

QUANTITATIVE HISTOLOGY OF WALLERIAN DEGENERATION

II. NUCLEAR POPULATION IN TWO NERVES OF DIFFERENT FIBRE SPECTRUM

By G. A. THOMAS, *Department of Embryology, University College, London*

INTRODUCTION

Abercrombie & Johnson (1946), in Part I of this investigation of the quantitative histology of Wallerian degeneration, found that the number of nuclei in rabbit peroneal and tibial nerves increased to a maximum at about 25 days of degeneration, after which it declined somewhat, though at 100 days it was still five times as great as that of undegenerated nerve. They analysed the nuclear population into various sub-populations, those of endoneurial connective tissue, blood-vessel walls and Schwann tubes, dividing the Schwann tubes into those of large, medium and small calibre. Each sub-population was found to multiply to a different extent during degeneration. Since there were big differences in the amount of multiplication of nuclei of Schwann tubes of different sizes, Abercrombie & Johnson suggested that the multiplication of nuclei in any nerve undergoing degeneration would be found to depend, at least in part, on its fibre spectrum (that is, on the relative numbers of nerve fibres of different sizes which make up the nerve). The present investigation was undertaken, first, in order to discover whether a similar general pattern of rise and fall of nuclear numbers occurs in nerves other than the peroneal and tibial; and secondly, to find out whether there are quantitative differences in the magnitude of changes of numbers of nuclei which could be correlated with differences in the fibre spectra of the nerves. Both problems bear on the wider problem of the mechanism of mitotic stimulation.

In this paper the changes during degeneration in the number of nuclei in the nerve to the medial head of the gastrocnemius muscle (henceforward called the n.g.m.) and in the sural nerve of the rabbit are surveyed. The n.g.m. and sural nerve were chosen because they both occur in the same region of the thigh, immediately alongside the peroneal and tibial nerves previously studied, but are very different in fibre spectrum, the n.g.m. consisting mainly of large fibres, and the sural nerve mainly of small ones. The average fibre diameter of the peroneal and tibial nerves is similar and roughly intermediate between that of the n.g.m. and sural nerve. The anterior tibial nerve also was studied, but not in such detail as the n.g.m. and the sural nerve. The anterior tibial is the distal branch of the peroneal nerve in the shank; its fibre spectrum is similar to that of the sural nerve but, since it is in a different anatomical region, it gives some

opportunity of discovering whether factors other than the fibre spectrum of a nerve affect its changes of nuclear population during degeneration.

The nuclei of the different types of cell have as far as possible been considered separately, as was done by Abercrombie & Johnson. I have distinguished between nuclei within the Schwann tubes (tubal nuclei) and nuclei in the endoneurium. These latter have been analysed into connective tissue nuclei and blood-vessel wall nuclei. The tubal nuclei have not, however, been analysed according to the size of tube in which they were contained.

MATERIAL AND METHOD

The operative procedure was as described by Abercrombie & Johnson (1946). The nerve was cut in the thigh region and allowed to degenerate for the required period, after which the animal was killed and part of the peripheral stump removed and fixed. The centimetre of peripheral stump adjacent to the cut made at operation was not used for counting, since it was likely to have been affected by the trauma of the operation. For undegenerated material the corresponding region of nerves in unoperated rabbits was removed and fixed. Such undegenerated nerves are referred to as 0-day nerves.

The periods of degeneration studied were 5, 10, 25, 50 and 100 days for the n.g.m. and sural nerve. The nerves are correspondingly referred to as 5-day, 10-day, etc. In addition, sural nerves at 15 days of degeneration and anterior tibial nerves at 10 and 25 days were taken.

112 nerves from 43 rabbits have been used.

Histological treatment was as described by Abercrombie & Johnson (1946). Longitudinal and transverse sections at 7μ were used. The sural nerve was attached to a small piece of card to prevent distortion during fixation but, since the n.g.m. is firmly bound to the tibial nerve throughout the region used, there was no need to support it in this way.

