THE RELATIONSHIP BETWEEN INTERNODAL LENGTH AND GROWTH IN HUMAN NERVES

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INTRODUCTION

It has been shown in a number of animal species that the length between the nodes of Ranvier of peripheral nerve fibres increases with the diameter of the fibre (Key & Retzius, 1876; Boycott, 1904; Takahashi, 1908; Hatai, 1910; Kubo & Yuge, 1938; Hiscoe, 1947; Thomas & Young, 1949). Further, it is known that the slope of the line expressing this relationship is related to the growth of the part in which the nerve lies (Vizoso & Young, 1948). When a nerve regenerates in an adult animal, that is to say an animal no longer growing, the internodal length does not return to its original measurements but remains constant throughout the whole range of fibre diameters, even after the fibres have again reached their normal size (Young, 1945; Hiscoe, 1947; Vizoso & Young, 1948).

If internode length is so closely related to growth it should be possible to reveal differences between the nerves of parts of the body that grow to different extents. Such differences of growth of parts are very marked in man, and Shephard, Sholl & Vizoso (1949), in particular, have shown that the jaw grows very much less in absolute length than either the forearm or the leg in the period from birth to 20 years of age. The present paper records a study of internodal length in nerves taken from these three parts of the body. The nerves used were the anterior tibial at the level of the ankle joint, the ulnar at the level of the wrist joint and the facial immediately proximal to its entry into the parotid gland.

METHOD

The material used consisted of various sets of nerves taken in the post-mortem room as soon after death as circumstances permitted. The time between death and the removal and fixation of the specimens varied from 4 to 23 hr. Stretches of nerves (3–4 cm. in the case of the anterior tibial and ulnar, and 1 cm. approximately for the facial) were carefully placed on small cards and then fixed in 4 % formaldehyde in 0·9 NaCl, in which they were left until required. On removal from this solution the material was stained in 1 % osmium tetroxide in 0·9 NaCl. An alternative procedure was to fix and stain the specimens directly with 1 % osmium tetroxide in a solution of 0·9 NaCl, and then to store the specimen in 30 % alcohol until required.

Before the fibres could be dissociated it was necessary to place the nerves in water with glycerine (one-third of glycerine by volume) for several days. This tends to counteract the brittleness which results after the nerves have been in osmium tetroxide solution.

The remainder of the technique employed has been described already by Vizoso & Young (1948). The methods of measurement of the fibres, treatment of the data,

effects of fixation and dehydration, the mechanical effect of removing fibres, and errors of measurement were also dealt with in that paper.

RESULTS

(1) *Nine-year-old female*

Material from the anterior tibial and facial nerves of a girl 9 years old who died of peritonitis was measured. In Fig. 1. the lengths of individual internodal segments from the anterior tibial nerve are shown plotted against their diameters. The fibres

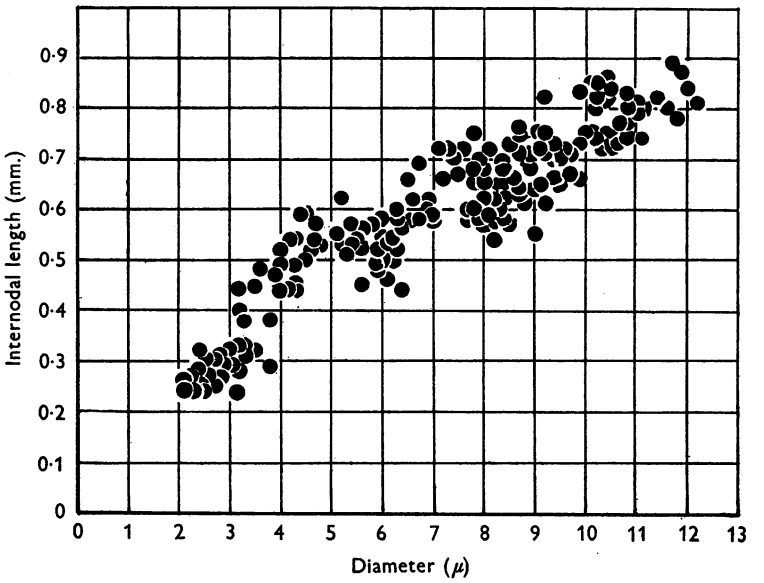

Fig. 1. Fibres from the anterior tibial nerve of a 9-year-old girl. Each point represents a single internode.

