matters arising

Dysmyelination in Jimpy mouse due to astroglial hyperplasia?

SKOFF[1] recently suggested a new explanation for the central dysmyelination in Jimpy mice. He suggested that astrocytic processes branch abnormally in these mutants before oligodendroglial proliferation. This branching continues until it surrounds most axons. It is further suggested that by this mechanism oligodendrocytes are prevented from reaching the axons, thus leading to secondary inhibition of oligodendroglial development and myelin formation. This concept, however, seems to be inadequately supported by the quantitative and qualitative data given.

The difference in the ratio of astrocyte cytoplasm to optic nerve tissue between hemizygous controls and Jimpys which were calculated in the planimetric study (ref. 1, Table 1) seems to be much too small to support the proposed thesis. A comparison against animals of a different strain is not valid. Considering the absolute cell counts (ref. 1, Table 2) the calculated surface area of six missing, non astrological cells (72 in hemizygotes, 66 in Jimpys) must be taken into account, if the ratio is to be interpreted as an expression of true astrocytic hyperplasia.

No illustration from the premyelination period showing the astroglial processes surrounding the axons is presented. The vast majority of axons in Fig. 2 ref. 1 are not in contact with astrocytic processes. Figure 3 in ref. 1 is irrelevant for Skoff"s argument because it is obtained from optic nerve at day 23, that is, 15 d after onset of myelination. The cited illustrations (ref. 2, Figs 7 and 8) are also irrelevant for the same reason. The effects which Skoff claims are probably concerned with pathologies following the primary event. The concept that reactive astrocytosis follows central nervous system pathology is well established.

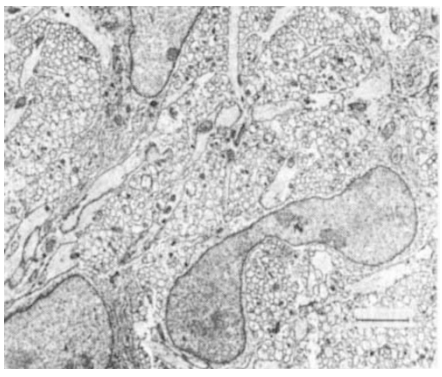

Fig. 1 8-d-old Jimpy mouse optic nerve exhibiting large groups of unmyelinated axons without contact to astroglial processes.

Can astrocytic processes block oligodendrocytes from contacting axons? This hypothesis seems questionable. Blakemore[3-5] produced degeneration of oligodendrocytes, demyelination and heavy astrocytosis in young mice with cuprizone. Demyelinated axons were ensheathed by astrocytic processes. Drug withdrawal led to clear remyelination induced by newly developing oligodendrocytes.

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SKOFF REPLIES,—Meier and Bischoff[1] say that the data used to support the hypothesis[2] that astroglial cells may interfere with myelination is inadequate. They claim that the astrocytic processes in Jimpy optic nerve do not contact the majority of the axons before the onset of myelination and that to show this condition afterwards is irrelevant. In the photograph of an 8-d-old Jimpy mouse optic nerve (Fig. 1 ref. 1), Meier and Bischoff state that large groups of axons are not contacted by astrocytic processes. Careful examination of this picture, however, shows that the large astroglial processes send out very fine branches into the fascicles of axons. I have calculated from the original photograph that 77% of the axons are contacted by astrocytic cytoplasm. At this stage, about 2% of the axons in littermates are in the process of being myelinated[3]. In my own 8-d material from Jimpy optic nerve, I have observed that the astrocytic processes not only contact the majority of the axons but they, in part, surround individual axons; this process continues throughout myelinogenesis[2]. I have demonstrated that the abnormal branching of astrocytic processes in the optic nerve begins 2–3 d before the onset of myelin formation. Since this astrogliosis (increase in processes and filaments) begins before myelinogenesis, it is reasonable to conclude that the astrocytic abnormality is not a reaction to abnormal myelination.

In response to the comments[1] that the ratio of astrocytic cytoplasm is too small to support the astroglial hypothesis, these ratios represent a 39% increase over the Swiss strain and an 18% increase over the heterozygote (the term hemizygote was used in the original paper). Concern over the effect of the missing cells on the above ratios is irrelevant since the area of the astrocytic cytoplasm was directly determined rather than by multiplying the number of astrocytes by an average area. The ratios were included to show that the total amount of astrocytic cytoplasm seems to be increased in electron microscopic preparations. It should be stressed that an increase in glial cytoplasm is not essential for an increase in the branching of their processes (two cells of a given volume can take on entirely different geometric configurations).

The Jimpy mice in this study were always compared with their littermates[2]. The Swiss mouse was used as a control for the entire strain because gliogenesis seems somewhat abnormal in most animals of the litter. Electron microscopic observations of Jimpy littermates show varying degrees of astrogliosis in both optic nerve and spinal cord; the number of axons being myelinated in the branchial spinal cord also varies considerably in littermates of identical body weights.

The model of demyelination using cuprizone[4] is important because it shows that normal animals can remyelinate after the drug has been removed from their diets. But this study does not explain the mechanism of remyelination, that is, whether the astroglial cells first withdraw their processes or whether the oligodendroglial cells displace them. In contrast to this model, most human demyelinating diseases[5-8] exhibit an astroglial reaction but the degree or remyelination is poor to nonexistent.

The earliest detectable morphological abnormality in this study of Jimpy mice lies in the astrocytes. To date, there is neither morphological nor biochemical evidence to suggest that the axons are abnormal at the onset of the astrogliosis. It remains to be deter-