

ON THE STRUCTURAL CHANGES OBSERVED IN THE ENDS OF THE TIBIAL NERVES FROM THE STUMP OF AN AMPUTATED LEG.*

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MORE than eighteen years ago, in the autumn of 1865, I took the opportunity of dissecting the stump of an amputated arm, for the purpose of ascertaining the changes that had taken place, since the amputation of the limb, in the cut ends of the brachial artery and the median nerve. The examination resulted in finding both the vessel and the nerve embedded in and fused with an organized exudate, forming a part of the cicatrix of the stump. Though the ends of the vessel and nerve were adhering to this organized material, I succeeded in separating them from the latter, finding moreover, the vessel, which had considerably lost in diameter, still open and containing some blood, while the end of the nerve presented a bulbous swelling about twice the diameter of the nerve. No particular changes were observed upon the nerve-fibres by microscopical examination. They were easily traced into the bulbous swelling, where, however, their demonstration was attended with more difficulty, on account of the newly formed connective tissue, of which the swelling chiefly consisted.

Although I have, since the above examination was made,

* Read before the New Orleans Pathological Society.

met with a few other stumps of amputated limbs upon the autopsy-table of the Charity Hospital, I omitted, for the want of time or other reasons, to repeat this examination in a more thorough manner, until about three years ago another very favorable case presented itself to me in the body of a man, who had lost his left leg while serving as a soldier in the Confederate army during the American Civil War, and who had died in the Charity Hospital but a few hours before I dissected the stump of his leg. This limb had been amputated at least seventeen years before the patient's death, and the stump appeared to have been in a healthy condition—that is, well formed and cicatrized. After a careful exposure of the posterior and anterior tibial nerves, I found that both ended in comparatively large bulbous swellings (figs. 1 and 2), while they were not fused, or in any other way connected with the cicatrix of the stump, except by some very loose areolar connective tissue. On the contrary, the surface of the bulbous enlargement presented the same appearance as that of the nerve higher up, representing, therefore, the natural envelope of the nerve, the epineurium, formerly known as the neurilemma; the very ends of the bulbs only were slightly attached to the neighboring tissues. The consistency of these bulbous swellings was about the same as that of the nerve higher up.

Slight bulbous enlargements of the cut ends of nerves, such as I met with in the first case which I examined, have frequently been observed in the stumps of amputated limbs; and it is even believed that in every case of amputation these nervous ends become slightly enlarged by the inflammatory process, accompanying the healing of the stump. In a number of cases even, the enlargement of the ends of the nerves met with has been more considerable, resembling in extent the case before us. As some authors

had regarded these swellings as true neuroma I was glad to meet with the opportunity of enquiring, myself, into their true nature, and, therefore, looked with interest to the facts which my own studies should reveal.

After the removal of the lower portions of the tibial nerves, with their bulbous ends, from the stump they were divided into four pieces, two of which were hardened in Mueller's fluid, while the others were put into a weak solution of osmic acid ; and, when the material had obtained the proper consistency, thin, microscopical sections were made from different points of the specimens, to be mounted, either unstained or stained, in glycerine, or in Canada balsam. The results obtained from the microscopical study of these sections, as well as from teased preparations, will form the subject of this paper.

Before, however, commencing to describe the structural changes which I observed to have taken place in the bulbous ends of the nerves in question, I prefer, in order to facilitate the demonstration and discussion of the subject, to briefly review the manner in which the nerve-fibres are arranged and held together in a so-called compound nerve, which is composed of a smaller or larger number of nervous fasciculi, and, also, the relationship of the component elements of the whole nerve. All the larger nerves, such as the tibial nerves under discussion, belong to this order, being composed, according to their thickness, of a smaller or larger number of fasciculi, or bundles of nerve-fibres. In examining these fasciculi in a thin, transverse section of nerve, a smaller portion of which is represented in fig. 3, it will be found that, besides considerably differing in diameter, each of them is subdivided into still smaller bundles of nerve-fibres by a system of connective tissue septa, which, in the drawing appear as delicate fissures throughout the sections of the fasciculi. But during their course in the

nerve from the nervous centre to the periphery, these fasciculi give rise to branches which reciprocally pass from one fasciculus to another. A constant interchange of bundles of nerve-fibres is thus established between the component fasciculi of the nerve, resulting in the formation of a continuous plexus throughout the entire course of the latter. I have purposely dwelt upon this plexiform arrangement of the component fasciculi of the nerve, as it will assist in explaining the formation of the bulbous swelling of the ends of the tibial nerves above mentioned.

