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DIET AND THE CENTRAL NERVOUS SYSTEM

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The influence of nutritional disorder on the lipid composition of the central nervous system

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In recent years there has been growing interest in the effects of malnutrition on the developing brain (Dobbing, 1967; Coursin, 1967). The proposition that undernutrition may be associated with impaired intellectual function is quite clearly a topic of considerable medical and social interest. From an economic standpoint nutritional disorder is also of importance, for failure to thrive in some farm animals can also be related to permanent damage to the developing central nervous system. In adults, damage to the central nervous system may result in demyelination, while, in developing animals, incomplete or faulty myelination may be produced by disease or nutritional disorder. Some indication of the nature and extent of such effects can be obtained from a knowledge of the metabolism of neural lipids and from an examination of changes in the lipid composition of brain and spinal cord, for more than half the total brain lipid is localized within the myelin sheath.

Myelin is particularly rich in lipid containing cholesterol, cerebrosides and phospholipids together with protein—the last accounting for about a quarter of the dry weight of myelin. The lipid and protein are firmly associated in fixed proportions within myelin and there are only small differences in its composition even between species (Cuzner, Davison & Gregson, 1965). Experiments using isotopic precursors indicate that the myelin sheath is one of the most metabolically stable structures in the body. Radioactive isotopes incorporated into the myelin of growing animals indicate little change in its constituents in more than a year (Davison, 1964). In addition, lipid biosynthesis is most active during the period of myelination and in the nervous system of adult animals the rate of synthesis of myelin lipid is slow. It has therefore been suggested (Davison & Dobbing, 1966) that the period of myelination may be regarded as a vulnerable period in development, for restrictions at this time could reduce the supply of suitable substrates and, by inhibiting lipid biosynthesis, interfere with the process of myelination. It would be expected that deprivation of the mature nervous system would have little effect.

This hypothesis explains the vulnerability of the developing nervous system and

accounts for the sparing of the adult brain from the effects of starvation. J. Dobbing (personal communication) has for example found that, in adult rats fed on a sucrose diet, very marked loss in body-weight is accompanied by no significant alteration in the composition or weight of the brain. Some evidence suggests that in avian species at least (Joel, Moser, Majno & Karnovsky, 1967) very severe starvation can produce changes in the proportions of tetraenoic and pentaenoic acid in the brain but, even so, no alteration was noted in other lipids. However, minor dietary restrictions applied to suckling rats (Dobbing, 1963–4) can produce significant changes in the cholesterol content and wet weight of the brain. It is of interest that there is depletion of cholesterol and other myelin lipids in the central nervous system of lambs with swayback and Border disease (Howell, Davison & Oxberry, 1964; Davison & Oxberry, 1966). Myelin aplasia in swayback lambs has been attributed to copper and cytochrome oxidase deficiencies (Howell & Davison, 1959) leading to impaired lipid biosynthesis. The sensitivity of the developing brain to nutritional disorder is also seen in phenylketonuria, for both histological and chemical evidence suggests that normal myelination may be impaired (Crome, Tymms & Woolf, 1962; Gerstl, Malamud, Eng & Hayman, 1967), although it is not established that there is a link between such effects and the mental retardation found to accompany the disease. It has been noted that children suffering from kwashiorkor soon become listless and apathetic. Any more lasting mental defects that may be found could possibly be related to the effects of protein undernutrition on the developing brain, for some deficits in myelin lipids have been found in children dying from the disease (Davison, 1967).

Some experimental evidence supports the idea that poor mental performance may be related to the effects of dietary restrictions on the developing brain. Thus, for example, changes in learning behaviour (Barnes, Cunnold, Zimmermann, Simmons, MacLeod & Krook, 1966) resulted from feeding undernourished weanling male rats for 8 weeks on a protein-deficient diet. Similarly the development of cortical electrical activity has been found to be retarded in malnourished pups compared to well-fed animals of the same age (Myslivecek, Fox & Zahlava, 1966).

The question as to the permanence or not of such effects on intellectual performance is clearly of considerable importance. Rehabilitation experiments have been carried out with developing rats and pigs after subjection to various periods of undernutrition (Dobbing, 1966). Dickerson, Dobbing & McCance (1966–7) underfed piglets for a year so that their body-weight was $3\frac{1}{2}\%$ that of controls. Rehabilitation for 2 years on an unrestricted diet failed to restore brain and body-weight to that of normal 3-year-old animals. When rats were malnourished for short periods or late in development it proved possible to restore both brain and body-weight to normal (Dobbing, 1966). There is, then, evidence for the hypothesis that permanent effects on the lipid composition of the brain may be produced by nutritional disorder only during the vulnerable period of development; the possibility that this may be related to diminished intellectual performances remains to be more extensively investigated.

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Observations on the histology and possible pathogenesis of lesions in the central nervous system of sheep with swayback

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Swayback or enzootic ataxia is an ataxic disorder of newborn and young lambs which is associated with low levels of copper in the tissues. Only one case of a similar syndrome has been reported in an adult (McDonald, 1942) and the concept of an insult during a vulnerable period in the development of the central nervous system (CNS) as postulated by Davison & Dobbing (1966) is clearly relevant.

Lesions may be found in three divisions of the CNS: the cerebral hemispheres, large neurones in the brain stem and spinal cord and in the white matter of the spinal cord (Innes & Shearer, 1940; Barlow, Purves, Butler & Macintyre, 1960; Howell, Davison & Oxberry, 1964).

Several changes have been reported in the cerebral hemispheres, including swelling, gelatinous softening and, more commonly, cavitation of the cerebral white matter. Such changes were found in 60% of the lambs examined by Innes & Shearer (1940), in 40% of those seen by Barlow *et al.* (1960), in 20% of lambs seen by us in Liverpool, but they appear to be rare in Australian lambs.

The gross lesion is similar to the cystic change found in human infantile encephalopathies (Courville, 1959; Spais, Palsson & van Bogaert, 1961), a lesion which may be caused by anoxia (Courville, 1959; Clarke & Anderson, 1961). It is also similar to the lesion found in infants who have survived the mother's attempted suicide by coal gas inhalation during late pregnancy (Schwedenberg, 1959). Howell & Davison (1959) found that the activity of the copper-dependent enzyme cytochrome oxidase was significantly lower in the CNS of swayback lambs than in normal controls. McDonald (1942) suggested that cerebral cavitation is found only