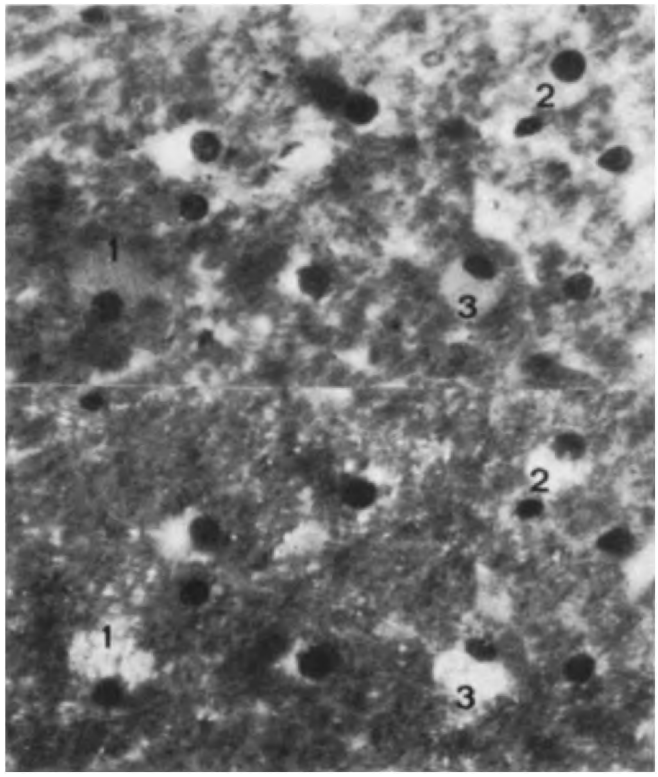

Fig. 3 Top: type 2 inclusion in the white matter around an acute plaque of multiple sclerosis. Note the intracellular site of these inclusions (1, 2, 3), which were stained metachromatically orange-brown in the section. Cresyl violet (×960). Bottom: same field viewed in polarized light.

The metabolic interpretation of the neuroglial lipid inclusions in multiple sclerosis is speculative. They could result from defective cerebroside synthesis and increased production of sulphatide or, possibly, by failure in extrusion of membrane from the myelin-formative cell, so that lipid accumulates intracellularly.

It is unlikely that the inclusions reflect remyelinating activity, because they occur in apparently normal white matter distant from the demyelinating edge and, moreover, their histochemical characteristics do not correspond with those of the lipids that temporarily appear within interfascicular oligodendroglia during myelination[23–26].

We thank Dr David Haler, Mr Douglas High, Dr Keith Mant, Professor Keith Simpson and Dr Peter Sylvester for brain samples.

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Received April 29; revised July 9, 1971.

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Nature of the Nerve Lesion caused by a Pneumatic Tourniquet

THE use of a tourniquet around a limb may be followed by damage to peripheral nerves. This lesion has been investigated experimentally in cats[1,2] and the results suggested that in most cases the nerve damage was limited to the portion of the nerve under the tourniquet. Nerve fibres conducted normally distal to this level, with either a conduction block or a reduced conduction velocity at the site of the tourniquet. Histological studies showed localized demyelination under the tourniquet with preservation of axonal continuity. A similar pathological change is believed to occur in many forms of human pressure palsy, and the conclusion that the nerve damage is due to ischaemia has been widely accepted.

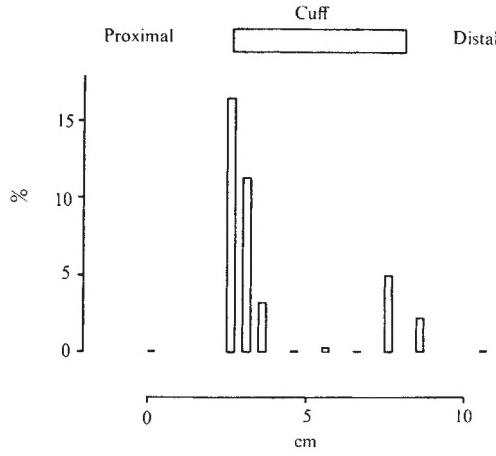

Fig. 1 Histogram to show proportion of abnormal fibres in transverse sections of medial popliteal nerve at different levels in relation to site of tourniquet (5 cm cuff inflated to 1,000 mm Hg for 75 min). Approximate position of cuff shown above. The specimen was taken 3 months after tourniquet. Nerve was fixed by perfusion with buffered glutaraldehyde and post-fixed with osmium tetroxide, 1 μm transverse sections were stained with toluidine blue, photographed, and counts made from enlarged prints[5]. Abnormal fibres (axon diameter 5 μm or greater, myelin thickness less than 1 μm) are expressed as a percentage of the large fibre population.

