THE STRUCTURE, FORMS, AND CONDITIONS OF THE ENDS OF DIVIDED NERVES:

WITH A NOTE ON REGENERATION NEUROMATA.

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(*A Report to the Medical Research Committee.*)

THE first steps in any undertaking should be to prepare the ground carefully, in order to form a sure foundation for subsequent work which may be built upon it. This is the object of the present preliminary report on the nerve endings in amputation stumps, and upon it the writer hopes to build a strong pathological and clinical superstructure.

When a nerve trunk is divided, it retracts—provided it has not previously been torn from its bed, as may easily be done. Of the two kinds of tissue thus divided: (1) The divided nerve fibres commence to degenerate and afterwards regenerate, undergoing two changes; and (2) The divided connective tissue (the endoneurium, perineurium, and epineurium) commences at once to repair, and, undergoing but one change, gets a considerable start as compared with the nerves. Consequently, in the early stages the end bulbs of a divided nerve consist very largely of fibrous tissue. Into that bulb of scar tissue the nerve fibres grow. The central part of the nerve bulb is formed from the repairing inner coats of the nerve (the endoneurium and the perineurium). Its outer and circumferential parts are largely formed from the outer coat (the epineurium). This connective-tissue bulb has partly ceased to contract by the time the nerve fibres grow into it, by reason of its early start, and it offers a substantial buffer to the regenerating nerve. The varying densities produced by the growth and contraction of this fibrous tissue give ever-varying patterns of the nerve fibres in it: some have been observed in serial sections to be completely turned round, apparently by the action of contracting fibrous tissue, into a U-shape (*Fig 271*); some of the loops hook over each other. Hence the ever-differing irregular arrangements of the nerve fibres within the bulb—the internal plexiform neuroma, as Professor Marinesco of Bucharest termed it.*

FIG. 271.—To illustrate how a nerve fibre growing alongside a bundle of scar tissue can be made to turn completely round and grow backward, forming a U. Also its appearance on section at the different levels.

The ascending neuritis—as evidenced by the increased amount of connective tissue between the nerve bundles, and its added vascularity—travels up between the fibres in the central part of the nerve trunk. In the nerve end there is little or no separation of the nerve fibres near the periphery. The bundles of central fibres become more tortuous and further separated from each other as they approach the bulb (*Fig. 272*). On reaching the bulb, they undergo more twisting, forming a well-marked ‘zone of twisting.’ Beyond this the nerve bundles come closer together, interlacing with the centrally-bent peripheral fibres to form a dense tissue in the central parts of the bulb,

* *Proc. Roy. Soc. Med.*, 1918, xi, p. 5.

the 'zone of lacing.' This tissue gives the bulb its hardness, and the small amount of closely-packed connective tissue between the bundles of nerve filaments allows of only a very little swelling before causing pressure on nerves and a painful sensation. This, then, is a situation where very little inflammation may cause much pain. The dense network produced by the interlacing and tortuosity of the central and peripheral nerve fibres becomes looser as the apex of the bulb is approached. Finally, the apex is penetrated by the terminal perforating fibres.

FIG. 272.—Scheme of nerve conformation in bulb.

On making a section of the bulb, the network of nerves, the 'zone of lacing,' protrudes in an irregularly convex form, the pressure on one side being relieved by the section.

The part of the end bulb formed largely from the inner and middle coats, the endoneurium and the perineurium—the core of the bulb—is not always central and symmetrical, and gives different shapes to the bulbs by its variations. Over this central mass and in continuity with it is the epineural cap of fibrous tissue. It is well to visualize this cap of connective tissue, which has begun to contract before the regeneration nerve fibres have

FIG. 273.—*a*, Nerve bulb; *b*, Nerve pencil; drawn from actual specimens removed by Major Chapple. The nerve which formed the bulb was cut across. The nerve which formed the pencil was amputated by the sleeve method.

FIG. 274.—*a*, Nerve bulb, formed mostly from the endoneurium and perineurium after nerve division by crushing. *b*, The above with a nerve pencil, formed by the amputation of the nerve with a sleeve of epineurium distal to the crushing. *c*, The regeneration from the point of the pencil end.

grown into it. Unfortunately a little contraction on an inflamed nerve fibre causes much pain. In the nerve pencils, as contrasted with the bulbs, the epineurium is preserved as a sleeve, and does not participate directly in the formation of the nerve endings.

