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A THEORY OF THE EFFECTS OF FIBRE SIZE IN MEDULLATED NERVE

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Our knowledge of the mechanism of nerve action is still insufficient to predict what happens in terms of electrical and chemical structure. If our theoretical knowledge were as weak in every aspect as it is upon the behaviour of the excitable membrane, we should not be able to predict confidently any relation but this—that two nerves which were exactly the same in structure, composition and properties, must behave in exactly the same way. However, both Ringer's fluid and axoplasm appear to be homogeneous conductors, so the current distribution in those regions is exactly defined by electrical theory. If, then, two nerves are not identical but have membranes with the same specific properties, it *might* still be possible to compare them exactly. For, though the properties of the membrane are unknown, they are the same in the two nerves, and though the distribution of current in Ringer and axoplasm is different it is precisely understood.

It turns out that there is only a very narrow range of conditions which will permit this argument being applied. It is when the two fibres are dimensionally similar, which is nearly the same as their being geometrically similar.

Now the interesting thing is that the nerve fibres do, in fact, exhibit the structural similarity demanded by the theory, and hence it is worth while to examine how far the variation in properties also accords with theoretical predictions.

THE ARGUMENT

The assumptions and definitions will first be set out, and then it will be demonstrated that it is only possible to argue from one nerve to another if certain proportions exist between their dimensions. Finally, it will be shown that if these proportions do exist, then the two nerves are dimensionally similar, and that everything which happens in one will, in 'similar' circumstances, happen to the other with appropriate scaling.

Assumptions

Regularity. The two nerves to be considered are assumed to have the usual cylindrical shape but to be quite regular, uniform in diameter, sheath thickness, internodal length, nodal gap-width, etc.

Homogeneous media. The axoplasm and external fluid obey Ohm's Law; the composition and specific properties are the same for the two nerves.

The cross-section area of the external fluid is assumed large compared to axon area, but the argument would remain essentially the same if it were assumed proportional to the axon area in each case.

The internodal sheath. This is formed principally by the myelin which is assumed to act passively as a leaky cable in the conventional manner. The specific properties of the myelin are the same in the two cases.

The nodal membrane. It is assumed that the current which escapes from the axon through the nodal cleft excites a cylindrical band of membrane through which it passes. This nodal membrane is the only 'active' structure in the nerve. Its specific properties are assumed the same for both nerves to be compared. This means that if we could observe independently a small element of membrane from each nerve when the current is passed through according to any time curve whatever, then, provided that the current density is at every instant the same in the two nerve elements, the potentials across the membrane will be found identical at each instant.

The resting potential. This is the same in both nerves.

Note. It has sometimes been suggested that the membrane at the nodes is a transverse one across the axis cylinder. Whatever may be the microscopic evidence for such a structure, and electron microscopy does little to support it (Rozsa, Morgan, Szent-Györgyi & Wyckoff, 1950, Fig. 16), excitability relations are quite inconsistent with a transverse membrane being the one stimulated by an applied current. For such a current must be axial to affect this membrane, and excitability should be best where the axial current is strongest. But with bipolar stimulation the axial current is strongest half way between the electrodes where the excitability is zero and with symmetrical tripolar stimulation (cathode in the middle) the excitability is maximal at the cathode and the axial current zero at this place.

Definitions

Let l = internodal length; d = internal diameter of myelin, = axon diameter; D = external diameter of myelin, = fibre diameter; a = area of nodal membrane.

Corresponding points. Events take place in the two nerves upon a different scale of distances, and in order to compare them it is convenient to consider 'corresponding points'. These are indicated in Fig. 1 where corresponding points lie on the same line radiating from O. For instance P_1, P_2 are corresponding points, and so are Q_1, Q_2. As is clear from the figure, the scaling is proportional to the internodal length. We are not assuming that fibre thickness and nodal gap are necessarily scaled in the same proportion, so there is a departure from precise geometrical similarity at the nodes.

Corresponding states. For nerves to be in 'corresponding states' all pairs of corresponding points must be equipotential. But this is not a sufficient definition, since the nodal membranes are not necessarily in corresponding states when the membrane potentials are the same, e.g. just at the beginning of an action potential as compared with some point at the end. The specific properties of the membranes have to be defined in terms of the time curve of current density, and the present definition must also involve the history of the nerve potentials in addition to their instantaneous values. It will be sufficient here to define two nerves as being in 'corresponding states' when all corresponding points are equipotential and have been so for a long time. This means that though the potentials have in general varied, they will have varied along the same time curve in corresponding points.

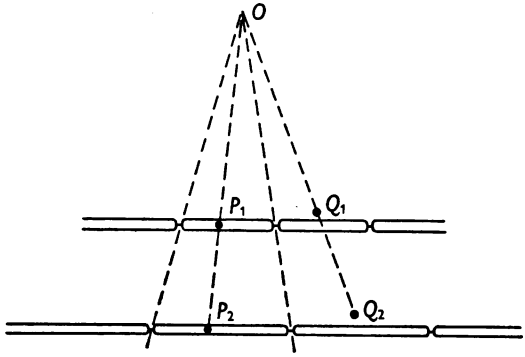

Fig. 1.

This idea is fundamental to the present treatment. Only if corresponding nodal membranes are in, and remain in, corresponding states can we argue at all from one to the other. If they are, we can argue exactly. Only if all the rest of the nerve is in, and remains in, corresponding states will this nodal condition be fulfilled. The problem thus reduces itself to this—what are the necessary conditions that two nerves in corresponding states should remain in corresponding states.

Deductions

There are four regions where the current flow must be considered: (*a*) the external fluid; (*b*) through the nodes; (*c*) along the axis cylinder; (*d*) across the myelin.

(*a*) The potentials of all corresponding points are the same and may result from externally applied stimuli. The current need not concern us.