Transverse sections only have been used for counting the nuclear population. To determine the changes in the total population, total counts, i.e. counts of all the nuclei visible in one transverse section, were made. For differential counts, i.e. counts in which the nuclei are analysed into tubal, endoneurial, and blood-vessel wall nuclei, complete transverse sections of the n.g.m. were counted, but for the larger and more densely populated sural nerve a number of fields selected at random was counted. When the population of a whole transverse section was to be estimated it was usual to average the counts of three complete sections, selected at random, of each nerve. When fields only were counted, four to ten fields from each of three sections were used.

In the tables which follow, the figure for degenerated nerves has in most cases been expressed as a percentage of the mean number of nuclei in undegenerated nerves. In the analysis of the sural nerve, however, it was found to be impossible to make satisfactory differential counts of undegenerated nerves. But at 5 days of degeneration endoneurial oedema makes the different kinds of nuclei more easily distinguishable. The differential counts of all nerves have, therefore,

been expressed as a percentage of the number of nuclei in 5-day degenerated nerves, at which time the total population has already increased, but only between $1\frac{1}{2}$ and 2 times.

Estimations of the statistical significance of differences between means have been made by *t* test, the level of significance used for a conclusion that the samples concerned do not come from the same population being a probability (*P*) that they do so, of 0.01.

The necessity for standardizing the nuclear counts for alterations during degeneration in the volume of the whole nerve and in the average length of nuclei was pointed out by Abercrombie & Johnson (1946). The methods used by them, and by Abercrombie (1946), to achieve this standardization have been applied in the present paper.

Changes in volume of the nerve produce misleading results only when the data consist of counts of the number of nuclei per microscopical field. When counts of all the nuclei in a complete transverse section of the nerve have been made there is no need to standardize for changes in the volume of the nerve, since changes in volume will not affect the total number of nuclei present. In the differential counts of the sural nerve, the percentages of the various types of nuclei obtained from sample fields have been converted into actual numbers of each of these types of nuclei in a complete transverse section, by applying the percentages to the total counts made separately, of all nuclei in a transverse section of the nerve. Any effect of volume changes on individual fields will thus be allowed for.

The method for allowing for changes in nuclear length, used by Abercrombie & Johnson (1946), was used for the sural and anterior tibial nerves, except that the length of the nuclei of every individual nerve was not measured, but the average nuclear length in longitudinal section at each time of degeneration was obtained from a sample of the nerves degenerated for that length of time. Since the small amount of stretching involved in fixing the sural nerve to a piece of card might have affected the length of the nuclei and, therefore, the number of nuclei which appeared in a transverse section, counts of the sural nerve fixed in this way were compared with the counts of nerves which had not been so treated. The difference between these counts was so small, averaging only 6%, that the effect of fixing on cards can be regarded as unimportant in relation to the scale of differences dealt with here.

It was found to be impracticable to cut longitudinal sections suitable for measuring nuclear lengths of the very small n.g.m. and, therefore, the method given by Abercrombie (1946) of counting the nuclei in transverse sections of 5μ and 12μ was used.

The nuclei of all the nerves studied shorten during early degeneration, and the maximum shortening was found at 10–15 days of degeneration in the sural nerve, and at 25 days in the n.g.m. The nuclei of the n.g.m. shortened most, then those of the peroneal and tibial nerves, and the nuclei of the sural nerve shortened least of all.

RESULTS

Changes in total nuclear population

Table 1 shows the mean number of nuclei in a complete transverse section of the n.g.m. and sural nerve at different times of degeneration, corrected for changes in nuclear length, and expressed as a percentage of the mean total number of nuclei in undegenerated nerves. Column 3 shows the figures for the nuclei of the n.g.m. and column 5 those for the nuclei of the sural nerve. The data are shown graphically in Text-fig. 1 along with the data for peroneal and tibial nerves obtained by Abercrombie & Johnson (1946) (henceforward referred to as peroneal-tibial data).

