J. Physiol. (1980), **308**, *pp.* 125–157
With 2 plates and 14 text-figures
Printed in Great Britain

ULTRASTRUCTURAL DIMENSIONS OF MYELINATED PERIPHERAL NERVE FIBRES IN THE CAT AND THEIR RELATION TO CONDUCTION VELOCITY

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(*Received 5 January 1979*)

SUMMARY

1. The ultrastructure of all the afferent fibres, or all the efferent fibres, was studied in selected nerves from chronically de-afferentated or de-efferentated cat hind limbs perfusion-fixed with glutaraldehyde.

2. The following parameters were measured: number of lamellae in the myelin sheath (n), axon perimeter (s), external fibre perimeter (S), axon cross-sectional area (A). Fibres were allocated to afferent groups I, II, III or efferent groups α and γ according to the number of lamellae in the myelin sheath.

3. The thickness of the myelin sheath (m) was linearly related to axon perimeter within the range $s = 4\ \mu$m to $s = 20\ \mu$m (groups II, III and γ). The relation $m = 0{\cdot}103\ s - 0{\cdot}26$ provided a good fit for all afferent and efferent axons in this range in several different anatomical muscle nerves in three cats. The myelin sheaths were thinner in a fourth, presumably younger, cat.

4. The myelin sheaths were relatively thinner for large fibres in groups I and α ($s = 20$–$50\ \mu$m). The results are interpreted in one of three ways. Either m tends to a limit of about $2{\cdot}2\ \mu$m, or m is linearly related to s such that for large fibres $m = 0{\cdot}032\ s + 1{\cdot}11$.

5. Alternatively, m may be considered to be proportional to $\log_{10} s$ for all sizes of axon so that $m = 2{\cdot}58 \log_{10} s - 1{\cdot}73$. The interpretation that there are two separate linear relations for large and small fibres is favoured.

6. The ratio of axon to external fibre perimeter (g) falls from about 0·70 for group III and small γ fibres in the cat to about 0·62 for group II and large γ fibres and then rises again to 0·70, or even 0·75 for group I and α axons.

7. The above relations between m and s are combined with the observations of Boyd & Kalu (1979) that $\theta = 5{\cdot}7\ D$ for groups I and α and $\theta = 4{\cdot}6\ D$ for groups II, III and γ. It is shown that $\theta = 2{\cdot}5\ s$ approximately for all sizes of axon (s from material fixed for electron microscopy) in rat, cat and man. The accuracy of this equation may be improved by deducting 3 m/sec in the case of small fibres. This conclusion is compatible with experimental observations of the relation between l and D (Hursh, 1939; Lubinska, 1960; Coppin, 1973) and between l and θ (Coppin & Jack, 1972).

8. From the theoretical analyses of Rushton (1951) and others θ should be proportional to the external dimensions of the fibre rather than to axon size. It is shown

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0022-3751/80/2080-0936 $07.50

that the thinning of the myelin sheath ought to affect θ substantially. Thus some other factors must compensate for the thinning of the sheath.

9. Small fibres are significantly more non-circular than large fibres. From the quantitative data of Arbuthnott *et al.* (1980) it is concluded that non-circularity may contribute to the fact that $\theta \propto s$ rather than $\theta \propto S$, but cannot wholly account for it. Other possibilities considered are that axoplasmic resistivity or specific nodal conductance may differ for large and small fibres.

10. It is suggested that myelinated peripheral nerve fibres may fall into two distinct classes with different properties, one comprising groups I and α and the other groups II, III and γ. The conclusion predicted from theory may apply to each of these classes separately so that $\theta = 2{\cdot}0\,S$ for the large-fibre class and $\theta = 1{\cdot}6\,S$ for the small-fibre class.

INTRODUCTION

The scaling factor for converting external (or total) fibre diameter in microns into conduction velocity in metres per second for the largest myelinated fibres in normal cat nerves was shown to be 6·0 by Hursh (1939). The scaling factor for different functional groups in chronically de-afferentated or de-efferentated nerves in the cat was subsequently shown to be 5·7 for group I afferent fibres and α efferent fibres, but considerably less, 4·6 in fact, for group II and III afferents and for γ efferents (Boyd, 1964, 1965; Boyd & Davey, 1968; Boyd & Kalu, 1979). Not only was the factor different for large and small fibres, but it did not increase progressively with fibre diameter. Thus, it had the constant value of 4·6 for all fibres up to about 11 μm in external diameter and 5·7 for all fibres over about 11 μm. In the overlap zone of 10–12 μm there appeared to be a discontinuity in the scaling factor which suggested that fibres in groups I and α must have distinctly different structural or functional features, or both, from fibres in other groups. An ultrastructural study of all the individual fibres in a number of chronically de-afferentated or de-efferentated nerves was undertaken to identify any structural differences between fibres in different functional groups. Preliminary results were published (Arbuthnott, 1972; Boyd & Kalu, 1973; Arbuthnott, Boyd & Kalu, 1975, 1977) and the details are given in the present paper. The following parameters were measured for every fibre in each nerve save those cut through clefts of Schmidt-Lanterman; axon perimeter, external fibre perimeter, the number of lamellae in the myelin sheath and the cross-sectional area of the axon.

METHODS

The left hind limb of two cats was chronically de-afferentated and that of two further cats de-efferentated, and the limbs were perfusion-fixed with glutaraldehyde, as described by Boyd & Kalu (1979). Details of the preparation of material for electron microscopical study of every fibre in each nerve, using the one-hole mount technique of Arbuthnott (1974), were given by Arbuthnott, Ballard, Boyd & Kalu (1980). Individual fibres were photographed at a nominal electron-microscopic magnification of 3000 or 5000 times for large fibres and 7500 times for small fibres. The AEI EM6B microscope was calibrated using polystyrene beads of known diameter. The axon and external perimeters of each fibre were measured with a Pathfinder Map Measure. Axon cross-sectional area was measured with a Stanley hand planimeter. All measurements were converted to microns. Counts of myelin lamellae for small fibres were made on prints of the whole fibre (usually $\times$ 2·5), while for large fibres part of the sheath was photographed at a

nominal electron-microscopic magnification of 10,000 times. Counts of lamellae were made at a point on the fibre where resolution of the lamellae was greatest and as distant from marked convexities or concavities in the sheath as possible. In the case of small fibres the innermost layer of the sheath, which is further from the adjacent layer than the distance between the major period lines elsewhere in the sheath, was excluded from the measurements.

Symbols used in this paper are as follows:

s, axon perimeter
S, external fibre perimeter
n, number of lamellae in myelin sheath
m, thickness of myelin sheath
d, axon diameter
D, external (total) fibre diameter
A, axon cross-sectional area
l, internodal length
R_i, resistivity of axoplasm

$$g = \frac{s}{S}$$

θ = conduction velocity

$$\phi = \frac{\text{cross-sectional area of axon}}{\text{area of circle with same perimeter}} = \frac{A}{s^2/4\pi}$$

The relation of the thickness of the myelin sheath to the size of the axon has been expressed in the past as the ratio, g, of axon diameter to external fibre diameter. Since axons are non-circular to a varying degree it is more meaningful to use the ratio of axon perimeter to external fibre perimeter, and g, defined in this way, is used throughout this paper. The term 'fibre' generally refers to an axon and its myelin sheath.

RESULTS

All the afferent fibres were studied in one sample of each of the nerves to the flexor digitorum longus lateralis (f.d.l.l.) and soleus muscles from two different cats. These nerves were chosen because their afferent fibre-diameter histograms frequently show three distinct peaks corresponding to afferent fibre groups I, II and III (Boyd & Davey, 1968; Fig. 1*C* and *D* of this paper). All the efferent fibres were studied in the nerves to the tibialis posterior, soleus and peroneus longus muscles in two cats. These nerves were chosen because of the known variations in their γ fibre populations (Boyd & Davey, 1968). For example, the nerves to soleus and peroneus longus tend to have γ populations of relatively small and relatively large diameter, respectively, whereas the γ fibres to tibialis posterior often resolve into two groups, large and small, the thickly and thinly myelinated γ fibres of Boyd & Davey (1962, 1968). Thus it was possible to compare the relation between axon size and myelin thickness in several different nerves in the same cat, and also to determine whether or not the same relation applied to afferent and efferent fibres in four different cats.

The designation of individual motor fibres as α or γ presents little difficulty as there is usually little overlap between their external fibre diameter distributions and in some nerves there is a clear separation between the two groups (Boyd & Davey, 1968). Afferent groups I, II and III tend to overlap considerably, however, even in nerves showing three distinct peaks in their afferent fibre-diameter histogram. Since fibres are rarely circular and vary in cross-sectional area along the internode (Berthold, 1968; Arbuthnott *et al.* 1980) fibre diameter is not a very reliable criterion for the

subdivision of fibres into groups. The number of myelin lamellae, however, is almost constant along an internode, and Friede & Samorajski (1967) suggested that it was a better criterion to employ. This has been done throughought this paper. It can be seen from Fig. 1 that not only do afferent fibres resolve into three groups in a histogram of the number of myelin lamellae, as they do in one of external diameter, but furthermore the three peaks may be more distinct in the histogram of the number of lamellae (cf. Fig. 1 *A* and *C*). No attempt was made in the present work to estimate the overlap between the three afferent groups as at best such an estimate can be very approximate only. It was felt useful, however, to indicate where the minima in the histogram of myelin lamellae occurred by using different symbols for groups I, II and III, and for

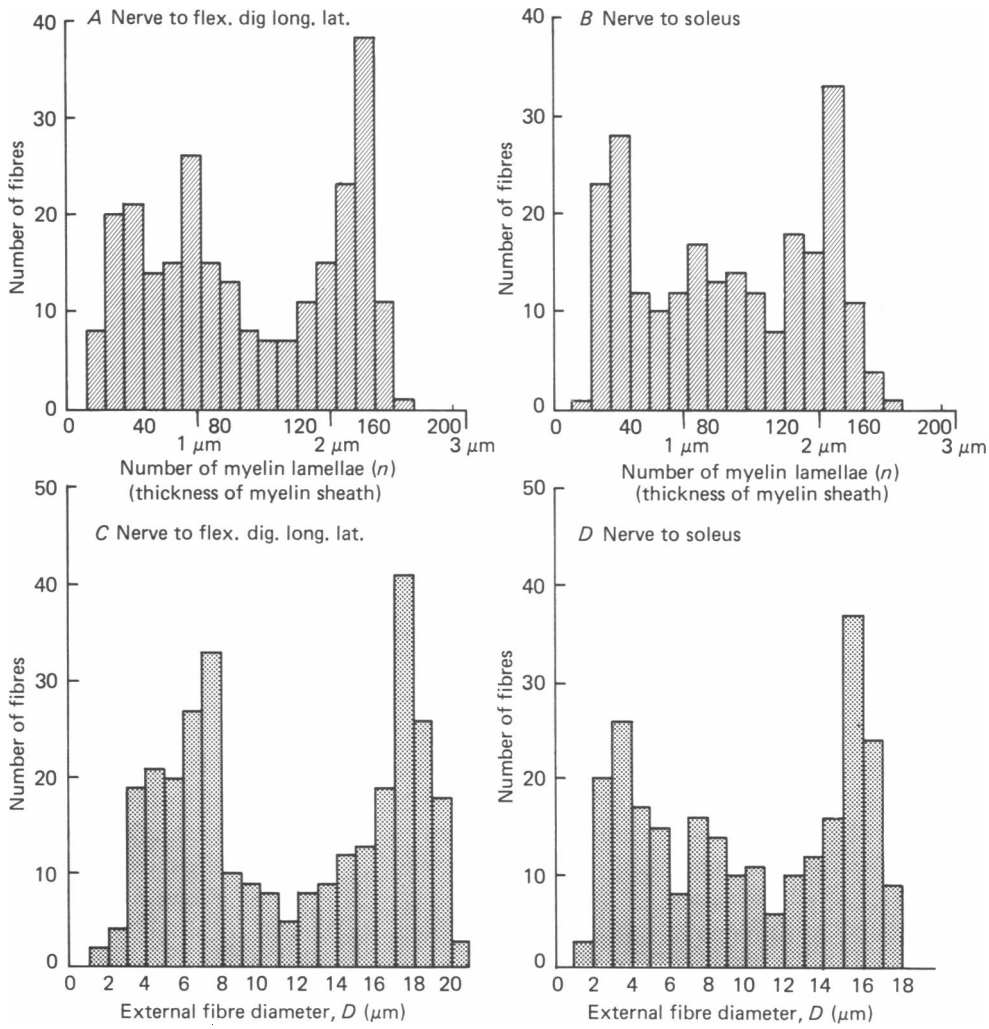


Fig. 1. Comparison of histograms of external fibre diameter (*D*) and number of lamellae (*n*) in the myelin sheath for all the afferent fibres in two muscle nerves chronically deefferentated 40 days previously. *A* and *C*, nerve to flex. dig. long. lat., cat 3. Myelin period 14·1 nm. *B* and *D*, nerve to soleus, cat 4. Myelin period 14·2 nm. Note presence of group I, II, III peaks in both forms of histogram.

α and γ fibres, in the other figures. It should be remembered, however, that in the case of afferent fibres in particular the division into functional groups is not as clear-cut as the figures suggest.

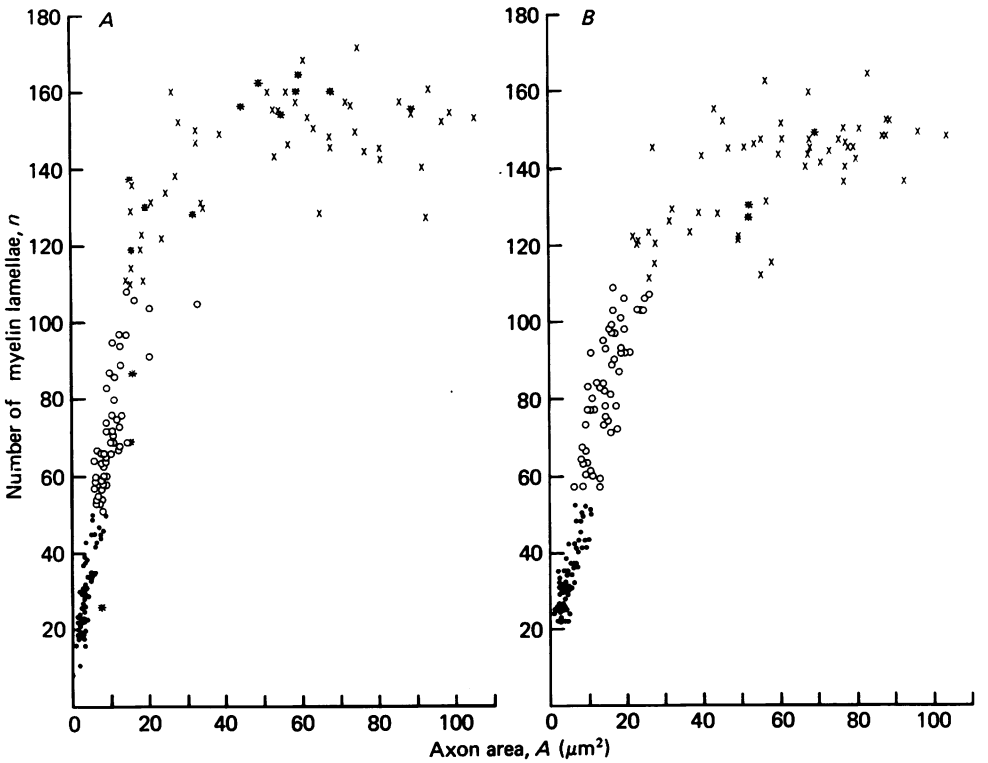


Fig. 2. Relation between axon cross-sectional area (A) and number of myelin lamellae (n) for all the afferent fibres in (A), nerve to f.d.l.l., cat 3 and (B), nerve to soleus, cat 4, both de-efferentated 40 days previously. ×, group I fibres. ○, group II fibres. ●, group III fibres. *, fibres cut through paranode. Note linearity in groups II and III and limiting thickness of myelin sheath in group I.