The fasciculi with their communicating branches,—which, in a transverse section of a nerve are represented by those fasciculi presenting a smaller diameter,—are surrounded by a distinct, well-defined sheath, the *perineurium* (fig. 3, *a*), which, according to the respective size of the fasciculus, consists of a smaller or larger number of delicate layers, or lamellæ, of connective tissue, mingled with elastic fibres. It is this peculiar arrangement of the perineurium which induced Ranvier to call it the “lamellar sheath” (*gaine lamelleuse*). These lamellæ, however, are not strictly concentrically placed around the fasciculus, but communicate with one another by others more narrow; though, from the changes which I observed the lamellar sheath to undergo in the bulbous swelling of the posterior tibial nerves, it appears to me more probable that the lamellæ themselves run into one another, instead of being connected by smaller bands, as it is stated. Both the outer and inner surface of the lamellæ are covered with a delicate layer of endothelial cells.

From the inner surface of the lamellar sheath another system of delicate layers of connective tissue arises, which, in the form of septa, not only divide the nerve-fibres of the fasciculus into smaller, or primary bundles, but, moreover, pass between the individual nerve-fibres themselves (fig.

3, *b.*). Around the latter the fibrils of the connective tissue run parallel with their axis, forming the so-called "fibrillar sheath" of the nerve-fibre, which on its inner and outer surface is said to be also covered by endothelial cells; it, of course, is connected with the foregoing septa. The connective tissue forming the septa and the fibrillar sheath is called the *endoneurium* (Key and Retzius), or, as Ranvier has termed it, the "intrafascicular tissue" (*tissue intrafasciculaire*). As this intrafascicular tissue is continuous with the connective tissue layers of the lamellar sheath, the spaces, left between the endothelial linings must also communicate with one another; that such a communication really exists has been demonstrated by the injection of colored materials into these spaces. They have, therefore, justly been regarded as lymph-spaces, representing the lymphatic apparatus of the nerve.

The nervous fasciculi, forming the larger nerves, finally, are bound together by membranous layers of connective tissue, loosely arranged and intermixed with fibres of elastic tissue. To this part of the connective tissue of the nerve (fig. 3, *c*), the term *epineurium* (Key and Retzius) has been applied of late years. Ranvier calls it the "perifascicular tissue" (*tissue perifasciculaire*). It is slightly adherent to, and consequently connected with the perineurium, and not only binds the component fasciculi of the nerve together; but, also, fills up the spaces left between their communicating branches; it moreover gives support to the larger blood vessels of the nerve (fig. 3, *d*).

In casting a final glance over the connective tissue elements of the nerve; we find that they are continuous throughout the different nervous elements just described, and that, in reality, they form but a single framework for the support of the nerve-fibres and blood vessels. The surfaces of this framework are, like the connective tissue

bundles elsewhere, imperfectly covered by endothelial cells.

Having thus far recalled to the memory of the reader the manner in which the nerve is built up by its component elements, I shall now enter upon the description of the pathological changes which I observed on these elements in the bulbous ends of the tibial nerves from the stump of the amputated leg, represented in their natural size by figs. 1 and 2. Before, however, passing to the consideration of the minute histological changes, let us first enquire into the manner in which the cut ends of the nerves were most probably so much enlarged.

Although it may be reasonable to presume, at first sight, that the enormous enlargement of the cut ends of the nerves, which we witness in this case, could only be caused by an increase of some of the histological elements of the nerves, this is but true to a certain extent. But even if the enlargement depended upon this cause, the disproportion existing between the bulbous swelling and the natural diameter of the nerve would hardly have been as great as it is, nor would its form have been so regular and so nicely rounded as we find it. We must, therefore, look for another cause. This may be found in the plexiform arrangement of the component fasciculi of the nerve above referred to, and, moreover, in the presence of elastic-tissue fibres in the lamellar sheath itself, and in the perifascicular connective tissue. These elastic fibres, in truth, may represent the chief factor in the formation of the bulbous enlargement, though the hyperplasia of the connective tissue, particularly of the endo- and epi-neurium, the latter filling up and enlarging laterally the interspaces of the plexiform fasciculi, may also play a considerable part in the formation of the bulbous swellings in question. That such a displacement of the fasciculi really takes place during the formation of the bulbs, may be distinctly seen by examining fig. 4, which