Table 1. *Mean populations of all nuclei of nerves at different times of degeneration, expressed as percentages of the mean populations of undegenerated nerves, with standard errors*

(1) Days of degeneration	N.g.m.		Sural	
	(2) No. of nerves	(3) Mean population (%)	(4) No. of nerves	(5) Mean population (%)
0	8	100 ± 9	9	100 ± 5
5	8	202 ± 13	9	140 ± 6
10	7	740 ± 30	9	319 ± 22
25	8	1860 ± 97	9	470 ± 21
50	6	1370 ± 60	7	289 ± 10
100	6	1120 ± 36	6	252 ± 13

In all three nerves the population increases quickly to a maximum and thereafter declines, more rapidly at first, less rapidly later. But though the changes in nuclear population of the three kinds of nerves have the same general trend, there are considerable differences in the amounts of multiplication which the nuclei of the different nerves undergo. The nerves with the larger fibres show the greater degree of multiplication. Pl. 1, figs. 1-4, showing degenerated and undegenerated sural nerves and n.g.m., illustrate the differences.

Taking the n.g.m. or sural nerve separately, the differences between total populations at different times of degeneration are all statistically significant, except for the differences between the populations at 50 and 100 days in both nerves. At 25, 50 and 100 days of degeneration, but not at 5 and 10 days, the percentage increase of the nuclear population of each kind of nerve is significantly different from that of either of the other kinds.

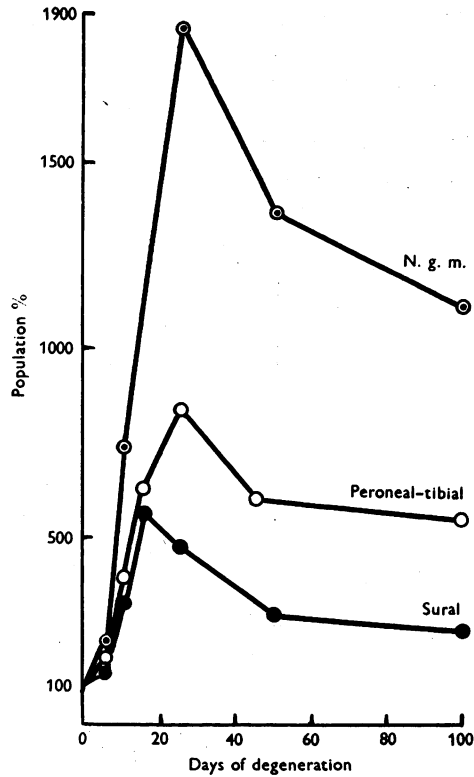
The main nuclear estimations were made at 0, 5, 10, 25, 50 and 100 days of degeneration and of these the highest for all nerves were those obtained at 25 days of degeneration. Since, however, measurements have been made at only one time between 10 and 50 days, it is possible that the true peak of population is earlier or later than 25 days. In supplementary experiments it has been shown for the sural nerve that in fact it is earlier. Four sural nerves of 15 days of degeneration, together with the corresponding nerves from the other side of the animals (contralateral controls) of 25 days of degeneration, were prepared. The populations of the nerves degenerated for 15 days were

respectively 118, 126, 122 and 121 % of the populations of their 25-day contra-lateral controls. The difference between the populations at 15 and 25 days is statistically significant. Further investigation would probably show that the population peaks of the n.g.m. and peroneal-tibial nerves are not exactly at 25 days of degeneration, though it is improbable that the maximum populations have been seriously underestimated.

At its maximum (at 15 days of degeneration) the nuclear population of the sural nerve has increased 6 times, while that of the n.g.m. has at its maximum (at 25 days) increased 19 times. In comparison the peroneal-tibial population has increased 8 times by 25 days. The maximum recorded n.g.m. population increase is therefore more than 3 times that of the sural nerve and more than twice that of the peroneal-tibial nerves.