Relation between axon size and myelin thickness

A typical example of the relation between the number of myelin lamellae and the cross-sectional area of the afferent axons in two nerves from different cats is shown in Fig. 2. Values for *all* the fibres in each nerve are included in this and later figures save for those sectioned through a Schmidt-Lanterman incisure, or which deviated widely from circularity because of the proximity of the Schwann cell nucleus (see Arbuthnott *et al.* 1980). Fibres cut through the region of paranodal folding are indicated by stars. It is immediately obvious that while n and A are linearly related throughout groups II and III, a quite different situation applies to group I where above $A = 40\ \mu m^2$, n and A appear to be randomly related. Thus, the myelin sheath appears to reach a limiting thickness even though axons continue to increase in cross-sectional area.

The linearity of the relation between myelin thickness and axon size is even more evident if the number of myelin lamellae is plotted against axon perimeter as in

Fig. 3 which refers to the same two nerves as Fig. 2. Furthermore, the gradient of the linear regression line between n and s for fibres in groups II and III is quite close to 7·0 in both the nerves which are from different cats, and the intercept in both cases occurs near $s = 3$ μm. Deviation from linearity is very obvious when s exceeds 20 μm, so that group I afferent axons have relatively thinner myelin sheaths than group II axons (Pl. 1*A*). The regression equations in this and other similar figures were obtained on the basis that error was present in both n and s and the error ratio was equal to the slope of the line.

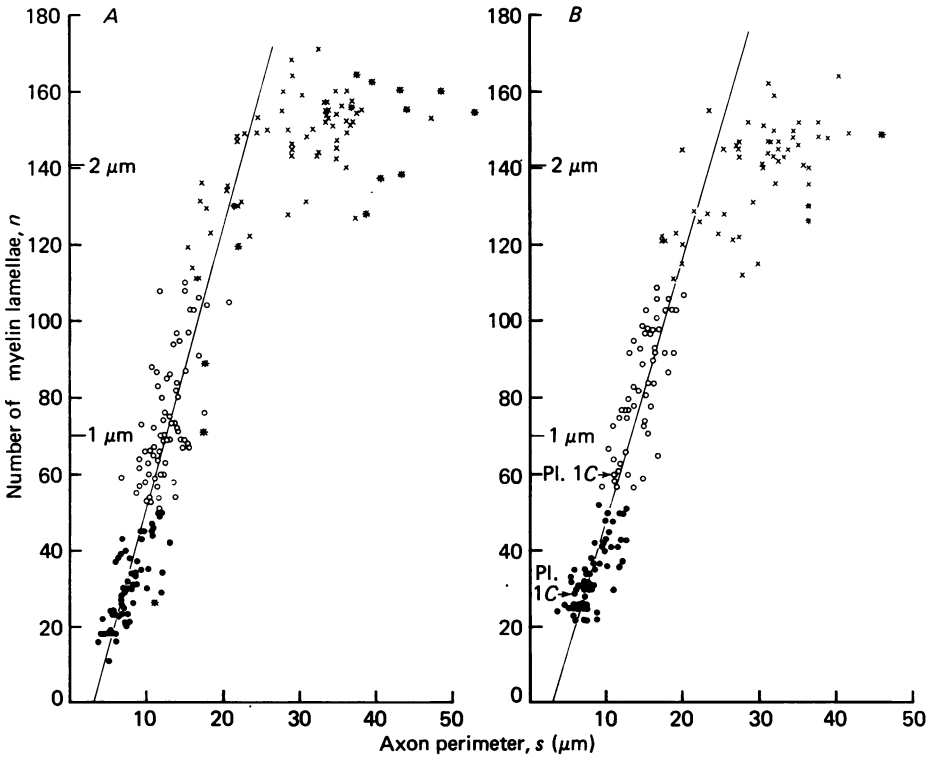


Fig. 3. Relation between axon perimeter (s) and number of myelin lamellae (n) or myelin sheath thickness (m) for all the afferent fibres in the same two nerves to *A*, f.d.l.l. and *B*, soleus, as in Fig. 2, ×, group I. ○, group II. ●, group III. *, fibres cut through paranode. Regression line for groups II and III had equation (*A*) $n = 7{\cdot}45\,s - 24$ and (*B*) $n = 6{\cdot}91\,s - 20$. Error assumed to be present in both n and s with error ratio equal to the slope of the line. The gradient is almost the same in the two cats.

Similarly, n and s for motor fibres are linearly related throughout the γ group, whereas the relative thickness of the sheath of α axons is much less and for the larger α axons at least is unrelated to axon perimeter (Figs. 4 and 5; Pl. 1*B*). The gradient of the linear regression line between n and s for γ axons in Fig. 4*A* is again close to 7·0 as it was for the afferent axons in groups II and III in two other cats in Fig. 3. The myelin sheaths in a fourth cat (Fig. 4*B*) were relatively thinner, however. That the relation between n and s is approximately the same for all axons with $s < 20$ μm in all the limb nerves in the *same* cat is evident from a comparison of Figs. 4*A* and 5

and from Table 1 in which all the results were aggregated. For groups II, III and γ in all three nerves in cat 1, and for those in cats 3 and 4, the gradient is about the same (Fig. 6) and a good fit is provided by the relation

$$n = 6{\cdot}9\,s - 17 \quad \text{or} \quad m = 0{\cdot}103\,s - 0{\cdot}26.$$

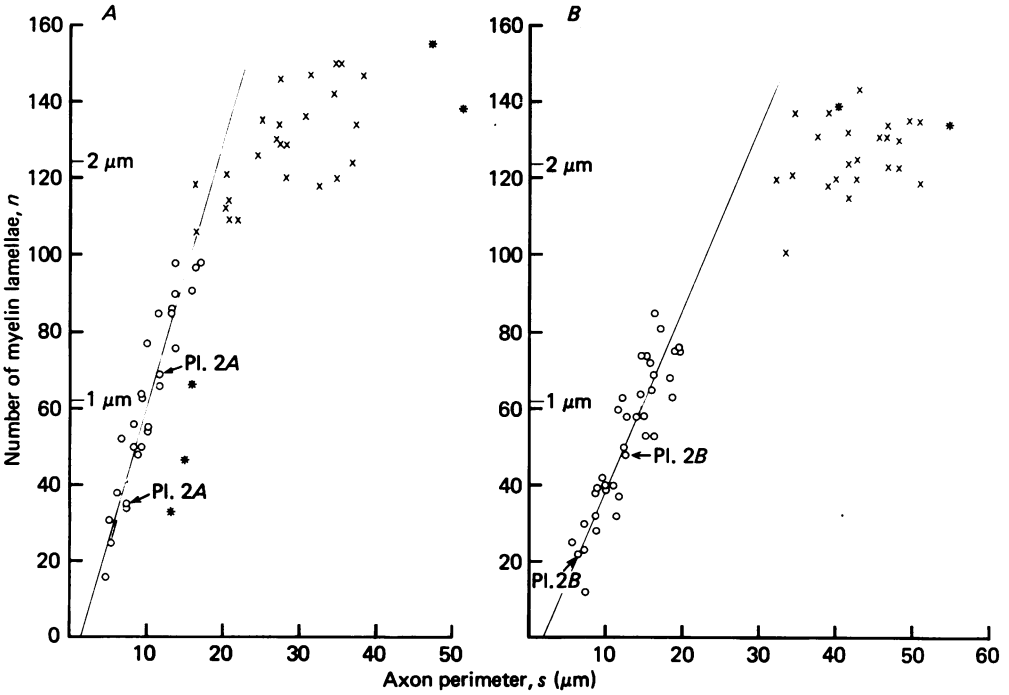


Fig. 4. Relation between axon perimeter (s), and number of myelin lamellae (n) or myelin thickness (m) in two nerves de-afferentated 35 days previously. *A*, nerve to tibialis posterior, cat 1. *B*, nerve to tibialis posterior, cat 2. ×, α fibres. ○, γ fibres. Values of s for γ axons in *B* are mean of measurements for each fibre in five transverse sections at 25 μm intervals; paranodal values excluded. Values of s in *A* and in other figures are from a single section. Regression equations for γ fibres: (*A*) $n = 6{\cdot}92\,s - 10$ and (*B*) $n = 4{\cdot}85\,s - 11$. Note different gradient in cats 1 and 2, but similar gradients for cats 1, 3, 4 (cf. Fig. 3).

The above and later equations relating m and s were derived on the basis that the myelin period was 15 nm. In fact it was 14·2 nm in cats 3 and 4 and 15·6 nm in cats 1 and 2. This degree of approximation does not affect the final equations appreciably.

In every nerve in cats 1, 3 and 4 the intercept of the regression line on the s axis occurred at between 0 and 4 μm, consistent with the fact that myelination commences when axons are about 3 μm in perimeter, or 1 μm in diameter. In nerves such as these from adult animals, however, there are rarely any myelinated fibres with less than ten myelin lamellae (Figs. 3, 4 and 5) and frequently none with less than twenty lamellae (Figs. 3*B*, 5*A* and *B*), and all the fibres are mature fibres. In two nerves from cat 2 there was a small negative intercept on the s axis; in both cases there was a relatively large scatter in the data.

Clearly the relation between n and s for group I afferent and α efferent fibres is different from that for smaller fibres. Three ways of interpreting the data suggest

themselves. First, myelination proceeds linearly from $s = 4$–$20\ \mu m$ approximately and then sheath thickness tends to a limit. This view is supported by the fact that if all values below $s = 25\ \mu m$ are rejected then the correlation coefficient (r) for larger fibres is $< 0{\cdot}1$ for the nerves to tibialis posterior (C_1; Fig. 4*A*), soleus ($C_{1,2}$; Fig. 5*B*) and flexor digitorum longus lateralis (C_3; Fig. 3*A*). For the nerve to soleus in cat 4,

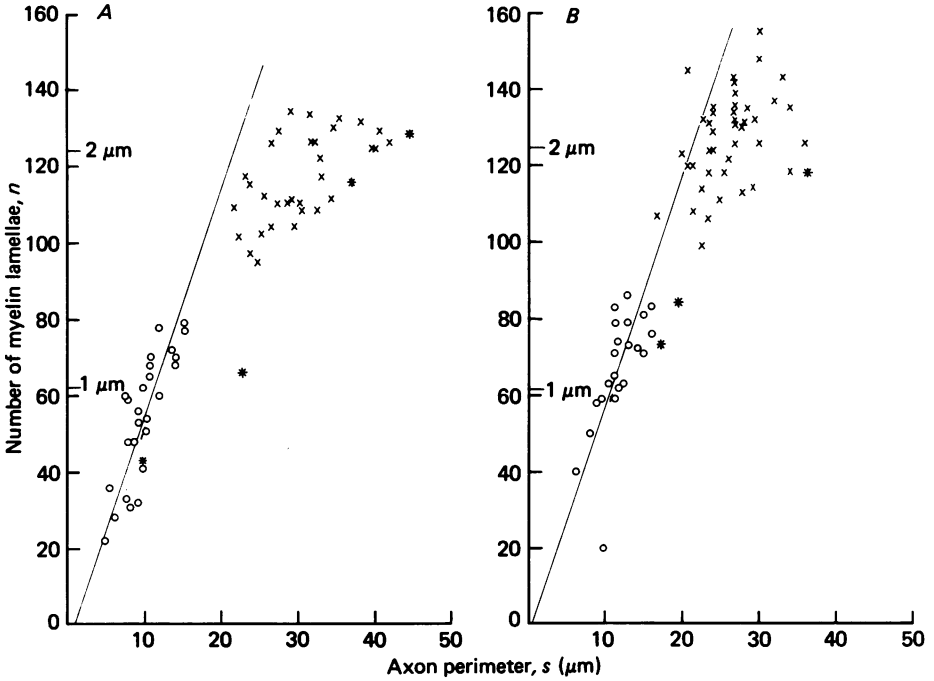


Fig. 5. Relation between axon perimeter (s) and number of myelin lamellae (n) or myelin thickness for two further nerves from cat 1. ×, α fibres, ○, γ fibres. *A*, nerve to peroneus longus, γ regression line equation $n = 5{\cdot}93\,s - 6$. *B*, nerve to soleus, $n = 5{\cdot}97\,s - 2$. Note similar gradient in both nerves as in Fig. 4*A* from same cat.

$r < 0{\cdot}2$ if all values of $s < 30\ \mu m$ are excluded (Fig. 3*B*). For all α fibres in the nerve to tibialis posterior in cat 2, $s > 30\ \mu m$ and r is only 0·29 (Fig. 4*B* and Table 1). The only nerve which showed a reasonable positive correlation between n and s for large α fibres was that to peroneus longus in cat 2 in which $s > 25\ \mu m$ for all α fibres and $r = 0{\cdot}57$ (Table 1). If this interpretation that sheath thickness tends to a limit is correct then it appears that the limiting value may be less for motor fibres ($n = 130$ lamellae, Figs. 4 and 5) than it is for afferent fibres ($n = 150$ lamellae, Fig. 3), despite the fact that the maximum axon perimeter is usually about 40 μm for both afferent and motor fibres, and may sometimes be greater for motor fibres (Fig. 4*B*). Since only four cats were studied it is not possible to say, however, whether this difference between afferent and motor axons is significant, and the limiting value will be assumed below to be 150 lamellae ($m = 2{\cdot}2\ \mu m$).

