

## NOTES OF TWO CASES OF PERIPHERAL NEURITIS, WITH COMPARATIVE RESULTS OF EXPERIMENTAL NERVE DEGENERATION AND CHANGES IN NERVE CELLS.

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IN this paper I wish to give an account of several cases of peripheral neuritis, mainly from the pathological point of view, to give a brief *résumé* of the results of my experimental nerve sections in dogs and rabbits, with a note of the changes found in nerves of stumps at varying dates after amputation, the changes in nerve cells of ganglia and cord on the affected side, and thereafter to show the bearing of certain of the results on peripheral neuritis.

So much has been written about peripheral neuritis—so many views formulated only to be afterwards demolished—that a disease of such varied modes of origin and clinical history requires to be attacked from many different stand-points. Perhaps there is no better method of approaching the problem than from the experimental side, and, although rabbits' nerves differ from those in man, the results obtained appear to me to throw an instructive light on the pathological anatomy of peripheral neuritis.

By the term "peripheral neuritis" I understand an affection primarily of the neuron, in whole or in part, and not a disease having its origin in some other part of the spinal cord.

The cases referred to will be published in full at a later date; all I wish to do here is to bring out the prominent

features, clinical and pathological, for the purposes of this paper. I wish to draw special attention to the changes in the vasa nervorum and the minute fibres in the affected nerves and in the nerve cells of the cord in one of the cases. No reference is made to the bibliography of the subjects discussed. I did not have the opportunity of examining Case I. during life.

*Case I.*<sup>1</sup>—Mrs. H., aged 38, admitted to Ward 25, Royal Infirmary, Edinburgh, on April 2, 1894, complaining of debility, great weakness of the hands, with almost complete loss of power in the feet and legs, with numbness and a sensation of "pins and needles" in the legs and arms. The weakness in the legs had lasted a fortnight; the numbness and loss of power in the lower limbs had been present for four days. She had six healthy children, all living—no miscarriages, and nothing to report in the family or personal history of special interest. Her last labour occurred three months before the commencement of the illness for which she was admitted, but it appears to have been normal in every respect.

The illness began a fortnight beforehand with a shivering attack, and she was confined to bed for one day. She resumed her household duties with difficulty for one week, and then was compelled to take to bed again. She had now severe pain in the back, relieved on sitting up. She tried to get up several times, but was unable to do so.

She had not been well fed, and was given to drink, locking herself into her room for the apparent purpose of indulging in that vice, and she admitted that during New Year week they had consumed nine bottles of whisky without help from visitors. There was no history of diphtheria or sore throat.

On admission—

*Sensory Functions.*—Pain in small of back, increased by palpation; numbness in hands and feet, and "pins and needles" sensation in hands.

*Tactile Sensibility.*—Unimpaired localisation and rate of conduction perfect.

*Pain Sensation.*—Apparently perfect.

*Temperature Sense.*—Impaired; delayed conduction, but she could distinguish heat from cold.

<sup>1</sup> History of case abstracted from Edinburgh Hospital Reports, vol. iii., p. 417.

Case I.  
CERVICAL ENLARGEMENT.

Group.	RIGHT ANTERIOR CORNU.				LEFT ANTERIOR CORNU.			
	Cell.	Nucleus.	Nucleolus.	Endo-Nucleolus.	Cell.	Nucleus.	Nucleolus.	Endo-Nucleolus.
Ventro-mesial {	56 $\mu$ x 40 $\mu$	22 $\mu$ x 20 $\mu$	8 $\mu$	2.5 $\mu$	84 $\mu$ x 60 $\mu$	26 $\mu$ x 26 $\mu$	8 $\mu$	8 $\mu$
	44 $\mu$ x 24 $\mu$	14 $\mu$ x 12 $\mu$	8 $\mu$	8 $\mu$	80 $\mu$ x 44 $\mu$	22 $\mu$ x 22 $\mu$	6 $\mu$	8 $\mu$
Ventro-lateral {	80 $\mu$ x 34 $\mu$	20 $\mu$ x 16 $\mu$	10 $\mu$	9 $\mu$	76 $\mu$ x 50 $\mu$	26 $\mu$ x 20 $\mu$	8 $\mu$	3.5 $\mu$
	80 $\mu$ x 24 $\mu$	14 $\mu$ x 12 $\mu$	8 $\mu$	2.5 $\mu$	68 $\mu$ x 60 $\mu$	24 $\mu$ x 24 $\mu$	10 $\mu$	4 $\mu$
Dorso-lateral {	64 $\mu$ x 40 $\mu$	20 $\mu$ x 14 $\mu$	10 $\mu$	4 $\mu$	60 $\mu$ x 50 $\mu$	9 $\mu$ x 9 $\mu$	6 $\mu$	3 $\mu$
	44 $\mu$ x 30 $\mu$	14 $\mu$ x 12 $\mu$	8 $\mu$	9 $\mu$	50 $\mu$ x 40 $\mu$	16 $\mu$ x 14 $\mu$	8 $\mu$	4 $\mu$

NOTE.—The measurements of the cells and nuclei represent their greatest length and breadth, and in the case of the cells are taken from the roots of the processes.

*Muscular Sense.*—Noted as markedly impaired.

*Skin Reflexes.*—Plantar on each side abolished; others present.

*Tendon Reflexes.*—Patellar reflex absent on both sides.

*Voluntary Movements.*—Distinct pointing of the toes on both sides, due to a condition of talipes equinus since birth. Patient could not draw up her knees, but, if flexed, she could extend them. The inability to use her flexors was most marked on the right side. Grasp was feeble, and the flexors and extensors of the forearm were weak. The muscles of the upper arm were a little stronger.

Muscles of lower extremity did not react to faradism; but reaction was obtained in the upper extremities, though weak, but was specially deficient on the right side.

Vasomotor symptoms were absent, except a slight cyanosis of the feet and distension of the superficial veins.

Patient became extremely weak and irritable; complained of great pain in the back, which precluded a thorough investigation of the case.

Patient became cyanosed on April 5, at 9.15 a.m., from paralysis of the diaphragm and lower intercostal muscles, and artificial respiration, by Silvester's method, was kept up continuously for sixty-eight hours, when she died from exhaustion. Ether and strychnine were administered subcutaneously. She could swallow up to a late stage. Muscular weakness rapidly increased, the right arm being much weaker than the left.

Micturition and defæcation remained unaffected up to a late stage.

*Post-mortem examination* performed by Dr. Leith yielded nothing worthy of note.

### *Microscopical Examination.*

The pathological examination of the nerves, etc., I made in the Practice of Physic Laboratory, Edinburgh University. The brain, pons, medulla, cord, and the following nerves were examined:—The brachial plexuses; the right ulnar; the sciatic, posterior tibial, and the right anterior crural nerves; the nerve to the left gastrocnemius muscle, with a portion of the muscle attached; the fourth right intercostal nerve; the phrenic nerves, with portions of the diaphragm; the vagi nerves and the sympathetic on the right side, with the superior cervical ganglion. Unfortunately, the external popliteal nerves were not obtained, nor any of the ganglia on the posterior nerve roots.

The changes met with were more remarkable than any I have seen described in the literature of peripheral neuritis, and the case was a unique one, inasmuch as the disease only lasted about twenty days from the commencement of symptoms, and the function of the intercostals was only seriously affected from seventy to eighty hours. On examining the brain I thought it might be worth while to try a modification of Golgi's method, described by Berkeley,<sup>1</sup> for the demonstration of dendrites, in a paper on lesions produced by the action of ethylic alcohol on the cortical nerve cells. Even though my specimens were somewhat over-hardened for this purpose in Müller's fluid, I found, in thus treating a portion of the left cortical motor area for the arm, that several of the ganglion cells showed the same marked bulging on their dendrites which has been described by Berkeley. The terminal dendritic swelling is the most marked, though, on close examination, other small moniliform swellings can be seen affecting several dendrites. None of the swellings appeared quite close to the cell body. These dendritic changes are best marked in the cortex of the motor areas, but were also noted over a wider area, and were seen in the cell groups forming the ganglia of the cranial nerves. The gemmulæ of the dendrites did not come out well, but they appear to be diminished in number, at least on the affected processes.

