HANDBOOK OF CLINICAL NEUROLOGY

VOLUME 29

METABOLIC AND DEFICIENCY DISEASES
OF THE NERVOUS SYSTEM
PART III

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Edited by

P. J. VINKEN and G. W. BRUYN

in collaboration with

HAROLD L. KLAWANS

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Foreword to volumes 27, 28 and 29

When planning these volumes on Metabolic and Deficiency Diseases, the Editors had to decide what, for their purpose, constitutes a metabolic disorder of the nervous system – the exact boundaries of this subject being difficult to define.

The clinical disorders they wished to bring together were those in which an alteration in metabolism, occurring within or outside the central nervous system, plays a major role in producing clinical dysfunction of the nervous system. Such disorders range from those of heredo-degenerative origin to toxic or systemic diseases.

Nervous system dysfunctions related to toxins have been excluded unless the major effect of the toxin is metabolic or the toxin itself is an important metabolite. Vitamin toxocities, in addition to deficiencies, have been dealt with. The numerous neurological problems associated with alcoholism are the only organic toxicities which have been included. The remaining toxicities will be presented in a future volume of this Handbook: 'Intoxications of the Nervous System'.

The neurological manifestations of systemic diseases have been included if the disease results in a metabolic disorder (whether or not this has been elucidated) leading to some form of nervous system dysfunction. Hence, the effect of uremia, liver failure and electrolyte imbalance are discussed, but problems caused by collagen vascular disorders, hematological disorders, sarcoidosis, etc. will be presented in the volume, 'Neurology of Systemic Disease'.

It will be obvious from the foregoing that these volumes are not limited to the inborn errors of metabolism; in fact, many inborn errors have been absorbed into other volumes – for example, 'Leucodystrophies and Poliodystrophies' (Volume 10). It is, of course, an artefact to define some hereditary disorders as metabolic and others as degenerative, since the latter may well be metabolic disorders awaiting elucidation. In general, we have included only those disorders in which there is some evidence of a known metabolic deficit.

In this Handbook, a major concern of both the Editors and their collaborators is to keep the time between completion of a chapter and its publication as short as possible. The main problem has always been the failure of some contributors to complete their manuscripts within the given deadline. Especially in this rapidly growing field, time is an important factor, as new inborn errors of metabolism are being identified every 4–5 months. In two ways, we have managed to overcome this recurring headache of delayed submission. The first was the editorial decision to restructure the internal

organization so that instead of delaying an entire volume for a single chapter, groups of chapters were moved to facilitate rapid publication. The second was the willingness of new contributors to take over the writing of chapters at short notice when the initial authors were unable to fulfill their obligations. We are indebted to Professor Klaus Kunze who stepped into the breach when the untimely and violent death of Professor Erbslöh prevented him from working with Dr. Leitenmaier on Vitamin B_{12} deficiency. We are also grateful to Drs. Donna Bergen, Stanley Fahn, Oleh Hornykiewicz and Peter Huttenlocher for preparing their contributions within a short space of time.

The Editors feel that these three volumes provide a comprehensive review of biochemical neurology in diseased states, which will be useful as a background to, and a basis for, further developments. The success of biochemical research in this rapidly growing field is clear, and it has become evident that the future of neurological understanding lies largely in the hands of the neurobiochemist and the developmental technologist.

P.J.V.
G.W.B.
H.L.K.

Acknowledgement

Several illustrations and diagrams in this volume have been obtained from other publications. Some of the original figures have been slightly modified. In all cases reference is made to the original publications in the figure caption. The full sources can be found in the reference lists at the end of each chapter. The permission for the reproduction of this material is gratefully acknowledged.

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CHAPTER 1

The effect of nutritional deprivation on the developing nervous system

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Questions about the effects of nutritional deprivation on the developing nervous system are relevant not only because a significant proportion of the world's population suffers from protein-calorie malnutrition, but also because nutritional deprivation represents one model of how a change in the exogenous environment can alter the carefully programmed development of the brain.