Alternatively, the relation between n and s for group I or α axons may be considered to be linear but with a much shallower slope than applies to smaller fibres. The linear regression equation constants for group I or α axons in individual nerves

are given in Table 1 and the regression equations which provide a good fit for all the nerves in each cat are plotted in Fig. 6. The slope of the relation is close to 2·0 in all four cats though cat 2 clearly differs once again in having α axons with myelin sheaths which are much thinner than those in the other cats. In this interpretation, in which α and group I fibres are considered to be discretely different populations from those in groups II, III and γ, it should be noted that the correlation coefficients are much

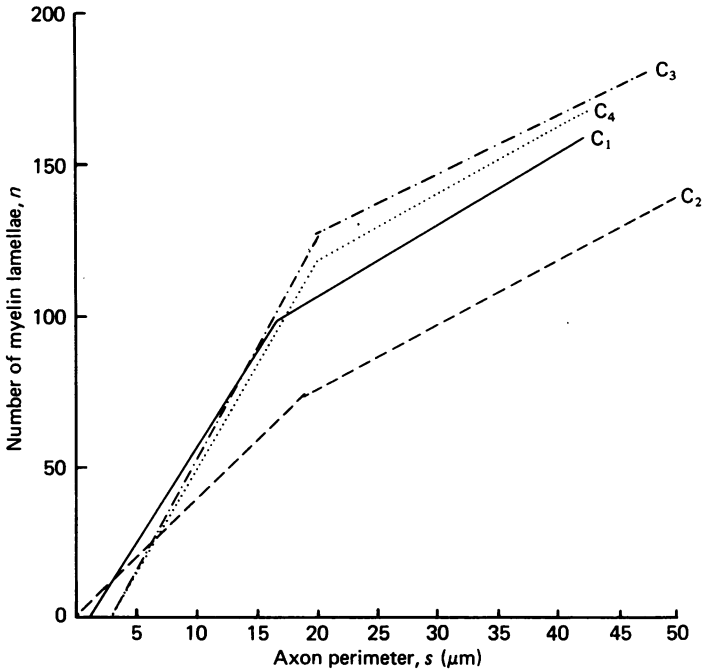


Fig. 6. Linear regression equations for all the data from cats 1, 2, 3 and 4 relating n and s, in which group I or α fibres were treated separately from groups II and III or γ fibres. Note close similarity of the relations for cats 1, 3 and 4, and distinctly different relations for cat 2 in which the myelin sheaths were thinner. For regression equations, see Table 1.

lower for the large fibres than for the small fibres. A good fit for the group I and α fibres in all the nerves in cats 1, 3 and 4 is provided by the equation

$$n = 2{\cdot}15\,s + 74 \quad \text{or} \quad m = 0{\cdot}032\,s + 1{\cdot}11.$$

The third alternative interpretation is that large and small fibres form a single population in which the thickness of the myelin sheath is related to the logarithm of the axon perimeter. Table 1 and Fig. 7 show that such a logarithmic relation provides a good fit for all the nerves ($r > 0{\cdot}92$). It should be remembered, however, that the high correlation coefficient is in part due to the relatively large number of data points, and that the fit is not always very good for the smallest fibres (Fig. 7*A*). On this interpretation, a good fit for all the nerves in cats 1, 3 and 4 is provided by

$$n = 172 \log_{10} s - 115 \quad \text{or} \quad m = 2{\cdot}58 \log_{10} s - 1{\cdot}73.$$

This is the dashed line in Fig. 7*A* and *B*.

TABLE 1. Relation between axon perimeter (s, μm) and number of myelin lamellae (n) for afferent or efferent nerve fibres in different functional groups in the cat. Equal error is assumed in s and n, with error ratio equal to the slope of the regression line. r, correlation coefficient. N, number of fibres. Fibres cut through a paranode, a Schmidt-Lanterman cleft, or passing a Schwann cell nucleus were excluded

	$n = xs+y$					$n = xs+y$					$n = p \log_{10} s+q$				
	Group	x	y	r	N	Group	x	y	r	N	Group	p	q	r	N
Tib. post. cat 1	α	2·17	69	0·61	25	γ	6·92	−10	0·94	27	$\alpha+\gamma$	152	−89	0·96	52
Soleus cat 1	α	2·96	50	0·40	42	γ	5·97	−2	0·75	22	$\alpha+\gamma$	166	−108	0·93	64
Per. long. cat 1	α	2·02	55	0·60	32	γ	5·93	−6	0·82	27	$\alpha+\gamma$	128	−72	0·96	59
Mean cat 1	α	2·38	58	—	—	γ	6·27	−6	—	—	$\alpha+\gamma$	149	−90	—	—
F.d.l.l. cat 3	I	1·91	89	0·58	60	II, III	7·45	−24	0·86	126	I, II, III	186	−129	0·95	186
Soleus cat 4	I	2·15	76	0·66	53	II, III	6·91	−20	0·92	115	I, II, III	181	−127	0·96	168
Tib. post. cat 2	α	1·46	65	0·29	23	γ	4·85	−11	0·89	37	$\alpha+\gamma$	140	−100	0·97	60
Soleus cat 2	α	2·07	25	0·50	84	γ	3·17	+6	0·74	69	$\alpha+\gamma$	96	−57	0·93	153
Per. long. cat 2	α	2·85	7	0·57	28	γ	3·44	+8	0·76	21	$\alpha+\gamma$	123	−82	0·96	49
Mean cat 2	α	2·13	32	—	—	γ	3·82	+1	—	—	$\alpha+\gamma$	120	−80	—	—

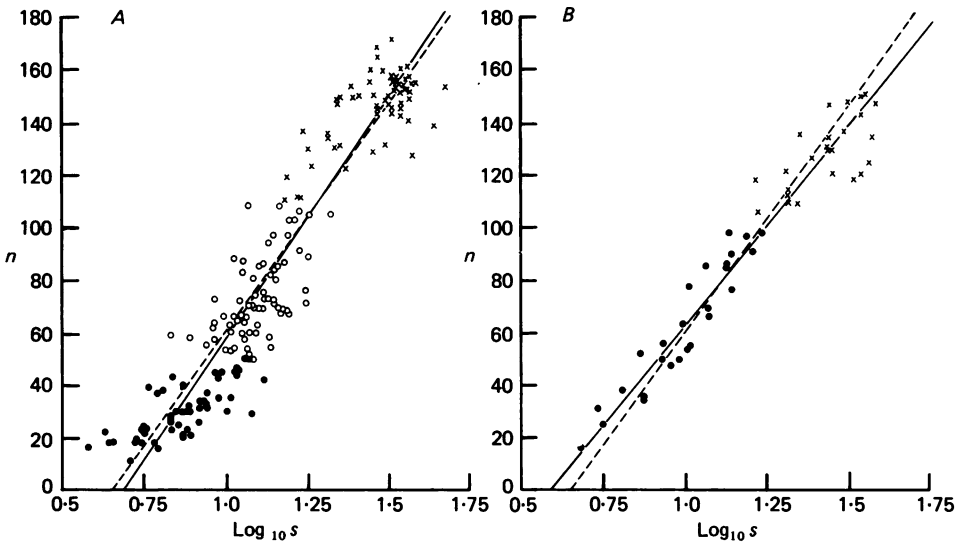


Fig. 7. Relation between n and $\log_{10} s$ for nerves to A, f.d.l.l., cat 3. ×, group I. ○, group II. ●, group III, and B, tib. post., cat 1. ×, α fibres, ●, γ fibres. Fibres showing paranodal folding excluded. Continuous lines, regression equations assuming equal error in n and s, error ratio equal to slope of line (see Table 1). Dashed lines, relation providing best fit for all nerves in cats 1, 3 and 4 (see text).

Ratio of axon perimeter to external fibre perimeter (g)

Since m is linearly related to s for $s < 20$ μm, it seems at first sight that g should be constant for this range of axon size. In fact, the intercept of the relation between m and s on the s axis has a profound effect on the value of g for small fibres. Thus, in Figs. 8 and 9 the dashed curves indicate the expected value of g if s and m are linearly related according to the regression equations given in Table 1 for the four nerves in question and the axons are assumed to be circular. The value of g should fall steeply from a value in excess of 0·75 and level out at about 0·6 for the nerves from cats 1, 3 and 4 (Fig. 8). In practice most of the values of g for α and group I fibres (×) lie well above the dashed curve as expected because of their relatively thin sheaths.

In the case of the nerve to tibialis posterior from cat 2, which had thinner myelin sheaths, g should fall from about 0·8 and level out at about 0·7 (Fig. 9A). The regression lines for γ fibres, calculated with the assumption that there was equal error in n and s, in the other two nerves in this cat had a small negative, rather than a positive, intercept on the s axis. It follows that g should *rise* as shown by the dashed line in Fig. 9B. In fact, this negative intercept is not typical of cat peripheral nerve and is due, in part, to the relatively large scatter in the data for γ fibres in these two nerves and, in the case of the nerve to peroneus longus, to the almost complete absence of axons less than 10 μm in perimeter. The regression lines for s as a function of n for γ fibres in these two nerves both had positive intercepts on the s axis. In any case, it is clear that the actual values of g for small fibres with s = 10–20 μm were lower than those for large fibres (Fig. 9B) as was the case for all the other nerves studied.

The actual values of g for fibres in groups II and III (Fig. 8A, ○, ●) are distributed about the dashed curve as expected, though more occur below the dashed curve

than above. In the case of γ fibres (Figs. 8*B*, 9*A* and *B*) the value of g lies below the curve for almost all the fibres.

Some scatter about the dashed curve is to be expected since there is a corresponding scatter about the linear regression line relating s and n (Figs. 3, 4 and 5). This is in part due to variations in s along the internode and is reduced by deriving a mean

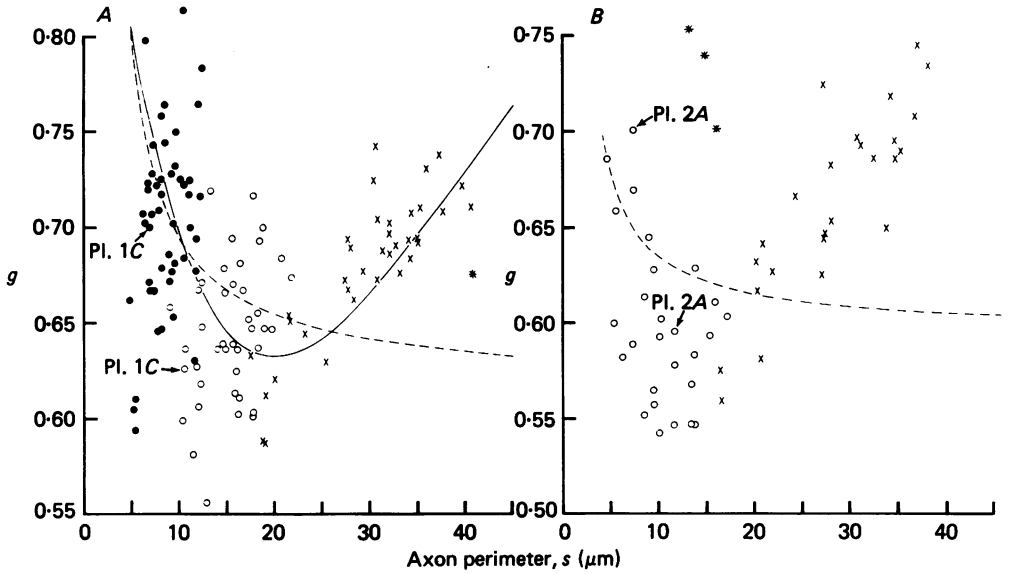


Fig. 8. Relation between axon perimeter (s) and ratio of axon perimeter to external fibre perimeter (g) for all the *A*, afferent fibres in soleus nerve, cat 4. ×, group I. ○, group II. ●, group III. *B*, motor fibres in nerve to tib. post., cat 1. ×, α fibres. ○, γ fibres. *, fibres cut through paranode. Dashed curves give relation between s and g predicted from *A*, $n = 6{\cdot}91\,s - 20$ and *B*, $n = 6{\cdot}92\,s - 10$. Values for group I and α lie above dashed curve because of relative thinness of myelin sheath. Values for other groups fall below dashed curve because of non-circularity (see text). Continuous curve in *A*, eqn. (1) giving g in terms of s.

value for s from a number of sections at different points in an internode as in Fig. 4*B*. Values for measurements at a paranode lie well to the right of the regression line (Figs. 3, 4 and 5, *) since s increases by about 70% in the proximal paranodal bulb relative to its value in the internode (Williams & Landon, 1963). This large increase in s without any increase in n accounts for the fact that g for paranodes is well above the dashed curve in Figs. 8 and 9 (*) since the myelin sheath is relatively thinner. The more non-circular an axon, on the other hand, the lower the value of g. For example, if a circular axon with $g = 0{\cdot}6$ became an ellipse with major axis twice the minor axis, and s and n remained unchanged, then for the ellipse $g = 0{\cdot}5$. This substantial effect accounts for the fact that so many of the points in Figs. 8 and 9 lie below the curve predicted from the linear relation between s and n and also for the fact that this is more obvious for motor axons (Figs. 8*B* and 9), which are more non-circular, than it is for afferent axons (Fig. 8*A*).

In practice, therefore, g is a minimum, occasionally as low as 0·55, when s lies between 10 μm and 20 μm and has a greater value not only for large fibres but also

for very small fibres. Thus, group III afferent axons tend to have relatively thinner sheaths than group II axons (Fig. 8*A* and Pl. 1*C*), though there is a large amount of scatter from fibre to fibre. If there are very few γ axons with $s < 10\ \mu$m, as in the nerve to peroneus longus, then all the γ axons have relatively much thicker sheaths than the α axons, and this is reflected in the mean value of g for each group (Fig. 9*B*

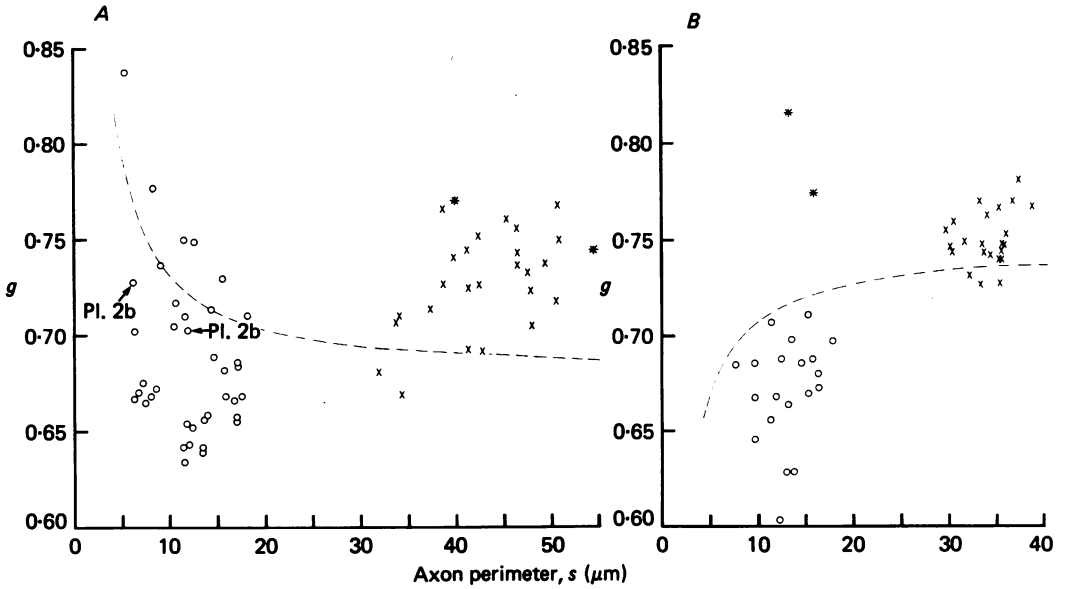


Fig. 9. Relation between s and g for two nerves from cat 2. ×, α fibres. ○, γ fibres. *, fibres cut through paranode. *A*, nerve to tib. post., dashed curve derived from $n = 4{\cdot}85\,s - 11$. *B*, nerve to per. longus, curve derived from $n = 3{\cdot}44\,s + 8$. Note γ fibres with $s < 8\ \mu$m in *A* but absent in *B*.

and Table 2). If, on the other hand, there are an appreciable number of γ axons for which $s < 10\ \mu$m, these axons have relatively thinner sheaths than those of the larger γ axons (Figs. 8*B* and 9*A*). In particular, if the γ fibres contribute to two distinct peaks in histograms of external fibre diameter, or of the number of myelin lamellae, as is not infrequent in the nerve to tibialis posterior (Boyd & Davey, 1968; Arbuthnott, 1972), then the group of small γ axons will be relatively thinly myelinated, and the group of large γ axons will be relatively thickly myelinated. Electron microscopy thus confirms the existence of the 'thickly myelinated' and 'thinly myelinated' γ fibres which were described for certain nerves in the light-microscopic study of Boyd & Davey (1962, 1968). In such cases (e.g. Figs. 8*B* and 9*A*; Table 2, tib. post.) the mean value of g for the whole γ group may not be so very much less than that for the α group, but g for large γ fibres only is much less than that for the α fibres or small γ fibres. Thus, in the nerve to tibialis posterior from cat 1 the value of g for the groups of large γ (thickly myelinated) and small γ (thinly myelinated) fibres was 0·58 and 0·65, respectively (Pl. 2*A*), while for the same nerve in cat 2 it was 0·67 and 0·71, respectively (Pl. 2*B*).