*In the Cord.*—The changes here are of the greatest interest. There are a great number of recent and older hæmorrhages best marked in the cervical and dorsal regions, and mostly found in the grey matter. At the level of the cervical enlargement a small encapsulated hæmorrhage is seen in the right antero-lateral ground tract, and is evidently from a centrifugal arteriole. The extravasation is surrounded by a laminated, hyaline wall, and there are a small number of leucocytes in the neighbourhood. In the course of the same arteriole, and nearer the anterior cornu, are several other smaller and apparently more recent hæmorrhages.

In the dorsal region, at the level of the second dorsal segment, one of the main branches of the anterior spinal artery to the right side of the canal is cut transversely and is seen to be blocked with a recent thrombus surrounded by numerous leucocytes. At the level of the ninth dorsal segment a large recent hæmorrhage is seen along the line of a branch of the anterior spinal artery, running to the outer side of the posterior cornu, in one of the septa. Here there is no great emigration of leucocytes.

<sup>1</sup> BRAIN, Part VI., 1895.

These hæmorrhages are limited to the anterior spinal artery and to the right side of the cord. Beyond the hæmorrhages of recent date, there are no vascular changes such as are seen in the nerves. The tracts of white matter show practically nothing. The nerve cells in the cord, although fixed in Müller's fluid, and, therefore, not so capable of showing nuclear changes, still demonstrate certain interesting facts, because the multipolar cells on the two sides of the cord show distinct differences. On the left side the cells are practically the nerve cells of a normal specimen hardened in Müller's fluid. On the *right* side we find great shrinking of the cells as a whole (see table of measurements). The nuclei are much smaller, and, in place of having a distinctly rounded contour, their outline is jagged and totally irregular. On the *left* side the cells show a clear, distinct nucleolus and endonucleolus, and a rich refractile chromatin network (see fig. 1). On the *right* side the whole nucleus stains more deeply and homogeneously, the nucleolus is with difficulty made out, and it is sometimes impossible to distinguish the endonucleolus. There are one or two healthy cells in each cell group of the *right* anterior horn; and there are rather larger numbers of degenerated cells in the groups of the *left* anterior horn; still the degenerated cells on the one side and the apparently normal cells on the other are quite characteristic. Anilin blue black reveals further that the affected cells possess fewer processes.

The ventro-mesial group of nerve cells is believed by Kaiser and others to be the centre for the nerves of the dorsal muscles, and the ventro-lateral group for the lateral and ventral muscles of the trunk and the muscles of respiration. In the cervical region the spinal accessory nerve is supposed to arise from the lateral group, the phrenic from the mesial. Now in this cord the ventro-lateral cell group is very markedly affected, and the inference is obvious. In this case, the patient had paralysis of the diaphragm on the right side more markedly than on the left, and the right intercostal muscles appeared also more markedly affected than the left. The greater number of degenerated cells at this level on the left side are in the ventro-lateral group, although there are a number of apparently healthy multipolar cells in addition.

As I chanced to have another cord with hæmorrhages at more than one level, and especially in the region of the cervical enlargement, I took several sections and made measurements of the cells and nuclei, selecting the largest cells from the different groups, and I noted that the mere effect of hæmorrhages being present in proximity to the cell groups made no difference in the

respective size of cells and nuclei, although the hæmorrhages in this case were very extensive.

The nerves were examined with particular care, and not merely were a few sections made from each, but many series of sections were examined, and portions of the same nerve were investigated at different levels.

In not a few of these nerves, the same description will suffice. In the *right sciatic, right anterior crural, left sciatic*, etc.

The Weigert-Pal specimens show many changes with only about half the fibres stained, and many that stain do so in a manner suggestive of an early stage of degeneration. Whereas this method stains most deeply the peripheral portion of the medullary sheath of a normal fibre, leaving a clear and faintly-stained central part, sometimes with a darker ring closely surrounding the axis-cylinder itself, a fibre in an *early* stage of degeneration stains often uniformly throughout and uniformly deeply. In fact, with a carefully-stained section, if properly decolourised, a uniformly black fibre, with sometimes a clear central spot representing the axis-cylinder, would point to the degeneration of the myelin alone, or what Gombault describes as the condition constituting periaxial neuritis, whereas disappearance of the clear spot in the centre implies that the continuity of the axis-cylinder is broken as well as the myelin.

The most degenerated fibres are in groups arranged throughout the funiculi. The fibres staining a uniform colour are close to these groups, or are intimately mixed up with the fibres composing them. The healthy fibres are also generally arranged in groups together. Specimens stained with hæmatoxylin and eosin show a considerable number of comparatively healthy fibres in most of the funiculi, and the grouping of the degenerated fibres is very marked. Careful examination of the various funiculi shows that there are very few fine fibres, and that those which are degenerated appear to take their place. These fine fibres occur in groups, and I shall have to refer to them again at length.

In connection with the degenerated groups and the funiculi generally, there are a number of nucleated cells. Some of these nuclei are very large in size.

(a) Many belong to the spindle-shaped cells, whose protoplasm is very small in amount, staining brightly with eosin and showing marked signs of mitosis; these are newly-formed, connective-tissue cells.

(b) Many are leucocytes, and these are chiefly in the neighbourhood of vessels, although they have spread amongst the

surrounding nerve fibres, being specially numerous near the little degenerated groups mentioned already. (See fig. 2.)

(c) A smaller proportion are enlarged and proliferated segmental nuclei, but, unless in fibres which have broken down, these can be seen inside the sheath of Schwann, and projecting into the lumen of the nerve fibre.

The axis-cylinders do not stain so sharply, and may be seen, even in transverse section, to be finely granular. There are few signs of proliferation of the segmental nuclei, though they are generally much distended, bulging into the lumen of the fibre. The larger septa of the endoneurium are not thickened; the finer septa, especially those separating individual fibres or smaller groups, show greatly enlarged and evidently proliferated connective tissue nuclei, but only in the neighbourhood of degenerated fibres, and these are also very marked in the proximity of vessels, and near the inner surface of the perineurium. The perineurium is very slightly thickened, but only in parts. The thickening is limited to the inner layers, and where vessels of small size are met with in the sheath, the newly-developed connective tissue nuclei are very numerous.

The epineurium shows little that is abnormal. The vessels are specially interesting because they illustrate the changes described by Minskowski in 1888, and later by a number of writers. Almost all the smaller arterioles and capillaries in the endoneurium or perineurium of those funiculi showing many degenerated fibres demonstrate the changes about to be described, though comparatively few in the epineurium do so. These changes are—distension and proliferation of the nuclei belonging to the endothelial cells of the intima, and to a less extent a similar nuclear increase in the media and adventitia. Comparatively few capillaries are so nearly blocked by the huge endothelial nuclei as in the more peripheral nerves. A considerable number of these nuclei show karyokinetic figures. The walls of the smaller arteries and arterioles are distinctly thickened. Almost every vessel within the perineurium seems to be surrounded by a greater or smaller number of leucocytes, and a huge diapedesis is shown in fig. 2, taken from one funiculus of the nerve. There is evidence of a considerable amount of exudation, which is greatest between the perineurium and the nerve fibres, and also in the neighbourhood of the arterioles and capillaries, well seen in fig 3.

In the more peripheral nerves the arterioles and capillaries have suffered even more markedly, whether in endo-, peri-, or



epineurium; they all show marked proliferation of nuclei, especially those in the intima, being greatly enlarged and showing very distinct mitotic figures. Many capillaries are so occluded that a red blood corpuscle could scarcely, if at all, pass through their lumen. The venules also show proliferation of endothelial nuclei. Corpora amylacea are present in many of the nerves more markedly degenerated.

