The Cause of Nerve Damage in Acute Compression

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Experimental results presented at a previous meeting (Gilliatt, Fowler, and Ochoa, 1972) threw doubt on the classic concept that acute pressure lesions of peripheral nerves are due to obliteration of the neural blood supply, and thus to ischaemia of nerve fibers. Using a cuff inflated to 1000 mm Hg round the leg of the baboon for 1 to 2 hours, it had been found that the anatomical lesions were concentrated under the edges of the cuff, with sparing in the centre (Ochoa, Fowler, Danta, and Gilliatt, 1971). Furthermore, the lesions themselves involved displacement of structures within the nerve fibres, suggesting that there had been axoplasmic movement from the site of compression towards uncompressed tissue.

These results emphasised the importance of direct pressure in causing the nerve damage and cast doubt upon the role of ischaemia (Ochoa, Fowler, and Gilliatt, 1972). It seemed possible that a similar mechanism might operate in human pressure palsies, although there appeared at first to be some discrepancy between the high cuff pressure necessary to produce the lesion in the baboon and the relatively mild pressure that often seems to be sufficient to produce neurapraxia or "Saturday-night" palsy in man. Accordingly, we looked for a method of applying pressure to peripheral nerves in the baboon which would simulate the human syndrome more closely. In the method we have selected, a thin (1.6 mm diameter) nylon cord with a weight attached is placed on the skin at right angles to the course of a superficial peripheral nerve such as the ulnar just below the elbow, or the anterior tibial nerve at the ankle. With a weight of 1.5 to 2.0 Kg attached, the pressure of the cord through the skin for two hours was usually sufficient to produce a conduction block in the nerve that lasted for several weeks. In these cases, the pressure on the skin under the cord ranged from 1.6 to 2.1 Kg/cm^2. By reducing the area of contact between the cord and the skin to that part which lay directly over the nerve, it was possible to produce partial blocks in the anterior tibial nerve with a weight as small as 0.5 Kg, the pressure on the skin under the cord being approximately 1 Kg/cm^2. In one of our anterior tibial nerves, mild histological changes (without a conduction block) were produced by only 0.75 Kg/cm^2.

In comparing these figures with our previous results obtained by using a pneumatic tourniquet, it should be remembered that the pressure on the skin under a cuff inflated to 1000 mm Hg would be

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1.36 Kg/cm^2. From the two sets of experiments it therefore appears that pressure palsies of a similar type are likely to occur in man when pressures of more than 1.0 - 1.5 Kg/cm^2 are developed on the skin and allowed to operate for periods of 1 to 2 hours.

Histologic study of the lesions produced by the nylon cord confirmed that they were similar in character to those produced previously by a pneumatic cuff. In the large myelinated fibres, there was displacement of the nodes of Ranvier away from the site of pressure, with buckling and stretching of the paranodal myelin and subsequent paranodal demyelination. In the anterior tibial nerve, up to five nodes of Ranvier on a single fibre might be affected at each edge of the lesion, with one or two unaffected nodes at the centre. Thus, this lesion, which approximates more closely to human pressure palsies than the previous tourniquet lesion, makes the role of ischaemia even less significant. This follows from the fact that the nodes of Ranvier are normal at the centre of the compressed zone where ischaemia would be expected, whereas nodal damage can extend for several millimetres along the nerve beyond the part directly compressed by the nylon cord.

Does the characteristic histologic lesion described above occur in man? Our present evidence for this rests on a single human case. In the course of a separate study of chronic entrapment in man, we obtained at autopsy the median nerve of a 39-year-old man who died of intracerebral haemorrhage. For several hours before death the patient had been in a state of decorticate rigidity with extension of the elbows and flexion of the wrists. This posture, which was maintained after death, had resulted in pressure on the median nerve under the distal part of the flexor retinaculum at the wrist. The nerve was not macroscopically abnormal but loosely teased bundles showed abnormalities extending over a distance of approximately 7 mm. In single fibres there had been movement of the nodes of Ranvier away from the centre of the lesion with stretching and invagination of paranodal myelin, similar to that seen in our experimental preparations. No demyelination had occurred, suggesting that the lesion was only a few days old. An early cellular reaction was present, indicating that the lesion had occurred during life.

The presence of these distinctive histologic features in a human nerve, thought to have been compressed during life, supports the view expressed earlier in this paper, that the mechanisms we have studied in experimental animals also operate in human pressure palsies.

DISCUSSION

Peter Dyck (*Rochester, Minn.*): Several years ago, while studying the effect of repeated applications of a tourniquet on nerve of rats in an attempt to produce the

histologic feature of "onion bulbs," we found that we could produce paranodal demyelination and some of the histologic features described in this paper, from a momentary application of a specially devised cuff. We did not, however, discover the curious displacement and invagination of nodal regions as described here. The fact that such typical lesions can be produced by applications lasting less than 1 minute seems to be evidence that mechanical compression rather than anoxia causes these lesions. It would be interesting, I think, to hear the authors' views on the mechanism of nerve fiber damage. Is the axoplasm partially squeezed out of the compressed region? Is there disruption of the microtubules of the axoplasm? Is there an arrest of axonal flow? Would you comment on your views of the mechanism?