A *nerve bulb* is formed by dividing the epineurium, perineurium, and endoneurium at the same level. (Figs. 273 *a*, 274 *a*.)

A *nerve pencil* is formed by dividing the perineurium and endoneurium at one level and the epineurium lower down, so as to cover the stump with a sleeve of epineurium. (Figs. 273 *b*, 274 *b*.)

A *nerve spindle* is formed by partially dividing both the endoneurium and perineurium and leaving the epineurium intact. (*Fig. 274 c.*)

The several forms of bulb are fashioned by the varying parts which the different nerve coats take in their formation. When the fibrous core to the cap just referred to is in the centre of the bulb, the peripheral nerve fibres are distributed symmetrically around it; but if it is eccentric, the fibres situated on the periphery of the nerve trunk pass it by asymmetrically, more on one side than on the other, and being curved round its surface, as directed by the fibrous tissue of the cap, some interlace and others escape at the apex of the bulb. Thus, the end bulb ceases to be an end of the nerve. Regenerating fibres pass it by; some escape by the side of the bulb, and some from the apex. The more eccentric the core, the more peripheral fibres will be on one side or the other.

Practically, the end bulb is not an end of the nerve fibres: these can grow into any adhesion or along any scaffolding of connective tissue. The adhesion of a nerve bulb to a muscle is a very frequent event in painful conditions, and the scar tissue of the adhesion offers a scaffolding for the nerve fibre to grow along and infiltrate the muscle, every contraction of which must jar the bulb. This has been demonstrated, and in addition Professor Marinesco has shown new nerve fibres from the median nerve infiltrating the tendon fibres of the flexor sublimis digitorum. In these cases the adhesions are almost always lateral to the bulb, being particularly frequent on that side of the bulb where there are most peripheral fibres. Of all the nerves of the body, adhesions to muscles are most frequently found on the stump of the sciatic.

It is chiefly the fibres which escape from the sides of the bulb that infiltrate the surrounding structures through the adhesions to the latter. From the apex of the bulb fibres strain out, and, like a river, seem to follow the line of least resistance. Usually this is by the old course of the nerve, or else along the vessels. Thus, the internal saphenous nerve from Hunter's canal on the front of the thigh may communicate with a regenerating sciatic behind via the course of the vessels.

Regeneration Neuromata.—Should the flowing growth of the regenerating fibres meet an obstruction, they bank up, as a stream forms a lake, so causing a tumour of new growth, a regeneration neuroma. The regeneration neuromata are far more often found on small nerves of devious course than on large nerves which run a plain easy path. On small nerves they are multiple and coursal, along the nerve's course, whilst on large nerves they are simple and terminal. These regeneration neuromata have been found most often—and multiple, three or four—on the internal saphenous nerve; less often and less in numbers on the small sciatic nerve. Never have they been found multiple in the arm, though there is no apparent reason why they should not so exist; perhaps the true reason is that the arm in general produces simple and straightforward problems and conditions as compared with the leg. Regeneration neuromata grow mainly in the leg; they may be multiple; as single tumours they form the terminations of all large nerve trunks formed by regeneration, and consist of a large and varying amount of fibrous tissue and a small and varying amount of nervous tissue.

Nerve-bulb Pain.—What makes the nerve ends painful? There are several theories. The first has been most recently and loudly advocated by Captain Sydney Cone in a long and learned paper.* After much labour and research he has found and elaborated a specific stain for neurokeratin. From a study of the results he has concluded that "three-fourths of each (painful bulb) consists of young nerve fibres," and that "they cause pain apparently by their excessive proliferation against resistance" of scar tissue. One can follow this theory quite well, and easily understand that, within reason, the older the bulb the more numerous the nerves within it. But as a clinical explanation the theory fails, because after section every nerve end is tender for four to six weeks. In normal cases the tenderness disappears just at the time when the intrabulbous nerve pressure

* *British Journal of Surgery*, 1918, v, No. 20, p. 524.

from the growth of young nerves should be coming into operation. In such a common and normal case the theory of neural-growth causation of nerve-end pain fails.

