

TRANSPLANTATION OF THE SPINAL GANGLION, WITH OBSERVATIONS ON THE SIGNIFICANCE OF THE COMPLEX TYPES OF SPINAL GANGLION CELLS

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FIVE FIGURES

One may no longer look upon the spinal ganglion as containing only simple unipolar cells with T-shaped axons. The researches of the past ten years have shown that from this fundamental type all sorts of variations occur. A glance at Dogiel's ('08) monograph shows how great is the number of such variations and how completely they baffle any attempt at logical classification. From the cell body may arise short, thick processes, or fine fibers ending in pyriform or spherical expansions. Other cells present elevated loops of protoplasm which are attached to the cell body at both ends. When such loops are numerous, the cells are spoken of as fenestrated. In other cases the axon at or near its origin from the cell may be broken up into a number of fibers, which unite with each other to form a plexus, and which are finally assembled into a single axon. Other axons give off collaterals with terminal enlargements called end-bulbs.

Although these complicated structures have been much discussed, we are still in doubt as to their functional significance. In this connection, we should not forget that, although obscured by all these variations, the fundamental characteristic of the spinal ganglion cell remains unchanged; i.e., the cell possesses an axon which, dividing dichotomously, puts the cell into relation with the periphery on the one hand and the central nervous system on the other, and, so far as we understand the physiology of the spinal ganglion, this simple type seems to answer all the requirements for the conduction of afferent impulses.

It is possible, of course, that these complex formations in the spinal ganglion may furnish points of contact for the transmission of nervous impulses between afferent neurones or even between afferent and sympathetic neurones. But there is no physiological evidence that such an interchange of impulses does occur in the spinal ganglion. Furthermore, these branches, bulbs, and plexuses seem to be arranged in a manner unfavorable for the occurrence of points of contact between neurones. Only in a few cases, as where the end bulb on the branch of one cell lies under the capsule of another cell, has the possibility of such contact been demonstrated.

It must also be remembered that these multiple processes, bulbs, and plexuses vary greatly in their development in different animals. In the dog the simple unipolar type represents the vast majority of the cells, while in man the more complex forms predominate. In view of this great variation in their development, it is clear that whatever function these accessory structures may have, it can not be of a fundamental character.

It was at first supposed by Cajal and others that it would be possible to classify the spinal ganglion cells into functionally separate and distinct groups according to these variations in their external form. This position is still maintained by some, but it is becoming evident that it is untenable. Two reasons for abandoning this position have already been presented; namely, the apparent ineffectiveness of these processes for transmitting nerve impulses, and the great variation in their development in closely related groups of animals.

The third reason for abandoning the conception that these alterations from the simple type represent the outward characteristics of fixed and functionally distinct groups of spinal ganglion cells is found in observations on pathological and transplanted spinal ganglia. These observations show that the form of a given spinal ganglion cell is not fixed, that it may undergo rapid changes, and that under proper stimulation cells of the simple unipolar type may be transformed into complex cells similar to those seen in normal ganglia. Such observations have been made by a number of observers.

Nageotte ('06) was the first to make observations of this sort on pathological ganglia. Studying the dorsal roots and spinal ganglia from cases of tabes dorsalis, he found in the dorsal roots many very fine non-medullated fibers, on the ends of which could be seen bulbs similar to those seen by Cajal on the tips of regenerating nerve fibers. Some of these fibers were processes from the body of the spinal ganglion cells, others were collaterals from the axons. He regarded these findings as an evidence of a collateral regeneration in contradistinction to regeneration from the end of the surviving portion of an injured axon. He believed that such a collateral regeneration was responsible for the similar structures seen in normal ganglia.

These observations on tabetic material have been confirmed by Marinesco and Minea ('07), and Bielschowsky ('08). In a case of carcinomatous metastasis, where the lesion was within the spinal ganglion, Bielschowsky found many atypical cells with multiple processes and many fine, new-formed fibers. He believes that the fenestrated cells, the cells with fine multiple branches, and the cells whose axons give off collaterals with end bulbs, seen in normal ganglia, are similar to those produced under pathological conditions, and accepts Nageotte's theory of collateral regeneration. Dejerine and André-Thomas ('07) report numerous collaterals with end bulbs in a case of herpes zoster.