(*b*) Since the nodes are in corresponding states, two corresponding nodes have the same membrane potential, and hence the same membrane current density; thus the total nodal current is proportional to the area of nodal membrane:

$$\text{nodal current} \propto a. \qquad (1)$$

(*c*) The potential of corresponding axial points is the same, but the distance between them varies as l, the internodal length. The axial current will thus vary as the conductivity of a cylinder of length l and diameter d:

$$\text{axial current} \propto d^2/l. \tag{2}$$

Since (2) gives the scale of axial current at any point on a nerve, it will also give the scale of the change in axial current between one point and another. In particular, if we take two points one close on either side of a node, the difference in the axial currents here must be equal to the nodal current. Hence we must equate expressions (1) and (2) obtaining

$$d^2/l \propto a. \tag{3}$$

We have seen that the change of axial current between corresponding points is given by (2), and that corresponding points are separated by a factor l, thus

$$\text{change in axial current per mm.} \propto d^2/l^2. \tag{4}$$

(*d*) The current flow across the myelin is due to leak and capacity. The potential difference across the myelin is the same at corresponding points, and hence the leak current per mm. is proportional to the conductivity per mm.

$$1/\log_e (D/d),$$

according to the well-known formula for radial leak through a cylinder. But if the condition is to be realized that the nerves continue to remain in corresponding states, then the rate of change of myelin p.d. must be the same for corresponding points and hence the capacity current per mm. will be proportional to the capacity per mm. which also is proportional to

$$1/\log_e (D/d).$$

Hence the total current flow per mm. across the myelin varies according to this expression. But this flow is equal to the change in axial current per mm. which is given in (4).

Hence

$$\frac{d^2}{l^2} \propto 1/\log_e (D/d). \tag{5}$$

The sufficiency argument

Starting with nerves in corresponding states we have seen that relations (3) and (5) are necessary if the nerves are to remain in corresponding states. It is easy now to see that if (3) and (5) do obtain (with the other assumptions) the nerves *must* remain in corresponding states.

For (3) secures that the current passing through the nodes is equal to the change in axial current there, and (5) establishes that the change in axial current per mm. (which is the sum of the leak current and the capacity current per mm.) is proportional to $1/\log_e (D/d)$. But the leak current itself is proportional to $1/\log_e (D/d)$, since this is the myelin conductivity per mm., the

sheath p.d. being the same for corresponding points. It follows that the capacity current per mm. must also be proportional to $1/\log_e(D/d)$.

But since capacity current per mm. is the product of $1/\log_e(D/d)$ and the rate of change of myelin potential per sec., it follows that not only the potential but also its rate of change must be the same at corresponding points, and hence that the nerves will continue to remain in corresponding states, at the next and all subsequent instants.

COMPARISON WITH OBSERVATION

We have started with the assumption simply that all the nerves to be compared are made of the same specific materials upon the same uniform pattern, and we have reached the conclusion that if (and only if) the dimensions are related by equations (3) and (5), the electrical behaviour will be predictable.

In this case the activity of any nerve may be exactly predicted from observations on another nerve simply by suitable scaling. It is thus important to consider whether (3) and (5) are in fact true. Equation (5) may be rewritten

$$\frac{l}{D} \propto \frac{d}{D}\sqrt{\left[\log_e\left(\frac{D}{d}\right)\right]}. \tag{6}$$

This expression then relates the internodal length l with the fibre diameter D and the axon diameter d, all of which have been carefully measured and compared by several independent workers.

Consider first the ratio (axon diameter)/(fibre diameter). This ratio g is d/D and the right-hand side of (6) is entirely determined by it. The ratio has been studied by Donaldson & Hoke (1905) who considered it constant, and more recently by Arnell (1936), Schmitt & Bear (1937), Gasser & Grundfest (1939), Taylor (1942) and Sanders (1948) who found it to increase systematically with fibre size. The results of Taylor (cat) by the birefringence method fit rather closely those of Sanders (rabbit) by direct histological measurement. Both methods are hard to apply to the smallest fibres.

In Sanders's fig. 3 more than two-thirds of the fibres had g between the limits 0·47 and 0·74, and all Gasser & Grundfest's fibres lay within this range.

Now if from equation (6) we compute how much variation there is in the ratio l/D, when d/D varies within the range mentioned, it turns out to be only a change of 5%. The ratio is highest when g is 0·6 and falls away on either side. This nearly stationary value of l/D is interesting. It follows at once from the ordinary procedure for finding a maximum.

For if
$$k\frac{l}{D} = g\sqrt{\left[\log_e\left(\frac{1}{g}\right)\right]} = g\sqrt{(-\log_e g)}$$

where k is some constant, l/D will be maximal when

$$\frac{\partial}{\partial g}\left[g\sqrt{(-\log_e g)}\right] = 0,$$

i.e. when $$\sqrt{(-\log_e g)}\left[1+\frac{1}{2\log_e g}\right]=0.$$

Obviously this is satisfied when

$$2\log_e g=-1,$$

or $$g=0{\cdot}6.$$

It is therefore because the ratio d/D is centred around the maximalizing value 0·6 that l/D is nearly independent of what the ratio is.

It can hardly be a coincidence that the ratios are centred around this value. If the materials of which a nerve is made are fixed, and if the external diameter is fixed, there is an optimal value for the thickness of the myelin in order that as much current as possible should spread from one node to the next. For if the sheath is too thin a large fraction of the current will leak through before arriving at the next node, and if it is too thick there will be hardly any space left for axoplasm and hence high core resistance will reduce the current flow.

The problem is in fact to make λ, the space constant, maximal.

Now $$\lambda^2=\frac{\text{conductivity of the core}\times\text{mm.}}{\text{admittance of the sheath/mm.}}.$$

Since we have seen that both the capacity current and the leak current of the sheath are proportional to

$$1/\log_e (D/d),$$

the admittance of the sheath will be proportional to this expression independent of the wave form of the pulse admitted, therefore

$$\lambda^2=A^2d^2\log_e (D/d),$$

where A^2 is a constant which depends upon the specific conductivity of the myelin and axoplasm but not upon dimensions. Since the external diameter is assumed fixed, we may divide the above expression by D^2 and obtain

$$\frac{\lambda}{A}=\frac{d}{D}\sqrt{[\log_e (D/d)]}. \tag{7}$$

It will be observed that since the specific conductivities of the nerve materials enter this expression only under the constant A, they can alter the height of the maximum but not the value of d/D where the maximum occurs. The optimum value of d/D is thus independent of the specific materials out of which the nerve is made.