*The nerve to the left gastrocnemius muscle* shows beautifully the effects of a recent large exudation, best marked in the neighbourhood of the vessels. It is present not merely between the nerve fibres and the perineurium, but it is well seen also along the septa. The specimen has been extremely well fixed, and the paraffin sections give what I believe to be a truthful picture. The effects of the exudation are very apparent; those fibres which have been pressed upon show marked degenerative changes, namely, granular myelin and irregularly distended and granular axis-cylinders. The fibres of the endoneurial septa and the inner lamellæ of the perineurium are separated by the effusion, and present an open network-like appearance. The exudation itself forms fibrinous threads or strands, here and there replaced by newly-formed connective tissue cells, and a considerable number of leucocytes are in its vicinity. The nerve fibres at some distance from the exudation are mostly normal, but still some show granular changes in the myelin and distended irregular axis-cylinders, staining feebly with eosin or benzo-purpurin. On the other hand, certain larger fibres appear to resist pressure more than others, but the comparative rarity of these, where the exudation is great in amount, is very striking. The fine fibres have evidently suffered most severely, and the connective tissue nuclei, increased in size and number all over the funiculi, are specially prominent near groups of what had once been these fibres. The segmental nuclei are enlarged, but there is little evidence as yet of proliferation.

The vessels of the endo- and perineurium show marked nuclear increase in the intima. The media of the arterioles in the same localities is thickened.

All the funiculi have not suffered alike, but all show some exudation, appearing first around the vessels in the neighbourhood of the perineurium.

Some of the nerves—as, for instance, the right ulnar, and especially the intercostals—show much more advanced changes in the myelin and axis-cylinders; and in these nerves, corpora amylacea are extremely numerous.

In several of the nerves of this case I endeavoured to study:—

(1) Whether the leucocyte emigration was confined to parts of the nerve or was generally met with throughout its length?

(2) Whether the diapedesis of red blood corpuscles was local?

(3) Whether the degenerated fibres (which could be fairly well followed in groups by noting their relationship to the blood-vessels) were healthy at any part of their course; or, if not, whether the degeneration varied at different levels as stated by many writers?

(4) Whether the nuclear changes in the blood vessels varied at different levels, and if they had any relationship to the phenomena noted under the other three headings?

The *phrenic nerves* were selected because they were small, and there was some chance of recognising the approximate position of fibres, or even identical fibres, in each section. My results are, in brief:—

(1) The leucocyte emigration varied greatly in different portions of the nerve, and where one vessel showed marked evidence of emigration most of those in the funiculus did the same. The leucocyte emigration tended to increase in the phrenics from above downwards—being most marked close to the diaphragm.

(2) The diapedesis of red blood corpuscles was equally local, and the emigration of leucocytes and diapedesis of red blood corpuscles in the nerves generally occurred together; but diapedesis of red blood corpuscles was less frequent.

(3) The degenerated fibres in the phrenics showed the most interesting changes. The fine fibres very gradually appeared to decrease in number from above downwards to the diaphragm, probably leaving the nerve to supply minute vessels *en route*. The larger fibres seemed to suffer more from the effects of pressure at a higher level than from a true parenchymatous degeneration. They were more dropsical-looking, *i.e.*, more distended, and of less regularly round and oval outline below as compared to the most

proximal sections. The medullary sheaths were granular in appearance, but the axis-cylinders were generally perfectly recognisable. One or two groups of markedly degenerated fibres in the right phrenic I followed carefully. These at one level were compressed together, by a large exudation and many leucocytes, so as to form a mass of myelin with unrecognisable sheaths of Schwann, with segmental and connective tissue nuclei, a few leucocytes, and even one or two axis-cylinders apparently unaffected. At a lower level these fibres had not recovered from their compression, and, although they gradually separated to some extent, they remained distended, and were not, in this nerve at least, absolutely normal-looking below. Apparently, with the possible exception of a few fibres, the changes in this nerve were not due entirely to a parenchymatous neuritis, but were largely the result of pressure, causing a secondary descending degeneration.

(4) The nuclear changes in the vessels vary very considerably at different levels, being much better marked where the emigration of leucocytes and red blood corpuscles were most in evidence, and less marked between.

*Case II.*—Mrs. M., aged 38, was admitted to Ward 25, Royal Infirmary, Edinburgh, on November 4, 1895, suffering from paralysis of the arms and legs, difficulty in swallowing, and loss of the power of speech.

She had a healthy family history, has had ten children, eldest aged 19; youngest, 3 years. Three are dead—one of bronchitis, and two of chest disease; the others are strong and healthy.

Patient has had no other illness, but had suffered from an occasional sore throat, yielding generally to local applications. Her mother suffered in the same way, and, in both cases, any slight exposure to cold was sufficient to bring on an attack. Mrs. M. had been very alcoholic, but to what extent could not be ascertained; though it is admitted that, during the greater part of her married life, she had been imbibing larger and larger quantities of spirits, beer, &c. She was rarely actually drunk, but often slightly stupefied.

There was no diphtheria in the district at the time of patient's illness, nor had the patient anything suggestive of the disease. She simply complained of one of her usual sore throats, which she

attributed to exposure to cold, and which on this occasion rapidly yielded to treatment. The patient never had any serious illness since childhood. There was no history of influenza as an antecedent to her condition, nor had she previously been attacked by it.

Three months ago the patient complained, for the first time, of numbness of the legs and swelling of the feet. These gradually increased, and patient was known to have resorted to an extra allowance of alcohol in the hope of curing the unpleasant symptoms. Patient took to bed on October 21, 1895, having only previously been laid up when the numbness and swelling incommoded her, as it did to an increasing extent; and she found a day's rest appeared to give some relief. She now had shooting pains and twitchings in her left arm, and, to a less extent, in her legs. On October 29 she found great difficulty in swallowing, and the power of speech was gradually lost. The patient, in a few days, became semi-comatose.

*Notes on Admission.*—She is a stout, flabby woman, with a somewhat bloated expression of countenance. There is nothing specially worthy of note in any system, excepting the nervous. The heart and lungs show nothing of special interest; the temperature, which was normal when the patient was admitted, rose to 102° Fahrenheit, where it remained for two days before death, and the pulse became at the same time correspondingly rapid.

*Sensory Functions.*—As the patient is almost unconscious, can be only with difficulty roused to the slightest extent, and is totally unable to speak, her subjective symptoms are unobtainable. Pain is evinced on pressure over the nerve trunks, and over certain muscles. The pupils are equal, and react sluggishly to light. The fundus of both eyes is normal.

*Motor Functions.*—Swallowing being almost impossible, the patient is fed by the rectum. Breathing is slow, somewhat stertorous, and from time to time simulates the Cheyne-Stokes type. The bowels and bladder are evacuated involuntarily. Skin reflexes and tendon reflexes of the legs and arms are abolished.

*Electrical Reactions.*—In examining the electrical reactions, I had the assistance of Dr. Garbut. On the first occasion the patient's skin was extremely hyperæsthetic, and it was very difficult to get accurate results, but our later efforts were more successful. One of the outstanding features was that a very powerful faradic current had to be used, far in excess of what a normal individual could endure. We tried at first a current which was too weak, although producing considerable pain when applied to our own persons, and with this we only got, almost universally,

a negative result. We next tried as powerful a current as we could obtain from a large induction coil; and when the skin was sufficiently anæsthetic to permit of observation, we noted that with nearly every muscle which had given us negative results before we now got a contraction, though, in some cases, an extremely feeble one; and this contraction was sometimes coincident with the qualitative change in the reaction of degeneration. Where the qualitative change, constituting one of the phenomena of the reaction of degeneration, was observed, the contraction was invariably noticed to be very sluggish, and obtainable with a smaller number of cells than usual.

The muscles of the extremities were examined in detail. It seems hardly necessary here to give the tables I prepared. Suffice it to say that the peronei and the tibialis anticus muscles of the left leg especially and some of the extensors and flexors of the fingers and the small thumb muscles of both arms gave the reaction of degeneration.

*Vaso-Motor and Nutritive Functions.*—There is slight cedema of both ankles. There is no evidence of any bed sore. None of the muscular groups are very markedly wasted—certainly the tibialis anticus and the calf muscles show considerable atrophy. The right leg is slightly smaller in circumference than the left. Both buttocks are flattened. The muscles of both fore-arms are flabby. Sweating is profuse, and has the peculiarly sour smell so often noted in cases of multiple neuritis.