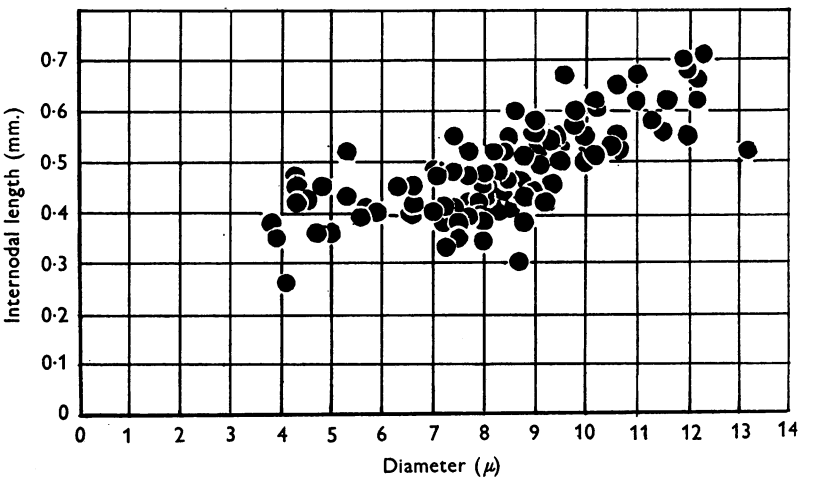

Fig. 2. Single internodes from the facial nerve of a 9-year-old girl.

measured range in diameter from 2 to 12 μ and in internodal length from 0·25 to 0·85 mm. There is a direct relationship between diameter and internodal length (Fig. 1), but some of the fibres of the 3 μ group and most in the 4 μ group appear to fall above the line observed for the other groups. A greater degree of scatter is found in the observations for fibres of larger diameter.

Fig. 2 shows individual internodes for the facial nerve of the same subject. Unfortunately, there were few fibres recorded below 4 μ in diameter, and none at all in the 2 μ group. The scatter is larger than observed for the anterior tibial, and is most apparent in the 7–9 μ group. The direction of the line suggested by the points is not as clear as it was for the anterior tibial, and a tendency to depart from linearity around the 7 and 8 μ groups is visible.

(2) *Eighteen-year-old female*

Fig. 3 shows the individual internodes plotted against their corresponding diameters for the anterior tibial nerve of a girl 18 years old who died of pulmonary tuberculosis and diabetes. The trend suggested by the points is very similar to that in Fig. 1 for the 9-year-old girl; there is a suggestion of a kink in the line here, as in the previous case, but it appears at a higher level, among diameters of 5, 6 and some of 7 μ.

In Fig. 4 the mean average internodal length is plotted against the mean fibre diameter in 1 μ groups, ranging from 3 to 12 μ. Comparing this line with that for the anterior tibial in Fig. 1 it will be seen that there is a kink present in both cases; in groups 3, 4 and 5 μ in Fig. 1 and groups 5, 6 and 7 μ in Fig. 4. The lines of the two graphs are similar, but in Fig. 4 there is a suggestion of a steeper rise.

Fig. 5 gives readings for the ulnar nerve of the 18-year-old girl. The range of fibre diameter extends to 13 μ, and the internodal length to 1·1 mm. As in the anterior tibial, the relationship between diameter and internodal length is well marked. There seems to be a sudden increase in internodal length between the 4–5 and 5–6 μ groups. The rate of increase of internodal length per diameter group appears to be somewhat less rapid above the 7 μ diameter group than in the smaller ones. The grouped data (Fig. 4) show the sudden increase in internodal length more clearly. The results for the third nerve of this set, the facial, are shown in Fig. 6, where individual internode lengths are plotted against the corresponding diameters. The diameter range extends to the 13–14 μ group. Although the scatter is probably wider than for the ulnar nerve, the majority of the readings fall close to the main line suggested by all the observations. There is no visible kink or step in the line but the slope is markedly less steep than in the ulnar and anterior tibial nerves.

The relationship existing between the different nerves studied in the 18-year-old subject can be seen in Fig. 4. From a common starting-point the anterior tibial and the ulnar nerves have a similar slope of line but the facial has a much more slowly rising gradient. It should be noted that a suggestion of a kink in the slope of the line for the facial nerve at the 5 μ diameter group depends on a single observation.