Now the right sides of equations (6) and (7) are identical, and it thus can hardly be doubted that nerve fibres have developed their ratio d/D around 0·6, because this is the ratio which will cause the action current at one node to stimulate the next most strongly. According to equation (6) the ratio l/D should be constant within 5% over the greater part of the medullated fibre range.

Now the relation between internodal length and fibre diameter has been studied by many workers: Key & Retzius (1876), Boycott (1904), Takahashi (1908), Kubo & Yuge (1938), Hursh (1939*a*, *b*), Tasaki, Ishii & Ito (1943), Vizoso & Young (1948), Thomas & Young (1949). All these workers agree that l is nearly proportional to D over the entire range of fibre sizes and in a variety of species. There is rather a large scatter as between one fibre and another in

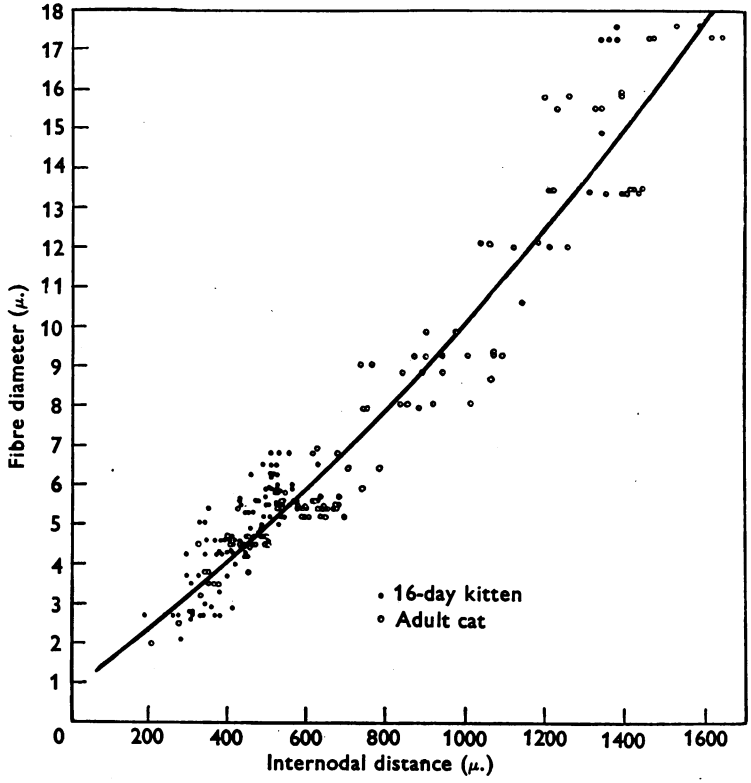

Fig. 2. Hursh's observations relating fibre diameter to internodal distance. Theoretical curve obtained by putting Sanders's observations of g into equation (6·1). Horizontal scaling arbitrary.

the same animal and even between one region and another on the same fibre, and the relation does not hold at all as between say a frog's nerve and a rabbit's. But within the rather wide limits imposed by scatter, there seems no doubt that l/D is fairly constant.

Fig. 2 is a reproduction of Hursh's observations (cat) relating D and l. The points fit fairly well a straight line through the origin. They fit perhaps slightly better the curve drawn. This curve is derived from Sanders's Fig. 3 which gives g ($=d/D$) for various values of D. Thus the value of l for each value of D may be calculated from equation (6) which may be rewritten

$$l \propto Dg\sqrt{(-\log_e g)}. \qquad (6{\cdot}1)$$

The curve therefore gives the relation between l and D which should exist if the theory of 'corresponding points' is to apply to actual nerves.

The observations of Vizoso & Young* (rabbit) indicate that small fibres have l greater than required by the theory; Thomas & Young (fishes) find small fibres with l less than the theory requires.

On the whole, the evidence is that in the frog (e.g. Tasaki *et al.* 1943) l/D is constant. In the mammal small fibres have l slightly greater than required by equation (6). But according to most observations the equation holds pretty well down to $D=4\mu$.

With regard then to the two relations which would have to be fulfilled if the argument about 'corresponding points' could be applied, (5) appears to be fairly well substantiated by plain histological measurement. Equation (3), on the other hand, can neither be proved nor refuted by this kind of observation since the value of a, the area of excitable membrane at the node, has not been adequately measured.

We shall therefore assume this relation to be true, since without it we cannot make any deductions, but with it we may predict other verifiable relations.

GENERAL NERVE PROPERTIES IN RELATION TO FIBRE SIZE

From the foregoing assumptions the following simple relations emerge:

A. Space relations are all increased in proportion to l, the internodal length.

B. Time relations are unchanged.

C. Voltage relations at corresponding points are unchanged.

A (i) *Conduction Velocity*

The space is increased l-fold and the time is unchanged, hence the velocity should be proportional to the internodal length and hence nearly to fibre diameter. This is a matter upon which there has been disagreement among investigators. The most direct measurements in the mammal are those of Hursh (1939*a*, *b*), who assumed (what is universally admitted) that the largest fibres conduct fastest, and measured in various nerves of the cat the fastest velocity and the largest fibre. His results are shown in Fig. 3, where velocity is plotted against D. Now if velocity is proportional to l, it is clear that velocity plotted against D (Fig. 3) should be the same curve as l plotted against D (Fig. 2) with suitable scaling. The theoretical curve of Fig. 2, obtained by introducing Sanders's measurements of g into equation (6) fits the points adequately. It is redrawn in Fig. 3, and is seen to fit these results also. Thus in the cat there is good proportionality between velocity and internodal length. Even more direct measurements were made by Tasaki *et al.* (1943) in single dissected fibres of the frog. They obtained the same relationship, which in frogs is a straight line through the origin.