In this review, we have focused our attention on the most commonly studied laboratory model of the effects of nutritional deprivation, the undernourished developing rat. We will consider the following parameters:

- Methods of producing nutritional deprivation
- Parameters of brain development
- Effect on body weight and brain weight
- Effects on cell proliferation
- Effects on neuronal processes and synapses
- Effects on myelination
- Other metabolic effects
- Effects on neuromotor development and behavior.

METHODS OF PRODUCING NUTRITIONAL DEPRIVATION

There are a number of ways in which nutrition can be altered, such as increasing litter size, decreasing feeding time, decreasing maternal food intake, or causing specific deficiencies of proteins, amino acids or vitamins.

Models of nutritional deprivation

In utero:
- Decreased protein or total diet to mother.
- Deficiency of specific components in mother's diet.

Before weaning:
- Decreased protein or total diet to mother.
- Large litter.
- Decreased feeding time.
- Fewer feeding stations.

After weaning:
- Decreased protein (8% vs. 24%).
- Decreased total intake.
- Deficiency of specific dietary components –
  - essential fatty acids
  - essential amino acids
  - vitamins.

All of these methods have certain uncontrolled variables, such as overcrowding, the quantity of milk production by the mother, the degree of milk consumption by the offspring, temperature regulation and unstudied psychological and emotional factors. Of greater significance is the relevance of these animal models to the developing nervous system of the human brain.

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PARAMETERS OF BRAIN DEVELOPMENT

The effect of nutritional deprivation on any particular parameter of brain development is related to the timing during development, the severity and the duration of the insult. The choice of denominator to express data, particularly biochemical data, is critical. Often significant changes are observed for a given parameter when the total quantity per brain or region of brain is utilized. Conversely, the concentration of the same parameter, expressed as amount per gram of tissue or milligram of protein, is not significantly altered because the denominator, the weight of the brain or the amount of protein in brain, is also altered.

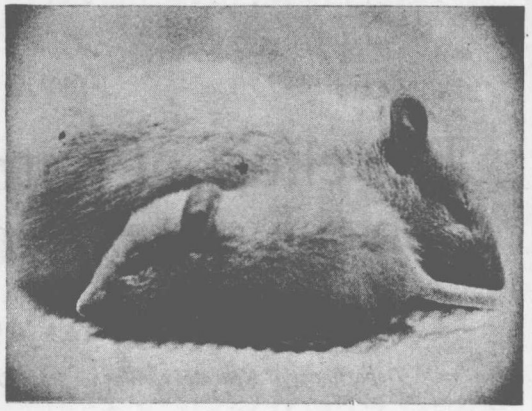

Fig. 1. These animals are litter mates. The smaller animal was nutritionally deprived. (Shoemaker and Wurtman 1971.)

Parameters of brain development

Gross parameters:
- Brain weight
- Number of cells – DNA
- Protein content and pattern
- Lipid content and pattern
- RNA

Specialized cell types:
- Neurons –
  - axons and dendrites
  - synapses
  - transmitters
  - receptors
- Oligodendroglia –
  - myelin
- Astrocytes

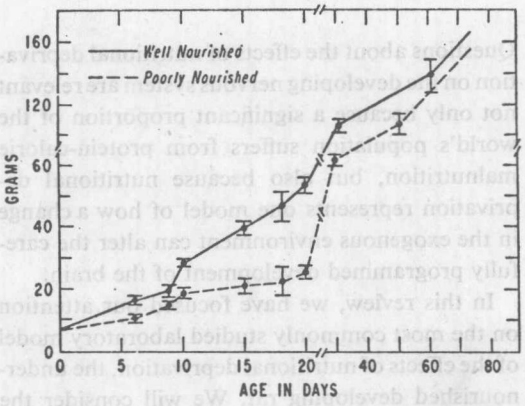

Fig. 2. Body weights of well-nourished and poorly nourished animals. Poorly nourished animals were members of large litters (16–18). (Chase et al. 1967.)

EFFECT ON BODY WEIGHT AND BRAIN WEIGHT

Regardless of the means of producing nutritional deprivation, there is a profound effect on body growth (Figs. 1 and 2). There is a less striking but significant effect on brain weight with postnatal undernutrition (Fig. 3). Prenatal undernutrition produces as much as a 20% decrease in weight of cerebrum of newborn pups (Siassi and Siassi 1973), while other studies found smaller deficits (e.g. Zamenhof et al. 1971), depending on the type of deprivation.