(3) *Sixty-seven-year-old female*

In Fig. 7 individual internode length measurements are plotted against diameter values for the anterior tibial nerve of a woman 67 years old who died from a

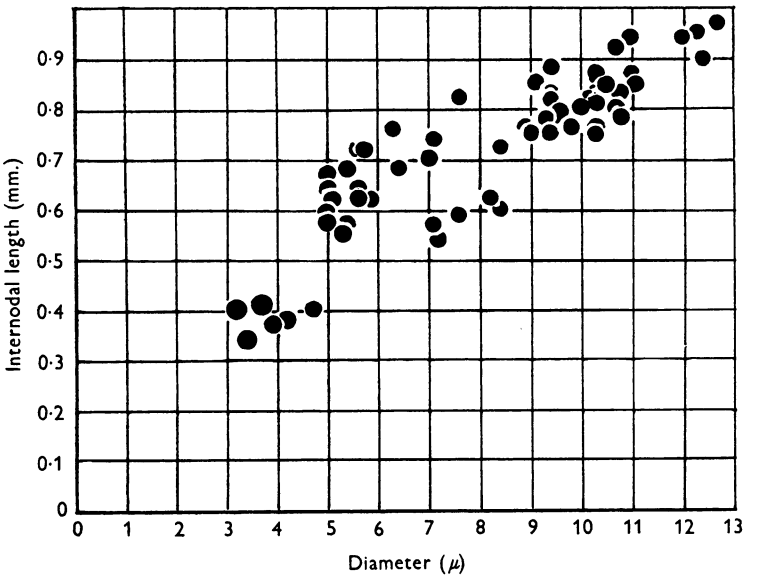

Fig. 3. Single internodes from the anterior tibial nerve of an 18-year-old girl.

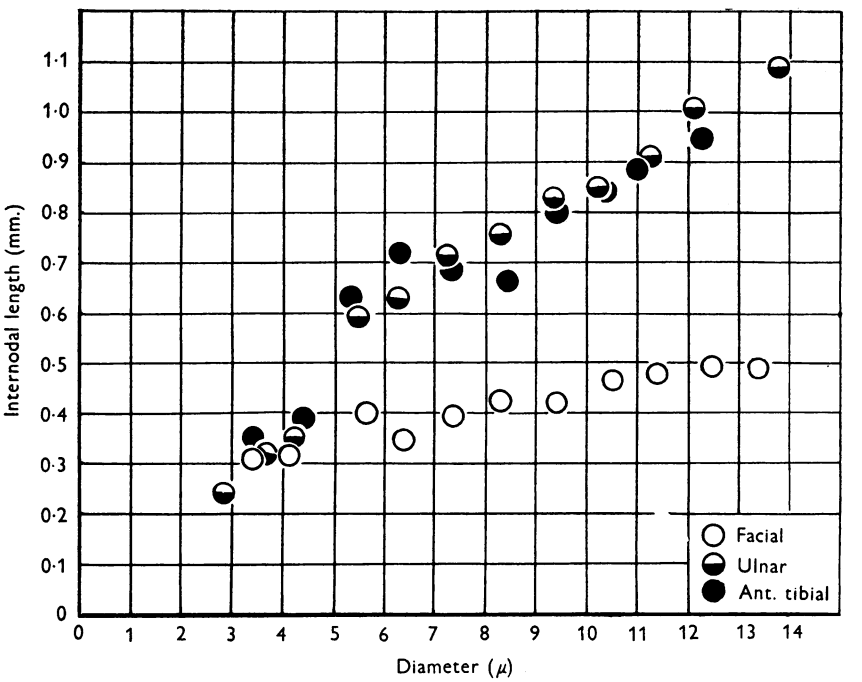

Fig. 4. Three sets of points representing mean values for 1 μ diameter groups for the anterior tibial, ulnar and facial nerves of an 18-year-old girl.

strangulated femoral hernia. This is clearly somewhat different from previous graphs for this nerve. First, the degree of scatter is appreciably larger; secondly, although the range of fibre diameter is the same as for younger individuals greater internodal lengths are observed, many being over 1·2 mm.