In general, then, the value of g falls as s increases and then rises again. There is considerable variation in the range of g from one nerve to another, in part due to

TABLE 2. Mean values of axon perimeter (s, μm), external fibre perimeter (S, μm), number of myelin lamellae (n) and ratio of axon to external perimeter (g) for individual fibre groups in chronically de-afferentated (α and γ groups) and de-efferentated (groups I, II and III) cat nerves. Mean $\pm$ S.D. * from ratio of mean s to mean S. Number of fibres in parentheses includes every fibre in the nerve except those cut through paranodes, Schmidt-Lanterman incisures or very non-circular because of proximity to Schwann cell nucleus

		α efferent fibres				γ efferent fibres			
Nerve	Cat no.	s	n	S	g	s	n	S	g
Tib. post.	C_2	**43** $\pm$ 6 (28)	**128** $\pm$ 8 (25)	**59** $\pm$ 7 (27)	**0·73** $\pm$ 0·03 (27)	**12** $\pm$ 4 (40)	**50** $\pm$ 19 (39)	**18** $\pm$ 6 (40)	**0·69** $\pm$ 0·04 (39)
Per. long.	C_2	**34** $\pm$ 2 (23)	**103** $\pm$ 16 (32)	**46** $\pm$ 3 (23)	**0·75** $\pm$ 0·01 (23)	**13** $\pm$ 3 (23)	**52** $\pm$ 11 (23)	**19** $\pm$ 4 (21)	**0·67** $\pm$ 0·03 (20)
Soleus	C_2	**26** $\pm$ 5 (84)	**80** $\pm$ 9 (88)	**37** $\pm$ 5 (81)	**0·71***	**11** $\pm$ 3 (69)	**41** $\pm$ 10 (69)	**17** $\pm$ 5 (72)	**0·65***
Tib. post.	C_1	**28** $\pm$ 7 (25)	**130** $\pm$ 14 (27)	**42** $\pm$ 7 (25)	**0·66** $\pm$ 0·05 (26)	**11** $\pm$ 3 (29)	**60** $\pm$ 24 (32)	**18** $\pm$ 6 (30)	**0·60** $\pm$ 0·04 (27)
Per. long.	C_1	**31** $\pm$ 6 (32)	**118** $\pm$ 11 (37)	**43** $\pm$ 7 (34)	**0·73** $\pm$ 0·03 (32)	**10** $\pm$ 4 (28)	**57** $\pm$ 15 (30)	**17** $\pm$ 5 (27)	**0·59** $\pm$ 0·06 (26)
Soleus	C_1	**26** $\pm$ 2 (42)	**127** $\pm$ 12 (43)	—	—	**12** $\pm$ 3 (22)	**68** $\pm$ 15 (24)	**21** $\pm$ 4 (24)	**0·57***

		Group I afferent fibres				Group II afferent fibres			
		s	n	S	g	s	n	S	g
F.d.l.l.	C_3	**31** $\pm$ 7 (66)	**146** $\pm$ 14 (66)	—	—	**13** $\pm$ 3 (70)	**74** $\pm$ 16 (70)	—	—
Soleus	C_4	**30** $\pm$ 6 (35)	**139** $\pm$ 13 (56)	**43** $\pm$ 7 (36)	**0·68** $\pm$ 0·04 (35)	**15** $\pm$ 2 (54)	**83** $\pm$ 16 (54)	**24** $\pm$ 4 (42)	**0·64** $\pm$ 0·04 (41)

		Group III afferent fibres			
		s	n	S	g
F.d.l.l.	C_3	**8** $\pm$ 2 (55)	**31** $\pm$ 10 (55)	—	—
Soleus	C_4	**8** $\pm$ 2 (61)	**34** $\pm$ 9 (61)	**12** $\pm$ 3 (42)	**0·70** $\pm$ 0·04 (41)

differences in the degree of non-circularity of individual fibres, and in part to differences between cats. But if cats 1, 3 and 4 are taken as typical, and cat 2 as having unusually thin myelin sheaths, then it may be concluded that g is about 0·70 for group III and small γ fibres, falls to about 0·62 for group II and large γ fibres and then rises again to 0·72 for group I and α fibres (Fig. 10 and Table 2). For the largest fibres g may rise, in fact, to 0·75, and occasionally even to 0·80.

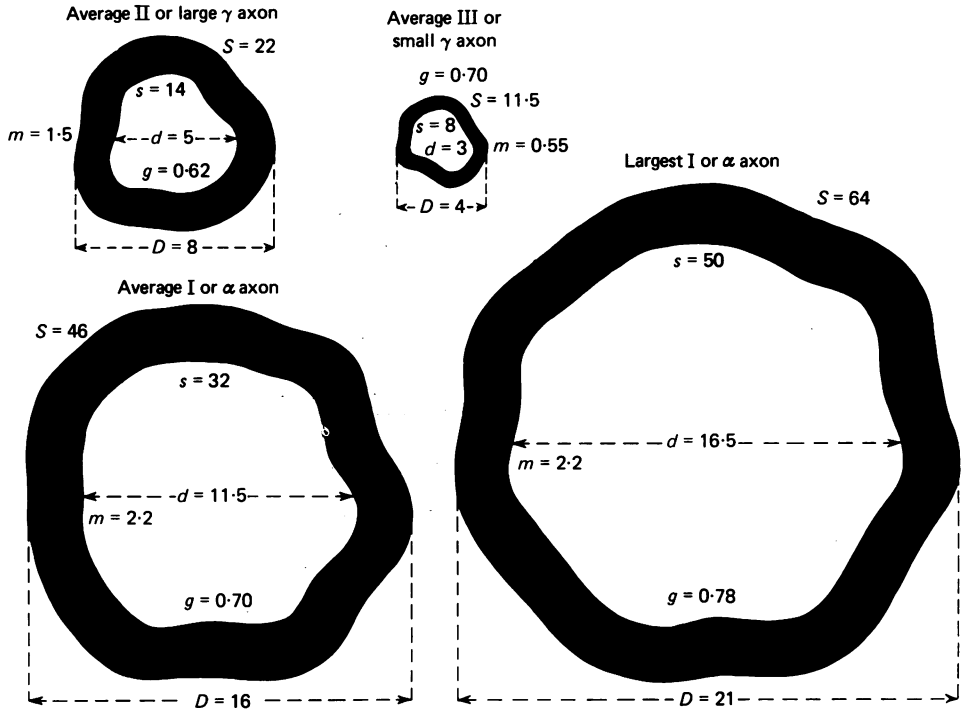


Fig. 10. Typical parameters for nerve fibres in different functional groups derived from data of the present work. Largest group I or α axon may be nearer $s = 45$ μm, $g = 0{\cdot}75$ in many nerves. Note relative thinness of myelin sheath on small fibres and large fibres relative to that on medium sized fibres.

DISCUSSION

Axon perimeter and myelin sheath thickness

Axon perimeter and number of myelin lamellae are linearly related for *all* sizes of axon in peripheral nerves in the mouse and rat (Friede & Samorajski, 1967, 1968), in rat ventral spinal roots (Fraher, 1972) and in central tracts in rat and cat (Samorajski & Friede, 1969; Bishop, Clare & Landau, 1971). There are few axons larger than 20 μm in perimeter in most mice and rats. In the present work on the cat the relation between s and n was linear, also, for $s < 20$ μm but the same relation did not apply to larger axons. It can be seen from Table 3 that, for axons with $s < 20$ μm, the increment in axon perimeter which is accompanied by the addition of one turn to the myelin spiral (gradient a) of 0·13 μm–0·16 μm in cats 1, 3 and 4 of the present work is not greatly different from that found in peripheral nerves and spinal roots in rats and mice. The same appears to be true of the human sural nerve if both large and

TABLE 3. Comparison of the gradient and intercept on the s axis of linear relations between axon perimeter and number of myelin lamellae, $s = an + b$, in fixed nerves from different species, and the range of s throughout which linearity applied. *, see text. **, if the myelin period is assumed to have been 12 nm or 15 nm, respectively

Authors	Tissue	Age and number of animals	a (gradient) (μm/lamella)	b (intercept) (μm)	Range of linearity
	Peripheral nerves				
Friede & Samorajski (1967)	Mouse vagus and sciatic nerves	Adult (46 weeks; 6)	0·14–0·19	1·5–1·7	All sizes, 3–15 μm
Friede & Samorajski (1968)	Rat sciatic nerve	4–16 weeks (4)	0·15–0·20	About 3	All sizes, 4–23 μm
Fraher (1972)	Rat ventral root	8 and 17 days (2)	0·15 and 0·22	2·8 and 1·8	All sizes, 3–20 μm
Arbuthnott, Boyd & Kalu (present work)	Cat hind-limb muscle nerves	Adult C_1, C_3, C_4; C_2	0·13–0·16; 0·26	1·0–3·2; 0·3	4–20 μm
		Adult C_1, C_3, C_4; C_2	0·42–0·52; 0·47	−24 to −47; −15	20–50 μm
Behse & Buchthal (1977)	Human sural nerve	Adult (6)	0·35	−4·4	3–14 μm
		Adult (6)	s and n unrelated		9–25 μm
Schröder, Bohl & Brodda (1978)	Human sural nerve	11–14 years (3)	0·15–0·24	−0·15 to +5·5	3–27 μm*
	Central tracts				
Samorajski & Friede (1969)	Rat pyramidal tract	4–12 weeks (3)	0·25–0·22	1·6–1·1	All sizes, 1–9 μm
Bishop, Clare & Landau (1971)	Cat cervical dorsal column	? adult (1)	0·19 or 0·23**	0	All sizes, 3–25 μm
	Cat cuneate area	? adult (1)	0·19 or 0·23**	0	All sizes, 3–38 μm

small fibres are considered to form a single population (Schröder, Bohl & Brodda, 1978). Some difference in the gradient is to be expected due to differing shrinkage with various fixation procedures, but the higher value of a in cat 2 than in cats 1, 3 and 4 in the present work is unlikely to have been due to this since the myelin period was the same for cats 1 and 2 whose nerves were processed by the same individual

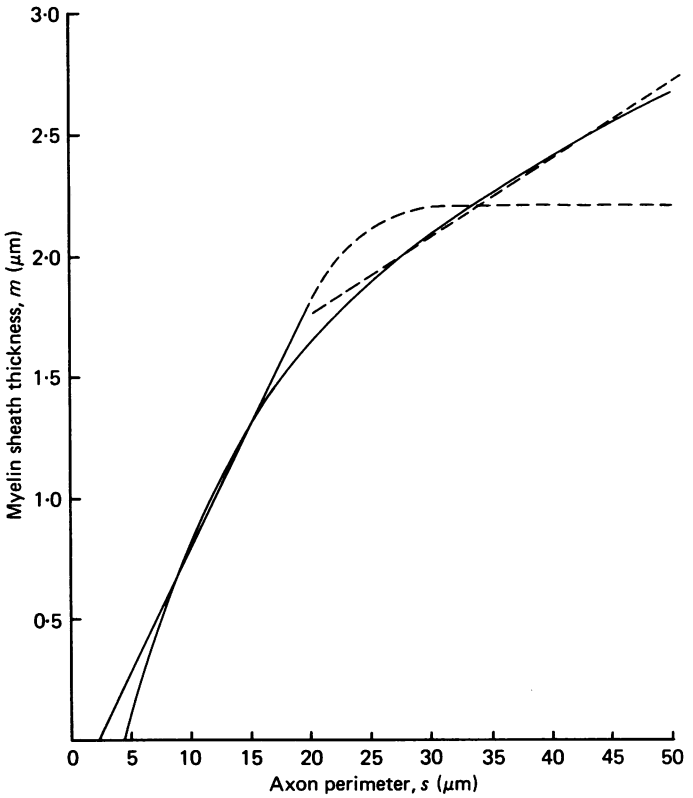


Fig. 11. Mean relation between m and s for all the nerves from cats 1, 3 and 4 in the present work. Straight line, eqn. (2) $m = 0{\cdot}103\,s - 0{\cdot}26$, linear regression equation for groups II, III and γ. Dashed line, eqn. (5), $m = 0{\cdot}032\,s + 1{\cdot}11$, linear regression equation for groups I and α. Continuous curve, eqn. (9), $m = 2{\cdot}58 \log_{10} s - 1{\cdot}73$, linear regression equation for all fibre groups on a semi-logarithmic plot. Dashed curve, relationship estimated by eye for data for group I and α if m tends to a limit of 2·2 μm.

using an identical technique. There is evidence that the gradient, a, is greater in younger animals in the rat (Friede & Samorajski, 1968, 1969) and in man (Schröder *et al.* 1978; J. M. Schröder, personal communication). We are inclined to think that the higher value of a in cat 2 was due to the fact that this animal was younger than the others although, unfortunately, only the weights, and not the ages, of the cats were known. Accordingly, the results for cats 1, 3 and 4 have been taken to be typical of adult animals.

It has been shown in the Results that axons in groups I and α in the cat (s, 20–50 μm) have relatively thinner sheaths than the smaller axons in other groups, and that the data can be interpreted in at least three ways. Either the thickness of the myelin

sheath tends towards a limiting value, or there is a linear relation between s and n with a quite different slope (a about 0·5; Table 3) for group I and α axons from that for other groups, or n is proportional to $\log_{10} s$ for all sizes of axon (Fig. 11). The most readily understandable explanation would appear to be that the driving force for the process of myelination diminishes or ceases as axons grow larger, and that myelination stops at different times in different axons although the axons continue to increase in perimeter. In small mammals like the mouse and rat in which few axons exceed 20 μm in perimeter the driving force is adequate to ensure that they all myelinate to a degree proportional to axon size.

