

EDITORIAL ARTICLE.

THE HEALING OF NERVES.¹

THE very uncommonplace way in which this work by Ballance and Stewart has been published will be a surprise to many in these days of hurried and ephemeral book-making. To some its appearance—the ample page, the excellent type and paper, the elaborate care taken in every line and in each of the sixteen elaborate plates by authors and publishers alike—will recall the “*Ligation of the Great Arteries in Continuity*,” published in 1901, Mr. Ballance then having Mr. Edwards as his fellow-worker. Those who are familiar with the earlier will find in the later work the same endeavor to make each chapter complete and each statement accurate. In a note, Mr. Ballance states that the number of preparations, each prepared by the best modern microscopical methods, on which this paper is based, are due to the knowledge and energy of Dr. Purves Stewart. In the preface we learn that the original drawings for the illustrations were made by Mr. M. H. Lapidge, the same artist who made the plates and drawings for the “*Ligation of the Great Arteries in Continuity*.”

We have spoken above of this work as being eminently uncommonplace. In these days of competition and hurry, it is as refreshing as it is striking to find on the second ample page four quotations from the Bacchylides, Manilius, the “*Merchant of Venice*,” and R. L. Stevenson’s “*El Dorado*.”

The time was ripe for a fresh work on the vexed question of the Healing of Nerves. In 1872, Dr. Weir Mitchell published

¹ THE HEALING OF NERVES. By C. A. BALLANCE, M.S., F.R.C.S., Assistant Surgeon, St. Thomas’s Hospital, and Lecturer on Surgery in the Medical School; and PURVES STEWART, M.D., M.R.C.P., Assistant Physician, Westminster Hospital. Quarto. Macmillan & Co., 1901.

his "Injuries of Nerves," rich in realistic descriptions. In 1889, Mr. Bowlby placed before the profession his "Injuries and Diseases of Nerves and their Surgical Treatment." Both these books were written from a clinical aspect, and will still repay careful study, Mr. Bowlby's having the especial merit that, like the late Professor Ollier and his cases of excision, large numbers of patients were kept under observation for many years. In the work before us the research has been mainly on histological grounds, and the observations having been chiefly made upon animals, the number of clinical observations here recorded is not large. But while this restriction is somewhat disappointing, it must be remembered that in this work we have for the first time, as far as the English tongue is concerned, experimental operations carried on, on the one hand, by one thoroughly skilled in operative and aseptic surgery, and on the other, the histological results of these experiments examined and recorded by an expert in modern microscopical methods.

It will facilitate our review of this book and render clear the objects of the authors, if we turn first to Chapter vi, p. 92, where it is stated that workers on the manner in which regeneration takes place in a divided nerve may be classified into two schools; these may be termed the "central" and the "peripheral" respectively. Of these the "central" school, to which the great majority of writers belongs, maintains that the new axis-cylinders are direct outgrowths from those in the central segment, the young axis-cylinders sprouting downward and worming their way into the empty neurilemma sheaths of the distal segment to replace the old axis-cylinders previously degenerated and absorbed. According to this school, the peripheral segment plays an entirely passive rôle, and no regeneration can take place in it unless it has been united to the proximal one.

The "peripheral" theory, on the other hand, is that the new fibres in the distal segment—axis-cylinders, medullary sheaths, and neurilemmata alike—are formed from pre-existing cells in

the distal segment itself. The young axis-cylinders and medullary sheaths are laid down in the first instance in the distal segment, and they become attached later to those of the central segment, thus restoring the conductivity of the nerve-trunk. To this latter view Mr. Ballance and Dr. Purves Stewart unhesitatingly declare their adherence. We propose now to see, in some detail, how the writers arrived at the above most important conclusion, and how far it is justified.

To begin with, the *chief objects of their research* were:

(1) The process of degeneration in a peripheral nerve after injury; (a) without and (b) with immediate suturing of the proximal to the distal segment.

(2) The process of regeneration in a nerve-trunk, which has been divided and subsequently reunited by suture.

(3) The process of regeneration, if any, in the distal segment of a nerve-trunk which has been divided, but in which the proximal and distal segments have not been brought into apposition.

(4) The changes which occur in nerve-grafts.

Methods Employed.—The specimens obtained from monkeys, dogs, and cats, and, in some cases, during operations on the animal subject, after being fixed in Müller's fluid or solution of formalin, were stained by one of the following four methods:

(1) Weigert's method for the selective staining of the medullary sheaths.

(2) Cox's modification of the Golgi method for the impregnation of the axis-cylinders.

(3) Stroebe's method for the staining of the axis-cylinders.

(4) Van Gieson's method for the staining of the cellular and protoplasmic structures, *e.g.*, leucocytes, connective-tissue corpuscles, and neurilemma cells.