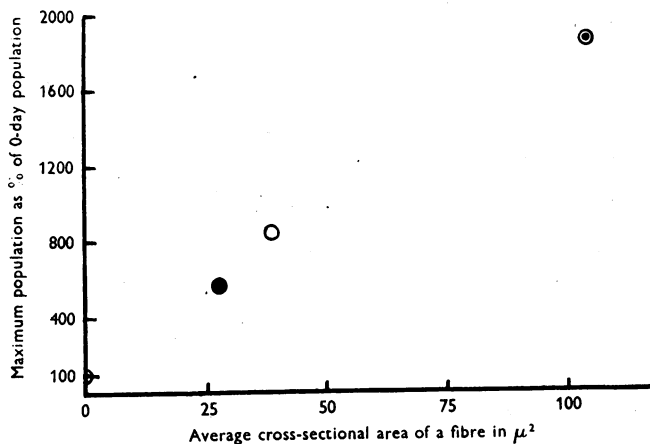
By 100 days of degeneration the nuclear population of the n.g.m. has declined to 60 % of the peak population, that of the sural nerve to 44 % and that of the peroneal-tibial nerves to 64 %, the decline being most rapid immediately after the presumed peak of population has been reached.

An undegenerated sural nerve averages 211 nuclei per transverse section of 7μ thickness and an undegenerated n.g.m. averages 41 nuclei, the cross-sectional areas of the two kinds of nerve being roughly similar. Since the n.g.m. has a higher rate of nuclear multiplication than the sural nerve the populations of the two nerves become more and more alike numerically as degeneration proceeds. Thus, at 25 days of degeneration, the sural nerve averages 990 nuclei per transverse section and the n.g.m. 770. In 1 cu.mm. of undegenerated nerve there are roughly 90,000 nuclei in the case of the sural nerve, 27,000 in the n.g.m. and 43,000 in the peroneal-tibial nerves. By 25 days of degeneration the differences between the number of nuclei in the different nerves is much less, the sural nerve population being 440,000, the n.g.m. 450,000 and the peroneal-tibial 330,000 nuclei per cu.mm. These figures refer of course to fixed material.



Text-fig. 1. Mean populations of nuclei of three different nerves at different times of degeneration, expressed as percentages of those of undegenerated nerves. ● Sural nerves; ○ peroneal-tibial nerves; ⊙ n.g.m.

Abercrombie & Johnson (1946) suggested that the changes in nuclear population during degeneration of any nerve are likely to depend at least in part on its fibre spectrum. The above data show such a relationship. One aspect of the fibre spectrum which we can examine is the average cross-sectional area of a myelinated fibre of the nerve. In Text-fig. 2 the nuclear population of each kind of nerve, when it is at its maximum (as far as my data reveal the maximum), is plotted against an estimate of the average cross-sectional area of a fibre. The figures for the n.g.m. and sural nerve average fibre areas were very kindly supplied by Dr G. Causey, and those for the peroneal-tibial nerves were calculated from data published by Gutmann & Sanders (1948).



Text-fig. 2. Maximum populations of nuclei of four different nerves expressed as percentages of the nuclear populations in these nerves when undegenerated, plotted against the average cross-sectional area of a nerve fibre of the respective nerves. \odot N.g.m.; \circ peroneal-tibial nerves; \bullet sural nerves; \oplus anterior mesenteric nerves.

The histological method used by Dr Causey to obtain the average fibre areas was that used by Aitken, Sharman & Young (1947). It involves a shrinkage of the living fibre diameter probably not exceeding 10%. In measuring the diameters, the nerve fibres were divided into groups which differed from each other in diameter by 2μ . The number of fibres in each group was then multiplied by a figure for the cross-sectional fibre area calculated from the median fibre diameter of the group. The weighted mean of the average fibre areas so obtained for each group is the average fibre area of the whole nerve.

The points on the graph in Text-fig. 2 represent the maximum percentage increase of the nuclear populations of the n.g.m., the peroneal-tibial and sural nerves, and since Joseph (1947) showed that the nuclei of an unmyelinated nerve do not increase in number at all during degeneration, the zero point can be put in, representing the anterior mesenteric nerve which he used. As a rough approximation it appears that the amount of nuclear proliferation in the nerves is directly proportional to the average cross-sectional fibre area.

