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Inherited Characteristics Affecting Neurotropic Behaviour of Scrapie

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A genetic influence has been shown to exert part control on the incidence of scrapie disease in sheep (Dickinson, Stamp, Renwick & Rennie, 1968). The clinical stage of the disease is caused by neurotropic damage, namely neuronal vacuolation and astrocytic hypertrophy. Whatever may be the nature of the agent (see Gibbon & Hunter, 1967) this lethal degeneration can be considered as initiated by an interaction between agent and nervous tissue producing malfunction in a chain of metabolic processes. The distribution of lesions in brains from affected sheep is variable and related to the combination of breed and scrapie type. A similar situation has been found in scrapie passaged in mice; the effects are highly dependent on the mouse strain and the source of the scrapie inoculum (Dickinson, Meikle & Fraser, 1968). In terms of the extent of development of lesions, each mouse within a random-bred strain appears to have an individual response with time after inoculation (Mould, Dawson, Slater & Zlotnik, 1967). With inbred strains the spread is much smaller. Changes in enzymic activity in brain tissue during the long period of development of the disease also show these individual variations. For example, the pattern of decrease in brain acetylcholinesterase with time differs between a random-bred Swiss White strain and an inbred C57 strain. It is probable that reported changes in other constituents would show such variability.

Recent work has confirmed that in lymphoid tissue, e.g. spleen and salivary gland, an appreciable increase in scrapie activity can appear at an earlier stage before comparable activity is reached in the brain. No histopathological change has been described in these tissues. This raises the possibility that there may be genetically controlled conditions determining the passage of scrapie from lymphoid tissue to the nervous system. Genetic control, manifest in the presence or absence of specific components, almost certainly influences the final

process of brain damage in any individual susceptible animal. These characteristics need to be considered in speculations as to the nature of the agent.

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Development of Metabolic Compartmentation in Rat Brain

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The maturation of the cerebral cortex takes place in the rat within a short well-defined period when morphological, electrophysiological and biochemical changes are observed (cf. Himwich, 1962). The capacity for rapid conversion of [^{14}C]glucose into glutamate develops in the rat brain between 10 and 21 days after birth (Gaitonde & Richter, 1966). This phenomenon reflects the final co-ordination of the different pathways of energy metabolism characteristic of the adult brain. It has also been reported that the signs of compartmentation of glutamate develop in the cat neocortex 3–4 weeks after birth (Berl, 1965). In the present work we investigated whether or not the development of these two characteristics of the adult brain coincides in one species. Labelled leucine was used since there was evidence that compartmentation of glutamate can be observed after administration of [^{14}C]leucine (Roberts & Morelos, 1965).

Porton rats (newborn to 35 days old) were injected subcutaneously with [$\text{U-}^{14}\text{C}$]leucine ($10\text{ }\mu\text{C}/100\text{ g}$. body wt.; specific radioactivity 31 mC/m-mole), and at 10 min. after the injection the free amino acids of the brain were separated and analysed. The specific radioactivity of alanine relative to that of glutamate was very low at each age (about 0.1); thus conversion of [^{14}C]leucine into glucose, which might enter the brain via the circulation, was probably negligible, and the incorporation of ^{14}C into amino acids was mainly through conversion of [^{14}C]leucine into [^{14}C]acetyl-CoA in the tissue. The index used for the metabolic compartmentation of glutamate was the high incorporation of ^{14}C into glutamine (relative specific radioactivity > 1) relative to glutamate. The relative specific radioactivity of glutamine was found to be about 0.5 up to the age of 9 days; it reached a value of 1.0 at 15 days and