*Cerebral and Mental Functions.*—Patient lies semi-comatose, as already described, and cannot be roused so as to comprehend questions asked of her. She evinces feelings of pain by a slight cry and a feeble, lethargic attempt to remove the limb from the source of the irritation.

*Locomotory System.*—There is nothing worthy of note as regards the joints. There are occasional slight jerking movements, especially of the arms.

The patient continued much in the same condition at first, gradually losing ground, then more rapidly after her temperature rose to 102° Fahrenheit. On the night of the 7th inst. her breathing became more difficult, the pulse more rapid and weaker, and she died on November 8th.

It is to be regretted that a more complete history of the patient's condition before admission to the hospital was not obtainable in this case. *Post-mortem examination* by Dr. Leith showed nothing worthy of special note here.

The following organs, &c., were examined microscopically.

The brain and cord, the eleventh and twelfth dorsal posterior nerve roots with ganglia, the right and left sympathetics, the optic nerves; the brachial plexus, the ulnar, median, musculo-spiral, musculo-cutaneous, sciatic, external popliteal, internal popliteal, posterior tibial, and the anterior tibial nerves of both sides were examined along with the extensor communis digitorum, extensor hallucis, and the tibialis anticus muscles; also the phrenic nerves, with diaphragm; the seventh intercostal nerves and muscles; the semi-lunar ganglia; pieces of the ventricular wall of the heart, the liver, &c. The specimens were all preserved in Müller's fluid, and unfortunately the ganglia were put into the same solution.

The motor areas of the brain were examined by the same method as used in Case I., but without any conclusive result.

The cord gave considerable trouble by not hardening properly. The multipolar cells in the anterior cornua show, however, the same changes as those described in Case I. There are no patches of degeneration in the white substance, and there are no hæmorrhages. The medium-sized vessels, especially between the cord and the membranes, show great thickening of the middle coat—the thickening having a hyaline appearance. Anterior and posterior roots are alike normal. The nerves showed the same arrangement of degenerated fibres in groups. The description of the right sciatic will suffice for the larger nerves.

*Right Sciatic Nerve.*—Many nerve fibres are normal, many show granulation or more advanced segmentation of myelin, and these fibres are mostly arranged in groups. They are associated with the presence of a greater number of segmental and connective tissue nuclei, and also leucocytes. There are some fibres which show loss of axis-cylinders; and, generally, these are in or near the groups referred to. Very few fine fibres are seen to be normal; most appear to be included in these groups. There is homogeneous pink-stained (eosin) fibrinous exudation between many of the fibres. This is most marked in connection with these groups of degenerated fibres, and they bear a distinct relationship to the position of the smaller arterioles and capillaries, from which the exudation may have originated. There are, however, far fewer leucocytes in connection with the exudation than might be expected, and these are mostly seen nearer the degenerated groups and the vessels. The segmental nuclei, especially near the degenerated groups, are greatly distended, and show evidence of proliferation, some of them showing well-marked mitotic figures.

The connective tissue nuclei have also increased in size and number, but only near the bundles of degenerated fibres. The smaller arterioles and capillaries show very marked enlargement and proliferation of the nuclei of the endothelial cells of the intima; most of the smaller vessels appear almost entirely blocked by these nuclei projecting into their lumen, and the nuclei may be seen in all stages of karyokinesis. These vascular changes, mainly involving the intima, and, to a much less extent, the media and adventitia, are best marked in the endoneurium, and are noticeable also in the perineurium and epineurium, but to a less extent.

The larger arteries in the endoneurium show a marked hyaline change in the media, a structureless-looking coat, often with few nuclei and staining feebly with eosin, and thus strongly contrasted with the fibrous tissue of the intima and adventitia. Arteries so affected measure in total diameter  $80\mu$  or thereby: the larger vessels do not show this change, nor do those which are much smaller in calibre than the measurement given. This hyaline appearance of the media is almost entirely confined to the arteries in the endoneurium. The perineurium is somewhat thickened in part, but almost entirely by the increased number of young connective tissue cells in the inner lamellæ of the sheath. Speaking generally, whereas all the funiculi show the vascular changes as regards nuclei, some do so much more markedly than others, and in those in which they are best developed the degenerative changes in the nerve fibres are much more in evidence.

*Right Anterior Tibial Nerve.*—This nerve is very markedly degenerated. The normal fibres are in little groups, but by far the greater proportion show segmentation of myelin, sheaths distended with droplets of myelin, and axis-cylinders very few in number. Where the axis-cylinders are seen, they extend generally for a short distance alone, and these small portions show typical vacuolation and granulation.

Fig. 4 represents the very advanced segmentation of the myelin in the fine fibres, as compared with the ordinary-sized fibres, and in peripheral neuritis, so far as my experience goes, these fine fibres nearly always suffer at an early date, and very severely.

The nuclei are increased in number, especially those of the connective tissue: there are a few leucocytes near the vessels, and the segmental nuclei are greatly enlarged, and, in not a few instances, proliferated.

The vascular changes are most typically seen in the endoneurium, also in the epineurium. Fig. 3 shows in transverse section the appearances just described, especially the vascular changes and the exudation.

*The Right Ulnar Nerve* is the last nerve of this case I shall describe here. It is much more markedly affected than the brachial plexus. Two-thirds of the fibres in all the funiculi show degenerative changes by Marchi's method. This nerve presents very different appearances at different levels. The axis-cylinders are much less interfered with than the medullary sheaths, although the latter are considerably thinner than normal. The degenerated fibres in a section which, at first sight, might be mistaken for a healthy nerve, are best marked round the periphery of each funiculus near the septa, and especially near the vessels. Those fibres show distension of sheath and loss of axis-cylinders, and are probably nerve fibres destroyed by pressure higher up, and in which the axis-cylinders may be actually broken across. Those fibres are not more numerous than one-tenth of the total number in the section at the level referred to. Many of the fibres possessing axis-cylinders have an irregular outline and seem somewhat separated the one from the other.

A longitudinal section shows all the appearances at different levels, the localised bulging of the sheath of Schwann by segmented myelin, the effusion between the fibres, and yet many of these very fibres appear above and below with fairly normal axis-cylinders. These changes may depend on vascular conditions, as an effusion is distinctly present along the line of certain of the vessels, and where these vessels run across the funiculus the exudation appears to spread widely. In the gap between the vessels and the neighbouring nerve fibres there are the fibrinous-looking remains of an exudation staining very feebly with eosin, and the marked changes in the medullary sheaths of the contiguous nerve fibres (segmentation, bulgings of wall, etc.), all bear witness to the detrimental effects of the pressure, while the connective tissue and segmental nuclei are enlarged and proliferated, but not very extensively. There are a few leucocytes.

The vessels in the endoneurium show marked nuclear changes, especially those vessels probably causing the exudation—but they are not so evident in the epineurium.

As a good instance of the change in the muscles of the affected limb, I describe the right tibialis anticus muscle.

*Right Tibialis Anticus Muscle.*—The transverse striation is better marked than could be expected, but many fibres show it



somewhat feebly. There are many nuclei, but these are mostly in the walls of the lymphatics and the capillaries. The sarcolemma nuclei are slightly increased in number, especially those belonging to the fibres which have lost, to some extent at least, their transverse striation. These nuclei may be seen in all the different stages of proliferation. The capillaries between the fibres are strikingly empty of blood, and many of them are blocked with enormously swollen endothelial nuclei.

These cases are most instructive, because while differing in some respects they yet agree in others.

*Firstly.*—We have in both cases the same effusion. This effusion is most characteristic; it is found specially around the arterioles and capillaries in the endoneurial septa, often between the nerve fibres and the perineurium, and separating the inner lamellæ of the perineurium. It is not, in these cases at least, a typical inflammatory exudation. In Case I., where in many nerves it is less in amount, it is accompanied by a far greater number of leucocytes than in Case II., where the exudation is much more excessive. This exudation, where referred to at all in most text books on neuritis, is manifestly regarded as an evidence of inflammation, and is not accorded a prominent position. In both cases I have endeavoured to demonstrate that this exudation is greater in one part of the nerve than in another, and that it acts injuriously by compressing the nerve fibres in its neighbourhood, thus causing degenerative changes in them, not merely at the level where it occurs, but also to a greater or less extent peripherally. The exudation tends in time to organise, as many of my preparations show. (See fig. 3.)