The relationship which thus appears to hold between the average fibre area and the amount of proliferation in a nerve has been further checked on the anterior tibial nerve. If the relationship really exists, then the anterior tibial nerve should show changes in population more like those in the sural nerve than those in the peroneal from which it arises, since the average fibre area of the anterior tibial nerve (Sanders & Young, 1944) is very similar to that of the sural nerve. This proved to be the case. At 25 days of degeneration six anterior tibial nerves had a nuclear population which was 146 % of the nuclear population of six other anterior tibial nerves at 10 days of degeneration. The comparable figure for sural nerves is 150 %. The n.g.m. and peroneal-tibial nerves, with their very different fibre spectra, showed increases in nuclear population of 260 and 215 % respectively.

Differential counts of nuclear multiplication

In order to discover to what extent each of the nuclear categories present was responsible for the differences in the amount of proliferation in the different nerves, the populations have been analysed into tubal nuclei (i.e. those nuclei which lie within the Schwann tubes), endoneurial connective tissue nuclei, and blood-vessel wall nuclei.

The difficulties involved in the recognition of the different kinds of nuclei in the undegenerated sural nerve, which has a large number of small fibres, were found to be insuperable. Therefore, in considering these differential counts, the figure for a nerve of 5 days of degeneration has been used as a standard from which to calculate the relative amount of nuclear increase.

The figures for the populations of different nuclear types have been standardized for changes in nuclear length during degeneration, though for this standardization the average length of all the nuclei in the nerve was used and not the average length of each individual type.

The nuclei of the sural nerve were not counted differentially at 15 days of degeneration, but in the light of the total counts at this time, it should be remembered that the peak population of each of the different categories of its nuclei is likely to lie nearer to 15 days than to 25 days.

Changes in numbers of tubal nuclei

The population of tubal nuclei in both kinds of nerve shows, like the population of all nuclei, a rise to a maximum followed by a decline. As with the total population, the n.g.m. tubal nuclei show a much greater increase than those of the sural. They reach 17 times the 5-day population at 25 days. The peroneal-tibial tubal nuclei increase 8 times and those of the sural nerve only 4 times.

The third columns in Tables 2 and 3 show the changes in tubal populations with time of degeneration.

Taking each kind of nerve separately, at each time of degeneration studied the tubal nuclear population is significantly different from the tubal nuclear population at either the preceding or the following times of degeneration.

After 10 days of degeneration the tubal nuclear population of any of the three kinds of nerve is significantly different from that of either of the others.

Table 2. *Nervus gastrocnemii medialis*. Mean populations of various nuclei of nerves at different times of degeneration, expressed as percentages of the mean populations of 5-day degenerated nerves, with standard errors

(1) Days of degeneration	(2) No. of nerves	(3) Tubal nuclei	(4) Endoneurial nuclei	(5) Blood-vessel wall nuclei
0	8	47 ± 5	53 ± 5	45 ± 5
5	8	100 ± 5	100 ± 8	100 ± 7
10	7	606 ± 18	188 ± 12	107 ± 9
25	8	1680 ± 96	336 ± 18	193 ± 22
50	6	1220 ± 67	260 ± 12	143 ± 17

Table 3. *Sural nerve*. Mean populations of various nuclei of nerves at different times of degeneration, expressed as percentages of the mean populations of 5-day degenerated nerves, with standard errors

(1) Days of degeneration	(2) No. of nerves	(3) Tubal nuclei	(4) Endoneurial nuclei	(5) Blood-vessel wall nuclei
5	8	100 ± 6	100 ± 6	100 ± 13
10	7	286 ± 15	158 ± 9	109 ± 8
25	8	435 ± 29	230 ± 17	120 ± 10
50	6	254 ± 17	144 ± 9	107 ± 8