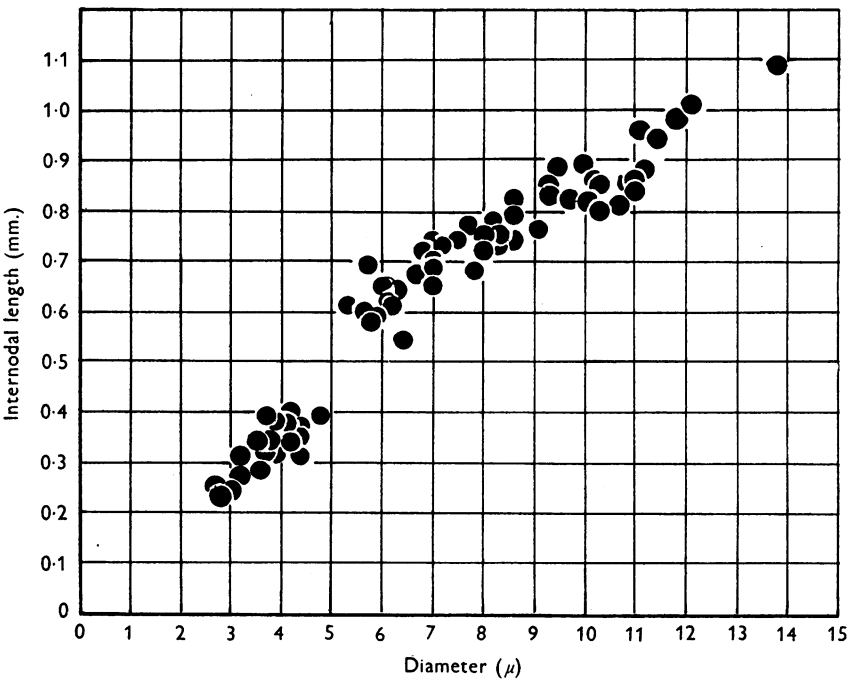

Fig. 5. Single internodes of the ulnar nerve of an 18-year-old girl.

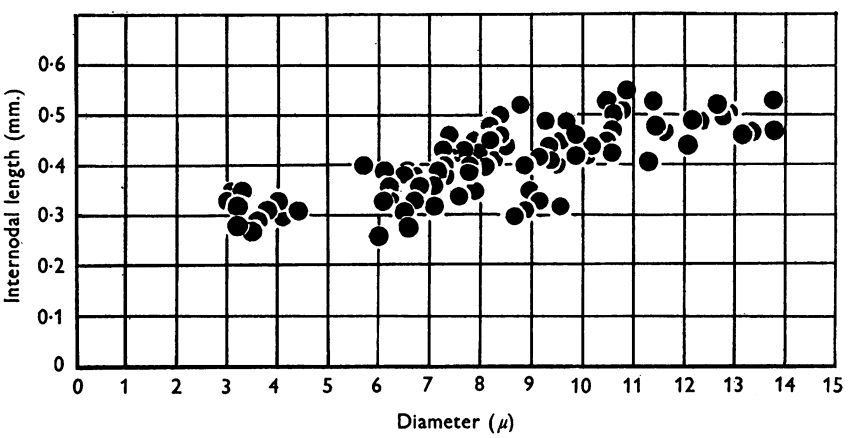

Fig. 6. Single internodes of the facial nerve of an 18-year-old girl.

These long internodes were mostly found in fibres of 11 μ or more in diameter. Still more striking is the fact that there are a number of relatively short internodes in

the 6–11 μ range, suggesting a second trend in the data. The slope of the line is somewhat steeper than in the anterior tibial nerve of the 18-year-old girl.

Results from the ulnar nerve of this 67-year-old woman are plotted in Fig. 8. Although there are less observations here than for the anterior tibial nerve a fair amount of scatter is apparent. The upwards trend is close to linearity, but as in the anterior tibial there are some short internodes in the 6–10 μ diameter groups.

