Possible Annular Distribution of Copper in the Myelin of Spinal-Cord Nerves with Special Reference to the Sheep

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Our recent neurochemical studies of congenital myelin disorders in lambs and piglets have included fairly detailed chemical analysis of the spinal cord both in experimental (Patterson et al., 1971a) and the naturally occurring form (Patterson et al., 1974b) of Border disease in lambs. The aetiological, pathological and other characteristics of the disease have been reviewed by Patterson (1974) but essentially it is a neonatal disease of lambs arising through infection of the foetus in utero with a virus. Clinically, the affected lambs are seen as 'hairy-shakers', i.e. the birth coat is hairy instead of woolly and they exhibit tonic-clonic muscular spasms. Histologically, sections of spinal cord show a generalized deficiency of myelin.

We have noted that affected lambs are mildly hypocupraemic (Patterson & Sweasey, 1973; Patterson et al., 1974a) and the above-mentioned neurochemical study of field cases showed that the spinal cord possessed both the characteristics of retarded development and demyelination. The one conclusion was based on spinal-cord weight, DNA and myelin lipid contents and the other on the presence of esterified cholesterol (none normally detectable at birth), the fatty acid composition of these esters and the relatively greater decrease of the plasmalogen content compared with other myelin lipids. A striking observation was that the spinal cord of affected lambs was actually richer in copper (when expressed as μg/g) than normal healthy cord (see Table 1) although, in both cases, approx. 80% of copper was located in the myelin.

Purified myelin was isolated in much lower yield from affected compared with healthy lambs but it was much richer in copper (59.2 and 17.7 μg/g respectively for pooled preparations).

Lambs affected with Border disease suffer from generally retarded morphological development [together with certain specific features of dysmorphogenesis: see Terlecki et al. (1973)] as well as hypomyelinogenesis of the central nervous system, and it was considered that, from the above-mentioned copper data, Border disease may be a useful model system from which to deduce the distribution of copper in the myelin of normal spinal-cord nerves.

It has already been proposed that there are two phases of myelination in the spinal cord of the lamb (Patterson et al., 1971b) and this observation has been confirmed for the pig by Foulkes & Patterson (1974ab). In the lamb, the first phase of activity occurs in the central nervous system at about 20 days before and the second 10–20 days after birth. Our recent study of field cases of Border disease suggested that, neurochemically, the spinal cord of newborn affected lambs had developed to a stage approximately equivalent to 124 days conceptual age (i.e. about 20 days less than the usual full-term lamb). We

Table 1. Spinal-cord weight, myelin and copper contents in normal newborn lambs and lambs affected with Border disease

The values are means±s.e.m. with the number of observations in parentheses.

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<th>Healthy (10)</th>
<th>Affected (16)</th>
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<tr>
<td>Cord weight (g)</td>
<td>10.65 ± 0.40</td>
<td>8.39 ± 0.29*</td>
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<tr>
<td>Isolated purified myelin (mg)</td>
<td>641 ± 36</td>
<td>208 ± 23*</td>
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<td>Copper concentration in cord (μg/g of dry matter)</td>
<td>5.92 ± 0.45</td>
<td>9.63 ± 0.48*</td>
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<tr>
<td>Total spinal-cord copper content (μg)</td>
<td>14.68 ± 1.04</td>
<td>14.92 ± 0.93</td>
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* P value for the difference <0.001.

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had already suggested that neonatal swayback arose through a deficiency in the supply of copper from the dam to the foetus during the first phase of myelination (Patterson et al., 1971b) and the present data for Border disease now suggest that, during this phase of activity in normal and affected lambs, the axons of spinal-cord nerves are usually surrounded with spiral layers of myelin (Peters, 1960) that are rich in copper. Afterwards the layers of myelin with a low copper content are formed and in Border disease these probably lack stability as indicated by the neurochemical evidence suggestive of demyelination. The comparison between normal and Border-disease myelination is made schematically in Fig. 1.

Thus it is proposed that in normal myelination of the lamb an annulus of copper-rich layers of myelin is formed and completed before birth. Later, the successive layers formed perinatally and particularly during the postnatal phase of myelination contain very little copper. These proposals are consistent with our observations on the neurochemistry of normal and Border-disease spinal cord. However, there is at least one alternative hypothesis. The protein of 'early' myelin in Border-disease lambs might contain approximately three times the number of copper-binding sites compared with normal lambs but, against this, no increase in the proportion of protein or change in the electrophoretic behaviour of myelin lipoprotein and basic proteins have been found in isolated myelin from Border-disease lambs. Also, the fact that spinal cords of normal newborn and affected lambs contain virtually identical total amounts of copper would seem to support our preference for the former hypothesis.

Foulkes, J. A. & Patterson, D. S. P. (1974b) Brain Res. in the press
Patterson, D. S. P., Sweasey, D. & Hebert, C. N. (1971b) J. Neurochem. 18, 2027–2040