In order to determine if similar changes could be produced experimentally, Nageotte ('07) transplanted spinal ganglia beneath the skin of the ear in young rabbits. Fifteen days after transplantation he found that some cells at the periphery of the transplanted ganglion had survived, but that they had taken on an appearance very different from the normal. The cell body was distorted, the nucleus excentric, and the glomerulus missing; but there were a number of processes, both fine and coarse, running in every direction from the cell. Many of these branches had bulbed extremities. There is no essential difference, according to Nageotte, between these and the similar cells found by Cajal under normal conditions. Nageotte also describes in a graft of eight days' standing: (1) cells with persistent axons from which collaterals arise; (2) cells, the bodies of which are

divided into several lobes connected by narrow necks; (3) complicated pericellular networks formed of great numbers of fine branches and collaterals; and (4) glomeruli of fine fibers occupying the capsules of dead cells, and formed by collaterals from adjacent axons.

Similar observations on transplanted ganglia have been made by Marinesco and Minea ('07-'08), and by Agosti ('11). Quite similar changes have been seen when spinal ganglia have been cultivated *in vitro* (Lengendre and Minot '11, and Marinesco and Minea '12, '14).

Our own observations confirm those of previous investigators that simple unipolar cells may be transformed under experimental conditions into complex multipolar cells. An additional fact of importance brought out by this investigation is that such multipolar cells can return again to their original simple form.

In this work white rats were used, two for each experiment. The animals receiving the graft varied in age from one month up. The grafts were taken from animals of varying ages, some only one week old. The head of the recipient was prepared and a small strip of bone removed parallel to the superior sagittal sinus, and an incision made in the cerebral cortex in line with the bone defect. A warm pack was then placed over the wound and the second cervical spinal ganglion removed from the neck of the second rat. The ganglion was grasped with fine forceps by a short stretch of attached nerve and inserted into the brain wound in such a way that the nerve was deepest in the wound and the ganglion just beneath the cortex.

The first experiments were made in 1905. At that time three successful transplantations were made. In each of these experiments the recipient was one month old, and the donor a week old. Two animals were allowed to live ten days and one two months. The brains from the first two animals were examined for the site of the graft and this with a piece of the surrounding cortex was excised. Paraffin sections from these were stained with toluidin blue and erythrosin. The third brain was prepared by the Pal-Weigert method and counterstained with Upson's carmine.

The sections from the brain of Rat I containing a graft of ten days' standing shows the spinal ganglion imbedded in the substantia alba just dorsal to the radiations of the corpus callosum. It is easily recognized by the abundance of connective tissue and by the presence of the round or polygonal cells characteristic of the spinal ganglion. These are arranged in the shape of a horseshoe, two or three cells deep, around the periphery of the ganglion on the side toward the corpus callosum. All nerve cells have disappeared from the interior of the ganglion. The surviving cells are in various stages of chromatolysis, but the majority of the cells show only partial solution of the tigroid masses. These cells are much swollen and their nuclei are excentric. No small nerve cells can be seen. These are more susceptible to injury than the larger cells and rapidly disappear from the transplanted ganglia.

Substantially the same conditions are to be seen in Rat II, also representing a ten-day graft.

The spinal ganglion which was allowed to remain in the brain for two months is shown in figure 1. The graft was not as deeply placed as the others, but was imbedded in the cortex near the great longitudinal fissure and covered over by a proliferation of the pia mater. The ganglion is much decreased in size and surrounded by scar tissue. It contains only a small fraction of the number of cells to be found in a normal ganglion, but these few cells are of normal appearance, so far as can be ascertained by the carmine stain. The shape and size of the cell body, the position, size and contour of the nucleus and the absence of any proliferation of the nuclei of their capsules justify one in assuming that these cells are not undergoing degeneration but have survived the transplantation and would continue to exist indefinitely in their new position.

A few medullated nerve fibers can be seen in the ganglion. These are gathered together in a bundle which can be traced for some distance in the scar when a series of these sections are studied. It is not possible to say whether these are regenerated fibers or fibers which have persisted from the time of transplantation of the ganglion.