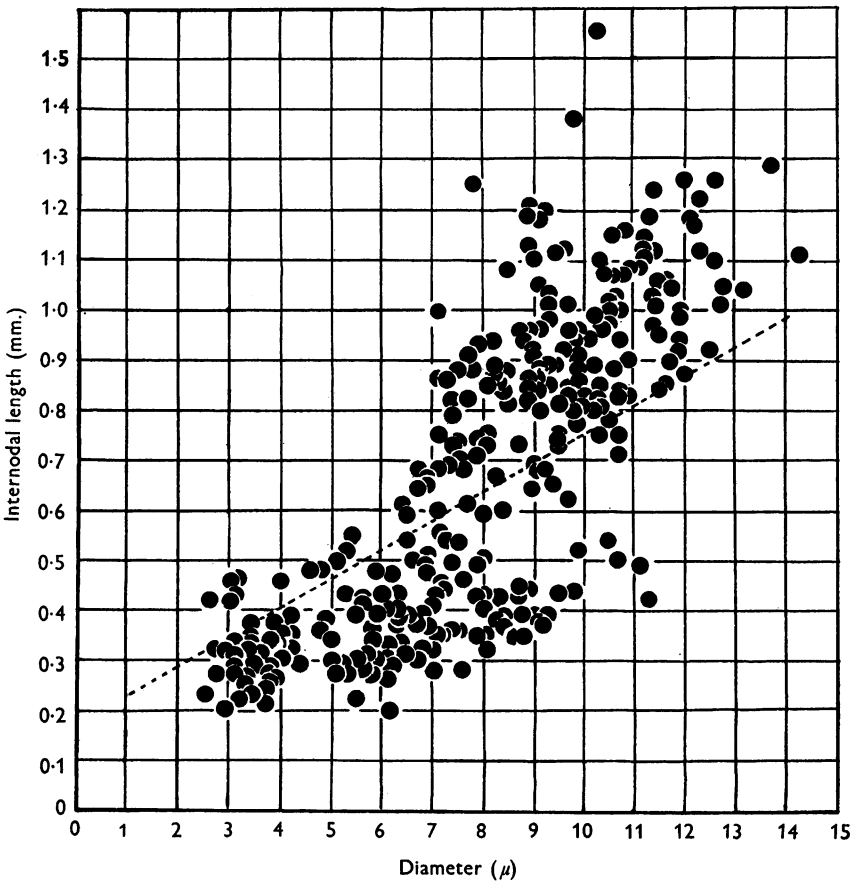

Fig. 7. Single internodes of the anterior tibial nerve of a 67-year-old woman. The broken line corresponds to an hypothetical line calculated from initial internodal length measurements and the size of the lower leg (see p. 352).

(4) *Eighty-year-old male*

Results from the fibres of the anterior tibial nerve of a man 80 years old who died of cerebral injury are plotted in Fig. 9 as single internodal length observations against corresponding fibre diameters. The picture obtained is strikingly different from those of younger subjects, and even from that of the 67-year-old woman.

The line starts with diameter readings of about 4 μ corresponding to internodal lengths shorter than any recorded, even for the thinner fibres of younger subjects.

A very steep rise leads to readings for internodal length of 1·1–1·2 mm. in diameter groups ranging from 8 μ. The scatter is large and may be compared with that for the anterior tibial nerve at 67 years of age in Fig. 7.

The ulnar nerve of this old individual, shown in Fig. 10, shows similar conditions. The degree of scatter is large. The line relating internodal length to diameter is less steep than that for the anterior tibial, especially after the 13 μ group. However, in view of the great scatter the grouped results do not adequately express the relations found.

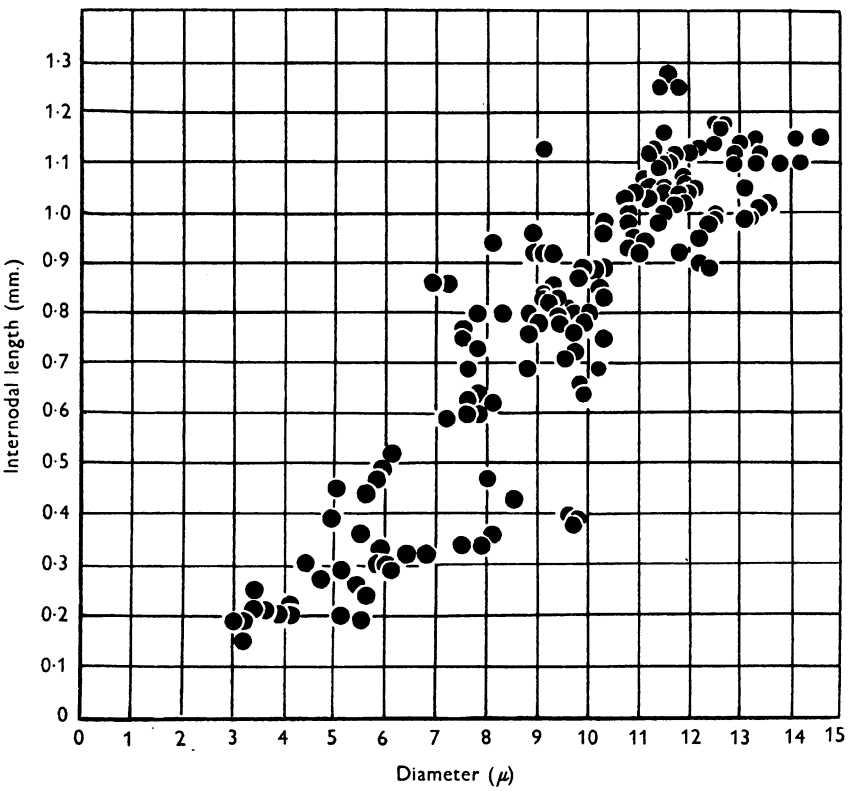

Fig. 8. Single internodes of the ulnar nerve of a 67-year-old woman.