represents a longitudinal section of the smaller bulbous enlargement, that of the anterior tibial nerve, stained with picro-carmin, and magnified about four and a half diameters. In this drawing we observe the fasciculi—enlarged by the hyperplastic connective tissue, not only of the epineurium but also by that of the endoneurium—diverging after entering the bulb to converge again at its rounded end. Not only this, but, by examining the drawing a little closer, it will be found that the fasciculi, besides diverging and converging, form, within the bulbous swelling, numerous curves in different directions. In the centre, even, they are more crowded and curved than at the extremity of the bulb. In the latter locality, on the contrary, they will, to a certain extent, be found missing, the bulb consisting here only of loose connective, and of some adipose tissue. The darker spots, scattered throughout the drawing, represent the transverse section of fasciculi running at right angles with the axis of the bulb.

As regards, now, the free ends of the nervous fasciculi, produced by the section of the nerves during the operation, it will be difficult to decide whether they have remained free, or whether they may not have united to one another, forming loops throughout the bulbous swellings. For, as in transverse, as well as in longitudinal thin microscopic sections, fasciculi, cut transversely or in different degrees obliquely, or running even longitudinally throughout the section, are met with, no definite conclusion can be drawn from the examination. Nevertheless, if I may judge from a number of fasciculi which, in longitudinal sections of the bulbous swelling of the posterior tibial artery, I have traced from one side of the bulb around its rounded extremity to the other, I am inclined to the view that their cut ends have become united to one another to form loops around the lower portion of the bulb. The arrangement of the fasciculi, as seen in fig. 4, also points to this view.

Let us now pass to the study of the more minute histological changes observed in the anatomical elements of our subject, and commence with the examination of a transverse section of the posterior tibial nerve, taken from about one inch above the bulbous enlargement. In this section some changes were already observed to have taken place, consisting in an increase of the connective tissue of the endoneurium throughout the whole fasciculus. Thus the septa between the primary fasciculi, or nerve-bundles, were rendered thicker, and the spaces which they occupy appeared, in consequence, very distinct under the microscope. That layer of endoneurium, arising from and being in contact with the inner layer of the perineurium, as well as the larger septa, occupying the larger fissures seen in the section, particularly, had been considerably thickened. Not only this, but the so-called fibrillar sheath was here and there observed enlarged around some nerve-fibres, giving rise to a subdivision of the primary nerve-bundles. In a thin section of the same nerve, taken from just above the bulbous swelling, the same changes were observed in a somewhat higher degree. Besides, the fibrillar sheath around a greater number of nerve-fibres had now increased in thickness; though the thickening did not always extend around the whole nerve-fibre, but more in one or the other direction. The different parts of the connective tissue of the nerve, however, had still preserved their individual typical forms and relative distribution throughout its section. The perineurium, with its component layers, or membranes, closely applied to one another, therefore, was still observed to surround the fasciculus in the form of a distinct ring.

A totally different view I obtained in examining a thin transverse section, taken from the middle of the bulbous enlargement of the posterior tibial nerve, a small portion of which, enlarged about twenty-five diameters, will be

found represented in fig. 5. The first abnormality striking my eye was a complete disarrangement of the fasciculi and their lamellar sheaths; for, instead of the regular, round, or oval sections of the larger or smaller fasciculi, I now observed a great number of islands (fig. 5, *a*), very irregular in form and size, and surrounded by strata of connective tissue, distributed throughout the section. In a few places only, traces of the original fasciculi (fig. 5, *d*) were still met with, which, however, had also undergone considerable changes. The connective-tissue layers of the endo-, peri-, and epi-neurium, in fact, had become fused—or, in other words, had been converted one into the other; for all the connective tissue of the nerve showed the same character throughout the section. In some places small bundles of nerve-fibres were met with enclosed within some strata of connective tissue, resembling the remains of a lamellar sheath and presenting the appearance of having newly arisen there (fig. 5, *e*). As it can hardly be supposed that bundles of nerve-fibres would be newly formed between the membranous layers of the perineurium, this phenomenon somewhat perplexed me when I first beheld it, though I soon found an explanation for it, which will be stated in its proper place. Besides the fasciculi, presenting their transverse sections in the drawing (fig. 5) before us, there are others observed, cut obliquely, or running longitudinally in the plane of the transverse section of the bulbous swelling (fig. 6, *b*). How these obliquely and longitudinally running bundles of nerve-fibres got into the plane of a transverse section of the bulbous swelling, is easily explained by reflecting upon the course of the fasciculi in the latter, as above stated, and illustrated by fig. 4.