We will take first the authors' conclusions as to the way in which regeneration of the medullary sheaths takes place when staining by the Weigert method has been employed.

Regeneration in Nerves that have been United.—The earliest date at which any new sheaths are discoverable is at the end of the second week. These are developed in the *proximal* segment close above the plane of division. The new sheaths lie not in the axis of the old ones, but eccentrically and in close apposition to the cells of the neurilemma. These cells do not share in the degenerative process. The new sheaths are not outgrowths, branches, or continuations from the old sheaths of the normal nerve-fibre above. They are formed entirely apart from them. Tracing the process from the plane of division upward, small isolated groups of new sheaths are visible, whose general direction is sinuously longitudinal. It is particularly to be observed that each group is an island which has at first no physical continuity with the peninsula of the normal medullary sheath above, to which, however, it is subsequently guided during its growth within the neurilemma tube. At a higher level, adjacent islands of the same longitudinal series have become a continuous tubular plexus within the neurilemma, and, higher still, the plexus is continuous with the end of the normal sheath.

On the *distal* side of the plane of reunion no new myelin sheaths are visible at the end of three weeks, but at the end of four weeks they are to be seen in great abundance in the entire extent of the nerve. It is important to observe that whilst there are, at the end of four weeks, numerous new myelin sheaths both in the proximal and distal segment, they are relatively scanty in the *intervening scar-tissue*. These new sheaths, seen in the *intervening scar-tissue* at the end of the fourth week, are more numerous than in the adjacent part of the central segment and much less abundant than in the distal segment. It cannot, therefore, be claimed that regeneration is a process of sprouting from the proximal segment, otherwise the new medullary sheaths would progressively diminish in number instead of increasing from above downward.

Transplantation Experiments.—Of these only four were performed. Degeneration occurs in the graft exactly as in the distal segment of the divided nerve. The graft itself is a dead tissue, and is gradually absorbed and replaced, like blood-clot, by a living tissue. At the end of four weeks the graft is degenerated, and there are no new myelin sheaths in its substance, such as have been formed in the distal segment of the nerve-trunk below. But by the end of five weeks, in the monkey numerous young myelin sheaths are present in the graft, chiefly in the neighborhood of the ingrowing blood-vessels. The neuroblasts from which the embryonic sheaths are derived do not originally belong to the graft itself, but are to be numbered among the cells which invade and replace the graft from the distal as well as the proximal segment. The invading neuroblasts travel into the graft alongside the blood-vessels, for the embryonic sheaths are found in greatest abundance in their immediate vicinity; this method of entrance facilitating nutrition of the actively growing sheaths. The graft is, therefore, a scaffolding invaded equally throughout its length by neurilemma cells¹ from without, both from the proximal and distal segments. These enter along the blood-vessels, their path being one of minimum resistance and maximum nutrition.

We take next the results of the authors as to the regeneration of *axis-cylinders*, the nerves being stained by the Golgi method, a method which was found, when successful, to give striking results, but one in which success was difficult of attainment. The specimens obtained presented a striking confirmation of the results given by the Weigert method. In the normal nerve prepared by the Golgi method, a few "spider-cells" can be seen, scantily distributed. In a divided nerve the earliest stage of regeneration occurs in the proximal segment at the end

¹ The derivation of the neuroblasts or young axis-cylinders from the neurilemma cells in the distal as well as in the proximal segment is dealt with again, at some length, below.—REV.

of the second week, and consists in an increase in the number of the "spider-cells." In the intermediate scar-tissue at this date no axis-cylinders or "spider-cells" can be distinguished, but at the end of the third week regenerative changes are well marked both in the scar-tissue and in the distal segment. In the proximal segment the processes of the "spider-cells" run longitudinally; in the intermediate scar-tissue they form a delicate interlacing network, and in the distal segment they are both larger and more numerous than in the proximal segment, and are arranged with longitudinal parallel processes growing out from opposite ends of each cell. They approach the processes of the next cell of the same longitudinal series, but do not anastomose. At the end of the fourth week the processes of the "spider-cells" in the distal segment are much longer than at three weeks, but do not yet anastomose, though they often overlap. The writers consider they have clearly established that the regeneration of the axis-cylinders does not take place by a process of outgrowth from the proximal segment, but is commenced and completed by the activity of cells already existing in the trunk of the nerve. We shall see shortly that these "spider-cells" are again the neuroblasts or young axis-cylinders, and that they are derived from neurilemma cells. On the results obtained by Mr. Ballance and Dr. Purves Stewart on the regeneration of axis-cylinders in nerves stained by the method of Stroebe for differentiation of the above cylinders, we do not propose to dwell, as the authors found this method to be very uncertain in its results.