* The fact that the curves are plotted with the l-axis passing through $D=1$ instead of through the origin, should not mislead the reader, as it has the authors (p. 115 bottom).

The other view is based upon the observation that spike-height varies in direct proportion to conduction velocity. If spike-height is also proportional to the area of the axis cylinder, as appeared plausible, then velocity should vary as the square of the fibre diameter. This was the view of Blair & Erlanger (1933) and of Zotterman (1937).

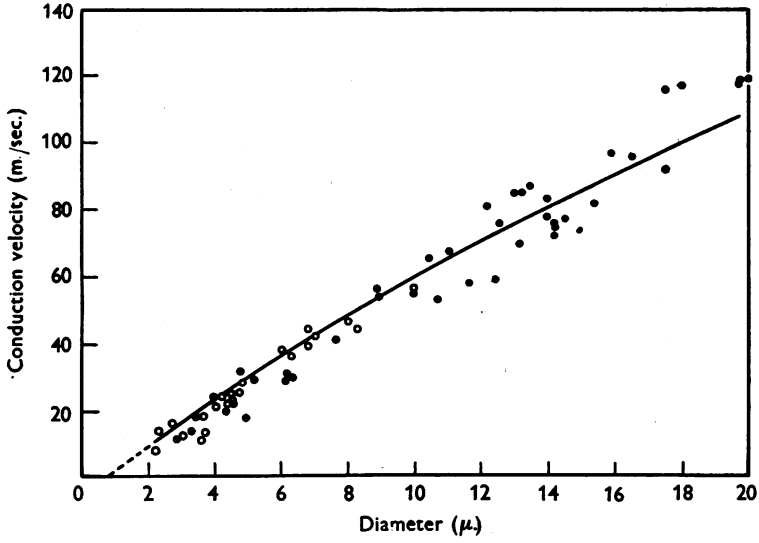

Fig. 3. Hursh's observations relating conduction velocity to fibre diameter. Theoretical curve as in Fig. 2.

The results of Zotterman, however, though interpreted by him as supporting Blair & Erlanger, actually do not show direct proportionality between spike height and conduction rate. The fact that a parabola fits these results excellently, on the other hand, cannot receive the obvious interpretation that velocity varies with diameter and spike height with area. For the velocity was calculated by measuring the time interval between the peaks of a diphasic and a monophasic recording with 20 mm. conduction distance. This must introduce a systematic error in a direction which could explain the divergence from the spike-height/velocity proportionality found by other workers.

The balance of evidence at the present time is probably rather strongly on the side of the direct measurements of Hursh and of Tasaki *et al.* and, according to these, conduction velocity is nearly proportional to fibre diameter, as required by the theory of this paper. One minor modification suggested by Gasser & Grundfest (1939) is that the proportionality should be between the velocity and the *axon* diameter, not the external fibre diameter. This is *not* the conclusion of the present theory in which the proportionality lies with the internodal length—all fibres conducting from one node to the next in the same time. As we have seen, the internodal length should be, and in fact is found to be, more nearly proportional to the external diameter than to the internal.

Their argument on p. 406 that the thinner the sheath the fatter the axons and hence the faster the conduction has a weakness which we have already

considered. For a given internodal length and external diameter the velocity will be greatest when the action current from one node spreads in greatest concentration to the next node. If the ratio d/D is either greater or less than 0·6 the conduction will be slower. But the variation is nearly stationary, and thus the *external diameter* is all that needs to be specified. Gasser & Grundfest's action potential reconstructions will be considered later.

It may be mentioned that with *non-medullated* nerve, the electrical theory predicts that velocity should be proportional to the square root of the fibre diameter. This has been found experimentally in the squid (Pumphrey & Young, 1938).

There is no conflict here either in theory or experiment. The mechanism of conduction and the relation to fibre size is different in medullated and non-medullated fibres, and experiment confirms the theoretical expectations in both cases. The brief proof which follows was shown to me by Mr Hodgkin in 1945. Though he has referred to it (Hodgkin, 1947) he has never published it. The same result has been derived by Rosenblueth, Wiener, Pitts & Garcia Ramos (1948).

If conduction velocity θ is constant, the membrane potential V will have some form $F(x-\theta t)$, where x is distance along the nerve. Thus the membrane current per mm. (outwards) will be

$$\frac{1}{R}\frac{\partial^2 F}{\partial x^2}=\frac{1}{R\theta^2}\frac{\partial^2 F}{\partial t^2},$$

where R is the resistance per mm. of axon. Now if D is the diameter of the fibre and r the specific resistance of axoplasm:

$$\text{Membrane current density } I=\frac{\pi D^2}{4r\theta^2}\frac{1}{\pi D}\frac{\partial^2 F}{\partial t^2},$$

$$\text{therefore } \frac{\theta^2}{D}=\frac{\partial^2 F}{\partial t^2}\Big/4Ir. \tag{7}$$

The second member of the equation describes the specific activity of the membrane during propagation which is the same from nerve to nerve. So θ^2/D is constant.

That velocity is proportional to $\sqrt{D}$, however, is not the conclusion of Gasser (1950) in his experimental study of mammalian C fibres.

A (ii) *Spatial aspects of excitability*

In the past it has not been fully appreciated that the epineurium is a substantial barrier to current flow so the potential distribution actually applied to the nerve fibre within may be quite different from that applied to the unstripped nerve trunk. When the nerve is stripped, however, it appears that current distribution satisfies the expectations from the simple cable theory (Rashbass & Rushton, 1949).

It follows that with different fibres, all spatial effects of current distribution will be the same when scaled in units of λ, the space constant of the fibre. But from the theory of this paper all spatial effects should be the same when scaled in units of l, the internodal length. The two theories will be congruent if, and only if, λ is proportional to l.