Before, however, proceeding still further with the consideration of the minute changes which I observed in the nervous and connective-tissue elements of the bulbous en-

largement, I must beg leave to diverge for a moment from the subject, in order to pass a few remarks on the probable cause of the hyperplastic process of the connective tissue, observed in this part of the tibial nerves.

I have already stated above, that in the sections of the posterior tibial nerve, taken from just above the bulbous swelling, the first pathological changes appear to take place in the connective tissue of the endoneurium. They consist in a thickening of those layers which arise from the inner strata of the perineurium, thence extending into the larger fissures of the fasciculus, to give finally rise to the septa which divide the latter into primary fasciculi, or bundles of nerve-fibres; at the same time, a hyperplasia of the fibrillar sheath, in one or the other direction of a number of nerve-fibres was already observed. Now, the more we approach the middle of the bulbous swelling, the greater we find the hyperplasia of the connective tissue of the septa of the endoneurium, which here is not only widening the spaces between the primary fasciculi, but, moreover, by extending into the latter, gives rise to new septa, dividing these primary bundles of nerve-fibres into still smaller ones. In some places, these newly-formed septa are observed to penetrate between the individual nerve-fibres, forming bundles or groups of three or four fibres, or isolating even a single nerve-fibre. While, however, the connective tissue of the septa thus proliferates into the primary bundles of nerve-fibres, that of the fibrillar sheaths, surrounding the individual nerve-fibres, also very considerably increases in quantity, contributing thus its full share to the formation of the bulbous enlargement of the cut end of the nerve. The same hyperplastic changes taking place in the connective tissue of the endoneurium, as just described, are also observed to occur at the same time in the epineurium throughout the whole thickness of the nerve, giving rise to the

formation of new connective-tissue layers, increasing still more the size of the bulbous ends of the latter.

The foregoing remarks on the probable course of the hyperplastic process in the connective tissues of the nerves relate only to two of the parts, or envelopes, formed by these tissues, viz.: The endo- and epi-neurium. Of the third part, the perineurium, which forms a special envelope around the nervous fasciculus, I have already stated that but a few traces are met with in the section taken from the middle of the bulbous enlargement. The question, therefore, arises, what has become of these lamellar sheaths, which, in the normal nerve, are so well developed and defined. In order to properly understand the disarrangement of the membranous layers of the perineurium and their fusion with the neighboring hyperplastic connective tissue of the endo- and epi-neurium, we must call to our mind that these layers are not strictly concentrically arranged around the fasciculus of nerve-fibres, but that they rather pass one into the other. In other words, each layer does not form a complete tube around the fasciculus, but only a portion of it. The free margins of this portion of tube are connected, not to the margin of the neighboring lamella, but to their surface; one lamella, therefore, runs into its neighbor, the whole forming a single framework around the fasciculus. While, however, those lamellæ forming the central part, or main bulk of the perineurium, are in this manner connected with one another, the free margins of the lamellæ, placed on the inner and outer surfaces of this envelope of the fasciculus, are continuous with the connective tissue lamellæ of the endo- and epi-neurium. It is in virtue of this relationship, existing between these connective-tissue envelopes of the nerve, that two of them, the endo- and epi-neurium, may, in a hyperplastic condition, separate the component lamellæ of the third, the

perineurium, by simply growing between them. If such an encroachment takes place from the side of the endoneurium, small bundles of nerve-fibres, enclosed by the latter, may be placed between the lamellæ of the perineurium, such as is represented in fig. 5, *c*. In this figure we behold the remains of a nervous fasciculus with the lamellæ of its perineurium separated by the hyperplastic endoneurium from a neighboring fasciculus, enclosing bundles of nerve-fibres. The whole fasciculus is seen to be broken up into very small primary bundles of nerve-fibres by the hyperplastic connective tissue of the endoneurium (fig. 5, *d*).

The separation of the lamellæ of the perineurium by the hyperplastic connective tissue of the endoneurium with small bundles of nerve-fibres inclosed, as I have demonstrated above, not only explains the presence of those bundles observed between these lamellæ in the section of the bulbous enlargement, but, moreover, also accounts for the disappearance of almost all the lamellar sheaths, and of the obliteration of the boundaries of the nervous fasciculi throughout the section. In the breaking up of these fasciculi into smaller bundles of nerve-fibres, as seen in fig. 5, the disarrangement of the lamellæ of the perineurium is not only effected by the encroaching hyperplastic connective tissue of the endoneurium, but also by that of the epineurium.