Last comes the result of the authors' investigations into the part played in the regeneration of nerves by the different cellular tissue elements, viz., leucocytes, connective-tissue cells, and neurilemma cells. Here Van Gieson's picrofuchsin and hæmatoxylin method was employed from its especial value in the study of the above cellular elements.

A. Leucocytes.

Specimens obtained six hours after the injury exhibit extravasation of blood and diapedesis of leucocytes, such as would occur in any injured tissue. At the end of eighteen hours, the leucocytic invasion reaches its maximum. It is particularly to be noted that the whole extent of the distal segment is invaded, whilst the proximal segment is only so affected in the vicinity of the wound. It is, therefore, evident that as a consequence of loss of function some chemical alteration has already occurred in the distal segment, sufficient to induce the leucocytes to wander into the dying tissue, and this in spite of the fact that no structural changes are detected either in the axis-cylinders or the medullary sheaths until the fourth day. The function of the leucocytes is apparently a transient one, for at the end of three days many of them have already been replaced by migratory connective-tissue cells.

B. Connective-Tissue Cells.

The proliferation of these cells, from whatever source derived (whether from the connective-tissue elements of the nerve-trunk, or from the surrounding structures), begins at a distinctly later period than the leucocytic invasion. A possible explanation may be offered in the fact that leucocytes, being already present in large numbers in the blood, form a standing army ready to move instantly in the direction of an irritant; whereas the connective-tissue cells must abandon their quiescent habit and proceed to multiply or mobilize before they can advance into a tissue which it is their function to absorb and replace.

C. Neurilemma Cells.

The rod-shaped nucleus of this cell stains with the same intensity as the connective-tissue nucleus; but when both varieties of cells are in great abundance, there is no difficulty in distinguishing the long rod-shaped nucleus of the one from the short oval

nucleus of the other. The earliest indication of proliferation occurs in the distal segment of a divided nerve at the end of two days. By this time, probably in response to some early chemical change in certain of the medullary sheaths with which they are in contact, the neurilemma cells abandon their resting condition and commence actively to multiply in discrete patches. Each parent-cell divides, so that the resulting daughter-cells somewhat overlap each other, and by successive division they form closely set longitudinal columns or chains. Putting aside the leucocytic invasion already discussed, the earliest cells observed to multiply in the degenerating segment of a divided nerve are not the cells of the ordinary connective tissue, but those of the neurilemma.

The proliferation of the neurilemma cells, at first patchy, soon becomes general. It has commenced at the lower end of the proximal segment by the end of the third day, but it does not extend in a central direction beyond the vicinity of the injury; whereas in the distal segment it takes place simultaneously, at this date, throughout the whole length of the nerve, whether it has been sutured or not. This proliferation of the neurilemma cells has for its immediate object the removal of the functionless fatty débris of medullary sheaths and axis-cylinders, in which work the neurilemma cells co-operate with the connective-tissue cells which come in, as already described, from the perineurium. The work of fat-absorption, however, though initiated by the neurilemma cells, is performed mainly by the connective-tissue cells, and even while this process is as yet unfinished, the neurilemma cells give up the struggle for the remaining spoil of food, and resign themselves to the formation of separate and compact columns, the individual elongated cells of which are arranged longitudinally. The elongated cells which form these columns proceed later to send out from their opposite poles fine protoplasmic processes which gradually increase in length. Thus, within each old neurilemma sheath numerous new fibres are laid down in short lengths; these afterwards blend and become con-

tinuous so as to form the regenerated axis-cylinder, which shows evidence of its youth by its greater sinuosity and by the existence of beaded thickenings at intervals. *The more the specimens are studied, the more is the conclusion forced upon the mind of the observer that for the regeneration of a peripheral nerve-fibre (not only the axis-cylinder, but also the medullary and neurilemma sheaths) the activity of one variety of cell, and one variety only, is responsible. That cell is the neurilemma cell.*¹ In support of this most important statement, we may refer to the account of the regeneration process as described above from specimens impregnated by the authors by the Golgi method. It will be remembered that they found that at the end of three weeks numerous longitudinal "spider-cells" could be seen in the distal segment, shooting out young, beaded axis-cylinders from their opposite poles. These new axis-cylinders, also met with at this date in the scar-tissue lying between the two segments, rapidly increase in length, and, at the end of four weeks, have grown so as to overlap and anastomose. *The writers have been able to convince themselves that the "spider-cells" or neuroblasts demonstrated by the Golgi method are identical with the proliferated neurilemma cells.*¹

The writers point out that on this subject the process of nerve-regeneration in the growing tail of the lizard bears a very striking resemblance to the results obtained in their series of observation. Galeotti and Levi (*Ziegler's Beiträge zur Path. Anat.*, 1895, xvii, pp. 369-412) studied the process of nerve-regeneration in lizards whose tails had been cut off, and in which (in sunny weather) new tails grew in about fourteen days. In the central stump the nerve-fibres degenerated upward for only a short distance. Regeneration then commenced, the first stage in the process consisting in a proliferation of the neurilemma nuclei, which became elongated and arranged in definite rows. The ends of adjacent cells later overlapped and fused together.