Now we have already seen that l is proportional to conduction velocity so we simply require to know whether λ is also proportional to conduction velocity. This has recently been studied in the A fibres of the frog by Lussier & Rushton (1951). Though the range of conduction velocities observed was only about 2 : 1 the measurements both of velocity and λ were fairly accurate and a rather exact proportionality found. It therefore appears that the spatial aspects of excitability satisfy the expectations of this paper to the extent that they have been measured.

A (iii) *The wave-length of the propagated impulse*

This should be proportional to internodal length, which follows at once from the velocity relationship we have considered and from the constancy of the duration of the action potential which we consider next.

B (i) *Time relations are the same in all fibres*

The duration of the action potential of fibres of the A group are shown in figs. 1 and 2 of Gasser & Grundfest (1939). Avoiding the effects of velocity dispersion by extrapolating back to the stimulus site they find that α and δ waves have about the same duration. Fig. 3 of their paper shows single axon spikes travelling at velocities ranging between 10 and 54 m./sec. and all having about the same spike duration.

The fact that B fibres have a different spike duration and, still more, quite different after-potentials (Grundfest, 1939) must be taken to mean that the fibres differ in qualities other than size. This view was taken by Bïshop & Heinbecker (1930), and in a more modern setting is given by Gasser (1946). It is the basis of separating the fibres into A and B groups. The relations of the present paper apply only to fibres within one group.

B (ii) *Chronaxie and summation time*

Blair & Erlanger (1933) have studied the properties of single axons in the plantaris preparation of the frog. Their results show that as conduction velocity decreases from 25 to 3 m./sec. the chronaxie and summation times both decrease by about 30%. Fibres slower than this have the times increased suddenly by more than tenfold. It would seem possible that we have here the transition between A and B fibres, which Bishop & Heinbecker (1930) placed at 4 m./sec. from investigations upon visceral nerves. Blair & Erlanger consider this suggestion, but tentatively reject it.

They suggest that the small change in chronaxie between fibres conducting at 20 and 3 m./sec. might be due to various aspects of the local circuit which is not scaled proportionally for various fibres. The present treatment gives us a precise idea of how to make the situation homologous for various sized fibres, and in recent experiments (1951) Lussier and I investigated the matter, using nerves stripped of epineurium, embedded in agar-Ringer (approximating to zero external resistance) and using half maximal α or β waves as index. We confirmed Blair & Erlanger's observation, and consider that it cannot be due simply to inappropriate scaling of the applied stimulus.

B (iii) *Refractory period*

It was largely upon the constancy of the refractory period in fibres A to B_1 and the sudden jump in the B_2 group of the same size and conduction rate that Bishop & Heinbecker's (1930) classification rested. The measurements upon single axons (Blair & Erlanger, 1933), however, show that the duration of the refractory period in the frog varies in a systematic manner, being undoubtedly shorter with large than with small fibres in the A group. The same relation has been found in mammalian nerves by Hursh (1939*b*) and by Gasser & Grundfest (1939).

It is much harder to get consistent results in measurements of recovery than in determinations of the resting threshold. The absolute refractory period requires intense shocks and involves propagation at the extreme limit of the safety factor. Late recovery, on the other hand, is complicated by subnormal or other phases which makes accurate comparison difficult. A more satisfactory measure would seem to be the interval from the first shock to the moment when a stimulus of twice threshold strength can first excite. If this is applied to the results shown in Fig. 12 of Blair & Erlanger's paper, it is found that there is still a systematic increase in the refractory time with slower fibres, but it is not very great. The velocities of the fibres cover the range 27·1 to 6·7 m./sec. and the refractory times vary between 2·1 and 2·8 msec.

Dr Tasaki has informed me that the increase in refractory period of the smaller fibres goes hand in hand with a difference in the shape of the monophasic action potential (frog). For although the duration of the rising phase is the same for all fibres, the falling phase is longer in those whose refractory period is prolonged. It thus appears that the rising time of the action potential, and with it the time of conduction from one node to the next, is the same over the whole range of medullated fibres. This signifies that energy is released by a mechanism which is specifically identical for all fibres. The falling time, on the other hand, and with it the refractory period, is longer in small nerves than in large. There appears therefore to be a specific distinction in the recovery processes between large fibres and small.

C (i) *Excitability*

If the electrodes are placed similarly with respect to the nodes, two fibres of different sizes should have thresholds at the same voltage. For instance, single fibres excited between one node and the next by Tasaki's ridge insulator method should require the same voltage independent of fibre size. This has been observed (Tasaki *et al.* 1943).

If fibres of various sizes are stimulated in one nerve through electrodes widely separated, then the stimulus must be increased inversely as the internodal length in order that the voltage drop per node may be the same for each fibre. The threshold measured in this way should therefore be inversely as the fibre size. This was found with reasonable exactness by Blair & Erlanger (1933), and more recently by Tasaki *et al.* on the frog. If the inter-electrode distance is less than the smallest internodal length concerned and the field uniformly applied, all fibres of whatever size which did not have a node between the electrodes should exhibit the same threshold. Those with a node between should have a higher threshold.

Lussier and I (unpublished) have found with stripped nerve and fairly uniform stimulating fields that the threshold for α fibres is about the same as for β when the electrodes are 1 mm. apart, but lower inversely as the conduction velocity when 10 mm. apart. With a method which permits the stimulation of a single fibre in the nerve trunk it was found that there is considerable variation between the excitability of one node and the next along the same fibre, and that the threshold rises by about 40% when the cathode is in the mid-internodal region as compared with the value at the node itself.

The relation between threshold and fibre size for various arrangements of electrodes is thus more or less as predicted by the present theory, but it is not very easy to secure similar placing of electrodes in relation to nodes, and there is a considerable variation in the 'specific excitability' from node to node which the theory excludes in its assumption of homogeneity of the fibre.