Other evidence suggests strongly, however, that different types of fibre fall into discrete groups which differ in the relative thickness of their myelin sheaths. Thus, myelinated fibres in the third cranial nerve of the rat form two distinct populations: small fibres (s, 2–7 μm) with sheath thickness scattered around 0·2 μm and large fibres (s, 7–17 μm) with sheaths around 0·6 μm thick (Bronson & Hedley-White, 1977; Bronson, Bishop & Hedley-White, 1978). For both groups taken separately the regression coefficient must have been very low indeed, i.e. m almost constant. Likewise, in a study of the human sural nerve, Behse & Buchthal (1977) concluded that they were dealing with two distinctly different groups of small and large fibres. For the small group III (or A_δ) cutaneous axons the gradient, a, was 0·35 (Table 3). The large fibres (group I or A_β) had relatively thick sheaths averaging nearly 150 lamellae, and m seemed to be unrelated to s. The data of Schröder *et al.* (1978), also derived from the human sural nerve, is similar. Although they plotted regression lines for all the fibres as a single population (Table 3), their data suggest that the large and small fibres again may have belonged to two separate populations. The relation between n and s for small fibres has a relatively shallow slope (a large) while for the limited sample of large fibres studied the sheaths are relatively thick and there is no obvious correlation between m and s. These results support the interpretation of the present results that group I afferent and α motor axons in the cat form discretely different populations from those containing axons in afferent groups II and III, or γ motor axons. If so, then it is quite likely that they may differ in respects other than just the relative thickness of their myelin sheaths.

Myelin sheath thickness and the ratio g

It has been shown in the present work on peripheral nerves in the cat that g, the ratio of s to S in fixed nerves declines from about 0·70 for small fibres to a minimum of about 0·62 for medium sized fibres and then rises again to 0·70 or perhaps 0·75 for large fibres. Coppin (1973, Figs. IX. 11, 12) obtained a very similar pattern from electron micrographs of two de-efferentated cat muscle nerves. Friede & Samorajski (1967) stated that they could not determine a definite trend in g with increasing axon size in the mouse but they thought that g ought to increase from about 0·6 for the thinnest fibres to about 0·8 for the thickest fibres. In fact, using the same reasoning as was used earlier for the present work, the linear relationship they obtained between s and n with a positive intercept on the s axis (Table 3) means that g should *fall* from about 0·8 for the smallest fibres to 0·7 for the largest ones. Such a trend is perhaps apparent in their Fig. 4 though it is obscured by the large scatter of individual observations. The value of g in the rat will not, of course, rise again for large fibres as it does

in the cat since s and n are linearly related throughout the entire range of axon size in rats. The positive intercept on the s axis in both rat and cat usually occurs at a value close to 3 μm, i.e. axon diameter about 1 μm. This is the critical size below which axons in peripheral nerves and spinal roots do not become myelinated. Myelination may commence, however, on axons with perimeters anywhere within the range 3 μm to about 8 μm (Fraher, 1972).

Measurements of g in thick sections, e.g. 5 μm fresh or fixed, viewed under the light microscope are much too low in small fibres, as was shown by Dyck, Gutrecht, Bastron, Karnes & Dale (1968). The myelin thickness is exaggerated due to the fact that an irregular cylinder is being observed end on and the effect is proportionately greater for small fibres. Dyck *et al.* (1968) showed that if g for a fibre in a section 1 μm thick was 0·6, it could be 0·4–0·5 in a section of the same fibre 4 μm thick, and 0·3–0·4 in a 6 μm section. For this reason the conclusion from work using thick sections that g *increases* with fibre size from 0·4 or less for small myelinated fibres in peripheral nerves to 0·7 or 0·8 for large ones is almost certainly incorrect (e.g. Gasser & Grundfest, 1939; Sanders, 1948; Sunderland & Roche, 1958; Williams & Wendell-Smith, 1971). Likewise, values of g obtained from teased fibres (Schmitt & Bear, 1937; Taylor, 1942; Schwartzacher, 1954) are suspect because the 'lens effect' of myelin makes the sheath appear thinner than it really is.

It should be noted, however, that if a linear relation between s and n passes through the origin then g will be constant. This seems to be true in central tracts in the cat where myelination takes place on very much smaller axons ($< 0{\cdot}3$ μm) than in peripheral nerve (Table 3; Bishop *et al.* 1971). It may be true for some peripheral nerves as in the work of Schnepp & Schnepp (1971) on rat, mouse, cat and dog, though some downward trend from 0·7 to 0·6 is apparent in their figures.

If a linear relation between s and n has a negative intercept on the s axis then g will rise with increasing s. This is, in general, true for groups I and α in cat and man (Table 3) where sometimes s and n may actually appear to be unrelated and the myelin thickness is scattered round a constant value. In the only two nerves in the present work in which g for small fibres in groups II, III or γ, calculated from the linear regression equation, appeared to increase with s, the actual values of g for individual fibres were so scattered that no trend in g was obvious (Fig. 9*B*). It seems, however, that an increase in g with s may occur within the group of small fibres in human sural nerve (Behse & Buchthal, 1977; Schröder *et al.* 1978) and in the third cranial nerve in the rat (Bronson *et al.* 1978).

It is concluded that, in general, g in peripheral nerves in cat and rat falls as axon size increases from 4 μm to about 20 μm. In the cat g rises again when the myelin sheath becomes relatively thinner as s increases from 20 μm to 40 or 50 μm. Although there is some variation in the actual value of g from nerve to nerve the form of the relation between g and s in the cat is quite well described by the equation

$$g = 1 - \frac{s}{20} e^{\frac{-s}{20}} \quad (1)$$

shown by the continuous curve in Fig. 8*A*. This curve has a minimum at $g = 0{\cdot}63$ when $s = 20$ μm.

Axon perimeter and conduction velocity

It has been shown in the present work that for axons in groups II, III and γ (s between 4 μm and 20 μm)

$$m = 0{\cdot}103\, s - 0{\cdot}26 \tag{2}$$

if it is assumed that cats 1, 3 and 4 were typical adult animals (Fig. 11 continuous straight line). It has been established previously that for fibres in these groups the ratio of conduction velocity in m/sec to external fibre diameter in microns is 4·6 (Boyd & Kalu, 1979). Thus, for II, III and γ fibres

$$\theta = 4{\cdot}6\, D = 4{\cdot}6\, (d + 2\, m) \tag{3}$$

and from eqns. (2) and (3)

$$\theta = 2{\cdot}41\, s - 2{\cdot}4. \tag{4}$$

If the interpretation that, for group I and α fibres (s between 20 μm and 50 μm), m and s are linearly related but the slope is substantially less than for fibres in other groups is accepted (Fig. 11 dashed straight line), then it has been shown that for cats 1, 3 and 4

$$m = 0{\cdot}032\, s + 1{\cdot}11. \tag{5}$$

The ratio of θ to D both for the peak and the maximum diameter of fibre in groups I and α is 5·7 (Boyd & Kalu, 1979). Thus, for group I and α fibres

$$\theta = 5{\cdot}7\, D = 5{\cdot}7\, (d + 2\, m) \tag{6}$$

and from eqns. (5) and (6)

$$\theta = 2{\cdot}18\, s + 12{\cdot}7. \tag{7}$$

Eqns. (4) for small fibres and (7) for large fibres are shown by continuous straight lines in Fig. 12.

If the results are interpreted as showing that m tends to a limit of 2·2 μm when $s > 30$ μm (Fig. 11 dashed curve) then for group I and α fibres of this size eqn. (6) becomes

$$\theta = 1{\cdot}81\, s + 25{\cdot}1 \tag{8}$$

shown by the interrupted straight line in Fig. 12.

If the interpretation that myelin thickness and axon perimeter are logarithmically related is accepted (Fig. 11 continuous curve) then for all sizes of axon

$$m = 2{\cdot}58 \log_{10} s - 1{\cdot}73 \tag{9}$$

Eqn. (9) combined with eqns. (3) and (6) for small and large fibres, respectively, gives rise to the relation between θ and s shown by the two dashed curves in Fig. 12.

Whichever interpretation of the results is employed it is clear that the difference in the scaling factor relating θ and D for large and small fibres is neatly explained by the difference in the relative thickness of their myelin sheaths if conduction velocity is proportional to axon size. Eqn. (4) derived for small fibres gives values of θ for most large fibres which are quite close to the true value.

The discontinuity at $s = 20$ μm in Fig. 12 (eqns. 4 and 7) arises from the apparent discontinuity in the θ/D scaling factor obtained by Boyd & Kalu (1979) in the range $D = 10$–12 μm. This discontinuity may not be present in one particular nerve, however. While the factor of 5·7 applied to both the largest and the mean size of group I or α fibre in every nerve and 4·6 to both

the largest and the mean size of fibres in groups II, III and γ, it is less certain that the factor of 5·7 applied to the smallest group I and α fibres. It was not possible to derive meaningful values of θ from the tail of the compound action potential of a particular fibre group. The values of θ in the range D = 10–12 μm for group I and α fibres in Boyd & Kalu (1979, Figs. 7, 8) were the conduction velocity of the *mean* size of fibre in nerves in which the fibres in these groups are relatively small (e.g. nerves to the foot). If the largest, and the mean size, of group I or α fibre in every nerve have thinner sheaths than the largest group II or γ fibres, it could still be true that in any particular nerve there is a smooth transition in scaling factor from 4·6 to 5·7 in the mid range. However, the undoubted anatomical discontinuity in the relation between m and s for large and small fibres in some rat and human nerves mentioned earlier suggests that this may also be true for the cat.

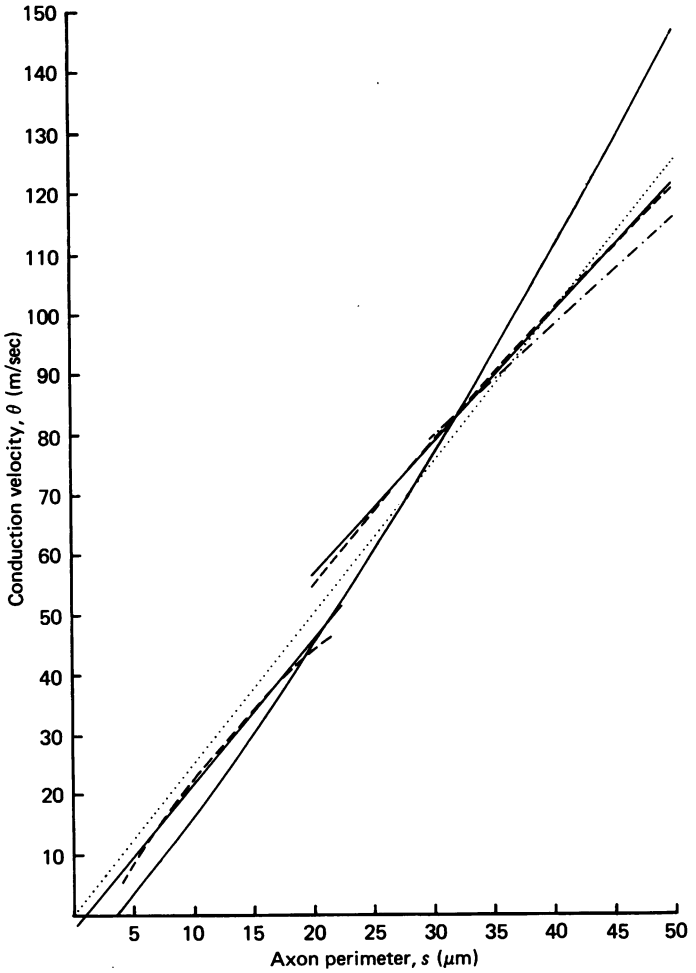


Fig. 12. Derived relations between conduction velocity (θ) and axon perimeter (s) assuming axons are circular. Lower straight line, eqn. (4), relation between m and s for groups II, III and γ from present work (eqn. 2) combined with $\theta = 4{\cdot}6\ D$ from Boyd & Kalu (1979). Upper straight line, eqn. (7), relation between m and s for groups I and α in present work (eqn. 5) combined with $\theta = 5{\cdot}7\ D$ from Boyd & Kalu (1979). Dashed curves, relation between m and $\log_{10} s$ (eqn. 9) combined with $\theta = 4{\cdot}6\ D$ and $5{\cdot}7\ D$ as above. Continuous curve, eqn. (9) combined with $\theta = 1{\cdot}5\ D^{1{\cdot}5}$ from Coppin & Jack (1972). Dotted line, $\theta = 2{\cdot}5\ s$ which gives approximate values of θ for all sizes of axon.

Thus, the relation between θ and s is approximately linear throughout the entire range of axon size in the cat. As a first approximation

$$\theta = 2.5\, s \tag{10}$$

shown by the dotted straight line in Fig. 12. The accuracy of this equation may be improved by deducting 3 m/sec for all axons with $s < 20\ \mu$m.

Variation in myelin sheath thickness also explains why the ratio of θ to D for human group I (or A_β) cutaneous afferents is 4·4 (Buchthal, Rosenfalck & Behse, 1975). The range of external diameter for this group is about the same in man and cat, 7–14 μm (Buchthal *et al.* 1975; Boyd & Davey, 1968). The corresponding *axon* diameters (d) in electron micrographs of human sural nerves range from 3 to 8 μm (Behse & Buchthal, 1977), and the myelin sheaths are relatively thick, averaging about 2·2 μm. The fastest conducting fibre in the human sural nerve of Buchthal *et al.* (1975) had a conduction velocity of 62 m/sec. This is the same as that for a fibre with $d = 8\ \mu$m ($s = 25\ \mu$m) derived from eqn. (10). Further, eqn. (10), with the 3 m/sec deduction for small fibres, gives a velocity of 18 m/sec for an axon with $d = 2{\cdot}8\ \mu$m, the peak axon diameter for group III human sural afferents (Behse & Buchthal, 1977). The corresponding total diameter is 4·0 μm (Buchthal *et al.* 1975), and the scaling factor of 4·4 gives a velocity of 18 m/sec. Thus, the conduction velocity of all human sural afferents is directly proportional to axon perimeter and is given by $\theta = 2{\cdot}5\, s$ as in the cat, with the appropriate 3 m/sec deduction for small fibres. The equivalent data do not appear to be available for human muscle nerves but it seems likely that, as in cutaneous nerves, the conduction velocities of human motor and afferent fibres are lower than those of corresponding fibres in the cat because they have smaller axons and thicker sheaths, the external diameters being about the same in the two species.

Likewise, myelin sheaths in the rabbit seem to be thicker than in the cat, according to the detailed study of 5 μm fresh frozen sections of Williams & Wendell-Smith (1961) using the light microscope. Unfortunately, m in sections of this thickness is usually over-estimated. However, thicker sheaths on smaller axons would be consistent with lower conduction velocities than in the cat for a given external diameter and hence the scaling factor between θ and D is 4·4 for large fibres in the rabbit (Cragg & Thomas, 1964), similar to that of man.