Were the exudation to occur in a healthy nerve, it would cause pain, and possibly interfere with the conduction of impulses, sensory or motor, or both; but it could not occasion degenerative changes similar to those seen in my two cases, unless from some cause the nerve fibres were interrupted, or the effusion, becoming organised, had contracted, so as to exert hurtful pressure. But in these cases the stage of organisation of exudation is in its infancy, and the effusion

could, by spreading upwards and downwards, against no very excessive resistance, be prevented from doing any great amount of damage—were it not that the fibres from their condition are specially prone to injury.

*Secondly.*—In Cases I. and II. the vascular changes were the same; the same increase in size and number of the nuclei of intima, media, and adventitia, limited to the smaller vessels, and first found in endoneurial vessels, and, as the periphery is reached, extending to the vessels of the perineurium and epineurium.

There is no point more difficult to determine with certainty than the existence or non-existence of proliferation of nuclei in vessels. Enlargement can be decided by measurement, but not proliferation. Many of my specimens show, however, mitotic figures in these nuclei, and this seems to me to be sufficient evidence.

I noted in both cases that the effusion, whether with or without many leucocytes, was always accompanied by the vascular change, and that these vascular changes became better marked as the nerves were traced peripherally. Then the larger arteries in the endo- and sometimes the perineurium showed thickening of the middle coat, and the thickening was homogeneous in appearance, and with few nuclei in its structure.

*Thirdly.*—The condition of the nerve fibres themselves. Taking almost any of the affected nerves, a transverse section shows that effusion and degenerated fibres are in conjunction, whereas the healthier fibres are those least affected by an effusion. Many of the nerve fibres situated near an exudation are greatly distended. Fibres in the presence of an exudation often swell up much as normal nerve fibres do when placed in water; probably it means endosmosis.

But sometimes groups of degenerated fibres are seen without any effusion. This indicates that the fibres are probably pressed upon by an effusion at a higher level. I do not mean to assert that all peripheral nerve fibres degenerate as the result of pressure alone, but this was the principal cause, in the two cases I have recorded.

To put this point in a different way, I contend that although in alcoholic neuritis the nerve cell suffers chiefly, and with it the process—*i.e.*, the nerve fibre—yet the cell intoxication is not the chief cause of the advanced changes met with more in one fibre in a nerve than in another, but that a local agent—the effusion depending on vascular conditions—greatly expedites the degenerative changes in the previously weakened nerve fibres.

A true parenchymatous degeneration may occur in toxic peripheral neuritis, but there is, in addition, an interstitial effusion which aids in the process, and the greater the effusion the less is the chance of subsequent recovery.

I have noted in several of the nerves the fact that the very fine fibres, which are, I believe, mostly vaso-motor in function, are nearly always markedly degenerated.

Comparing fig. 4, already referred to, we see how much further advanced are the changes in the fine fibres than in those of average size. I believe that it is to the early changes met with in these fibres that the vascular conditions are partly due, but as after nerve section effusion is not the rule, but the exception, and the vascular changes are much less pronounced than in peripheral neuritis, I do not believe that the degeneration of the fine fibres is the cause of the effusion, but only aids in the nuclear changes in the arterioles, capillaries, &c. The changes in the axis-cylinders are well shown in both cases, granulation, swelling, etc.

*Fourthly.*—I found in Case I. the diminution and alteration in shape of the nuclei in the multipolar cells of the most affected side of the grey matter of the cord, and in some cells on the other. Had all the cells shown the same characteristics I might be compelled to admit that the condition was artificial, but the contrast between the two sides, as shown in my photograph, is too marked to allow of such a conclusion. The fact that the cortical cells in Case I. agree with Berkeley's observation on rabbits is of interest, suggesting that these cells are also affected.

In Case II. the electrical reactions compare in a remarkable way with the pathological descriptions, and it is specially interesting to note that an extraordinarily powerful

Faradic current had to be used before contraction of the muscles under examination were obtained.

In conclusion, in Case I. there is, with less exudation, less change in myelin and axis cylinder, and less marked change in vessels, the same amount of paralysis as in Case II., which shows more exudation, more segmentation of myelin and destruction of axis-cylinders and greater vascular changes; therefore in Case I. we have probably a much more advanced change in the central cells than in Case II., and the inference is that, but for the effusion, Case II. might possibly have survived much longer.

In connection with these two cases just contrasted together, I should like to note the similarity of changes in the right posterior tibial nerve from a case of diabetic neuritis, a male, aged 36, who died from a pulmonary complication, and not of diabetic coma. I am indebted for the specimen to Dr. Alexander Bruce, of Edinburgh.

#### *Case of Diabetic Neuritis—Right Posterior Tibial Nerve.*

Many fibres appear normal. These are mostly seen in groups, and the groups form a more or less irregular pattern in the funiculi. Between these groups of fibres those that are degenerated appear also grouped together. The myelin is extremely granular and the neurolemma tends in certain fibres to give way. The axis-cylinders of affected fibres are distended, sometimes showing regular bead-like swellings, granular, often vacuolated, and stain feebly. Among these groups of degenerated fibres many nucleated connective tissue cells appear. Some of these show greatly distended nuclei with a very small amount of protoplasm, the protoplasm staining deeply with eosin. They show evident traces of proliferation, and it is possible that by their presence they may exert a prejudicial influence over the nerve fibres in their neighbourhood. Segmental nuclei are not markedly proliferated, although they are distinctly enlarged in size. The exudation described in Cases I. and II. appears here

also, being specially well marked between the perineurium and the nerve fibres and along the lines of the septa.

The vessels show the most typical enlargement and proliferation of the nuclei of the endothelial cells of the intima; to a less extent the nuclei of the media and adventitia are similarly affected. The smaller vessels suffer most, although every vessel in the endoneurium appears affected, the arteries much more markedly than the veins. The vessels of the perineurium are involved, but to a less extent. In some of the larger arteries a local proliferation of the endothelium seems to have occurred, the process thus formed suggesting an appearance not unlike little endothelial buds. This appearance suggests the possibility of these little processes becoming detached and forming emboli in the minute capillaries. There are certainly little cells apparently free in the blood stream which are somewhat suggestive of free endothelial cells.

The appearances noted in the muscles of Case II., especially the left tibialis anticus, strongly suggest that these little emboli do occur.

### *Ascending Degeneration in Nerves.*

A summary of the results of my experimental work on dogs and rabbits, and the observations made on the ulnar nerve of a stump ten years after the amputation of the arm, were given at the British Medical Association meeting in Carlisle last summer, and are to be found in the October number of the journal, and they appear in a more extended form in the January number of the *Edinburgh Medical Journal*. I shall, therefore, only give my conclusions in the briefest possible way.

In the ulnar nerve of the patient referred to, the fine medullated fibres have suffered most; they are markedly compressed by connective tissue. These fine fibres, which may be easily seen occurring in little groups, are most affected close to the terminal neuroma. The arterioles and

capillaries in the nerve (endo- peri- and epineurium) show the nuclear changes described in peripheral neuritis, but the changes become less obvious as the nerve is traced centrally. My inferences are that the fine fibres whose function is lost are replaced by connective tissue; that those fibres which have so lost their function become proportionately less numerous as the nerve is traced centrally; and that the nuclear changes in the vessels depend on the minute fibres whose function is not abrogated being compressed by the connective tissue replacing minute fibres whose function is abrogated. In other words, I believe that fine fibres are chiefly vaso-motor, and mainly suffer in ascending degeneration. The connective tissue increase around the larger fibres is extremely slight in proportion, even around fibres which must have lost their function. I should note that corresponding vascular changes occur in the muscles, &c.

In a large series of experiments on dogs and rabbits, mainly the latter, I find similar results.