Changes in numbers of endoneurial connective tissue nuclei

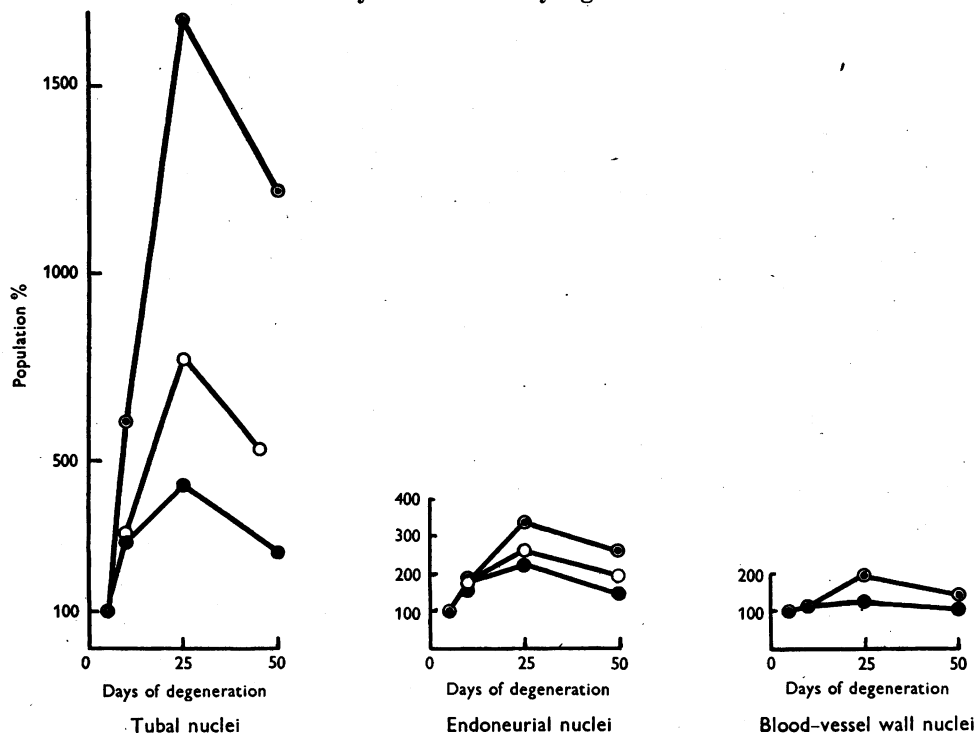
The numbers of endoneurial nuclei are shown in Tables 2 and 3, column 4, expressed as a percentage of the mean population of nuclei at 5 days of degeneration. It will be seen from Tables 2 and 3 and Text-fig. 3 that the endoneurial nuclei increase much less than the tubal nuclei, but there is still a peak at 25 days of degeneration. There is a difference in the amounts by which the endoneurial nuclei of the different nerves increase. In the n.g.m. at 25 days of degeneration the endoneurial nuclei are 3½ times as numerous as at 5 days, in the sural nerve twice as numerous, and in the peroneal-tibial 2½ times as numerous. In each case the 25-day figure is significantly different from the 5-day figure.

Changes in numbers of blood-vessel wall nuclei

It is possible to count blood-vessel wall nuclei (endothelial and smooth muscle nuclei) in undegenerated nerves and so the nuclear populations in this section are expressed as percentages of the 0-day population of nuclei. In the fifth column of Tables 2 and 3, however, and in Text-fig. 3 the nuclear populations of the blood-vessel walls have been expressed as a percentage of the population at 5 days, so that they can be compared directly with the figures for other nuclei.

At 25 days of degeneration the blood-vessel wall nuclei of the n.g.m. have increased to 470 % of the undegenerated population, the peroneal-tibial to 146 % and the sural to 145 %. At this time the increase in the blood-vessel wall nuclear population of the n.g.m. is significantly different from that in the

sural and peroneal-tibial nerve populations, though the increase of these latter are not significantly different from each other. The increase in blood-vessel wall nuclei between 0 and 25 days is statistically significant in each of the nerves.



Text-fig. 3. Mean population of tubal nuclei, endoneurial nuclei and blood-vessel wall nuclei of three different nerves at different times of degeneration, expressed as percentages of the respective nuclear populations in 5-day degenerated nerves. ● Sural nerves; ○ peroneal-tibial nerves; ⊙ n.g.m.

Synthesis of differential counts

The changes of populations of the different kinds of nuclei of the n.g.m. and sural nerve are brought together in Table 4, which gives the composition by cell type of a representative sample of 100 nuclei in 5-day degenerated nerves, and shows the number of nuclei which such a sample produces by multiplication as degeneration proceeds.