The facial nerve of the 80-year-old male provides the data for Fig. 11. Here individual measurements show a clearer trend of increase than in the ulnar and anterior tibial nerves.

In so far as conclusions can be drawn from the plots of the grouped data they show that the differences found in younger subjects between slopes of the lines for the facial and other two nerves have disappeared. However, a better way of expressing the result is to say that in older subjects in the nerves of the limbs, but not of the face, many of the larger fibres have relatively shorter internodes than in younger subjects.

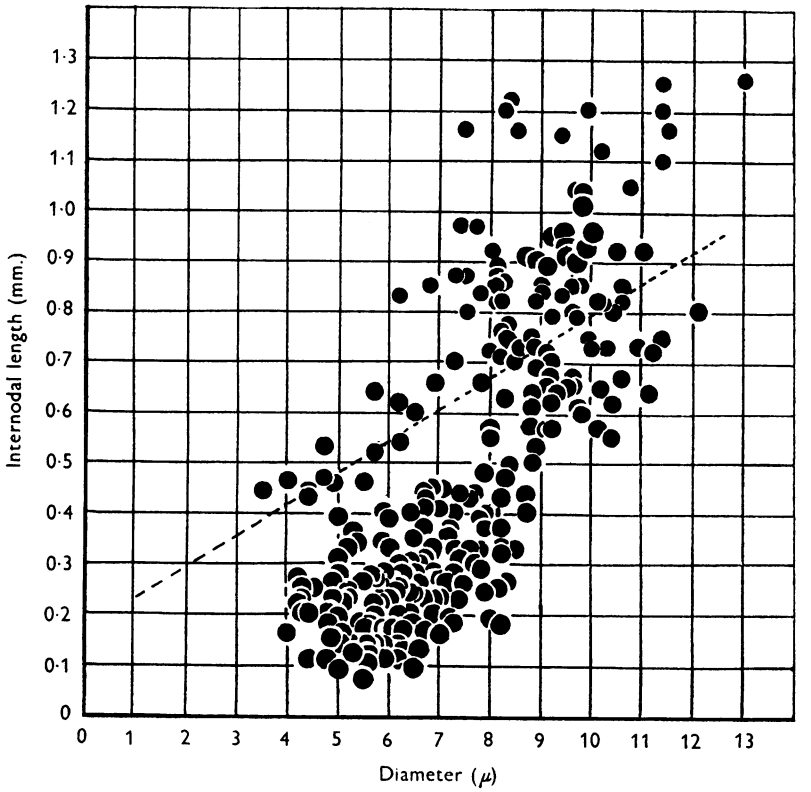

Fig. 9. Single internodes of the anterior tibial nerve of an 80-year-old man. Hypothetical line calculated as in Fig. 7.