Either prenatal (Zamenhof et al. 1971) or postnatal nutritional deprivation causes deficits in

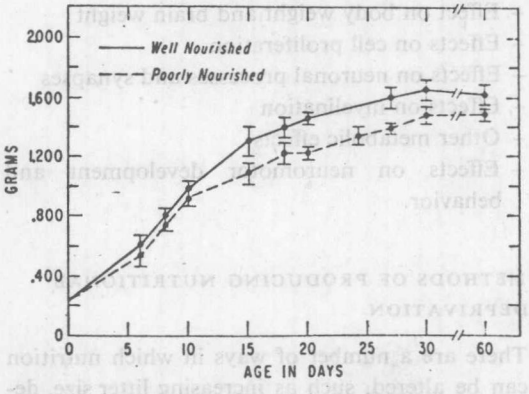

Fig. 3. Brain weights of well-nourished and poorly nourished animals. (Chase et al. 1967.)

body weight and to a lesser extent in brain weight. In some paradigms of deprivation, these deficits are permanent. For example, rats placed in large litters from birth to 21 days showed a 16% deficit in brain weight (Dobbing and Sands 1971). After refeeding, there was some recovery, but a permanent deficit of 8% still remained in the adult rats. At the same time, body weights showed a deficit of 60% at 21 days, which was reduced to 17% in the refed animals by adulthood. However, with a similar paradigm of deprivation, Benton et al. (1966) reported essentially complete recovery of both brain and body weight. Winick and Noble (1966) demonstrated that permanent deficit in brain weight resulted when deprivation occurred between birth and 21 days, but deprivation beginning after 21 days led to deficits that were completely reversible. Obviously, the severity of the deficit before refeeding, the details of the refeeding itself, and the great variability in recovery must be taken into account in interpreting the results of recovery experiments.

EFFECTS ON CELL PROLIFERATION

Undernutrition during a period of cell division in a particular region of brain may result in a permanent deficit in the cell type undergoing division (Winick et al. 1972b). Recovery might occur if a pool of cells with the potential to divide is left when refeeding starts. If the nutritional insult occurs after division of a particular cell type, the cell number may be normal, but cell size is reduced (Winick and Noble 1966). In addition, these cells may show decreased elaboration of processes, such as dendrites, axons or myelin (Dobbing 1972). Recovery will depend on the ability of cells to continue growth or process elaboration at the time of refeeding.

At birth, DNA content of rat cerebrum is about 50% of the maximal level, and continues to increase until 20 days after birth (Fish and Winick 1969). Division of most of the large neurons ends before birth, while postnatal cell division primarily gives rise to glial cells (astroglia and oligodendroglia) and short-axoned microneurons (Altman 1969). Thus, in rat cerebrum, either prenatal or postnatal restriction may lead to decreased DNA content (Zeman 1970; Zamenhof et al. 1971; Winick et al. 1972a; Patel et al. 1973; Smart et al. 1973). Winick et al. (1972a) and Smart et al. (1973) have shown that animals subjected to both prenatal and postnatal undernutrition have greater decreases in cell number than expected from summing the two. This indicates that the duration as well as the timing and severity of the undernutrition plays a role in determining the extent of damage during these periods of rapid cell division. As with brain weight, DNA levels show some recovery if refeeding of postnatally deprived rats begins at weaning; one report indicates complete recovery of both brain weight and DNA content if refeeding starts on day 10 (Winick and Noble 1966). When prenatally undernourished pups are fed normally after birth, some recovery occurs, but a deficit in total DNA content remains.

In rat cerebellum, DNA content is only 3% of maximal at birth, and increases rapidly to adult levels during the first 3 weeks after birth (Fish and Winick 1969; Patel et al. 1973). Some of the Purkinje cells and other large neurons are formed before birth, but many neurons as well as glia are formed after birth; basket, stellate and granule cells are all formed postnatally (Altman 1969). Postnatal undernutrition causes a greater deficit in both weight and cell number in cerebellum than in cerebrum, reflecting its later, more rapid growth (Chase et al. 1969; Dickerson and Jarvis 1970; Winick et al. 1972a).