Table 4. Changes which occur in the tubal, endoneurial and blood-vessel wall nuclear populations in a region of nerve which at 5 days of degeneration contains 100 nuclei

Days of generation	N.g.m.				Sural			
	Total nuclei	Tubal nuclei	Endoneurial nuclei	Blood-vessel wall nuclei	Total nuclei	Tubal nuclei	Endoneurial nuclei	Blood-vessel wall nuclei
5	100	45	41	14	100	57	36	7
10	366	274	77	15	227	162	57	8
25	920	755	138	27	340	248	83	9
50	677	550	107	20	206	146	52	8

DISCUSSION

It now seems that the general pattern of change in nuclear population found by Abercrombie & Johnson (1946) is by no means peculiar to the peroneal and tibial nerves, but that other myelinated nerves of very different fibre size, namely, the *nervus gastrocnemii medialis* (n.g.m.) and sural nerve, show this rise and fall of nuclear population with approximately the same time relations.

Although the nerves studied are similar in the general pattern of their multiplication, the amounts of increase are very different, and Abercrombie & Johnson's suggestion that the extent of the population increase in any nerve will depend at least in part on its fibre spectrum is amply borne out by these figures for a variety of nerves. The present work, together with that of Joseph (1948), indicates a very close correlation between the extent of the increase in size of the nuclear population of a nerve during Wallerian degeneration and the characteristic of the fibre spectrum which we use here, the average cross-sectional area of a myelinated fibre of the nerve. The larger the average fibre area, the greater is the increase in nuclear population relative to the initial population, the two variables being roughly linearly related.

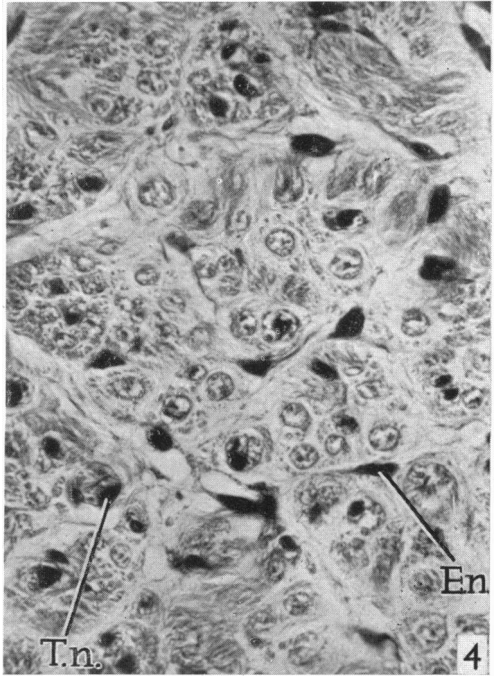
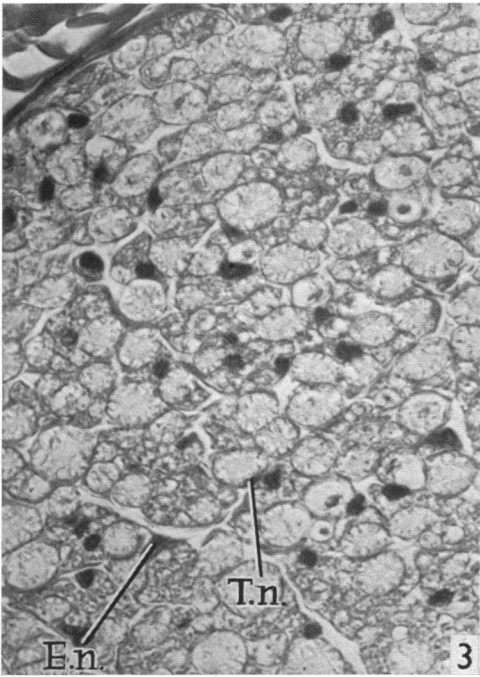
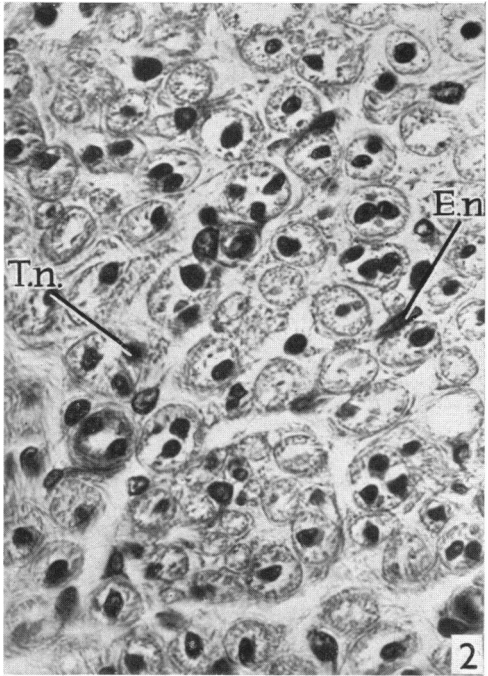
The cardinal problem which initiated the present studies of nuclear population is the causation of mitosis. Abercrombie & Johnson (1946) postulated a diffusing activator of mitosis produced by autolysis of nerve fibres. The results recorded here give no conclusive evidence for or against this hypothesis; though the fact that, in different kinds of nerve, the greater the nuclear multiplication is in the tubes the greater it is in the endoneurium is at least consistent with the view that both tubal and endoneurial cells are responding to the same activator. What the present work does demonstrate is a fundamental relation between nuclear multiplication and a quantitative characteristic of degenerating nerve fibre material. The discovery of this relationship clearly opens the way to further investigation of the mechanisms of mitotic stimulation involved.