C (ii) *Action potential*

Axial currents, as we have seen (equation 2), are proportional to d^2/l. Such a current returns through the external fluid and can be measured by a pair of electrodes placed close together on the surface of the nerve.

When action potentials are measured in this way, therefore, the height would be expected to vary as d^2/l and to be more or less proportional to fibre diameter.

Fig. 4 shows an instantaneous configuration of the action current in two fibres. Horizontally is plotted distance in mm. along the nerve, and vertically the axial current at each point. This is the current which, returning through the external fluid, gives rise to the action potential. This potential will be greatest when one electrode lies at the point O and the other far to the left. For a given external resistance, the recorded potential in this case will be proportional to

the area of the curve above the axis. The monophasic spike height will thus be proportional to this area if the electrodes are far enough apart. Now we have seen that the vertical scaling is proportional to d^2/l, and in section A (iii) we found that the horizontal scaling was proportional to l, so the area is proportional to the product of the scales which is d^2. We thus obtain the result that the monophasic spike height is proportional to d^2, that is to the axon area.

This is a very awkward conclusion because the evidence is strong that spike height is proportional to velocity, which we have seen is nearly proportional to D. The variation in the ratio d/D aggravates the discrepancy, and so does consideration of possible current deformation by the epineurium through which action potentials are usually recorded.

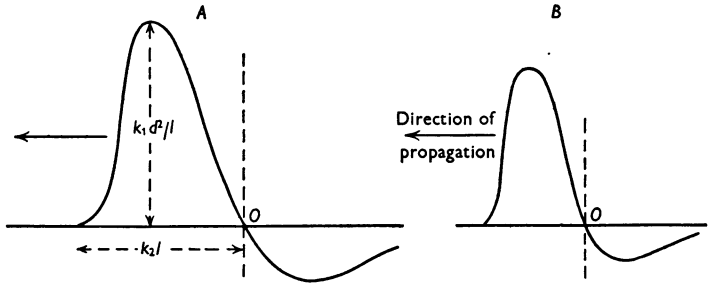

Fig. 4. Diagrammatic representation of the space configuration of the action current at one instant during propagation. Ordinates show the size of current flowing along the axis cylinder at each point (abscissae). *B* is a smaller fibre than *A*, so both spike height and wave-length are smaller.

Blair & Erlanger (1933) obtained a good proportionality between spike height and velocity in the frog, and Gasser & Grundfest (1939) did so in the mammal where their reconstructed action potentials are excellent.

These investigations do not state the conditions of the recording electrodes, and if in fact the wave were only propagated a mm. or two past the proximal lead, all these results would be consistent with the expectations of this paper.

But this is so unlikely a contingency, that it is more satisfactory simply to leave the question as an outstanding discrepancy between the present theory of fibre size and observation.

DISCUSSION

Every worker who has attempted to correlate fibre diameter with other measurements of structure and function has found that, despite a certain irregular variation, there are quite definite relations. That some theory could be hit upon to explain the regular features, at least as accurately as they are explained in this paper, would not be surprising if the theory were devised precisely to this end. What is remarkable in the present case is that the explicit requirement of the theory was not that it should correspond to observation but that it should satisfy an abstract problem. 'Given that nerves are made of

the same materials and upon the same kind of uniform pattern, what are the necessary and sufficient conditions that the behaviour of one nerve *can* be deduced from the known behaviour of another?'

It is so surprising that the solution of this problem actually corresponds with nerve structure and function, that one is tempted to speculate as to how the abstract problem which determines the one can relate to the evolutionary processes upon which the other must depend.

About evolution I shall say nothing more than that survival value attaches to optimum conditions so that we may postulate a tendency for nerves to be constructed optimally.

The idea of an optimum is not simple, and the nature of the compromises which are involved cannot be theoretically assessed. There is, however, one aspect of the optimum which conforms with the theory of this paper.

Suppose we have two fibres of the *same* internodal length l_1, and the first of them is optimal in its electrical behaviour according to some set of criteria. Then the second fibre must be made of the same specific materials and of the same dimensions and in fact be identical with the first if it is not to be inferior to it (excluding the remote case that two different systems could be equally good). Now if we consider a third nerve with internodal length l_2, it will behave in a way similar to the first nerve at corresponding points if it is made of the same specific materials and is dimensionally scaled according to equations (3) and (5). Otherwise, it will be similar to a nerve of internodal length l_1 which is inferior to the optimal fibre. It follows that nerves tend to conform to the abstract conditions of this paper because these are the optimal conditions for electrical behaviour consistent with the fibre size concerned.

The sort of optimum here involved is that the fibre should conduct as fast as possible or have as high a safety factor as possible consistent with its size. From this point of view the entire range of medullated fibres in a given animal constitutes one group, for the relation between conduction velocity and fibre diameter fits the curve of Fig. 3 throughout its length. An interesting point arises, however, with regard to non-medullated fibres.

The electrical theory (p. 110), supported by the observations of Pumphrey & Young (1938), leads to the conclusion that in non-medullated nerves conduction velocity is proportional to $\sqrt{D}$. This means that a very small fibre must conduct faster if it is non-myelinated than if it is myelinated, though the reverse will be the case for large fibres. Now it is possible to make some estimate as to the value of D when myelination first pays. The situation is shown in Fig. 5 where the dotted straight line is a replot on a larger scale of the dotted part of the line in Fig. 3. As we have seen, this theoretical line derived from Sanders's measurements of g fits well the observations of Hursh relating velocity and D. In Fig. 5 the line is extrapolated downward to give an idea of the velocity to be expected if the same relation held for the smallest sizes of nerve fibres.

Now according to the measurements of Gasser (1950) (who does not accept the $\sqrt{D}$ relation), the fastest C fibres conduct at 2·3 m./sec. and the largest C fibres have $D = 1{\cdot}1\,\mu$., hence the parabola which relates velocity and D must be the one which passes through the point (1·1, 2·3). It is drawn in Fig. 5. It at once appears that the parabola cuts the line at just about the diameter of the largest C fibre. As may be seen from the figure, all fibres smaller than this conduct faster if they are on the parabola, i.e. are unmyelinated. All fibres larger than this conduct faster if they are on the dotted line, i.e. are medullated. Now Duncan (1934) has shown that $1\,\mu$. or a little larger is the critical diameter above which all fibres are myelinated. Electrical considerations show that $1\,\mu$. is the critical diameter where myelination increases conduction velocity.