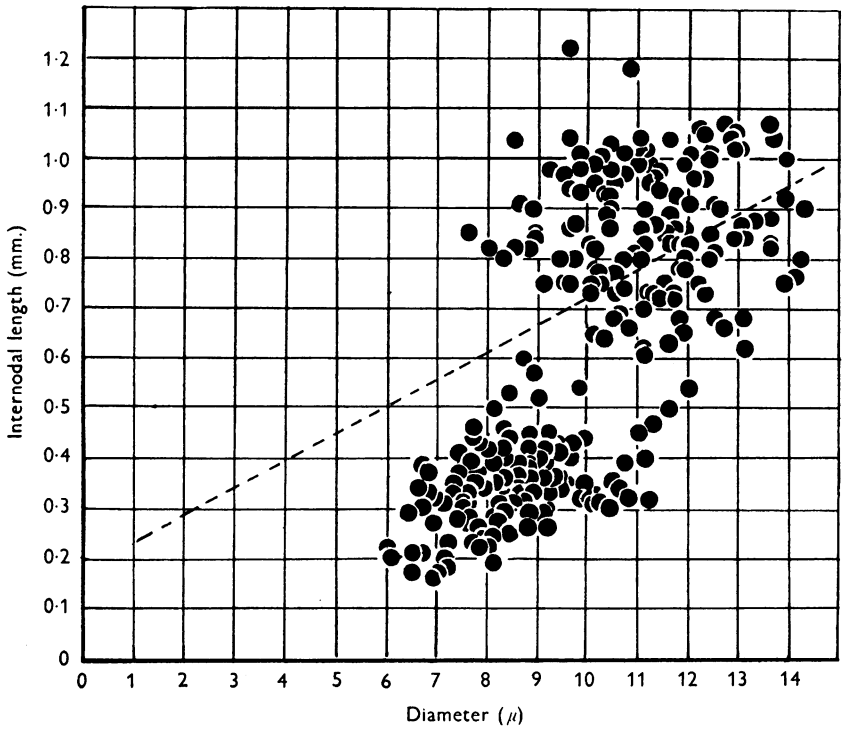

Fig. 10. Single internodes of the ulnar nerve of an 80-year-old man. Dotted line as for Figs. 7 and 9.

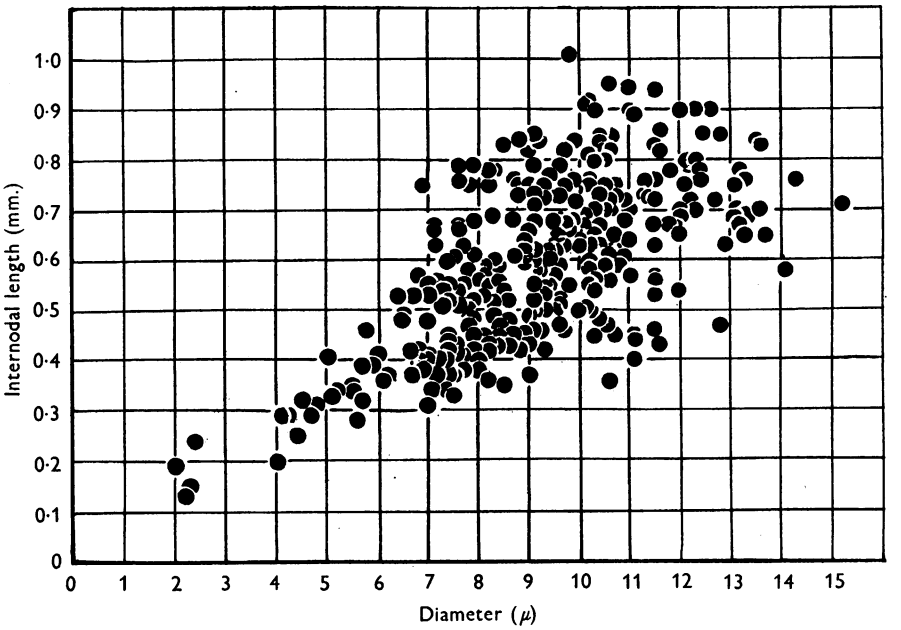

Fig. 11. Single internodes of the facial nerve of an 80-year-old man.

DISCUSSION

(1) *Increase of internode length with growth*

The data of the various nerves from the individual 18 years old clearly support in a general way the thesis that internode length increases with diameter faster in nerves lying in the parts of the body that have grown the more in length since birth. From the data collected by Shephard *et al.* the following figures have been obtained by finding the mean of all newborn and 18-year-old subjects measured.

	Birth (mm.)	18 years (mm.)	Increase (mm.)
Lower leg	130	522	4·0 ×
Forearm	139	462	3·3 ×
Jaw	59	119	2·0 ×

The nerves examined lie within the parts as defined by Shephard *et al.* and were therefore stretched approximately to the extent shown in the third column above. We cannot say exactly what increase has occurred in any given internode length, since the condition at birth is unknown in man. However, it is not unreasonable to suppose that the ultimately largest nerve fibres in each nerve will have medullated by the time of birth (Cottrell, 1940). The spacing at the nodes in a newborn rabbit was given by Vignal (1889) at about 250 μ, and by Vizoso & Young (1948) at 250–300 μ. Hiscoe (1947) gives 300 μ in the rat. The shortest internodes found in the 9- and 18-year-old individuals in the present study are about 235 μ, though the older individuals show shorter internodes. The data therefore suggest that the nodes are first laid down at a periodicity somewhat less than 250 μ—possibly at about 230 μ.

If this is so we have for the longest internodes of the 18-year-old subject the following figures:

	Birth (presumed) (μ)	18 years (μ)	Increase (μ)
Anterior tibial	230	980	4·3 ×
Ulnar	230	1100	4·8 ×
Facial	230	550	2·4 ×

There is clearly a general agreement with the relative increases in the length of the parts given above. The nodes appear to have separated slightly more than the bones have grown, but it must be remembered that the figures are for the whole parts and do not indicate the exact amount of growth for the region of nerve examined. The ulnar internodes have grown more than expected, but this appearance depends on the two very long internodes shown in Fig. 5. Exact correspondence with the growth figures can in any case hardly be expected, since the subject was a girl and the data of growth rate were for boys. Considering the known sources of error the results agree with the view that the internode length is related to the growth of the nerve.