Figs. 5 and 6 show longitudinal sections of the two sciatics from a rabbit. Fig. 5 is the normal nerve, and the fine fibres can be seen about the centre of the funiculus, forming a distinct strand. Fig. 6 is from the central end of the left sciatic twenty-three days after a double ligature was applied to the nerve. The well-marked connective tissue septa mark the site of fine medullated fibres, all of which suffered severely from the pressure, and there is little, if any, connective tissue increase elsewhere.

This change begins about the fourth day, and is observable in a week's time after operating; it occurs whether sections or ligatures be made, and is found in dogs and rabbits alike. The arterioles and capillaries show corresponding changes to those found in the human ulnar nerve after amputation. In short, the changes found in the central ends of rabbits' sciatics after section or ligature appear closely to correspond to those in the nerve of the stump in man. I have had the opportunity of corroborating these observations on the nerves of human stumps at different dates, but have still an insufficient number of cases at my disposal.

*Descending Degeneration in Mixed Nerves, after Section or Ligature.*

It is my intention only to refer to those changes which have any bearing on peripheral neuritis.

(1) Many nerve fibres in the peripheral end of a divided nerve in dogs and rabbits are distended. This distension, best marked within a few days after the operation, may be due to aggregation of myelin droplets; but where there has been an exudation from neighbouring vessels the fibres may swell up, probably from inhibition. This appearance is of very common occurrence in peripheral neuritis, although accidental in experimental sections.

(2) I do not propose to discuss at any great length the changes observed in the axis-cylinder. I have noted a granular, vacuolated, or distended appearance very commonly in the peripheral end of a divided nerve up to such a time as axis-cylinders are easily observed.

The life of an axis-cylinder in a severed nerve is of great interest. Observers state that they ought to become unrecognisable in three to four weeks, and disappear altogether (*i.e.*, are unstainable) in a period not exceeding six weeks. In the rabbit, the peripheral end of the axis-cylinder remains for a longer time nearly normal in appearance after ligature than after section, just as segmentation of myelin and proliferation of segmental nuclei are slower in taking place; but, whatever happens, an axis-cylinder appears to derive trophic influence of some nature from the segmental cells.

An axis-cylinder may be seen swollen and distended in a fibre with apparently normal myelin, although the distension might be artificial. An axis-cylinder may be healthy, or apparently so, where myelin is granular or broken up (to a very limited extent), but an axis-cylinder is rarely, if ever, found to be normal in function or appearance where segmental nuclei are proliferated. It is difficult to bring forward any photographic proof of this, but a careful study of many sections of many specimens gives strong corroborative evi-

dence in favour of the truth of this theory, however unlikely it may seem from an embryological standpoint.

(3) The change in the vessels of a nerve undergoing Wallerian degeneration is described as consisting in enlargement and proliferation of endothelial nuclei of arterioles and capillaries, and slighter nuclear increase in media and adventitia. Venules are less affected. I would only here point out that these changes are not nearly so well marked in most of my experimental sections and ligatures as in peripheral neuritis, and in many cases not marked at all.

(4) The question so much discussed as to where the degeneration process begins in the peripheral end of a divided or ligatured nerve is a very difficult one to answer. I made a large series of experiments on rabbits with double sections and double ligatures, so as to observe whether the middle or peripheral portion of the nerve degenerated first. The operations were done without displacing the nerve and as long a middle portion was left as possible between the two sections or ligatures.

Notwithstanding that the middle portion is at a disadvantage, because the blood supply is presumably more interfered with, the balance of my evidence is in favour of the peripheral part commencing to degenerate first.

In one rabbit, for example, in the middle part the segmental nuclei have not proliferated to nearly the same extent as in the peripheral. In another rabbit, 23 days after double ligature, the segmental nuclei have evidently only just ceased proliferating, whereas the process had long ceased in the peripheral. After four days ligature or section the degenerative process appeared to commence all along the severed nerve, but to be most advanced in the peripheral part, with the exception of certain fibres in that part which long retained a fairly normal appearance, though they also eventually suffered.

I cannot, however, leave this subject without referring again to fig. 4, which is taken from the right anterior tibial nerve of Case II. It shows what is likewise well seen in the peripheral ends of the divided or ligatured nerves—namely, that the fine fibres suffer most severely. In the photograph



they may be seen markedly segmented. Their medullary sheaths show far more advanced degenerative changes than the ordinarily-sized fibres. In only one of the whole series of experiments on rabbits was the evidence not corroborative.

I propose next to contrast peripheral neuritis with descending Wallerian degeneration.

If a nerve fibre be severed completely from its centre, it undergoes Wallerian degeneration, but in peripheral neuritis the fibre below the level of the degeneration is apparently normal. There may be several such degenerated patches in the same fibre, with intervening and almost healthy-looking portions, although it is not likely that the peripheral end organs, whether sensory or motor, could be entirely, if at all, responsible for these healthy intervening portions.

The obvious conclusions are, that the fibres which show these alternating changes are still nourished by the cells from which they arise, and that the local changes are due to a locally injurious, or toxic, agent acting only in a limited area.

It has been stated that these degenerated tracts are at points where the nerves are exposed to external injury or pressure, for example, the ulnar nerve at the elbow, but this is far from being a complete explanation of the difficulty.

These degenerated patches have an infinitely wider range than merely points of possible external pressure; they are more marked peripherally than centrally, but, what is of much greater importance, these changes bear a distinct relationship to the condition of the vessels.

Wherever an exudation is well marked the vessels show most distinctly enlargement and proliferation of nuclei, and the hyaline-looking thickening of the middle coat of the endoneurial arteries. Why may not these conditions be due to the toxic action of a poison on the vaso-motor cells in the medulla? It cannot be solely due to this, or else all the vaso-motor nerves would be simultaneously interfered with, and it is undoubtedly true that in Cases I. and II. the vascular changes varied greatly in the different nerves, as the pathological specimens demonstrate. But the toxic agent may act locally as well as centrally. An injury to a nerve, as, for example, a squeeze or any local irritant, may damage

the fine fibres, which are probably vaso-constrictor, much more markedly than the larger fibres; and in any of the cases of peripheral neuritis which I have had the opportunity of examining, these fine fibres, arranged in groups, seem to be the point where the earliest and most marked proliferation of connective tissue nuclei is observable.

Each individual fibre obtains its nutritive supply from lymph or blood. The toxine in the blood will act with great virulence upon these fibres brought into immediate contact with it. The nerve fibre may be deriving nutritive material, more or less throughout its whole length, whether by means of segmental cells or not we cannot say; still there seem to be certain points along its course where it comes more directly under the influence of the blood current. The fact of the existence of the nuclear changes may be due to the lymph surrounding the fibre being to a certain extent toxic, and specially at the points where a further nutritive supply is derived from the capillaries, and where the greater toxic effect may be produced. This may cause an effusion at the level of distribution of the fibres to the nerve vessels. When a bundle of fibres shows degenerative changes at one level it shows similar changes, not merely repeatedly as the periphery is approached, but with shorter and shorter intervals of more normal nerve fibre between.

*Changes in Nerve Cells. Ganglia on posterior nerve roots and multipolar cells in anterior cornua. (Rabbits and Dogs.)*

After a very considerable amount of experiment, I found that a solution of corrosive sublimate (saturated in a 0.75 per cent. solution of common salt) with equal parts of water, heated to the temperature of the tissues, was the most satisfactory fixing agent for the nerve cells of rabbits' ganglia and cord, and I succeeded in getting fairly satisfactory nuclear networks (as compared at least with my earlier specimens) and almost no evidence of cell shrinkage. I had control nerve cells to compare with those which were abnormal. The stains used were toluidin blue and eosin, a method for which I was originally indebted to Dr. Gustav Mann.

Quoting from my paper, read before the British Medical Association at Carlisle, the changes I obtained were—

(1) The cells of the ganglia on the posterior nerve roots undergo definite changes as the result of nerve section or ligature, and do so at a much earlier period than the multipolar cells in the cord—beginning probably as early as the fourth day, and certainly by the seventh day.