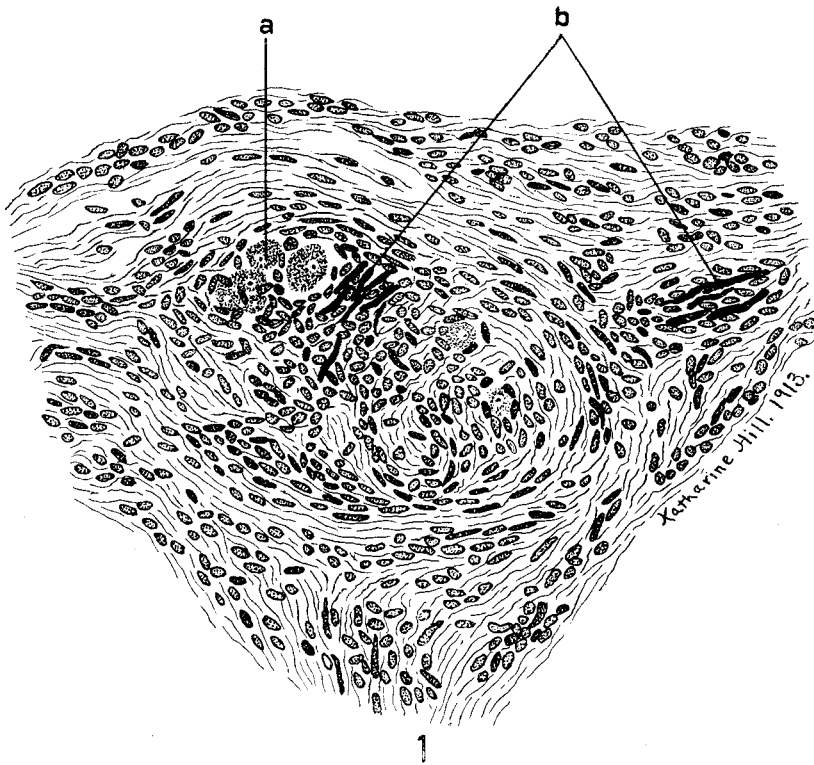


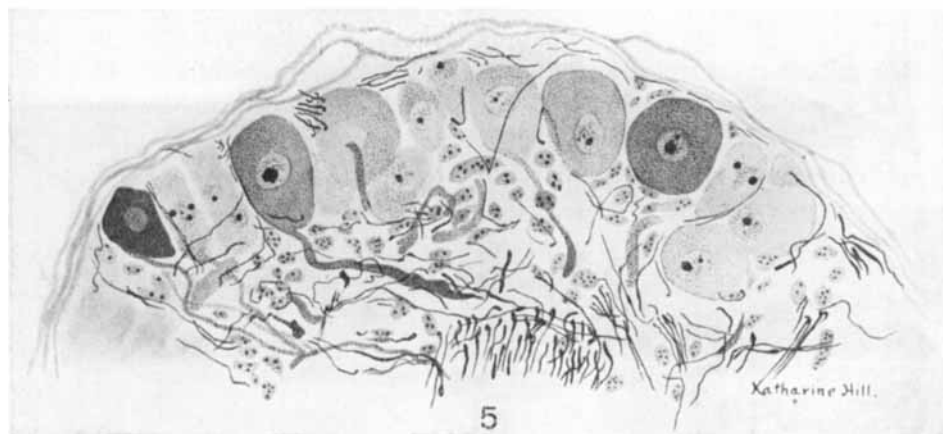
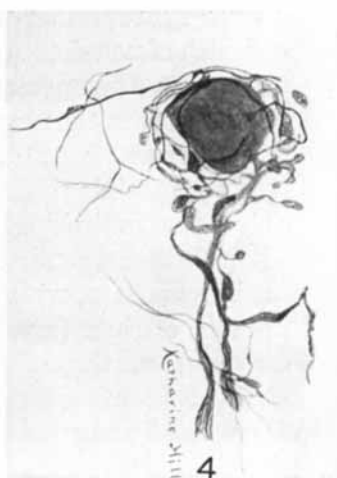
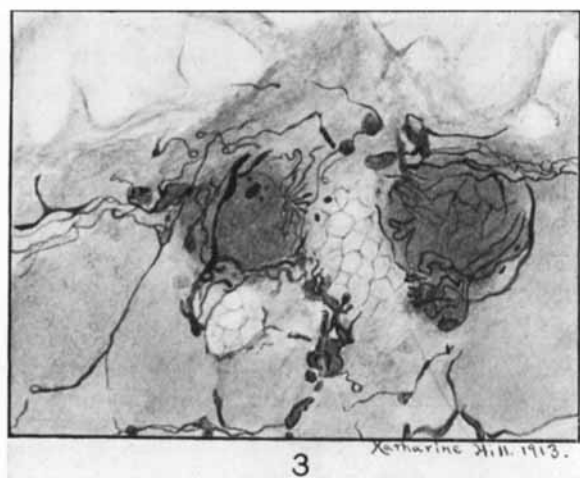
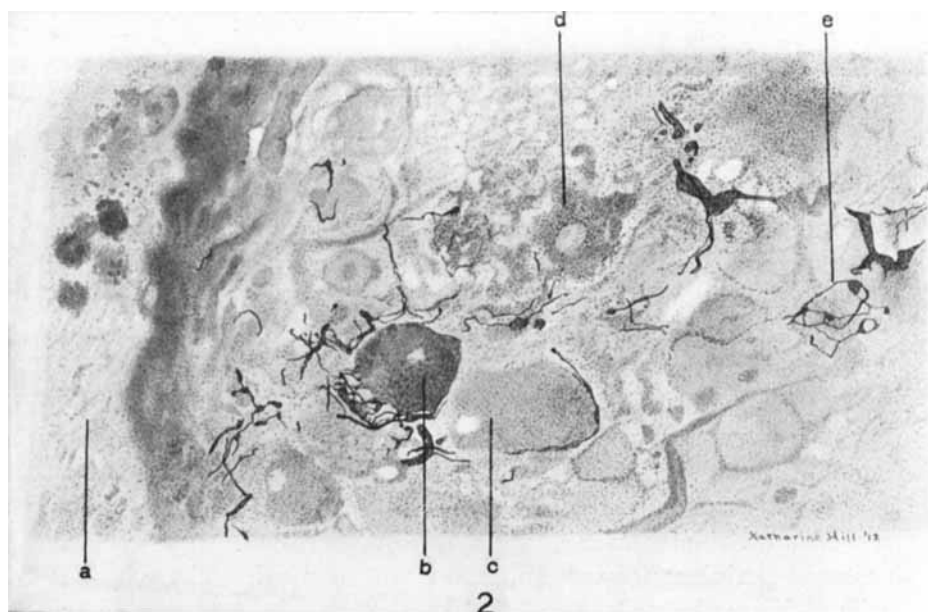
Fig. 1 Transplanted spinal ganglion of the rat; duration two months. Shows several spinal ganglion cells, *a*, and a bundle of medullated nerve fibers, *b*. Pal-Weigert and Upson's carmine. $\times 180$.

Fig. 2 Transplanted spinal ganglion of the rat; duration three days. *a*, coagulum surrounding the ganglion; *b*, living cell surrounded by new-formed fibers; *c* and *d*, disintegrating cells; *e*, plexus of new-formed fibers. Pyridine-silver. $\times 544$.

Fig. 3 Cells from a transplanted spinal ganglion of the rat; duration four days. Pyridine-silver. $\times 544$.

Fig. 4 Cell from a transplanted spinal ganglion of the rat; duration two days. Pyridine-silver. $\times 544$.

Fig. 5 Transplanted spinal ganglion of the rat; duration 17 days. Pyridine-silver. $\times 352$.



In a second series of experiments six successful transplantations were made. These fall into two groups according to the period of survival. In the first group of three, one rat was allowed to live two days, one three, and one four days. In the second group of three, one was killed on the 13th, one on the 17th, and one on the 18th day. In these six experiments all the animals used were half grown or young adults.