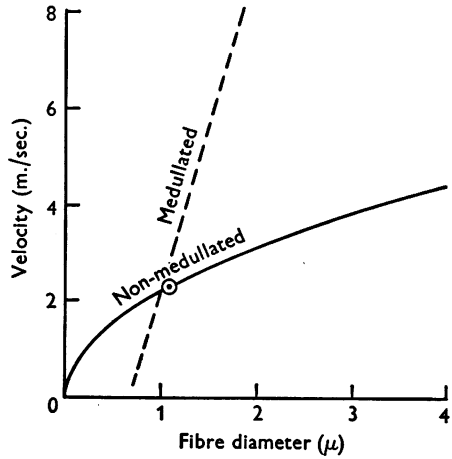

Fig. 5. Replot of part of Fig. 3 on a larger scale. Dotted line is the extrapolation of the relation between velocity and fibre diameter for medullated nerves. The parabola is the theoretical relation for non-medullated nerves passing through the point corresponding to the fastest C fibre (Gasser, 1950). No arbitrariness in scaling.

The fact that the entire range of medullated fibres constitutes a single group in respect of conduction velocity in no way invalidates the division into subgroups depending upon other functions. For example, a nerve with a pronounced supernormal recovery phase will be liable to discharge at the fixed frequency corresponding to the supernormal period whenever a constant stimulus attains threshold. This type of nerve would be suitable for sounding an alarm but unsuitable for signalling slow variations in the intensity of stimulus. It would be legitimate and might be convenient to make a division of nerves depending upon this property, especially since after-potentials and perhaps other phenomena would also be distinct.

In this way the division of nerves into A and B groups upon considerations of the recovery process may be made without disturbing the singleness of the relation between conduction velocity and fibre size.

So far we have considered structure only in relation to electrical properties. Clearly the optimum might involve the mechanical robustness of the fibre, its stability against surface tension (Young, 1944), the mechanics of plasmic flow (Weiss, 1943; Weiss & Hiscoe, 1948) and the relation of structure to metabolic changes. It is possible that certain aspects of these problems might present themselves as formally equivalent to the electrical problems already considered. If so these aspects will be solved by the 'dimensional similarity' which satisfies the electrical problem and which is, in fact, found to occur. But it is likely that for the most part quite different kinds of relation will arise in these mechanical and metabolic problems. We can only conclude that not these but the electrical considerations have determined evolution. Presumably there is a sufficient safety factor of robustness, metabolism, etc., for ordinary use, and the perfection of electrical working becomes the limiting factor.

It is interesting to compare this point of view with that of Young (1945; Vizoso & Young, 1948), where the growth and structure of medullated nerve are worked out without considering the electrical implications. The two approaches are complementary. Young finds that myelination appears when the axon diameter reaches 1–2 μ. and the myelin tube breaks (perhaps under the influence of surface tension) into segments about 0·2 mm. long. The number of these segments remains fixed, so that their length increases with the growth of the part of the body. If it be further supposed that all the fibres begin as non-medullated nerves and that they keep their diameters in fixed proportion to the length of the part of the body and hence to each other, then it will follow that the smallest which never attain 1 μ. will remain non-medullated, but that the others will have an internodal length proportional to diameter.

This describes the mechanics of myelination and accounts for the observed structural relations, but it does not explain why 1–2 μ. is the critical myelination diameter nor why diameter grows in fixed proportion to size of neighbouring bones. Electrical theory shows that both these characteristics have survival value, for below 1 μ. conduction is faster without myelination, and a nearly constant D/l ratio is needed for optimum conduction when myelination has occurred.

In regeneration after nerve damage there is a tendency for fibre diameters to return to their original values, but the regenerated internodal lengths are all about the same and only about half the length in the largest fibres originally.

Young rejects the idea that the nodes are of primary importance in nerve organization, because Sanders & Whitteridge (1946) found fully regenerated nerves to conduct at normal velocity when their diameter and myelin thickness had returned to normal, though the internodal length was halved.

The treatment of this paper has no exact contribution to make to this observation, since the regenerated fibres were not at all dimensionally similar to the controls. But it is obvious that if alternate nodes in the regenerated fibre were able simply to generate enough current to neutralize the flow which

otherwise would leak through them, then the conduction would be electrically exactly as in the normal fibre (though there would be energy degradation, Na^+ entry, etc., at the odd nodes). Now the node in fact could not do exactly this. It would be too late in starting its reaction and too vigorous in completing it. The effect of this upon the next node, however, might very well be to bring it into activity at just about the same instant as would occur in the normal fibre without the intermediate node. The result of regeneration then would not be expected to show so much in conduction velocity as in energy loss, which should be about doubled.

Huxley & Stämpfli (1949) have reached the same conclusion from a more analytical approach. They have worked out that for a given size there will be an optimum internodal length for maximum conduction velocity. Lengths somewhat greater or smaller than this will give nearly the same velocity. But the energy losses in propagation will be proportional to the number of nodes in the stretch of nerve. Hence it will be most economical if the normal nerve has an internode somewhat greater than the optimum, for this will appreciably reduce the energy necessary for conduction without much change in speed. It follows that the reduction of the internode to a length somewhat below the optimum (as occurs after regeneration) will not change velocity but will increase the energy of propagation—the conclusion reached above. So, although the relation 'velocity varies as l' holds exactly so long as fibre structure conforms to the pattern of this paper, it is far from the truth when the pattern is grossly modified as in regeneration. The relation 'velocity varies as D' on the other hand, seems a pretty good approximation over a wide range of structure patterns. The experiment of Sanders & Whitteridge thus goes very little way towards degrading the significance of the internodal length to a mere incident in the machinery of myelination. But it does raise a further question of interest. Since the regeneration experiment shows that conduction velocity can be much increased simply by increasing fibre diameter irrespective of internodal length, we are left with the question why normally developing nerves do not also increase their diameters out of proportion in the interest of speed.