(2) That one of the very first changes observed in the cells of ganglia and anterior cornu is a diminution in the size of the nucleus in proportion to the size of the cell, and that sometimes, but not in all cases, nucleoli also become smaller, and very frequently the nuclei take up an eccentric position, sometimes even bulging the cell wall.

(3) That in both sets of cells Nissl's granules, otherwise known as the chromatic granules, are either smaller in size, fewer in number, and scattered through the cell body tending to be most numerous round the nucleus, or else they are grouped together in large masses round the nucleus, leaving the periphery of the cell quite clear.

(4) That pericellular lymph spaces may become enlarged, especially around the ganglia cells, and where the enlargement is very marked the cells become proportionately smaller in size, although an actual atrophy may also occur. In several of my specimens I found large vacuoles—not the vacuoles described by many writers as occurring in the cells of the cord and cerebral cortex, which are probably to some extent artificial—but big vacuoles, more resembling hugely distended pericellular lymph spaces. They differ, however, inasmuch as they are surrounded by the remains of cell protoplasm containing chromatic granules.

(5) That in the multipolar cells not merely are there these changes in position and size of nuclei, and arrangements and number of chromatic granules, but there is, as a later phenomenon, marked disintegration of cell protoplasm, well seen in some of my specimens. This disintegration has been described by Marinesco as occurring in certain cord lesions in man. It consists of patches, which, with toluidin blue and eosin, are whitish in colour and surrounded by masses of chromatic granules.

This stage of disintegration follows only at a very late stage in the ganglion cells of the posterior nerve roots. It should, however, be stated that a varying number of normal cells occur in abnormal ganglia, and that a very few abnormal cells occur in normal ganglia. The changes in the cells most commonly observed in normal ganglia are an aggregation of chromatic granules round the nucleus, and more rarely in eccentric position of nuclei. By normal ganglia I mean ganglia of presumably healthy rabbits never submitted to any experiment at all, as well as ganglia unaffected by the experiments performed. The proportion of such abnormal cells in a normal ganglia rarely exceeds 2 per cent. of the whole. Vacuoles may also appear, but much more rarely, and their presence is quite exceptional.

Figs. 7 and 8 show the changes described in the ganglia on the posterior nerve roots—7 is the normal, 8 the affected side twenty-one weeks after double ligature of the sciatic. The ganglia are a pair belonging to the sciatics, and the operation in this case was successful in every way as regards healing by first intention and the subsequent health of the animal.

Fig. 9 shows the multipolar cells from the anterior cornua of a rabbit six weeks after a double ligature had been applied to one sciatic. The cells are taken from the same level of the cord in the "sciatic" region. The affected cells are to the left side of the photograph.

Tables of measurements showing the difference in size of nuclei and cells in the affected and normal sides will, I anticipate, be published in the March number of the *Edinburgh Medical Journal*. I may state, however, that with very few exceptions, in my forty to fifty experiments on rabbits, the changes recorded appeared in the affected side, and that the exceptional cases referred to were some two or three in number, in all of which the wound had become septic.

It seems quite comprehensible that the cells of the ganglia in the posterior nerve roots should suffer first, because nerve impulses pass normally up to them from the site of the lesion; whereas the cells of the multi-

polar cells in the anterior cornua normally send impulses downwards from them, although there is no question that impulses can pass in both directions along a motor nerve fibre.

Are the connective tissue changes along the lines of the fine medullated fibres in the central end of a divided nerve and the changes in the nerve cells of ganglia and cord due to irritation? This is a very difficult question to answer. I do not believe irritation from the site of the lesion is alone the cause, because very different results were obtained on examining the nerve cells in septic cases; and further, the rabbits never showed any signs of pain, eating a hearty meal whenever they recovered from the anæsthetic, and feeding regularly and well till the day of their death. I am about to try to eliminate still more the possible irritation factor in producing "ascending degeneration" in a new series of experiments, as irritation may not always be evidenced by pain.

The suggestions which may be culled from comparing the cases of peripheral neuritis and the nerve degeneration, and the changes in nerve cells as the result of experimental section or ligature, are:—

The fine medullated fibres, which appear to play such an important rôle in "ascending degeneration," degenerate very early in peripheral neuritis, and are associated with marked vascular changes.

The comparative absence of the vascular changes in Wallerian degeneration is evident from an examination of my series of specimens.

The limited nature of the vascular changes in the central end of the divided sciatic in dogs and rabbits, and in the nerves of stumps in man, suggests not merely the relationship of fine medullated fibres to the vessels, but is also a strong contrast to the great vascular changes found so frequently, at least, in peripheral neuritis.

Peripheral neuritis is different from either ascending or descending degeneration, and is manifestly caused by a toxine acting on cells as well as nerve fibres, and possibly vessels.

The fact that in Case I., and also Case II., the multipolar cells showed the same changes that appeared after experimental section (so far as the methods of fixing would permit of comparison), is most suggestive, and I would draw especial attention to the diminished size of the nuclei in the affected cells, a point I have not seen noted by other observers.

The changes which I found in the cells of the ganglia on the posterior nerve roots after a nerve section or ligature appeared at such a very early period, much earlier in fact than in the multipolar cells, that they suggest the theory that the division of an axis-cylinder process acts more rapidly in a prejudicial manner on that cell to which the process normally conducts nerve impulses.

This would naturally suggest that if the multipolar cells and ganglion cells were affected by a toxic agent, the processes normally conducting *from* the cell would suffer more rapidly than the processes normally conducting *to* the cell.

My results show that, up to a certain date after section or ligature, the ganglia will suffer most organic change, but that after three weeks the multipolar cells rapidly undergo alteration, and that in six to seven weeks, according to Marinesco, Golgi, and others, disintegration of protoplasm occurs. My results, however, only show distinct disintegration of protoplasm of the cells of the posterior nerve root ganglia after fifteen to twenty weeks, although it is well marked in multipolar cells in three to seven weeks. May not this explain why, in peripheral neuritis, long after paralysis is almost complete, sensation to pain may persist, to some extent at least?

In peripheral neuritis, the condition of these ganglia cells have not met with much attention, "vacuolation" and "hyaline swelling," &c., being referred to in only a few cases; but I trust to be able in a few months to have some work completed upon the condition of these cells, in one case, at least, of this disease.

In conclusion, I may state that I have been engaged upon the histology of these fine fibres, and their distribution, etc., at different stages of life, in human nerves. The results are

as yet incomplete, but this much may be asserted : that the connective tissue supporting the fine fibres becomes gradually increased as age advances, and that diseases causing arterial degeneration appear to expedite the process.

The methods used in the microscopical work were numerous ; nerves were, however, always fixed in Müller's fluid, and portions of cord, etc., in corrosive sublimate. Hæmatoxylin and benzo - purpurin were mostly employed for staining nerves, in addition to Weigert-Pal's method, and toluidin blue and eosin for nerve cells. I cannot close this paper without expressing my thanks to Sir Thomas Grainger Stewart and Dr. George A. Gibson for permission to give details of the two cases of peripheral neuritis which were under their care, and by whose courtesy I obtained the specimens described in the earlier part of this paper.

#### DESCRIPTION OF FIGURES.

FIG. 1.—Multipolar cells from the anterior cornua of the cervical enlargement of the spinal cord of Case I.

- a.* = Cells from left anterior cornu.
- b.* = Cells from right anterior cornu.
- nc.* = Multipolar cell.
- nu.* = Nucleus.
- nl.* = Nucleolus.
- enl.* = Endonucleolus.

FIG. 2.—Right sciatic nerve, Case I., showing recent leucocyte exudation around arteriole.

- arl.* = Arteriole.
- l.* = Leucocytes.
- ex.* = Exudation.
- n.* = Normal nerve fibre.
- nx.* = Degenerated nerve fibre.

FIG. 3.—Left sciatic nerve, Case II., showing exudation, with commencing organisation, and the change in coat of arteriole.

- arl.* = Arteriole.
- ex.* = Exudation.
- fn.* = Newly-formed connective tissue fibres.
- en.* = Endothelial nuclei.
- me.* = Media.
- ad.* = Adventitia.
- adn.* = Nuclei of adventitia.