Perhaps the most popular theory of nerve-bulb pain was that it was due to constriction and compression from the contraction of the scar tissue in and around the bulb. Many examples of this condition are to be found in studying the structure of nerve bulbs, both in those which clinically are painful and in those which are painless. The following may be cited :—

1. When a microscopic section is made of a nerve which has not been hardened as it lay stretched out, the fibres are seen to be waved. In the same section there are often both waved and straight fibres, showing that some are held out very taut—most probably by the fibrous tissue between the nerve bundles—whilst others are not so held. There is evidence of tight hold, if not of strangulation.

2. The interior of a nerve bulb is filled with a network of nerve fibres, loops of which knot with other loops, the knots so formed being more or less tightly drawn. A section of a painful neuroma showed this, and also the tortuosity of the fibres in the bulb, its

FIG. 275.—Showing nerve fibres crushed by the contraction of the surrounding fibrous tissue. Nerve fibres without a capsule, and uncrushed, are shown at the upper part of the section. ($\times 30$.)

great vascularity, and the large amount of œdematous fibrous tissue within it. The nerve bundles were very twisted.

3. The fibrous capsule of the bulb is not often contracted so as to be observable with the naked eye, like that of a hobnailed liver. Occasionally a bulb is seen to be wrinkled, with fibrous downgrowths into it. More frequently the contractions can only be seen with a microscope.

4. In another section there was a strangulated island of nerve tissue, the strangulation being suggested by the irregularity of the neural waves in the pinched 'island.' They were like those on boiling fluids.

5. A section of a sciatic nerve showed a very remarkable state of affairs. Growing down from the capsule of the bulb was a band of fibrous tissue, which divided, embracing many nerves in a kind of alveolar arrangement. By contraction of the walls the contained nerves were crushed. In the drawing (*Fig. 275*), crushed and uncrushed fibres may be compared.

6. A section of a strangulated nerve showed œdema of the interfascicular connective tissue, starting from the point at which the fibres were constricted. Œdema was present in all parts distal to where the lymphatic flow was impeded.

7. A section from another case also showed strangulation and twisting of an œdematous nerve bundle.

8. Another section was interesting as demonstrating a slight strangulation of two nerve bundles by a bridge of scar tissue, which only pressed sufficiently to damp off the size of the waving as the bundles passed under it.

9. In another section the nerve bulb showed a strangulated and twisted nerve bundle, with increased amount and vascularity of the connective tissue.

10. A section showed a strangulated nerve island, with increased size and irregularity of the waving. There was also a band over a nerve bundle, which was constricted at that point, the nerve-waving being damped off.

11. Another section showed very clearly a strangulated and twisted nerve bundle, with increased vascularity and quantity of interfascicular connective tissue.

12. Another section showed the presence of a large collar of scar tissue which by its contraction had bitten deeply into a nerve bundle, causing its severe strangulation.

13. In another section there was strangulation of a severely constricted nerve bundle.

Doubtless these two factors, the raising of the intrabulbar pressure by neural growth and the contraction of the fibrous tissue, have some significance. They can be found, however, when there is no complaint of pain, and consequently cannot be regarded as giving a pathological explanation of this clinical symptom. Professor Marinesco and I have shown* that the true explanation is to be found in the raised intrabulbar pressure and the irritation of an infective inflammation which is the characteristic of painful stumps, and that this is favoured by the presence of foreign bodies, reaching the nerve bulbs by direct extension if the nerve has not been cut short, or indirectly by the lymph stream if it has. If these foci of inflammation should be in the 'zone of lacing' of a nerve bulb, pain is quickly and easily caused, as there is little room between the nerve bundles for swelling. A swollen nerve is more susceptible to twisting, pressure, and strangulation, and more painful therefrom. Doubtless, therefore, increased intrabulbar pressure accounts in some degree for the pain of nerve endings; but the pressure and irritation of infective inflammation is the prime factor which produces the pain. As the presence and extent of this factor has been frequently demonstrated by me elsewhere,* no more need be said here. In this report I wish to consider the various shapes of nerve bulbs, their methods of production, and the zones of contraction around them, as these have not been detailed previously.

Nerve bulbs take four shapes; three of these are fairly well known, but one has been noted only recently, and is as yet imperfectly recognized. They are (1) The nerve bulb; (2) The nerve pencil; (3) The nerve spindle; and (4) The nerve drop.

