffected. These studies suggest the greater susceptibility of cerebellum to the effects of nutritional deficiency and the relative resistance of the brain stem to the effects of postnatal deficiency.

Some of the questions arising from above observations are high lighted below :

As mentioned earlier, a question arises as to how far results obtained on small animals such as the rat can be extrapolated to man with a different pattern of maturation and a far greater complexity of the brain. This question assumes special importance in interpreting the effects of maternal malnutrition and the consequent growth retardation of the fetus as brain growth in human is very rapid during the late fetal period (Winick, 1968). Alterations in the biochemical composition of the brain of small for date infants has been reported by Chase et al (1972) and Janardan Sarma and Subba Rao (1974).

Conflicting observations have been made with regard to psychological development of such infants. A greater incidence of psychological retardation has been reported by Knobloch and Pasamanik (1963), Drillen (1970) and Usha Parekh et al (1972). No such phenomenon was observed either in the studies of Ghosh et al (1972); Fitzhardinge and Steven (1972) or in previous studies in this laboratory (Rajalakshmi and Ramakrishnan, 1969c). In the latter case however, the incidence of IQ scores above 100 appeared to be somewhat less in such children.

The possibility of phylogenetic differences in the relative vulnerability of the brain to malnutrition cannot also be ruled out because of differences in the rate of development and also because of the location of the species on the evolutionary ladder. The brain increases in size and complexity as we go higher up the scale and the question arises as to whether it also enjoys a greater protection from the effects of deficiency. The situation is also complicated by the fact that in man the type of deficiency occurring during the neonatal period is generally different from that occurring during the postweaning period.

The observation that animals continue to grow in spite of severe undernutrition points to the operation of biological adaptation. Such adaptation is evident in the relative "sparing" of some organs from the effects of deficiency in body and brain weights. For instance, although both vary with the severity of deficiency, the ratio of brain weight to body weight is higher in nutritional deficiency and this ratio continues to be somewhat greater than normal even after rehabilitation (e.g. Winick and Noble, 1966; Dobbing, 1968) although one report has been made to the contrary (Dobbing and Sands, 1972). The question arises as to how far the permanent stunting observed with nutritional deficiencies in early life is due to the operation of an adaptive metabolism

designed to maintain this ratio. This may also account for the higher rate of basal metabolism in undernourished and rehabilitated animals, observed in some studies as the brain may account for a greater share of metabolism not reflected by body size or surface area in these animals.

Progressive deficits in brain weight with more severe degrees of deficiency are not associated with increasing deficits in brain enzymes which reach a certain minimal level and do not decrease further. This underlines the fact that the composition and metabolic activity of the brain show less variation than those of other organs.

The observation that the effects of postweaning undernutrition are modified by the nutritional status of the animal during the neonatal period is of great interest. In man, most children of poorly nourished mothers develop normally during the first few months of life and become undernourished only during the postweaning period. Similarly children with low birth weights show more than the normal increase in weight during the neonatal period (180% increase in body weight as against 140% in children of average birth weights) (Rajalakshmi, 1975). However, occasionally, children with low birth weights may fail to develop normally during the neonatal period as well. Similarly some children fail to develop satisfactorily prior to weaning. If such children

continue to be undernourished and malnourished during the postweaning period as well they may suffer from more serious consequences. In studies carried out by this department in Kerala children admitted for kwashiorkor and marasmus were reported by the mothers to have developed quite well during the first 8-12 months of age if not till later, so that such a combination of prenatal, neonatal and postweaning undernutrition may be rare. It is also possible that such a combination ends fatally so that they do not come in the purview of hospital practice.

In conclusion, the present studies demonstrate the effects of nutritional deficiencies in early life on selected metabolic parameters in the brain. They confirm the general impression that the effects of deficiency depend on the age of the animal and duration of deficiency. Although problems remain in extrapolating these results to man, they suggest the need for carrying out more systematic investigations in brain function in relation to age at onset of malnutrition and severity of the same.