In the rat, myelin sheath thickness tends to be slightly less than for the same size of axon in the cat ($s = 0{\cdot}20\, n + 3$, Table 3). The largest fibres in the rat hind-limb nerves have external diameters of 14–14·5 μm (Mellstrom & Skoglund, 1965; Tomanek & Tipton, 1967; Thompson, 1970). This corresponds to an axon perimeter of about 30 μm. The fastest conducting axons in hind-limb nerves in a number of rats were found by Andrew, Leslie & Thompson (1973) to have velocities between 70 and 75 m/sec. Hence eqn. (10) appears to apply to the rat also.

Thus, the conduction velocity of axons in all mammals so far studied appears to be proportional to axon perimeter and, if values of s are derived from tissue fixed for electron microscopy, $\theta = 2{\cdot}5\, s$ approximately. It is worth noting that as long ago as 1939 Gasser & Grundfest reached the conclusion that θ was proportional to d rather than to D on the basis of much more limited data. They concluded, however, that $\theta = 8{\cdot}7\, d$ whereas the result of the present work is equivalent to $\theta = 7{\cdot}9\, d$ for a circular fibre.

Relation between conduction velocity and fibre dimensions predicted from theory

Conduction velocity in a myelinated fibre depends on the time taken to generate the action potential at successive nodes of Ranvier together with the much shorter time taken to traverse the internode. The rate of depolarization of the nodal membrane by 'local circuit' activity clearly depends on the total nodal capacitance and nodal conductances and one might expect the area of exposed nodal membrane to be important. Secondly, the local circuit current intensity will depend upon the longitudinal resistance of the column of axoplasm between nodes, and the amount of leakage of current through the myelin sheath in the internode. Longitudinal resistance varies with axon cross-sectional area, and inversely with internodal length, while capacitative and ionic leak current per unit length of internode depends upon the thickness of the myelin sheath and, for a cylindrical fibre, should each be proportional to $(-\ln g)^{-1}$.

From a theoretical consideration of current flow, Rushton (1951), in his theory of conduction in fibres in 'corresponding states', deduced that

$$l/D \propto g(-\ln g)^{\frac{1}{2}}. \tag{11}$$

This function of g was a maximum at $g = 0{\cdot}6$ and was constant within 5% for g between 0·47 and 0·74, the range of g found experimentally at that time. Hence l was almost proportional to D. Since other factors such as θ scaled with l in the theory of 'corresponding states', Rushton concluded that θ should be almost proportional to D, the *external* diameter of the fibre.

Subsequent dimensional analyses, or simulations of conduction using experimental data for myelinated fibres in the frog, appear to confirm that $\theta \propto D$ (e.g. Goldman & Albus, 1968; Smith & Koles, 1970; Fitzhugh, 1973). In their recent computer simulation of conduction in frog fibres Moore, Joyner, Brill, Waxman & Najar-Joa (1978) studied the effect of changing many of the variables independently and came to some interesting conclusions. In the first place, for a fibre of a particular size, θ is almost independent of l. This is not altogether unexpected since Huxley & Stämpfli (1949) pointed out long ago that although there is an optimum value of l for which θ is a maximum for a fibre of a particular size, quite large variations in l around the optimum value might result in only a small fall in θ. This was confirmed by Goldman & Albus (1968), whose data was replotted by Coppin (1973) and by Jack, Noble & Tsien (1975, Fig. 10.10); θ was almost constant throughout a range of l/D from 50 to 200 in the frog. The increased delay resulting from the presence of more nodes per unit length of fibre is almost compensated by the smaller current leak in the internode and hence greater local circuit current bringing the next node to threshold more rapidly. The conclusion that, for a particular D, θ is almost independent of l appears to apply to all normal values of l/D including the situation in remyelinated peripheral axons where l may be only one half normal although myelin thickness and conduction velocity are normal (Sanders & Whitteridge, 1946). It does not apply, however, if l is very small relative to D, which may be the case in some C.N.S. fibres (Brill, Waxman, Moore & Joyner, 1977).

Secondly, Brill *et al.* (1977) found that θ is almost independent of exposed nodal area. This surprising conclusion was possibly due to the fact that the sensitivities

to nodal membrane capacitance and maximum number of sodium channels were equal and opposite.

Thus it appears that the principal factors influencing θ are the size of the axon and the thickness of the myelin sheath. It is obvious that increasing the cross-sectional area of an axon, while keeping the myelin thickness constant, will increase θ considerably since there is a marked reduction in the longitudinal resistance of the axoplasm. Brill *et al.* (1977) computed this effect for the frog and found that the percentage change in θ was 0·65 times that in s.

The effect on θ of increasing the thickness of the myelin sheath (m) on an axon of fixed size is also substantial. Smith & Koles (1970) computed the effect of increasing m on a frog axon 10 μm in diameter. They obtained a 30 % increase in θ for a fall in g from 0·75 to 0·6, the range of g found in the present work. Brill *et al.* (1977) found that under these conditions the percentage change in θ was about 0·3 times the percentage change in m.

It should be noted that the above situation is different from that in which external fibre diameter, D, is held constant and m is increased. It follows that axon diameter must decrease with consequent increase in longitudinal resistance. In this case there is an optimum value of g for maximum θ, deduced by Rushton (1951) to be 0·6 and found to be about 0·65 by Smith & Koles (1970) and 0·62 by Brill *et al.* (1977).

Brill *et al.* (1977) found that the greatest increase in θ occurred if both axon size and myelin thickness increased in proportion to one another (g constant) in which case the percentage change in θ was 1·1 times the percentage change in D. It follows that $\theta = x\ D^{1\cdot1}$ which is a curve very slightly concave towards the θ axis.

If the above theoretical conclusions apply to the cat, then we may estimate the effect of the known change in g on the relation between θ and fibre size. If g were constant the θ/D relation and θ/s relation should be slightly concave towards the θ axis. In practice g is a minimum for medium-sized axons (s, 15–20 μm) and rises for both small and large axons. Thus, θ should be proportionately smaller for small axons ($s < 15$ μm) and for large axons ($s > 20$ μm) than if g were constant, and the relation between θ and s should become linear for $s < 20$ μm and probably concave towards the s axis for $s > 20$ μm. If, in fact, m tends to a limit at values of s in excess of 30 μm, then the effect on θ should be considerable. Some appreciable fall away from a linear relation between θ and s should occur at large values of s. Thus, a linear relation between θ and s up to $s = 20$ μm such as occurs in practice (Fig. 12) is to be expected, but that the same linear relation should provide values of θ which are consistent with those found experimentally for large fibres is not what is predicted from theory. Note, however, that in the above theoretical considerations axons were assumed to be circular, axoplasmic resistivity was assumed to be constant for all sizes of fibre, and the possibility that different groups of fibre might have different specific membrane properties was not considered.

Experimental relations between l, D, m and θ

The relation between l and D in the cat is shown in Fig. 13 in which the histological measurements of Hursh (1939) and Lubinska (1960) on the lateral popliteal trunk are combined with the findings of Coppin (1973) in which l was measured electrophysiologically in the nerve to the semitendinosus muscle. In all three studies the

relation was not linear and there was appreciable fall-off in l at large values of D. In fact, as pointed out by Coppin (1973), a semi-logarithmic relation provides a good fit to the data and the linear regression equation for the semi-logarithmic plot

$$l = 1{\cdot}69 \log_{10} D - 0{\cdot}62 \tag{12}$$

is shown by the continuous curve in Fig. 13.

If eqn. (11), deduced by Rushton (1951), were correct in practice, then there should be a small fall-off in l at large values of D. If g is obtained from eqn. (1) and the constant is chosen such that $l = 1{\cdot}07$ mm when $D = 10\ \mu$m (i.e. to coincide with eqn. 12) then eqn. (11) becomes

$$l = 0{\cdot}25\, Dg\, (-\ln g)^{\frac{1}{2}} \tag{13}$$

shown by the dashed curve in Fig. 13. Clearly the experimental values deviate appreciably from this curve at large values of D or l so that Rushton's deduction in eqn. (11) is only approximately valid.

Since the myelin sheath is relatively thinner on large axons the form of the data in Fig. 13 replotted as l against s rather than D would clearly be very similar to that of m against s in the present work. If D in eqn. (12) is replaced by $(s/\pi + 2\ m)$, i.e. axons are assumed to be circular, and s in terms of m is derived from eqn. (9) of the present work, then the resultant relation between l and m is a curve slightly concave towards the m axis which approximates very closely to the linear relation $l = 66\ m$. Thus, internodal length is much more nearly directly proportional to myelin sheath thickness than it is to either axon perimeter or total fibre perimeter (or diameter in the case of a circular fibre).

Rushton's second assumption that $\theta \propto l$, which was supported by the dimensional analyses of Goldman & Albus (1968) and Fitzhugh (1973), is also not valid for all sizes of axon in practice. This is clearly evident from the data of Coppin & Jack (1972) shown in Fig. 14. Both θ and l were measured electrophysiologically in these experiments. These authors felt that the data was best fitted by a semi-logarithmic relation and the linear regression equation for the semi-logarithmic plot

$$l = 0{\cdot}97 \log_{10} \theta - 0{\cdot}70 \tag{14}$$

is shown by the continuous curve in Fig. 14. Coppin & Jack (1972) and Coppin (1973) corrected this equation to take account of the difference in the values of θ measured in the semitendinosus nerve compared with the over-all value from spinal roots to muscle and concluded that

$$l = 1{\cdot}12 \log_{10} \theta - 0{\cdot}98 \tag{15}$$

Eqn. (15), combined with the semi-logarithmic relation between l and D derived from the data of Hursh (1939) and Lubinska (1960), but excluding Coppin's own data, which was almost the same as eqn. (12) above, led them to conclude that

$$\theta = 1{\cdot}5\, D^{1{\cdot}5} \tag{16}$$

It is not obvious how they obtained the value 0·98 which, in fact, gives rise to a multiplying factor of 2·0. To obtain the factor 1·5 the intercept in eqn. (15) needs to be about 0·8 which is closer to that in the uncorrected eqn. (14).

Eqn. (16) gives values of θ which are valid in the mid range but are somewhat high for the largest group I or α fibres and low for group III or small γ fibres (Boyd &

Kalu, 1979). If it is combined with eqn. (9) from the present work, and it is assumed that axons are circular, then the resultant relation between θ and s is that shown by the continuous curve in Fig. 12. Conclusions based on linear regression equations through data plotted semi-logarithmically should be interpreted with caution, however, since linear regression equations are only strictly applicable to data which is distributed normally. In semi-logarithmic plots there tend to be a large number of points at the upper end of the graph.

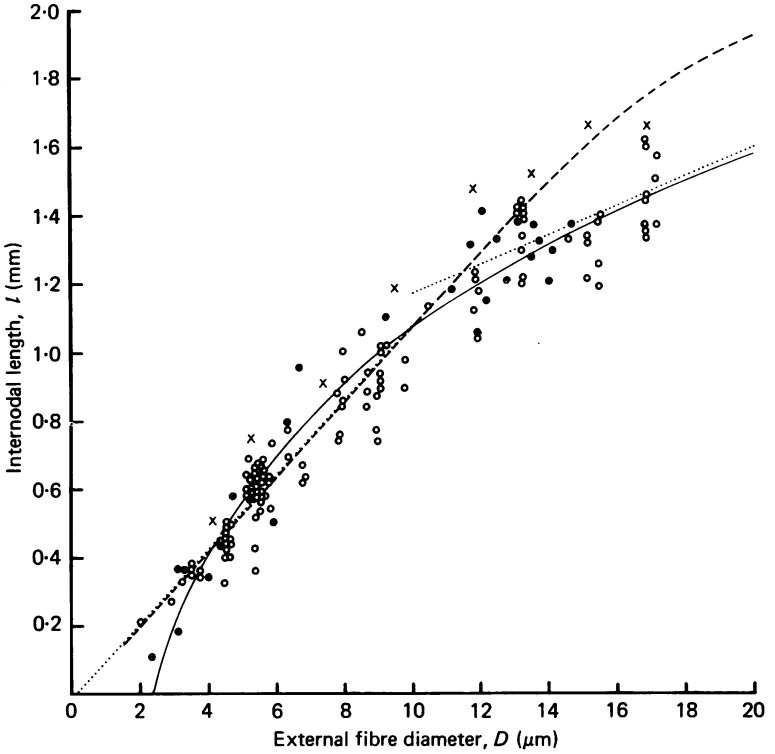


Fig. 13. Data relating l and D from Hursh (1939, ○), Lubinska (1960, ×) and Coppin (1973, ●), all replotted. Continuous curve, linear regression eqn. (12) for l in terms of D for all the data on a semi-logarithmic plot ($r = 0{\cdot}96$). Lower dotted line, linear regression equation (17) for l in terms of D for $D < 10\ \mu$m ($r = 0{\cdot}92$). Upper dotted line, linear regression eqn. (19) for l in terms of D for $D > 10\ \mu$m ($r = 0{\cdot}58$). Dashed curve, eqn. (13) relation between l and D deduced by Rushton (1951) combined with g from eqn. (1).

Although it is not true experimentally that $l \propto D$ or $l \propto \theta$ for all sizes of fibre, it could still be true for fibres within particular functional groups. The largest axons in groups II, III and γ have perimeters of about 20 μm (Figs. 3, 4 and 5) and myelin sheaths about 1·8 μm thick, so that their external diameter is close to 10 μm and their conduction velocity is between 45 and 50 m/sec. The data in Figs. 13 and 14 for fibres with $D < 10\ \mu$m or $\theta < 47$ m/sec are approximately linear. The regression equations for l as a function of D or θ are

$$l = 0{\cdot}109\,D - 0{\cdot}02 \tag{17}$$

$$\text{and } l = 0{\cdot}018\,\theta + 0{\cdot}19 \tag{18}$$

and are shown in Figs. 13 and 14 by the lower dotted lines. Eqn. (17) is not significantly different from a line through the origin, $l = 0{\cdot}106\ D$. The relation between l and θ if forced through the origin is $l = 0{\cdot}023\ \theta$. These two latter equations combine to give $\theta = 4{\cdot}6\ D$ which is precisely the same as that found by measurement of θ and D on the same nerve for groups II, III and γ by Boyd & Kalu (1979). Further,

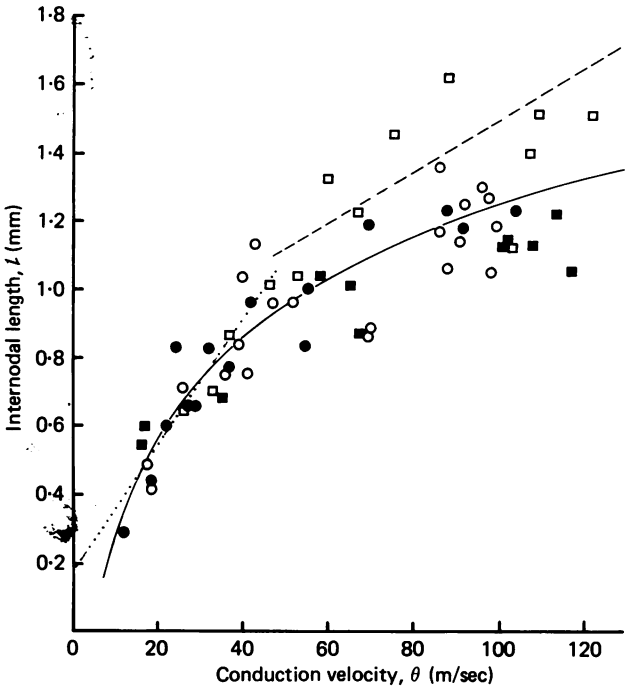


Fig. 14. Data of Coppin & Jack (1972) relating θ and l determined electrophysiologically for four cats denoted by different symbols (replotted). Continuous curve, linear regression eqn. (14) for l in terms of θ for all the data on a semi-logarithmic plot ($r = 0{\cdot}88$). Dotted line, linear regression eqn. (18) for l in terms of θ for $\theta < 47$ m/sec ($r = 0{\cdot}89$). Dashed line, eqn. (20) which when combined with eqn. (19) relating l and D leads to $\theta = 5{\cdot}7\ D$; note that it is not incompatible with the data for $\theta > 47$ m/sec (see text).

eqn. (13), shown by the dashed curve in Fig. 13, is almost coincident with eqn. (17) for $D < 10\ \mu$m. Hence Rushton's (1951) deduction given in eqn. (11) is valid, and l is almost proportional to θ, for these groups. So it seems that Rushton's theory of 'corresponding states' is applicable to axons in groups II, III and γ taken separately from those in groups I and α.