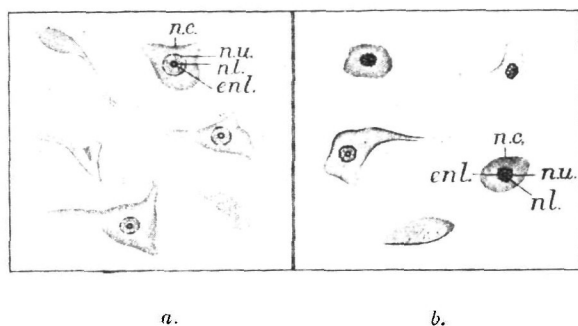


FIG. 1.

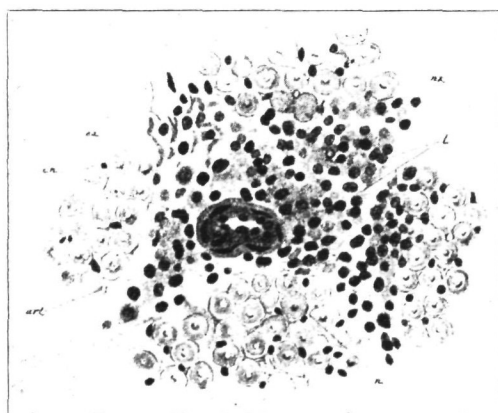


FIG. 2.



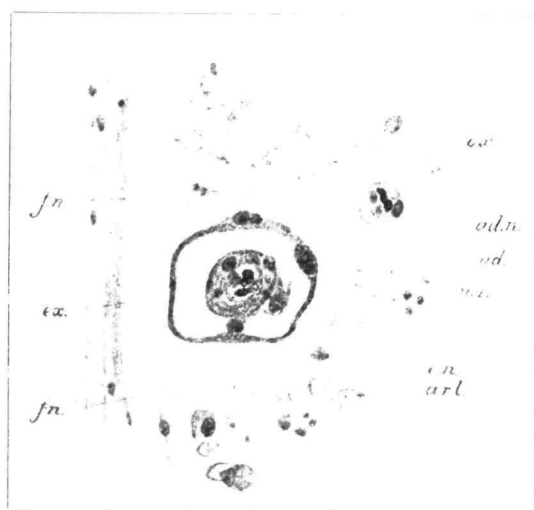


FIG. 3.

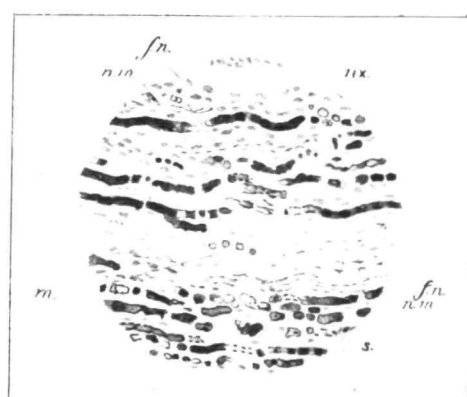


FIG. 4.

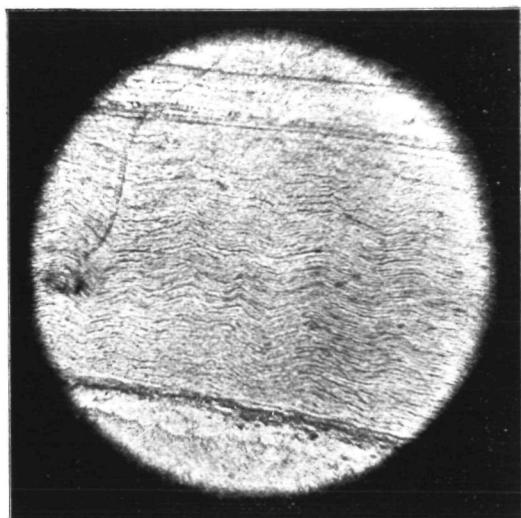


FIG. 5.

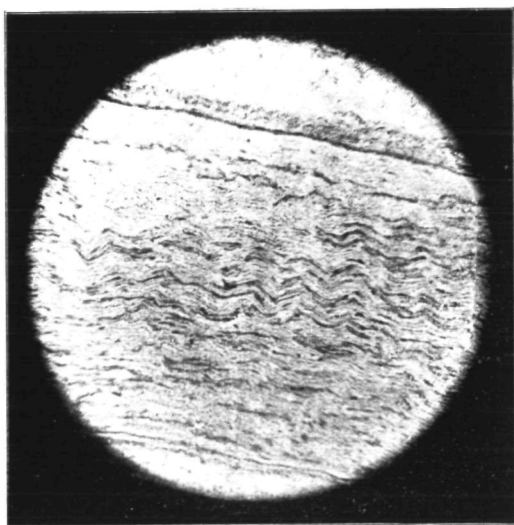


FIG. 6.

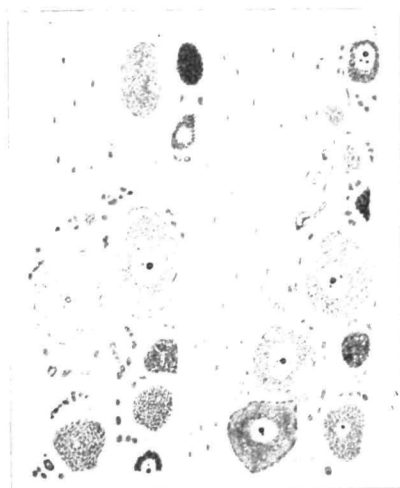


FIG. 7

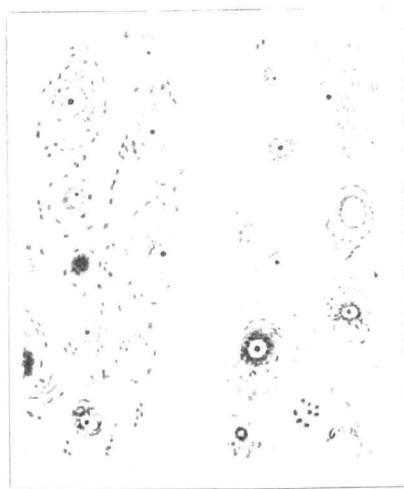


FIG. 8.

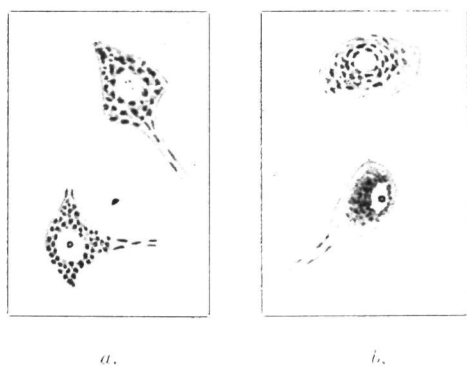


FIG. 9.



FIG. 4.—Right anterior tibial nerve, Case II, showing greater segmentation of fine than of average-sized fibres.

- nm.* = Degenerated fine fibres.
- fn.* = Proliferated connective tissue in relation to these fibres.
- s.* = Enlarged segmental nucleus.
- nz.* = Degenerated nerve fibres—average size.
- m.* = Myelin droplets.

FIG. 5.—Right sciatic nerve of rabbit—unaffected side—showing fine medullated fibres in groups or strands.

FIG. 6.—Left sciatic nerve of rabbit—central end, twenty-three days after application of a double ligature—showing thickened connective tissue septa replacing fine medullated fibres.

FIG. 7.—Ganglion on right posterior nerve root (sciatic region) of rabbit—unaffected side—stained with toluidin-blue and eosin.

FIG. 8.—Ganglion on left posterior nerve root (sciatic region) of rabbit—twenty-one weeks after double ligature—stained with toluidin-blue and eosin.

FIG. 9.—Multipolar cells from anterior cornua (sciatic region) of rabbit's cord.

- a.* = Normal side.
- b.* = Cells from affected side, six weeks after a double ligature had been applied to sciatic nerve.