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Endocrine Factors Affecting the Maturation of the Brain

Hormones affect the functional activity of the brain in a number of different ways. Adult behaviour is influenced reversibly by a deficiency or excess of thyroid hormone: it is influenced also by androgens or by treatment with adrenocortical preparations. Hormonal imbalance during the period of early growth and development can affect the pattern of neuronal organization of the brain and produce behavioural effects which are irreversible. Thyroid deficiency in early life leads to defective growth of the axons and dendrites of the nerve cells: it appears that thyroid hormone is needed for the differentiation of the neurones and hence for the development of the adult pattern of synaptic connexions in the brain (Eayrs 1968). Recent observations of Balázs and his colleagues have shown that thyroid deficiency delays the biochemical as well as the morphological maturation of the brain: thus thyroid deficiency during the postnatal period in the rat retards the development of the metabolic pattern and the metabolic compartmentation characteristic of the adult brain. Thyroid deficiency also decreases the average size of the neurones, as indicated by their content of protein and RNA, without greatly affecting the final cell number in the brain (Balázs *et al.* 1968). On the other hand administration of thyroid hormone (triiodothyronine) advances the morphological and biochemical maturation of the rat brain: it also leads to the premature termination of postnatal cell formation (as indicated by deposition of DNA) so that there is a significant reduction of 30–40% in the final number of cells. Glia and nerve cells are both affected. It appears that, by advancing the differentiation of the nerve cells, thyroid hormone promotes their migration from the germinating layer, and so causes a premature termination of cell division. This effect is especially marked in the cerebellum, which develops later than other parts of the brain.

Treatment with hydrocortisone in early life also results in a permanent decrease in the final cell number in the rat brain. The rates of synthesis and deposition of DNA are severely inhibited during the period of hydrocortisone administration; and active cell division ceases, as in the normal animal, at about 21 days (Balázs 1972). The end result of treatment with hydrocortisone on cell number is thus similar to that of treatment with triiodothyronine. Eayrs (1968) has observed that early treatment with thyroid hormone causes a later impairment of adaptive behaviour in the adult. However, treatment with corticosteroids has been reported to interfere with later emotional stability and with motor co-ordination in the adult, while leaving adaptive behaviour unaffected (Schapiro 1968). Balázs (1972) has suggested that the functional impairment in the adult may be due to the alteration in organization associated with a reduction in the normal proportion of microneurones so that the normal 'wiring pattern' is altered in certain parts of the brain. The different effects produced by treatment with thyroid hormone and corticosteroids may be due to their acting at different sites or at different times during development, depending on the experimental conditions used. The effects of hormones on the biochemical maturation of the brain have been reviewed elsewhere (Balázs 1972, Balázs & Richter 1972).

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Virus-related Mental Defect and Disorder

Although occasional examples of persistent brain damage had been recorded previously after measles encephalitis and the epidemics of encephalitis lethargica of presumed but unproven virus etiology, and more rarely in infants whose

mothers had contracted chicken-pox or undergone primary vaccination against smallpox during pregnancy, it was the observations of Gregg and Swann, and subsequently many others, on congenital rubella infection which drew attention to the important potential of virus infection as a cause of mental defect.

Gross congenital malformations are, of course, readily discernible at birth and in most instances will have resulted from infection in the first trimester when organogenesis is taking place so that even a virus like rubella, which at other times causes relatively trivial infection, may cause irrecoverable damage. Between the 8th and 12th weeks the cerebral cortex is undergoing its organization into the various molecular layers and this period is a critical time during which maternal stress would be apt to lead to those neuropsychiatric disabilities which result from cortical disorganization. However, although other organs are comparatively well developed in the second trimester, the development of the nerve pathways in the brain is a much more gradual process continuing at least until birth, as does the differentiation of some of the different types of cells in the brain, and myelination is not completed until after birth. Also, of course, in contrast to most other organs where repair or replacement of the essential cells may occur, a dead neurone is not replaced.

Congenital malformations are one expression of a spectrum of virus infections which includes intrauterine death, spontaneous abortion, premature labour and perinatal and even subsequent disease. Direct invasion of the fœtus by the virus may not always be a requisite to the induction of some of the latter results and the severity of maternal illness such as may occur in influenza or hepatitis may determine the outcome of the pregnancy and the effect on the fœtus by less obvious actions, such as anoxia, on placental and fœtal physiology which, in our ignorance, we label toxic or general systemic effects. As far as *in utero* infections are concerned I think that now we need to focus our attention on the possible effect on the brain, not only of possible inapparent infection in the first trimester of pregnancy but of apparent and inapparent infection in the second and even third trimesters. The results of infections in the brain at these times may result in quite subtle changes which may not become evident until the end of the first year of life, or later. The effect of some infections may not become evident until adult life. Any virus infection in which viræmia occurs may possibly affect the fœtus directly but, at least in temperate climates, most of the common virus infections occur before the child-bearing period. Rubella, herpes simplex and cytomegalovirus are the exceptions. Rubella antibody is absent in the sera of about 15%, herpes simplex in 30–60% and cytomegalovirus in about 30–40% of women of child-bearing age, depending on the socio-economic groups from which the women come. In some countries in temperate zones and in all countries in tropical areas insect-borne viruses are also an important cause of infection at all ages.