With postnatal undernutrition, the timing of the peak velocity of DNA increase is not delayed, but the magnitude of increase is reduced (Dobbing and Sands 1971). This is in contrast to hypothyroid rats, in which the peak is both lowered and delayed, and the period of cell division prolonged (Balazs 1972). The incorporation of radioactive thymidine in both cerebrum and cerebellum is greatly reduced in undernourished animals, more than would be expected from the decrease in DNA content (Patel et al. 1973). In further studies these investigators (Lewis et al. 1975) found that during the cell cycle, the period of DNA synthesis (S-phase) is prolonged more than doubling time in undernourished animals, accounting in part for the unexpectedly low incorporation of thymidine. In addition, these authors suggest that conversion of thymidine into

the proper DNA precursors might also be retarded.

Administration of [^{3}H]thymidine during a period of rapid cell division will permanently label neurons or glia undergoing their final cell division. Subsequent autoradiography and differential cell counting can indicate which cell types are affected by undernutrition, and whether normal migration has occurred. Winick et al. (1972) and Smart et al. (1973) have examined various brain regions, and found that postnatal undernutrition primarily affects glial division in cerebrum, while in cerebellum, both neuronal and glial division is decreased. Division of cells under the lateral and IIIrd ventricles is decreased, as is the subsequent migration of cells from these regions.

Using differential cell counts, Siassi and Siassi (1973) demonstrated similar effects in somatosensory cortex of rats: nonneuronal components (glia and endothelial cells) were reduced more than neuronal components, and prenatal restriction led to more severe deficits than postnatal. Following prenatal restriction, rat cerebral cortex at 10 days after birth showed decreases in cortical thickness, diameters of neuronal nuclei, and glia to neuron ratios, while cell density was increased. By 21 days, the cortex appeared similar to controls, except that the diameters of neuronal nuclei (indicative of neuron size) were still decreased. Numbers of glial cells had increased while neuronal and endothelial elements did not. With postnatal undernutrition, Bass (1971) and Siassi and Siassi (1973) found decreases in cortical thickness and numbers of glia, delayed stratification and increases in cell density.

EFFECTS ON NEURONAL PROCESSES AND SYNAPSES

The effects of undernutrition on the elaboration of neuronal processes and synapses have been studied by both morphologic and biochemical techniques. As Gambetti et al. (1974) and Sobotka et al. (1974) have recently summarized, these studies have given inconsistent results. Some of the differences can be related to differences in the duration and type of undernutrition used. However, the methods used to quantitate neuronal maturation also contribute to the reported inconsistencies.

Morphologic studies

With morphologic techniques, several studies of postnatal undernutrition in rat indicate less neuropil in cerebral cortex and fewer synaptic endings per neuron for this region (Bass et al. 1970a; Cragg 1972; Gambetti et al. 1972). From microchemical analyses of ganglioside content of cortical layers, Bass et al. (1970a) concluded that synapses and axodendritic processes were decreased in the regions examined. Light microscopic observations supported these conclusions; cortical thickness was decreased, with increased neuronal density and decreased neuropil, poor stratification, and fewer mature neuronal and glial cells as compared to controls.

Cragg (1972) examined by electron microscopy cortical areas of rats undernourished from birth to 3 or 7 weeks, and found a 22–33% increase in neuronal cell density. No change occurred in synaptic size compared to controls, but the average number of synapses per neuron was decreased by 38–41% compared to controls. Development of neuropil was also retarded. In contrast, direct isolation of synaptic endings (Gambetti et al. 1972) gave a higher yield per gram of brain in undernourished rats compared to controls (from 14 days of gestation to 24 days), suggesting that synaptic endings were spared relative to other brain components. However, in a later quantitative electron microscopic study of cortex (Gambetti et al. 1974), these same authors concluded that neuronal density was increased, neuropil decreased, and that synaptic endings were decreased in both size and density. The higher yield of synaptosomes in the earlier biochemical study may be due to better separation of synaptosomes from brains of undernourished animals with less myelin than controls.