The fitting of straight lines to the data for $D > 10\ \mu$m and $\theta > 47$ m/sec is less satisfactory because of the wide scatter in the data derived from different cats. Clearly the maximal internodal length in Fig. 13 is at least 1·4 mm, whereas in three of the cats in Fig. 14 it is 1·3 mm or less. The regression equation for l as a function of D for $D > 10\ \mu$m in Fig. 13 is

$$l = 0{\cdot}043\ D + 0{\cdot}74 \tag{19}$$

shown by the upper dotted line. The correlation coefficient is only 0·58, however (0·66 if the data of Hursh (1939) are taken by themselves). The following equation

$$l = 0{\cdot}0075\ \theta + 0{\cdot}74 \tag{20}$$

combines with eqn. (19) to give $\theta = 5{\cdot}7\ D$, the relation obtained experimentally for group I and α fibres by Boyd & Kalu (1979). Eqn. (20) is shown in Fig. 14 by the dashed line and it provides a reasonable fit for the data for the cat in which the maximum value of l was similar to that in Fig. 13. Thus, the data shown for large fibres is not incompatible with the concept that $l \propto D$, and $l \propto \theta$, and hence $\theta \propto D$, for group I and α fibres, in which case the Rushton theory is again valid within this class of fibres taken by itself.

The conclusion to be drawn from the above is that all the available experimental data suggest that for all sizes of axon θ is much more nearly proportional to s than to S (or D for a circular fibre). Thus, conventional theory of conduction in myelinated fibres is not applicable to all fibres treated as a single class. But if groups II, III and γ are considered as one like class, and groups I and α as a quite separate class, then theoretical analyses, which lead to the conclusion that θ should be almost proportional to the external dimensions of the fibre, may be true within these two classes which must differ in some fundamental respect.

It has not yet been explained, however, in what way large fibres and small fibres are fundamentally different. Certainly the relative thinness of the myelin sheath on large fibres explains why the scaling factor relating θ and D is 5·7 rather than 4·6 if, in fact, $\theta \propto s$. But it does not explain why the thinning of the myelin sheath does not have the expected effect of reducing substantially the conduction velocity of large fibres compared with what it would have been if m had continued to increase in proportion to s. Thus, there must be some other compensating difference between large and small fibres.

Most obviously, the theory outlined earlier, derived from data in one particular experimental situation in the frog, may not apply to all fibre groups in the cat. But even if it does, there are other possibilities. In the first place, it is usually assumed that axoplasmic resistivity (R_i) is the same for all sizes of axon. If R_i were substantially less for large fibres than small fibres this might account for the fact that they have a higher conduction velocity than expected. There is some evidence that R_i may differ from the value calculated from the concentrations of ions present due to ordering of intracellular water or ions, or both (Carpenter, Hovey & Bak, 1973). It is not considered worth pursuing this possibility at present, however. Secondly, although theory suggests that θ is almost independent of nodal area it could be that different fibre classes have distinctly different specific nodal conductances or specific nodal capacitance, most probably the former. This possibility is discussed by Jack (1975, 1976). Thirdly, axons are not usually circular and non-circularity may influence conduction velocity as described below.

The effect of non-circularity on conduction velocity

If, as suggested by Coppin (1973) and Jack (1976), there is a systematically greater degree of non-circularity in small axons than in large ones then the relatively small cross-sectional area of a very non-circular small axon would increase the resistance of the column of axoplasm between nodes appreciably, and θ for a given value of D would be less than if the axon were circular. This might explain why the scaling factor relating θ to D is less for small fibres than for large fibres.

In the derivation of eqn. (11) Rushton assumed that the conductance of the axo-

plasm between two nodes was proportional to d^2/l. For a non-circular axon this conductance is $\propto A/l$ and, as pointed out by Jack (1976), eqn. (11) must be rewritten

$$l \propto (-A \ln g)^{\frac{1}{2}}. \tag{21}$$

Non-circularity is expressed in the present paper by ϕ, the ratio of axon cross-sectional area to the area of a circle with the same perimeter. Thus

$$l \propto s\,(-\phi \ln g)^{\frac{1}{2}}. \tag{22}$$

Arbuthnott *et al.* (1980) showed that small axons are, in fact, more non-circular, on average, than large ones. This applied particularly to motor axons where the mean value of ϕ was 0·79 for α axons and 0·69 for γ axons, the difference being statistically highly significant. There was, however, a large amount of variability in the degree of non-circularity within both α and γ groups.

If we assume that $\theta \propto l$ within groups II, III and γ and within groups I and α, but that the actual relation differs within these two classes as discussed in the previous section then, from eqn. (22)

$$\theta \propto S\,g\,(-\phi \ln g)^{\frac{1}{2}} \tag{23}$$

within one fibre class. For a typical α axon (Fig. 10), $\phi^{\frac{1}{2}} = 0{\cdot}89$. For a typical γ axon, $\phi^{\frac{1}{2}}$ is 0·83. This difference in the degree of non-circularity could give rise to a slightly greater scaling factor relating θ to external fibre size for large fibres than for small ones, if the function of g in eqn. (23) were constant, but is not nearly enough to account for the size of the observed difference (1·24 times). In any case, the function of g in eqn. (23) is slightly greater for the typical γ axon than for the typical α axon, so that any difference in scaling factor for large and small fibres, due to non-circularity and change in g, should be very small.

In the case of afferent fibres the value of $\phi = 0{\cdot}84$ for group I fibres was not significantly different from that for group II fibres (Arbuthnott *et al.* 1980), so that non-circularity cannot contribute to the difference in scaling factor between these two groups (again 1·24 times). The difference between the value of $\phi = 0{\cdot}79$ for group III fibres and $\phi = 0{\cdot}83$ for group II fibres was statistically significant, but the scaling factor is the same for these two groups. Since g is larger for group III than for group II fibres the changes in ϕ and g ought to complement rather than oppose each other.

It is concluded that the observed difference in non-circularity between large and small fibres may contribute to the fact that $\theta \propto s$ rather than to S for all sizes of axon, but cannot wholly account for it. This is probably the case even if eqn. (23) is not strictly true in practice.

Non-circularity may also lead to an error in the conversion of measurements of D in light microscopy to values of S. It was shown by Arbuthnott *et al.* (1980) that, if D is the diameter of the circle which just contains a fibre, then $S = 0{\cdot}95\,\pi D$ for nearly circular large fibres in afferent groups I and II, $S = 0{\cdot}90\,\pi D$ for α efferent and group III afferent fibres, while $S = 0{\cdot}85\,\pi D$ for γ efferent fibres which are the most non-circular of all. The relations $\theta = 5{\cdot}7\,D$ and $4{\cdot}6\,D$ for large and small fibres, respectively, thus become $\theta = 1{\cdot}95\,S$ and $\theta = 1{\cdot}60\,S$, rather than $\theta = 1{\cdot}81\,S$ and $\theta = 1{\cdot}46\,S$, if the fibres were circular. The derivation of eqns. (4) and (7) relating θ and s for small and large fibres is also affected. The slope of the relation for small

fibres increases from about 2·4 to 2·6 whereas that for large fibres increases from about 2·2 to 2·4; the intercepts are not altered appreciably. Eqn. (4) for small fibres, corrected for non-circularity, gives a value of θ for the average size of large fibre very close to that given by the corrected eqn. (7). Thus, the effect of this correction for non-circularity is to bring the experimental data closer to $\theta = 2{\cdot}5\,s$ for all sizes of fibre.

Conclusion

The thinness of the myelin sheath on large axons does not have the expected effect of reducing θ for large axons relative to its value for smaller axons with thicker sheaths. In practice $\theta = 2{\cdot}5\,s$ approximately for all sizes of axon. The fact that large axons are more nearly circular than small axons may compensate to some extent for the thinning of the sheath on large axons, but cannot compensate for it completely. Some other basic difference between large and small fibres must be responsible, possibly a difference in specific nodal conductance. The evidence suggests that there is a genuine discontinuity in the relation between θ and fibre size, so that there may be two distinct classes of peripheral myelinated nerve fibre. One class comprises group I afferent and α motor fibres, and the other group II and III afferent and γ motor fibres. Theoretical analyses which suggest that θ ought to be proportional to the external perimeter of the fibre may apply to these two classes of fibre separately, but not to all myelinated fibres taken together. Thus $\theta = 2{\cdot}0\,S$ for the class of large fibres and $\theta = 1{\cdot}6\,S$ for the class of small fibres.

We wish to thank Dr D. J. Miller for helpful criticism of the manuscript and Dr V. Moss for assistance with statistics. We are indebted to Miss J. Wilson, Mr W. Biddlecombe and Mr I. Montgomery for technical assistance. We acknowledge gratefully financial support from the Muscular Dystrophy Group of Great Britain in the form of a research fellowship for E.R.A., technical assistance and materials.

REFERENCES

ANDREW, B. L., LESLIE, G. C. & THOMPSON, J. (1973). Distribution and properties of muscle spindles in the caudal segmental muscles of the rat together with some comparisons with hind limb muscle spindles. *Q. Jl exp. Physiol.* **58**, 19–37.

ARBUTHNOTT, E. R. (1972). Three groups of motor fibres in cat peripheral nerves differentiated by the number of lamellae in the myelin sheath. *J. Physiol.* **227**, 44–45*P*.

ARBUTHNOTT, E. R. (1974). Routine collection of flat large area sections for electron microscopy as applied to a detailed study of axon dimensions. *J. Microsc.* **101**, 219–222.

ARBUTHNOTT. E. R., BOYD, I. A. & KALU, K. U. (1975). Ultrastructure and conduction velocity of small, myelinated peripheral nerve fibres. In *The Somatosensory System*, ed. KORNHUBER, H. H. pp. 168–175. Stuttgart: Georg Thieme.

ARBUTHNOTT, E. R., BOYD, I. A. & KALU, K. U. (1977). The relation between axon area, axon circumference, total fibre circumference and number of myelin lamellae for different groups of fibres in cat hind-limb nerves. *J. Physiol.* **273**, 88-89*P*.

ARBUTHNOTT, E. R., BALLARD, K. J., BOYD, I. A. & KALU, K. U. (1980). Quantitative study of the non-circularity of myelinated peripheral nerve fibres in the cat. *J. Physiol.* **308**, 99–123.

BEHSE, F. & BUCHTHAL, F. (1977). Peroneal muscular atrophy (PMA) and related disorders. II. Histological findings in sural nerve. *Brain* **100**, 67–85.

BERTHOLD, C-H. (1968). A study on the fixation of large mature feline myelinated ventral lumbar spinal-root fibres. *Acta Soc. Med. upsal.* **73**, Suppl. 9, 1–36.

BISHOP, G. H., CLARE, M. H. & LANDAU, W. M. (1971). The relation of axon sheath thickness to fiber size in the central nervous system of vertebrates. *Int. J. Neurosci.* **2**, 69–78.

BOYD, I. A. (1964). The relation between conduction velocity and diameter for the three groups of efferent fibres in nerves to mammalian skeletal muscle. *J. Physiol.* **175**, 33–35*P*.

BOYD, I. A. (1965). Differences in the diameter and conduction velocity of motor and fusimotor fibres in nerves to different muscles in the hind limb of the cat. In *Studies in Physiology, presented to J. C. Eccles*, ed. CURTIS, D. R. & MCINTYRE, A. C., pp. 7–12. Berlin: Springer-Verlag.

BOYD, I. A. & DAVEY, M. R. (1962). The groups of origin in the nerves to skeletal muscle of the γ_1 and γ_2 fusimotor fibres present close to and within mammalian muscle spindles. In *Symposium on Muscle Receptors*, ed. BARKER, D., pp. 191–198. Hong Kong: Hong Kong University Press.

BOYD, I. A. & DAVEY, M. R. (1968). *Composition of Peripheral Nerves*. Edinburgh and London: Livingstone.

BOYD, I. A. & KALU, K. U. (1973). The relation between axon size and number of lamellae in the myelin sheath for afferent fibres in groups I, II and III in the cat. *J. Physiol.* **232**, 31–33*P*.

BOYD, I. A. & KALU, K. U. (1979). Scaling factor relating conduction velocity and diameter for myelinated afferent nerve fibres in the cat hind limb. *J. Physiol.* **289**, 277–297.

BRILL, M. H., WAXMAN, S. G., MOORE, J. W. & JOYNER, R. W. (1977). Conduction velocity and spike configuration in myelinated fibres: computed dependence on internodal distance. *J. Neurol.* **40**, 769–774.

BRONSON, R. T., BISHOP, Y. & HEDLEY-WHITE, E. T. (1978). A contribution to the electron microscopic morphometric analysis of peripheral nerve. *J. comp. Neurol.* **178**, 177–186.

BRONSON, R. T. & HEDLEY-WHITE, E. T. (1977). Morphometric analysis of the effects of exenteration and enucleation on the development of third and sixth cranial nerves in the rat. *J. comp. Neurol.* **176**, 315–330.

BUCHTHAL, F., ROSENFALCK, A. & BEHSE, F. (1975). Sensory potentials of normal and diseased nerves. In *Peripheral Neuropathy*, ed. DYCK, P. J., THOMAS, P. K. & LAMBERT, E. H., pp. 442–464. Philadelphia and London: Saunders.

CARPENTER, D. O., HOVEY, M. M. & BAK, A. F. (1973). Measurements of intracellular conductivity in *Aplysia* neurones: evidence for organisation of water and ions. *Ann. N.Y. Acad. Sci.* **204**, 502–530.

COPPIN, C. M. L. (1973). A study of the properties of mammalian peripheral nerve fibres. D.Phil. Thesis, University of Oxford.

COPPIN, C. M. L. & JACK, J. J. B. (1972). Internodal length and conduction velocity of cat muscle afferent nerve fibres. *J. Physiol.* **222**, 91–93*P*.