Arthur Asbury (*Philadephia, Pa.*): I'd like to congratulate Dr. Gilliatt and his group for bringing this series of studies to our attention. It seems to me that the important morphologic observation here is the telescoping of myelin at the nodes of Ranvier. This must be part and parcel of the mechanical lesion. As such, it provides extraordinarily strong evidence against ischemia mediating the conduction block or neuropathy produced.

The second thing is, as I understand it, with the nylon cord technique, the lesion is graded as one proceeds away from the center of the lesion, so that telescoping becomes less severe with each successive internode. At any given distance from the center of the lesion, all of the fibers appear to be affected more or less the same in terms of degree of nodal pathology.

If this is so, it seems that one might use this preparation to correlate the morphologic abnormalities at nodes of Ranvier with the electrophysiology of each node, using the technique of Rasminsky and Sears. One might make serial observations at successive nodes through one of these nylon cord lesions and see increasing and then decreasing degrees of delay, or perhaps block. Thus it might be possible, for the first time, to get a look at what has happened at a given node of Ranvier both electrophysiologically and morphologically.

Derek Denny-Brown (*Cambridge, Mass.*): I am, of course, greatly interested in these findings of Dr. Gilliatt. And I think the displacement of the node in different directions on either side of the compressed zone is very convincing. However, Dr. Gilliatt seems to have set aside too easily the very good correlation between duration of compression and degree of paralysis. Certainly, in the clinic, this is very obvious. How would he explain that it requires over an hour of tourniquet application to produce a lesion in man?

Also, the deduction seems to be that the loss of myelin is due to distortion of myelin. We found that with increasing degree of compression or duration it was possible to demyelinate half of each segment of the area compressed. How does Dr. Gilliatt explain the extension of loss of myelin away from the area of distortion at the node?

Dr. Gilliatt: If I can, I shall answer Dr. Denny-Brown's points first. There is no question that in the experimental animal, as is one's impression in the clinic, the duration of compression does affect the severity of the lesion. This might imply an ischemic component. Alternatively, it could imply that the effect of a mechanical force takes time to develop and that more extensive displacement occurs with longer periods of compression. There is no doubt that it is possible to produce these lesions with periods of compression that are only just sufficient to abolish conduction in the axons; something under an hour will produce these lesions with an appropriate compressing force, which is really a short time in relation to deprivation of blood supply. If one simply eliminates the blood supply to the limb for that period, the effect on conduction is always reversible.

On the whole, we think that we do not have positive evidence of an ischemic contribution in these or in the tourniquet experiments.

The extent of myelin loss is certainly a point of great interest because it is quite clear from Dr. Denny-Brown's experiments in the cat that this extends along the internode in a way that does not occur in the baboon; this requires further study and the application of the technique to other species.

As for Dr. Asbury's and Dr. Dyck's questions, I wonder whether Dr. Ochoa might be asked to reply to them?

Dr. Ochoa (*closing discussion*): I should like to answer Dr. Dyck's question briefly and then perhaps spend a minute in paying tribute to an obstinate Frenchman. This peculiar paranodal lesion of large-diameter, myelinated fibres appears to be the consequence of squeezing of the axoplasma along the nerve fibres. This is evidently caused by axial forces operating in opposite directions away from the site of compression. The axoplasm finds an obstacle in the normal narrowing of the axon at the node; the obstacle is pushed forward and dislocated. The myelin sheath follows passively (the lamellae are attached to the axonal membrane) and stretches on one end and infolds on the other, like an intussusception. Both the stretched and the infolded myelin at the paranodes are now detached from their Schwann cells and they disintegrate.

Having been concerned with the study of the fine anatomy of this lesion, I must now acknowledge the pioneer work of Ranvier. In the 1870s, he was determined to show that the so-called "incomplete nodes" were not normal structures, but artifacts. He set out to reproduce such nodes experimentally and he succeeded.

This picture [slide] from Ranvier's book published in 1878, illustrates five myelinated fibers, two of which show nodes without a nodal gap—"incomplete nodes." From the French text [slide] you may see that Ranvier was perfectly aware of the fact that such nodes resulted from displacement of the myelin from one segment into the next. It is interesting that Ranvier used local compression as the means of producing these nodes and, amazingly, he did so with this spring clip, as did Professor Denny-Brown and as Brenner did with this other famous spring clip [slide] in 1944.

An Outbreak of a Previously Undescribed Toxic Polyneuropathy Due to Industrial Solvent

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In June 1973, a 43-year-old employee of a plant that produced plastic-coated and color-printed fabrics was studied at Ohio State University Hospital for a motor neuropathy that had developed over a 6-week period. Upon identification of a similar neuropathy in 5 co-workers, a major clinical, toxicologic, and epidemiologic survey was begun with eventual screening of 1,161 employees and the finding of 182 persons with abnormal electrodiagnostic examinations and 79 with clinical evidence of neuropathy.

In all cases, the onset was insidious. Motor symptoms began with limb fatigue that slowly progressed to overt weakness. Sensory