There are certain sites in the brain which, usually unexplainably, appear to be more vulnerable than others to certain poisons, e.g. the globus pallidus in carbon monoxide poisoning, and to anoxia from convulsions or other cause, e.g. the hippocampus. Similarly, different viruses tend to attack certain areas and cells of the central nervous system presumably because of the presence of specific cell receptors and metabolic requirements, e.g. cytomegalovirus grows well in the ependyma and herpes simplex in glia and neurones anywhere.

Antenatal Infections

Rubella: The effect of rubella in the first trimester has been adequately described but the report of Hardy *et al.* (1969) on 19 children born to mothers who had rubella after the 16th week of their pregnancy indicates the need for further investigation of this group. Only 7 children could be considered completely normal when followed for periods up to four years. The principal anomalies consisted of hearing defects, retardation of physical, mental and motor development and associated difficulties in communication.

Cytomegalovirus (CMV): There have been reports of about a dozen cases of classical neonatal cytomegalovirus disease and 17 cases of atypical congenital infection in recent years (Stern 1971). Six of the survivors among the 29 patients were subsequently found to be mentally retarded. The first trimester is apparently the most dangerous period of infection for the fœtus. However, the majority of infections in women during pregnancy are subclinical and at least some of the fœtuses may escape infection. A number of very large long-term prospective surveys, such as that being undertaken by Stern and colleagues in London, will be required to determine the importance of intrauterine infection with CMV as a cause of mental retardation.

Herpes simplex virus (HSV): Intrauterine and immediately postnatal infection with HSV was regarded, until recently, as either a fatal disease or one causing gross mental defect in survivors. Evidence is accumulating that less severe in-

fections may occur also, sometimes only with skin lesions, but in a follow up of 14 such cases 5 were found to have psychomotor retardation.

Postnatal Infections
Infection with either rubella virus or cytomegalovirus after birth is not of any importance as a cause of mental retardation.

Herpes simplex: It has been apparent for some years that most patients who survive an acute attack of HSV encephalitis have some degree of permanent mental defect. Because of the well-known property of this virus to cause persistent latent infection which may be reactivated at any time the possibility that minor persistent infection in the brain is responsible for some well-known neuropsychiatric disorders is being investigated.

Successful transmission of the degenerative diseases of the brain, kuru and Jakob-Creutzfeldt disease to chimpanzees and New World monkeys (Gajdusek & Gibbs 1971), and the recently reported tissue culture of virus-like particles from the brain of a patient with progressive multifocal leukoencephalopathy (Padgett *et al.* 1971) have provided new opportunities for a better understanding of the etiology and possibly the future prevention of these diseases.

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Morphological Aspects of Mental Retardation

Some cases of mental retardation can be traced to a definite cause, such as chromosomal abnormality and infection, or they may be instances of an established syndrome, i.e. hydrocephalus, phenylketonuria or tuberous sclerosis. These are classifiable cases. Others are unclassifiable and can only be described as mental retardation with or without cerebral palsy and epilepsy. Innes *et al.* (1968) found that of 2,887 cases in North East Scotland, 447 (15·5%) were classifiable. On the other hand, in the smaller series of Angeli & Kirman (1971) 330 of 645 cases were regarded as classifiable.

Classified Syndromes
Phenylketonuria is an instance of morphological changes in such classified disorders. The brains of phenylketonurics tend to be small, chiefly, perhaps, on account of a reduction in the volume of the white matter, which may show astrocytic overgrowth and fibrous gliosis (Crome & Pare 1960). Most of the individual myelin sheaths stain normally but on chemical examination there may be excess of water in the white matter and a reduction of cerebrosides and cholesterol. This may be partly due to the presence of the already mentioned excessive glial tissue, but the findings are also compatible with hypomyelination or, even, slow demyelination. Small areas of frank demyelination have also been encountered and these may be ictal in origin. Some of the older patients develop widespread demyelination indistinguishable from sudanophil leukodystrophy (Crome 1962). On the other hand, some workers (Foote *et al.* 1965) have not been able to detect any significant morphological change in their series of older phenylketonurics. Thus, there is evidence that pathological changes in this condition reflect its clinical variability and are, perhaps, the result of genetic heterogeneity and success or failure of treatment.

Unclassified Cases
The brains of some 80–90% of the unclassified cases can be divided roughly evenly between malformations and gliotic (reactive) encephalopathies. The remainder show no ascertainable change.

Micrencephaly: The smaller the brain, the less intelligent the individual and the shorter his expectation of life. The micrencephalic brain may be equally small in all its parts, but more commonly some parts are more affected than others. Micrencephaly is often associated with other anomalies and with reactive changes. It is not always ascertainable at birth. The head circumference and the size of the brain may at first be well within standard range and then lag behind the normal rate of growth.

Hydrocephalus of the usual hypertensive type, particularly with cranial enlargement, should be regarded as a syndrome, but passive ventricular dilatation ('ex-vacuo') due to atrophy or underdevelopment of the overlying tissue is very common in unclassified cases, particularly in association with micrencephaly.

Prosencephaly: The cerebral hemispheres are normally formed by the transformation of the single prosencephalic vesicle into two telencephalic ones. Should this process be arrested,