CRAGG, B. G. & THOMAS, P. K. (1964). The conduction velocity of regenerated peripheral nerve fibres. *J. Physiol.* **171**, 164–175.

DYCK, P. J., GUTRECHT, J. A., BASTRON, J. A., KARNES, W. E. & DALE, A. J. D. (1968). Histologic and teased-fiber measurements of sural nerve in disorders of lower motor and primary sensory neurons. *Proc. Mayo Clinic* **43**, 81–123.

FITZHUGH, R. (1973). Dimensional analysis of nerve models. *J. theor. Biol.* **40**, 517–541.

FRAHER, J. P. (1972). A quantitative study of anterior root fibres during early myelination. *J. Anat.* **112**, 99–124.

FRIEDE, R. L. & SAMORAJSKI, T. (1967). Relation between the number of myelin lamellae and axon circumference in fibers of vagus and sciatic nerves of mice. *J. comp. Neurol.* **130**, 223–232.

FRIEDE, R. L. & SAMORAJSKI, T. (1968). Myelin formation in the sciatic nerve of the rat. A quantitative electron microscopic, histochemical and radioautographic study. *J. Neuropath. exp. Neurol.* **27**, 546–570.

GASSER, H. S. & GRUNDFEST, H. (1939). Axon diameters in relation to the spike dimensions and the conduction velocity in mammalian *A* fibres. *Am. J. Physiol.* **127**, 393–414.

GOLDMAN, L. & ALBUS, J. S. (1968). Computation of impulse conduction in myelinated fibres: theoretical basis of the velocity diameter relation. *Biophys. J.* **8**, 596–607.

HURSH, J. B. (1939). Conduction velocity and diameter of nerve fibres. *Am. J. Physiol.* **127**, 131–139.

HUXLEY, A. H. & STÄMPFLI, R. (1949). Evidence for saltatory conduction in peripheral myelinated nerve fibres. *J. Physiol.* **108**, 315–339.

JACK, J. J. B. (1975). Physiology of peripheral nerve fibres in relation to their size. *Br. J. Anaesth.* **47**, 173–182.

JACK, J. J. B. (1976). Electrophysiological properties of peripheral nerve. In *The Peripheral Nerve*, ed. LANDON, D. N. pp. 799–806. London: Chapman & Hall.

JACK, J. J. B., NOBLE, D., TSIEN, R. W. (1975). *Electric Current Flow in Excitable Cells*. Oxford: Clarendon Press.

LUBINSKA, L. (1960). Method of isolation of peripheral nerve fibres for quantitative morphological purposes. *Bull. Acad. pol. Sci. Cl. II Sér. biol.* **8**, 117–120.

MELLSTROM, A. & SKOGLUND, S. (1965). Calibre spectra of afferent and efferent fibers in muscle nerves of the albino rat's hind limb. *Acta morph. neerl.-scand.* **6**, 135–145.

MOORE, J. W., JOYNER, R. W., BRILL, M. H., WAXMAN, S. D., NAJAR-JOA, M. (1978). Simulations of conduction in uniform myelinated fibres. *Biophys. J.* **21**, 147–160.

RUSHTON, W. A. H. (1951). A theory of the effects of fibre size in medullated nerve. *J. Physiol.* **115**, 101–122.

SAMORAJSKI, T. & FRIEDE, R. L. (1969). A quantitative electron microscopic study of myelination in the pyramidal tract of rat. *J. comp. Neurol.* **134**, 323–338.

SANDERS, F. K. (1948). The thickness of the myelin sheath of normal and regenerating peripheral nerve fibres. *Proc. R. Soc.* B **135**, 323–357.

SANDERS, F. K. & WHITTERIDGE, D. (1946). Conduction velocity and myelin thickness in regenerating nerve fibres. *J. Physiol.* **105**, 152–174.

SCHMITT, F. O. & BEAR, R. S. (1937). The optical properties of vertebrate nerve axon as related to fibre size. *J. cell comp. Physiol.* **9**, 261–273.

SCHNEPP, P. & SCHNEPP, G. (1971). Faseranalytische Untersuchungen an peripheren Nerven bei Tieren verschiedener Grosse. *Z. Zellforsch mikrosk. Anat.* **119**, 99–114.

SCHRÖDER, J. M., BOHL, J. & BRODDA, K. (1978). Changes in the ratio between myelin thickness and axon diameter in the human developing sural nerve. *Acta neuropathol.* **43**, 169–178.

SCHWARZACHER, H. G. (1954). Markscheidendicke und achsenzylinderdurchmesser in peripheren menschlichen nerven. *Acta anat.* **21**, 26–46.

SMITH, R. S. & KOLES, Z. J. (1970). Myelinated nerve fibers: computed effect of myelin thickness on conduction velocity. *Am. J. Physiol.* **219**, 1256–1258.

SUNDERLAND, S. & ROCHE, A. (1958). Axon-myelin relationships in peripheral nerve fibres. *Acta anat.* **33**, 1–37.

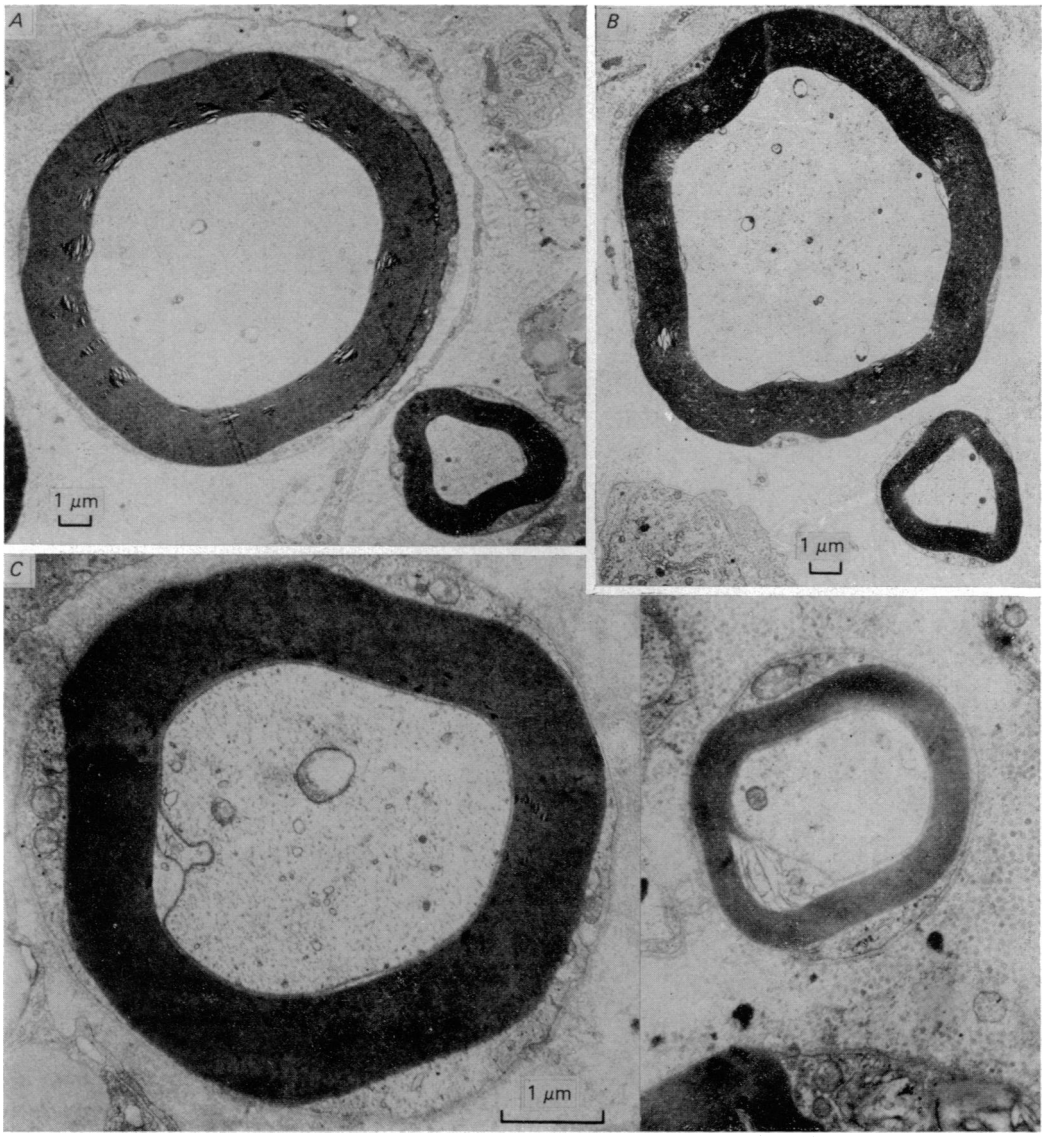
TAYLOR, G. W. (1942). The correlation between sheath birefringence and conduction velocity with special reference to cat nerve fibres. *J. cell. comp. Physiol.* **20**, 359–372.

THOMPSON, J. (1970). Parallel spindle systems in the small muscles of the rat tail. *J. Physiol.* **211**, 781–799.

TOMANEK, R. J. & TIPTON, C. M. (1967). Influence of exercise and tenectomy on the morphology of a muscle nerve. *Anat. Rec.* **159**, 105–114.

WILLIAMS, P. L. & LANDON, D. N. (1963). Paranode apparatus of peripheral myelinated nerve fibres in mammals. *Nature, Lond.* **198**, 670–673.

WILLIAMS, P. L. & WENDELL-SMITH, C. P. (1971). Some additional parametric variations between peripheral nerve fibre populations. *J. Anat.* **109**, 505–526.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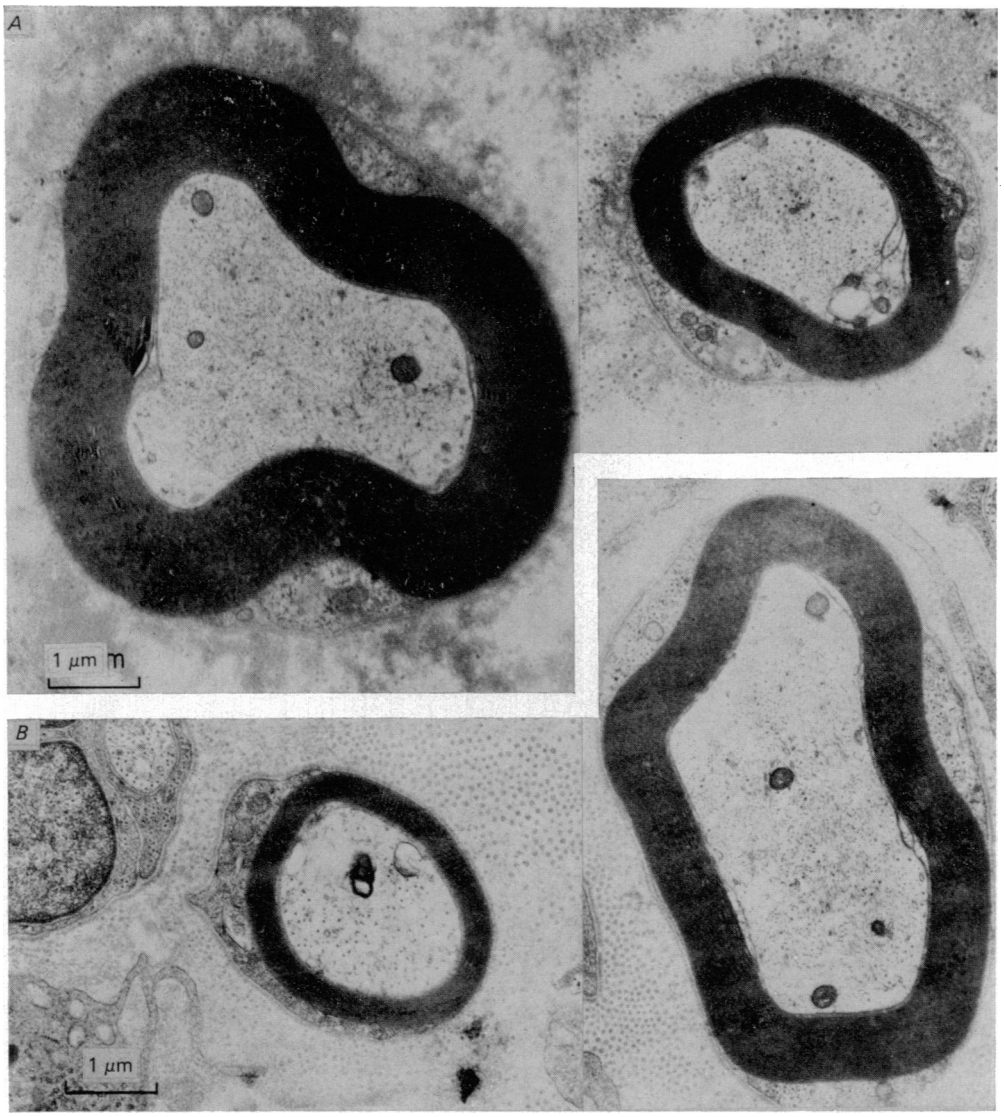

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PLATE 1

A, typical group I afferent and group II afferent fibres from nerve to flex. dig. long. lat., cat 3, de-efferentated 40 days previously, to show large size difference and relatively thicker sheath on the group II axon. group I fibre: $s = 32\ \mu m$, $n = 153$ lamellae, $g = 0{\cdot}70$. group II fibre: $s = 10{\cdot}5\ \mu m$, $n = 60$, $g = 0{\cdot}60$. *B*, adjacent α and γ efferent fibres from nerve to tibialis posterior, cat 2, de-afferentated 35 days previously, to show large size difference and relatively thicker sheath on the γ axon. α fibre: $s = 32\ \mu m$, $n = 100$, $g = 0{\cdot}73$. γ fibre: $s = 9{\cdot}5\ \mu m$, $n = 49$, $g = 0{\cdot}62$. *C*, typical group II and group III afferents from nerve to soleus, cat 4, de-efferentated 40 days previously, to show relatively thicker sheath on the group II axon. group II fibre: $s = 10{\cdot}5\ \mu m$, $n = 60$, $g = 0{\cdot}63$. Group III fibre: $s = 6\ \mu m$, $n = 29$, $g = 0{\cdot}70$. See also Figs. 3*B* and 7*A*.

PLATE 2

Typical thickly and thinly myelinated γ fibres from nerve to tibialis posterior from *A*, cat 1, de-afferentated 35 days previously; large γ axon: $s = 12{\cdot}5\ \mu m$, $n = 69$, $g = 0{\cdot}60$; small γ axon: $s = 7{\cdot}5\ \mu m$, $n = 35$, $g = 0{\cdot}70$ and *B*, cat 2, de-afferentated 36 days previously; large γ axon: $s = 11{\cdot}5\ \mu m$, $n = 48$, $g = 0{\cdot}70$; small γ axon: $s = 6\ \mu m$, $n = 22$, $g = 0{\cdot}73$. Note that myelin sheaths are thicker in cat 1 than in cat 2 but that the large γ axon has a relatively thicker sheath in both animals. See also Figs. 4*A*, *B*, 7*B* and 8*A*.