¹ The italics are our own.—REV.

Clinical Considerations.—The writers point out that the objects of their research being mainly histological, and their observations having been chiefly made upon animals, the number of clinical observations which they have recorded is not large.

As regards *primary suture* in dogs, they observed that when the nerve was reunited by immediate suture, motor power began to reappear in the paralyzed muscles after an interval usually of about four weeks. This date, it will be observed, corresponds to that determined by our authors as necessary for the process of regeneration to occur. The return of sensation was not recorded by the authors in their animals, owing to the difficulty of assuring themselves of the trustworthiness of such observations. With regard to man, it has been already recognized that two months at least must be allowed to elapse after *primary suture* before the return of function can be expected.

With regard to the employment of *nerve grafts*, it is well known that the results are highly contradictory. The writers' cases hitherto recorded, two in number, confirm the above. In one case, in which two inches of sheep's sciatic nerve were transplanted into a gap in the ulnar nerve in the human subject, sensation began to return twenty days after the operation, and was complete six months later. In another case of sciatic paralysis, where six inches of bullock's sciatic had been transplanted, no return of sensation had occurred up to five months after the operation.

A point of much interest, long observed after *secondary nerve suture*, is elucidated by the authors. We refer to the early return of sensation noted in some cases a few hours after the operation. This has been explained in different ways. A certain number of cases may be discounted as errors of observation, others may be explained by an unusual anastomosis or distribution of nerves. In the proportion of cases which remain unaccounted for, we must admit that restoration of conductive continuity (usually only a temporary restoration, though it may recur

later on) is to be explained by a process of what has been called "immediate repair" of the divided axis-cylinders on each side of the division. Mr. Ballance and Dr. Purves Stewart consider that "these cases of early return of sensation are readily explained when we remember the mode of regeneration in the distal segment, not by a process of down growth from the proximal segment, but as a pre-existent accomplished fact—immature, it is true—in the distal segment before reunion had been brought about. Secondary suture in those cases permits of restoration of conductivity in the new fibres already existent in the distal segment by joining thereto those of the central segment."

With all deference to these authorities, we cannot admit that this most interesting question of very early return of sensation after secondary nerve suture has been "explained" by their results. They throw a very interesting light upon it, but no more. This return of sensation, as is well known, takes place in some cases in some hours, only, as a rule, to disappear.

Now our authors have shown that the process of degeneration which must precede regeneration is taking place over a very much longer period. First, an invasion of leucocytes affecting the whole distal segment, but the proximal segment only near the wound. This invasion reaches its maximum about the eighteenth hour. After three days connective-tissue cells, wandering in, begin to take the place of the leucocytes; these proliferate, and on the fourth day begin to absorb the myelin. And so on. It is clear that the early, sometimes very early, return of sensation after secondary nerve suture remains, as yet, unexplained.

We trust that the above imperfect review of this most interesting and instructive work will lead other surgeons to study it with the care it deserves, and to weigh the fact that Mr. Ballance and Dr. Purves Stewart have given a most decided impetus to the views of the "peripheral" school of nerve regeneration. In other words, they have proved conclusively that the distal segment of a divided nerve is not, as hitherto believed, the inert, de-

generated, passive structure which depends for its repair solely on the shooting down into it of axis-cylinders from the proximal or central segment. They have shown as conclusively that it contains within itself, in its power of reproducing neurilemma cells, the ability to form neuroblasts and fresh axis-cylinders. The importance of this observation to surgeons cannot be too highly estimated. And be it remembered that this book, which in later years will probably be recognized as "epoch-making" or "path-making," is not by unknown men. It is the outcome of labors—and when the number of experimental operations, the hosts of sections to be cut and stained, from which those illustrating the sixteen exquisite plates have been selected, when these are weighed the word labor is hardly adequate—of a physician highly trained in histology and neurology alike, and of a surgeon whose name already stands very high on account of his operative skill, his wide view of modern surgery, and the scientific bent of his mind.

By the labors of such men, a firm foundation, trustworthy because consisting of the facts of the most recent histology, has been laid; it remains for surgeons working from the clinical side and by operation on man to raise a superstructure which shall be worthy of the foundation which we have in this work of Mr. Ballance and Dr. Purves Stewart.

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