Compared to the striking effects of postnatal undernutrition on morphologic maturation of cerebral cortex, cerebellar cortex appears less affected, at least in one study (Clos et al. 1973). At 10 days, no changes were found in yield of synaptosomes, density of synapses, density of dendritic spines, or axonal size.

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Biochemical studies

Transmitters. Synapse maturation and function in brains of undernourished rats have been evaluated by measurement of a) transmitter levels, b) uptake, synthesis and turnover of transmitters, and c) the enzymes involved in synthesis or degradation of transmitters. The level of a given transmitter may remain relatively constant in the face of marked changes in its handling at the neuronal or synaptic level. Thus, measurement of uptake, synthesis or turnover may be a more reliable index of its metabolism than tissue levels (Costa and Ness 1970; Lee and Dubos 1972).

The reported effects of undernutrition on cholinergic, adrenergic, and serotonergic systems are summarized below. The choice of denominator to express the data is critical to the interpretation of many of these results. Several investigators (Lee and Dubos 1972; Shoemaker and Wurtman 1973) have argued that the most appropriate way to express changes in components found primarily in neurons is on the basis of total content, since most of the lower weight in brains of postnatally undernourished rats is due to decreased glia and myelin; thus changes in brain weight, protein or DNA do not correlate with changes in numbers of neurons.

Acetylcholinesterase (AChE) activity has been used as an index of the quantity or maturity of cholinergic synapses. In cerebrum, postnatal undernutrition leads to reduced total levels of AChE, but not concentration, in pups 14 days or younger (Sereni et al. 1966; Gambetti et al. 1972). By 21–24 days, no significant differences from controls were found in the concentration of AChE (Sereni et a. 1966; Gambetti et al. 1972; Sobotka et al. 1974). In this last study, decreased total levels of AChE were still observed at 24 days (calculated from their data); also total AChE and its concentration were significantly decreased in cerebellum, suggesting greater sensitivity of this region. With combined prenatal and postnatal undernutrition, Adlard and Dobbing (1971a, 1972a) reported decreased cerebral levels and concentrations of AChE for a more prolonged period than with postnatal undernutrition alone. In the adult, the concentration of AChE was increased, suggesting a relative 'sparing' of cholinergic nerve endings compared to other brain components (Adlard and Dobbing 1971b, 1972b).

The effects of undernutrition on adrenergic neurons have been examined by measurement of both catecholamine content and metabolism. Decreased total levels of dopamine and norepinephrine have been found in brains of weanling rats exposed to undernutrition either 1 week before birth through weaning (Lee and Dubos 1972; Shoemaker and Wurtman 1973) or at birth through weaning (Sereni et al. 1966; Shoemaker and Wurtman 1973; Sobotka et al. 1974, as calculated from their data). Concentrations of norepinephrine and dopamine were decreased in the studies of Sereni et al. (1966) in which large litter size was used, and of Lee and Dubos (1972) in which mothers were put on 8% protein diets during the last week of gestation, while the other studies (Shoemaker and Wurtman 1973; Sobotka et al. 1974) found little change in concentrations.

Extending their studies, Shoemaker and Wurtman (1973) found the deficit in dopamine was localized primarily in the neurons of the basal ganglia. The initial uptake of norepinephrine into brain was used as an index of the number of catecholamine-containing neurons (or synapses); no change from controls was observed. One interpretation they offered is that numbers of catecholaminergic neurons are not reduced, but storage capacity is. They also found increased brain tyrosine hydroxylase activity, selective concentration of tyrosine and decreased turnover of norepinephrine, all suggesting that brain catecholamines are preferentially conserved during undernutrition. In their study, Lee and Dubos (1972) used a similar schedule of deprivation, but examined the undernourished animals at 2 months, several weeks after return to a normal diet. In agreement with the Shoemaker and Wurtman study, they found increased uptake of tyrosine; in contrast, they found increased norepinephrine uptake, no change in degradation, and decreased tyrosine hydroxylase. Whether these discrepancies are due to differences in age, nutritional states or some other factor is unclear.

Studies of serotonin metabolism during undernutrition are complicated by the acute effects of nutritional status on brain levels of tryptophan and serotonin; protein intake leads to lower

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