Ranvier (1875) was probably the first to realize that the increase in internodal length is related to the increase in size of the part in which the nerve lies. He compared the length of the segments in the newborn and adult dog, and found that it increased from 0·3 mm. to 1·3 mm. He then stated that the increases in the length of the nerves appeared to be due to the progressive elongation of their internodal segments.

This connexion was denied by Vignal (1889), but Young (1945) and Vizoso & Young (1948) have shown that it is supported by many further facts, for instance the slope of the line relating internode length to fibre diameter increases with the growth of the limb. Thomas & Young (1949) have produced further evidence by showing that in fishes the lateral line nerves have much longer internodes than have the branchial nerves.

The present study shows an exactly similar relationship in man, with the added advantage that the growth of the parts has been studied exactly. The factors that determine internode length may be complex, but there is no doubt that the amount of increase in length of the nerve subsequent to medullation is a very important factor.

(2) *Changes of internodal length in old age*

The evidence so far considered shows that the number of nodes on a fibre remains nearly constant in the earlier decades of life. The data from older people show that there is later a multiplication of nodes, presumably due to degeneration and reformation. The scatter of internode lengths for a given fibre diameter is greater in the 67-year-old, and especially in the 80-year-old subject, than in the one of 18. Data such as those of Fig. 7 suggest that we have two populations of internodes, those which have remained with the individual throughout life, and others which have formed later, after the growth period was over, and therefore remain close to the minimum length. Internodes of this other set are similar to those found in regenerated nerves of adult rabbits and rats by Young (1945), Hiscoe (1947) and Vizoso & Young

(1948), in that they are short, even on fibres of considerable diameter. Such new nodes might be formed on fibres which had either undergone complete degeneration and regeneration, in which case all segments are short, or have been formed between two retracted nodes. Probably both of these processes go on. Among those fibres that have retained the original internode length, there are some which have decreased in diameter (Figs. 7, 9 and 10) and have shifted towards the left on the graph, giving the appearance of a steeper slope than the one expressed by the line for a young adult. When the fibres continue to lose their diameters either the internodal segments may become unstable and divide into smaller segments or the fibres degenerate. The broken line in Figs. 7, 9 and 10 represents the hypothetical length/diameter relationship for a normal young adult having approximately the same limb measurements as the subject. It has been fitted through two points, one at 1 μ diameter, with the minimum internodal length 0·230 mm.; the other is the product of the original internodal length (0·230 mm.) by the number of times the limb has grown since birth for the maximum diameter. It is clear that these lines do not fit the data, that is to say that the process of ageing introduces a new factor in the control of internode length. Renaut (1881) described short segments in the nerves of old horses and donkeys, and suggested that they were new ones produced to replace elements 'dont l'évolution est terminée'.

There is some evidence that when there is a local degeneration the neighbouring segments may extend, for it is noticeable that the nerves of the old individuals, besides having many short internodes also show some that are longer than any found in the younger subjects.

Some of the internodes found in these old individuals are actually shorter than any found at younger ages. This may be due to a change in the nature of the myelin, producing a shorter minimum periodicity.

SUMMARY

1. The length of the internodes was measured in human nerves taken from parts of the body that differ in amount of post-natal growth.

2. In a subject 18 years old internode length was found to increase with fibre diameter faster in the ulnar and anterior tibial nerves than in the facial.

3. The increase of length of the largest internodes was estimated to be 4·3 × in the anterior tibial nerve, 4·8 × in the ulnar, and 2·4 × in the facial, the increases in the length of the corresponding parts being 4·0, 3·3 and 2·0 times. Internode length is therefore related approximately to growth.

4. In a subject 9 years old the increase of internode length with fibre diameter was less steep than in the 18-year-old, and there was less difference between the nerves from fast- and slow-growing regions.

5. A subject 67 years old showed some fibres with internodes unduly short relative to their diameter and these were still more numerous in a subject of 80. These short internodes presumably lie on fibres that have undergone either local demyelination or complete Wallerian degeneration and regeneration.

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The detailed data have been deposited in the Thane Library of the Faculty of Medical Sciences, University College, London.

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