1. The first of these is the best known by far, and is produced by merely cutting across the nerve transversely or obliquely. Roughly, it is made up by the coats of the nerve as follows: Near the regenerating fibres is a mass of scar tissue resulting from the repair of the endoneurium; outside this is a cap of perineurium; and most external is a cap of epineurium. Why has the trouble been taken to enumerate these facts? The answer is that only in the bulb and close to it is a regenerating nerve fibre in danger of compression. Once let the fibre penetrate beyond the cap of scar tissue furnished by the nerve coats, and it will have grown into a region where the scar tissue has largely ceased to contract and now merely acts as scaffolding along which the regenerating nerves grow. Only near the bulb does the regenerating nerve fibre run the risk of being compressed. Once beyond,

* In a lecture at the Royal Society of Medicine in April, 1918, and later, I have demonstrated to the Surgical, Neurological, and Electro-therapeutic Sections of the Royal Society of Medicine in May at the Welsh Metropolitan War Hospital, Cardiff, in April; and at St. Thomas's Hospital in May.—*Proc. Roy. Soc. Med.*, 1918, June; *Brit. Med. Jour.*, 1918, June.

it is safe, except for accidents, such as where it is strangulated and adherent to bone, as in a Syme's amputation.

2. The nerve pencil is a very definite structure which is produced by amputating the nerve so as to cover the stump with a sleeve of epineurium. This method only fails in its technique. Epineural flaps are sometimes 'holey,' and indeed inefficacious, in their fashioning. They are condemned by Captain G. M. Huggins in his excellent little book on amputation stumps.* Captain Huggins has had an unrivalled experience of amputation stumps at Brighton, added to an extended surgical experience at St. Thomas's Hospital, and later in South Africa. His opinion is therefore valuable. But undoubtedly the zone of certain compression around the tip of the nerve pencil is smaller than that around the nerve bulb (*Fig. 276*). A nerve pencil can be made by crushing the nerve and transfixing and ligating the crushed part with fine catgut. This method I have often used, and it is more certain than any epineural sleeve; but experiments often reveal that a number of the fibres were not divided by the crushing, the filaments only being compressed. The epineurium (outer coat) was rarely divided except by Kocher's crushing forceps. The best instrument I found was the smooth appendix clamp made for me in 1903 by Messrs. Allen & Hanburys.

FIG. 276.—Diagram to illustrate the zones of nerve-fibre compression by the cicatrization of the scars next to the nerve end. The innermost zone, mostly derived from the endoneurium, is that of certain compression. The middle zone, mostly derived from the perineurium, is that of possible compression. The outer zone, mostly derived from the epineurium, contains scar tissue which has ceased to contract, and its fibres act as scaffolding to the growing nerve shoots.

3. The nerve spindle is produced by crushing the nerve, the object being to divide the nerve fibres and not the connective-tissue coats. This has been accompanied by varying success. The vasa nervorum certainly did not bleed. But the method was discarded because the crushing caused a certain amount of epineuritis around the nerve, with subsequent pain, adhesions, and a generally unsatisfactory condition.

4. One of the most successful methods of nerve amputation for curing pain is by nerve anastomosis, but the method is too laborious for ordinary use. Its results are excellent, and seem to depend on the thoroughness with which the steps of the operation are done. It has been modified and made more generally useful by the L-operation. This method gives rise to a nerve drop; but it is too recent for its results to be really known yet. Its bulb is certainly very like the ordinary end bulb, but longer.

The usual method in my practice is that of the 'swing door.' The nerve is gently drawn down, divided by two cuts (one from either side), and then allowed to retract, the backward movement closing the flaps like swing doors. It forms a bulb like the ordinary bulb, but the nerve is shortened and its end closed cleanly and without stitches or manipulation.

Lastly, there is the nerve triangle to be mentioned. It is found particularly in the musculospiral and posterior tibial nerves, and is produced by the nerve becoming adherent to bone, its end being unable to expand to form a bulb. The result is a very flattened nerve end, often of triangular shape, as when a nerve becomes attached to a bony spur.

The zones of compression about a nerve end are clinically not much affected by the shape and fashion of the bulb. The cause of the pain is not compression of the nerve trunk: that only accentuates the pain already created by the foci of inflammation within the bulb, and is in no obvious way affected by the shape of the nerve end.

* Frowde, Hodder & Stoughton.