We have recently done some further experiments using a sphygmomanometer cuff inflated to 1,000 mm Hg around the hind limb of the baboon for 1–3 h. A brief preliminary account of the technique and of the resulting changes in nerve conduction has been published[3]. In the course of the experiments, it became clear that the role of direct pressure in producing nerve damage had been underestimated by previous workers. Two pieces of evidence for this can be cited.

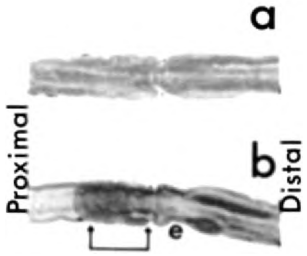

Fig. 2 Single fibres from medial popliteal nerve 1–4 days after tourniquet (5 cm cuff at 1,000 mm Hg for 90 min), to show different stages of invagination at nodes of Ranvier. Fibres were taken from a portion of nerve under the proximal edge of the cuff. Perfusion-fixation was carried out with buffered glutaraldehyde followed by post-fixation with osmium tetroxide; single fibres teased apart in 'Epon'. Symbol in *b* is as in Fig. 4.

(1) With the relatively wide (5 cm) cuff used, it has been found consistently that the nerve damage is maximal under the edges of the cuff or is restricted to these regions. This has been true of all stages of the pathological change in nerves studied for up to 6 months after the tourniquet had been applied. It has been demonstrated in single teased fibres and in transverse sections (Fig. 1). (2) The nature of the pathological change was best appreciated by examining single teased fibres by light and electron microscopy. In essence, the early change consisted of a dislocation of the nodes of Ranvier of the large-diameter myelinated fibres. The mildest form was a slight invagination of one paranode into the adjacent one (Figs. 2*a* and 3). Deeper invagination is illustrated in Figs. 2*b* and 4; it is accompanied by infolding of the myelin of the ensheathing paranode, with movement of the nodal axoplasm and axonal membrane away from the point of junction of the two Schwann cells. The dislocated nodal part of the axon could still be identified by the thickening of the axonal membrane and by the presence of characteristic transverse bands. The junction of adjacent Schwann cells was identified by their microvilli. If one assumes that the original site of the nodal axon was at the point of junction of the two Schwann cells, there must have been movement of the axon relative to the Schwann cell junction of approximately 30 μm, accompanying the invagination of the paranodal myelin.

A penetration of one paranode by another deeper than that shown in Fig. 4 may occur. In longitudinal sections of single fibres, it has not been unusual to see invagination and movement of the nodal axon which has proceeded for 100–200 μm. In such cases there is partial or complete rupture of myelin lamellae in the invaginated region.

All these changes are seen within the first few hours after the tourniquet and, by the end of the first week, invagination of myelin is beginning to be followed by demyelination. In our experience, the demyelination has usually been restricted to the region within 200 μm of the node of Ranvier. Demyelination of whole internodal segments has been rare. When teasing single nerve fibres, the striking feature of these lesions is that the changes described above have a clear polarity, the direction of invagination always being away from the cuff towards uncompressed tissue.

Fig. 3 Electron micrograph (LS) of nodal region shown in Fig. 2*a*.

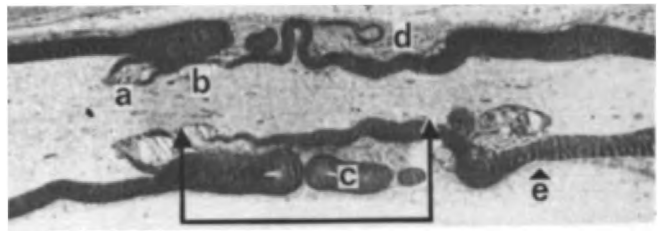

Fig. 4 Electron micrograph (LS) of nodal region shown in Fig. 2*b*. *a*, Terminal myelin loops of ensheathing paranode; *b*, terminal myelin loops of ensheathed paranode; *c*, myelin fold of ensheathing paranode cut tangentially; *d*, Schwann cell cytoplasm; *e*, microvilli indicating site of Schwann cell junction. Large arrows show length of ensheathed paranode (approximately 20 μm).

From the nature of the lesion, its polarity, and its distribution under the cuff, we therefore conclude that it is due to direct pressure and not to ischaemia. The principal evidence cited by previous authors against the possibility of direct pressure producing nerve damage is the experiment described by Grundfest[4], in which the pressure in an oxygenated chamber enclosing excised frog nerve was increased to approximately 1,000 atm before conduction was abolished. But this is a different situation from that which occurs when a pneumatic cuff is inflated around a limb. In the latter case there is a pressure gradient in the tissues between the portion under the cuff and that beyond its edge. Our results indicate that in these circumstances, longitudinal movement of the axon and its myelin occurs with respect to the Schwann cell. This change precedes demyelination.

This work was supported by the MRC and by the Muscular Dystrophy Group. J. O. is a Wellcome senior research fellow in clinical science.

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Received August 18, 1971.

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