SUMMARY

1. The changes in nuclear populations during Wallerian degeneration for different periods of two rabbit nerves of differing average fibre size, the *nervus gastrocnemii medialis* (n.g.m.) (large fibres) and the sural nerve (small fibres) are recorded.

2. The total nuclear populations of the nerves show changes similar to those established by Abercrombie & Johnson (1946) for the peroneal and tibial nerves, the growth curve showing a rise to a maximum population, followed by a fall which does not, however, reduce the population to that of undegenerated nerve.

3. After 25 days of degeneration the nuclear population of the n.g.m. had increased to 19 times its value in the undegenerated nerve, while the sural nerve had only increased to 5 times its value in the undegenerated nerve. By 100 days of degeneration the nuclear population of the n.g.m. had fallen to



11 times the population in the undegenerated nerve. In the same time the population of the sural nerve had fallen to $2\frac{1}{2}$ times the population in the undegenerated nerve.

4. The maximum amounts of nuclear multiplication in the different nerves, including also the peroneal and tibial nerves (Abercrombie & Johnson, 1946) and the anterior mesenteric nerve (Joseph, 1947), have been correlated with the average cross-sectional area of a nerve fibre of these nerves. There exists a roughly linear relation between the two variables.

5. The nuclei of the nerves have been analysed into those of the Schwann tubes, of the endoneurium and of the blood-vessel walls. Each category shows a rise followed by a slight fall in population. The extent of the rise is related to the average fibre size. The nuclei inside the Schwann tubes have, by 25 days of degeneration, increased to 17 times their population at 5 days in the n.g.m. and to $4\frac{1}{2}$ times in the sural nerve. Those of the endoneurium have increased to $3\frac{1}{2}$ times their population at 5 days in the n.g.m. and to $2\frac{1}{2}$ times in the sural nerve. Those of the blood-vessel walls have increased to twice the population at 5 days in the n.g.m. and to 1.2 times in the sural nerve.

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EXPLANATION OF PLATE 1

Preparations of rabbit nerves fixed in Susa, stained in Heidenhain's haematoxylin and light green, sectioned transversely at 7μ . *T.n.*, tubal nucleus. *E.n.*, endoneurial nucleus. Magnification $\times 640$.

Fig. 1. Undegenerated nervus gastrocnemii medialis.

Fig. 2. Peripheral stump of nervus gastrocnemii medialis degenerated for 100 days.

Fig. 3. Undegenerated sural nerve.

Fig. 4. Peripheral stump of sural nerve degenerated for 100 days.