It is part of the larger question as to why some nerves are large and some are small. Why are they not all large and very fast conducting? Gasser (1934) has given one answer in the suggestion that the fast fibres condition the C.N.S. to receive the later-coming impulses. Another suggestion rests upon the basis of economy. If there is only a limited amount of material available to make nerves of, or (more likely) a limited amount of space into which they can safely be fitted, then the choice lies between one fibre conducting at 90 m./sec. (say) and nine at 30 m./sec. The presence or absence of activity in the various nine fibres will theoretically distinguish between over 500 different peripheral arrangements. So for the sacrifice of some 2 or 3 msec. (in the rabbit) an enormous increase in detail may be supplied.

Now C.N.S. responses which involve choice reactions of any complexity demand a central reaction time of certainly some tens of milliseconds. It would therefore be gross mis-matching to supply the sensory input for such reactions by the 90 m./sec. type of fibre.

The consideration, then, simply of economy would suggest that large fibres should supply monosynaptic reflexes and other responses involving rapid reaction with little central analysis of the input. On the other hand, where the response depends upon a more exact appreciation of the sensory pattern, great speed is in any case impossible owing to the central delay, so it would be more economical to increase the detail of the sensory picture by multiplying the number of fibres at the expense of a small increase in conduction time. Whatever the size of fibre, however, the optimum arrangement will be for myelin thickness and internodal length to conform to the pattern of dimensional similarity.

Now this pattern is found not only in the nerves of adult animals, but in normal young ones at all stages, and in fact Hursh's results, reproduced in Figs. 2 and 3, were obtained from both young and adult nerves. So the generalization that a nerve impulse traverses one internode in a fixed time independent of fibre size applies to young animals too. And since the number of nodal segments in the total length of nerve remains fixed at all stages of growth, it follows that the duration of peripheral conduction time in the reflex arc will remain constant during growth. This might be an important factor in central reflex organization. For, as Merton (1951) has shown in human postural reflexes, the spinal cord is able to compensate for the conduction delay in the reflex arc presumably by some predictor mechanism, so that tension adjustments are performed without overshoot. This might be done by the central integration of responses from proprioceptors, some with fast and some with slow adaptation. Whatever be the manner in which the spinal cord integrates the information to give a dead-beat motor response, it might well be an advantage that the time round the servo-loop does not change with growth. For when once the central mechanism has developed, it will need no further modification due to increase in actual length of nerve pathway.

Conclusions of discussion

1. If nerves evolved to conduct as fast as possible for the size of fibre, they would be made of the same specific materials and have the dimensional similarity of structure with which this paper deals.

2. The fact that nerves are constructed approximately upon this pattern is an argument that the attainment of maximum velocity has been the controlling factor in the evolution of nerve structure.

3. Young's analysis of the mechanics of myelination goes some way towards explaining how the required structure is achieved.

4. Medullated nerves conduct at speeds roughly proportional to D, non-medullated nerves proportional to $\sqrt{D}$. It follows that the smallest nerves will conduct faster if un-myelinated, the largest if myelinated. The transition size where myelination first pays appears to be between 1 and 2μ. This is the size where fibres are, in fact, found first to acquire their sheath.

5. The principle that peripheral conduction time should match central delay leads to monosynaptic pathways being formed by fibres of the largest size. Where central delay is always long, it is advantageous to enrich the information by multiplicity of small sensory fibres which will but slightly increase total reaction time.

6. The growth of normal nerve is of such dimensions that the peripheral conduction delay in a reflex arc remains constant at all stages of growth. This permits of a *fixed* central mechanism suitable to compensate for the delay in the servo-loop at all ages.

SUMMARY

1. The following theoretical problem is propounded and solved: 'Given that all medullated nerves are made of the same specific materials, and upon the same kind of uniform pattern, what are the necessary and sufficient conditions that the behaviour of one nerve *can* be deduced from the known behaviour of another?'

2. The solution requires that the structure of all nerves should conform to a certain pattern expressed in equations (3) and (5), p. 104. To a rough approximation this is that the gap at the node should have the same width in all fibres (equation 3), and the internodes should all be geometrically similar in every dimension (equation 5).

3. There are insufficient data upon the size of the nodal clefts to check equation (3), but equation (5) is pretty well satisfied by the observed pattern of fibre structure. In particular the ratio axon diameter/fibre diameter is found to lie close to 0·6 ($=e^{-\frac{1}{2}}$) which is optimal for the spread of current from one node to the next.

4. Accepting then that the structure pattern required for the solution of the abstract problem corresponds to that of actual nerves, we may predict the way in which all properties depend upon fibre size. The results are very simple:

A. All space relations will be the same if scaled in units of the internodal length.

B. Time relations are the same for all nerves.

C. Voltage relations are the same after space scaling.

5. Experimental observations of the following quantities are considered in relation to fibre size:

A. Conduction velocity, space constant and the wave length of the nerve impulse, all of which are proportional to fibre size D. This is contrasted with the case of non-medullated nerve, where velocity is proportional to $\sqrt{D}$.

B. Duration of action potential, chronaxie, summation time and refractory period which should be the same for all fibres. This is not quite true, but the variations amount to about 30% in a fivefold range of fibre size.

C. Threshold measurements in various conditions. There is reasonable agreement with expectations, but the theory does not contemplate variations in specific irritability.

6. The monophasic action potential height from fibres in a small nerve twig should by theory be proportional to D^2. The observations show the relation to be proportional to D, the external fibre diameter. This is the only major discrepancy between theory and observation.

7. In the Discussion, fibre size and structure are considered in relation to survival value. The conclusions precede this Summary.

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