As the result of the hyperplasia pervading throughout all the connective-tissue elements of the bulbous enlargement, the characteristic features of the different envelopes of the nerves are almost entirely obliterated. Endo-, peri-, and epineurium have, as once remarked before, become fused into one another, so that the whole represents now but a single connective-tissue framework, enclosing the fragmentary bundles of nerve-fibres of the former original fasciculi, and extending throughout the entire bulbous swelling of the

nerve. The only distinctive feature still observed on this framework is that, like the original tissue, it is also built up by distinct connective-tissue layers, or lamellæ, which, similar to the original lamellar sheaths, surround, as seen in figs. 5 and 6, the larger and smaller bundles of nerve-fibres, derived from the original fasciculi of the nerve. But these layers do not run throughout the bulbous enlargement only in one direction; on the contrary, they frequently pass one another, in the form of bundles, more or less obliquely, as may be seen by referring to fig. 6, *c*, where the sections of the latter are indicated by short lines, or dots in the midst of the longitudinal bundles. Whilst, however, the hyperplastic connective tissue of the septa of the endoneurium, as well as that of the epineurium, appears arranged in layers, as just described, the fibrils of the hyperplastic fibrillar sheaths run still parallel with the long axis of the nerve fibres which they surround. In the transverse sections of the bundles of nerve-fibres, therefore, these fibrils are seen in the form of minute dots, or rings, representing their transverse sections. The difference in the appearance of the connective tissue of the fibrillar sheaths, and of that of the septa of the endoneurium, or of that of the epineurium, will be found sufficiently illustrated in fig. 6.

Throughout the whole hyperplastic connective tissue were found distributed a great number of proliferating small spindle-form or stellated cells with oval or round nuclei. In the transverse sections of the fascicular fragments of nerve-fibres (fig. 6, *a*), the form of these nuclei, scattered throughout the hyperplastic fibrillar sheath, appears round, while in the longitudinal sections of these bundles (fig. 6, *b*, and fig. 7) it appears oval.

With regard to the condition of the nerve-fibres embedded in the hyperplastic connective tissue above described, I may state, that I was *unable to discover any traces of degen-*

eration in their component parts. On the contrary, they showed distinctly everywhere their normal double contour, though they presented, in many places of their course, a varicose appearance (fig. 6, *b*, and fig. 7), which, to a certain extent, might be regarded as a deviation from the normal condition. The medullary sheath of these nerve-fibres was still rendered black by a weak solution of osmic acid, as shown in fig. 7.

There was a considerable number of blood-vessels met with, distributed throughout the hyperplastic tissue above described; they belonged to the smaller order of vessels, viz.: the arterioles, venules, and capillaries. Many of these vessels were filled with blood corpuscles, though the adventitia of the larger ones was observed to be also thickened by the hyperplasia, which affected the connective tissues already discussed. Judging, then, from the number and the condition of these vessels, we may presume that both the nervous and the connective-tissue elements were well supplied with blood.

In considering, now, the condition and nature of the histological elements of the bulbous enlargements of the tibial nerves in question, as revealed by my microscopical studies, I cannot but regard these enlargements as a product of a slow, inflammatory action; in other words, a hyperplasia of the connective-tissue elements of the nerve, caused by chronic neuritis. I chiefly base this view upon the fact that, notwithstanding the disarrangement of the original connective-tissue envelopes of the nerve, their characteristic structure was, to a certain extent, preserved throughout the hyperplastic tissue; and, furthermore, that no so-called embryonic tissue was anywhere met with. The whole process of the formation of the bulbous enlargements consisted in a simple increase, or hypertrophy, of the old, already existing connective tissue of the nerves.

The bulbous enlargements of the ends of the nerves in the stumps of amputated limbs have been regarded as one of the causes of the neuralgic pains which many patients suffer in their stumps, sometimes throughout the rest of their lives. Not knowing any thing of the ante-mortem history of the patient from whose stump I took the material for the above-described studies, I am unable to say whether he was subject to these pains or not. But, judging from the pressure which, in his case, the hyperplastic connective tissue of the bulbous enlargements must have made upon the apparently normal nerve-fibres, it is very probable that he also suffered, notwithstanding the rest of the stump presented a healthy appearance.

Explanation of the Illustrations.