Our observations on the first group confirm those of others on transplanted ganglia. The ganglion lies imbedded in the brain surrounded by a small amount of clot (fig. 2, *a*). All of the cells on the interior of the ganglion are dead. A few cells near the periphery of the ganglion have survived. These living cells stain much darker than the dead ones and sometimes show a clear neurofibrillar network. They are always surrounded by a wealth of new-formed fibers (fig. 2, *b*). Some cells seem to have undergone a temporary reaction and then succumbed (fig. 2, *d*). Everywhere in the neighborhood of reacting cells, branching fibers and plexuses (fig. 2, *e*) are to be seen. In most of these reacting cells it is not possible to distinguish the original axon, which has probably either entirely disappeared or broken up into fine branches. The cell is surrounded by a plexus of branching fibers, irregular in their contour, with swellings in their course, and often ending in bulbs or rings (figs. 3 and 4). The fine fibers may arise either directly from the cell body or from the coarse branches, and the fibers often unite in a true plexus formation. These new-formed fibers closely resemble those seen in the early stage of regeneration of a peripheral nerve.

The grafts of 13, 17, and 18 days' standing presented a very different picture, since the living cells in them had returned to a condition approaching the normal. This restoration was probably rendered possible by several favorable factors in the technique. In the first place, the second cervical ganglion of the rat is a very small piece of tissue, through which nutrient fluids can penetrate easily. It is readily isolated and handled without injury to itself by grasping the attached nerve with fine tissue forceps. No sutures were needed to hold it in place in the brain, and it seems probable that the brain may be a more favorable

site for the transplantation of nervous tissue than is subcutaneous tissue or muscle.

After two weeks most of the bizarre formations have disappeared from the transplanted ganglion. As seen in figure 5, which represents a graft of 17 days' standing, most of the dead cells have been removed; the ganglion has shrunk; and the living cells have been brought close together near the periphery of the ganglion. These cells have a smooth well-defined contour and have a single axon, running toward the center of the ganglion and showing practically no glomerulus. The multiple fine and coarse branches of the cells have disappeared, but there are numerous fine, even-contoured fibers running through the ganglion in every direction. Only in a small proportion of the cells could any process be demonstrated and this, when present, appeared to be a typical axon. In one section (fig. 5) a number of the cells showed axons running toward the center of the ganglion.

In each of the three grafts of two or three days' duration the surviving cells were multipolar and in each of the three of 13 to 18 days' duration the cells had returned to their normal form. The essential point in these results is that, under suitable experimental conditions, unipolar cells may transform themselves into multipolar cells and later return again to their original form.

The spinal ganglion cells do not undergo permanent changes in form after division of their axons at a distant point in a peripheral nerve. A month after division of the sciatic nerve in dogs the cells in the associated spinal ganglia were of normal form. Nor are such changes produced by cutting the dorsal root a short distance above the ganglion. In connection with a study of Lissauer's tract I have divided the dorsal roots of the sixth and seventh lumbar and first sacral nerves proximal to the ganglia in a number of cats, and have taken advantage of the opportunity to study the ganglia associated with the cut roots in four cats which had survived the operation, respectively, 24, 70, 74 and 74 days. On comparing these with the normal ganglia, no change in the external form of the cell could be observed. While these experiments show that division of the axon at a distance does not produce permanent changes in the external form of the spinal

ganglion cells, they do not exclude the possibility that transitory changes may occur during the first week or two after the lesion.

This question of the variation in external form of the spinal ganglion cells needs further study. Levi ('07) and Huber ('13) have shown that cells with fine processes ending in bulbs are to be found in the spinal ganglion during late foetal life and shortly after birth. The early appearance of these structures is an important fact to bear in mind in estimating their significance, and evidently points in the opposite direction from the evidence presented in this paper. But this much is clear, that under pathological conditions and in transplanted ganglia simple unipolar spinal ganglion cells become transformed into complex multipolar cells, due to the sprouting of new processes from the cell body and axon, and that these complex cells are very similar to, if not identical with, those found in varying numbers in normal ganglia. It is also clear that these new-formed processes can later disappear and the cell again be transformed into the simple unipolar type. In this way it is demonstrated that the form of the spinal ganglion cell is not stable and fixed, but is capable of undergoing marked alteration in a short space of time. It is probable that the similar complex cell types seen in normal ganglia in such varying numbers are not characteristic of this or that functionally distinct group of neurones, but rather a transient expression of the physiological condition of the neurone.

Just what the factors are which bring about such changes in form is here left unmentioned because we have no adequate means for forming a conception of them, and what theorizing has been done on the subject has only tended to obscure the essential fact that the spinal ganglion cells readily undergo striking changes in form.

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