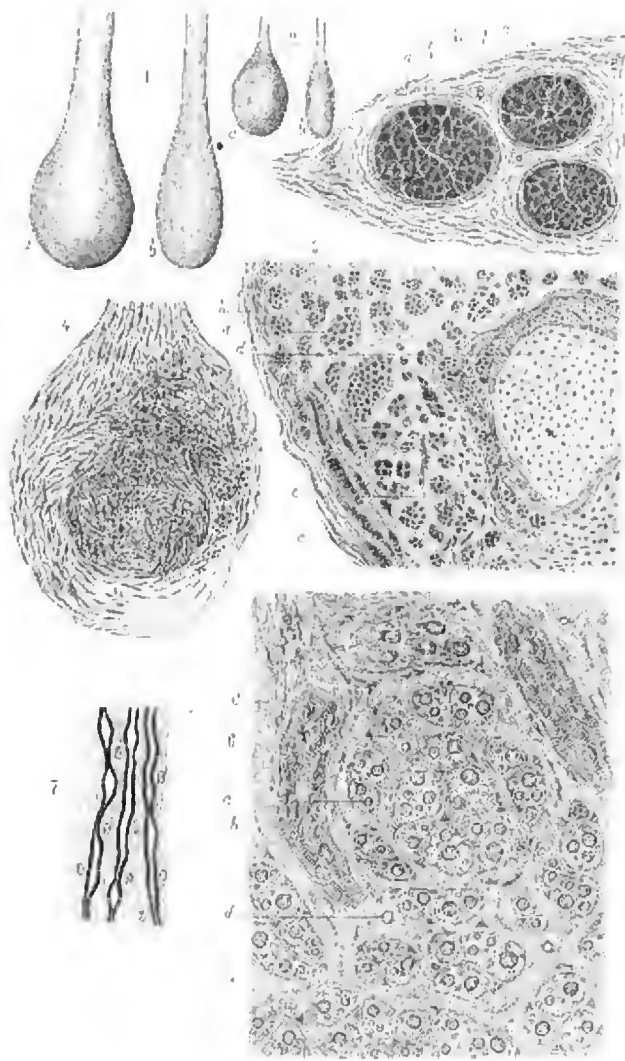
Fig. 1.—Bulbous enlargement of the posterior tibial nerve : *a*, front view ; *b*, side view (natural size).

Fig. 2.—Bulbous enlargement of the anterior tibial nerve : *a*, front view ; *b*, side view (natural size).

Fig. 3.—Small portion of a transverse section of a normal compound nerve, embracing three fasciculi of nerve-fibres : *a*, perineurium ; *b*, endoneurium ; *c*, epineurium ; *d*, blood-vessel (magnified about 25 diameters).

Fig. 4.—Longitudinal section of the bulbous enlargement of the anterior tibial nerve, illustrating the manner in which the ends of the nerves were enlarged, and how they assumed the form of a bulb, by showing the course of the fascicular fragments. These fragments of the nervous fasciculi, running in the bulbous enlargement in different directions, appear, of course, in the section cut either transversely or more or less oblique. The dots in the drawing represent the transverse sections of these fascicular fragments (magnified $4\frac{1}{2}$ diameters).

Fig. 5.—Small portion of a thin section taken from the middle of the bulbous enlargement, showing the distribution of the broken-up fasciculi throughout the hyperplastic connective tissue : *a*, fragments of the nervous fasciculi, cut transversely ; *b*, hyperplastic connective tissue of the the endo- and epi-neurium ; *c*, epineurium ; *d*, remains of a fasciculus ; its nerve-fibres have been subdivided into very small bundles by the hyperplasia of the endo-



neurium[†]; *c*, bundles of nerve-fibres, carried by the hyperplastic endoneurium between the lamellæ of the perineurium (magnified 25 diameters).

Fig. 6.—Small portion of the section fig. 5, higher magnified : *a*, transverse section of a fascicular fragment, showing the transverse sections of five nerve-fibres, a number of nuclei embedded into the hyperplastic connective tissue of the fibrillar sheaths, and the transverse sections of the fibrils of the latter ; *b*, longitudinal section of a fragment of a fasciculus, showing nerve-fibres, nuclei, and fibrils of connective tissue in its interior ; *c*, hyperplastic connective tissue with its spindle form and stellated cells embedded ; *d*, blood-vessel (magnified about 400 diameters).

Fig. 7.—Small portion of a fascicular fragment with three nerve-fibres embedded in the hyperplastic connective tissue ; the preparation has been taken from a portion of the bulbous enlargement that had been put into a weak solution of osmic acid, which has rendered black the medullary sheaths of the nerve-fibres (magnified about 400 diameters).