

## ORIGIN OF PERINEURAL FIBROBLASTOMA \*

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The crux of the discussion concerning the common encapsulated tumor of peripheral nerves centers about the nature of the type cell — whether it is a fibroblast of the connective tissue sheath (Mallory,<sup>1</sup> Penfield<sup>2</sup>), or whether it is of Schwann cell origin (Verocay,<sup>3</sup> Masson<sup>4</sup>). The former view rests on the morphological resemblance of the tumor cells to fibroblasts and the occurrence of a reticulum stroma similar to that of the connective tissue sheath of the nerve fiber. Mallory called these tumors perineural fibroblastoma, a term which was accepted by Penfield who recognized, however, that they might be derived from endoneurium as well as perineurium. The schwannian hypothesis is based largely on Masson's belief in the essential similarity of these tumors to experimental schwannomas produced in rabbits. Evidence for this view is entirely indirect since specific methods for the staining of Schwann cells were not employed. It was because of the uncertainty as to which of two components of peripheral nerves (fibroblasts or Schwann cells) gave rise to these tumors that Stout<sup>5</sup> introduced the term neurilemoma, by which he would indicate a derivation from either the Schwann cell or endoneurium. The objection to this designation becomes apparent when we consider the established usage of the term neurilemma, which refers to the membrane of Schwann although some authors have used it to indicate the endoneurium. Stout would broaden the term to include both the Schwann membrane and the endoneural sheath. Such liberty in the use of the term neurilemma seems unjustified in view of its established usage, and the designation neurilemoma, therefore, would appear to be unwarranted and confusing. These tumors have been called neurinomas (Verocay<sup>3</sup>) which means tumors of nerve fibers. Since it is agreed that these are not tumors of nerve fibers, the term neurinoma should be discarded.

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As far as we can ascertain, this is the first demonstration by direct staining methods that the type cell of these tumors is not the Schwann cell. Two perineural fibroblastomas of the vagus nerve roots will be discussed, the first, to our knowledge, that have been recorded. Study of the two tumors in serial section has presented the opportunity of making observations pertinent to the question in regard to the particular connective tissue sheath from which these tumors arise.

The method employed for the demonstration of Schwann cells was Dockrill's modification<sup>6</sup> of Hortega's silver impregnation technic. This method requires fixation in formalin-urea-potassium iodide and staining with undiluted silver carbonate. This technic, similar to other silver methods, is not entirely reliable, but it gives fair results in a high percentage of trials if the material is fresh and if the staining is done within 6 to 24 hours after fixation. It is imperative that the material be perfectly fresh and it must be placed in the fixative promptly after removal from the body. Schwann cells may be distinguished clearly from fibroblasts in preparations impregnated according to this method (Fig. 1).

By this technic Schwann cells have been impregnated along nerve fibers in a majority of trials (Fig. 2), but it has never been possible to reveal Schwann cells within any of the twelve perineural fibroblastomas examined. The cells impregnated by this technic in the perineural fibroblastomas presented clear-cut features of fibroblasts (Fig. 3). In a case of neurofibromatosis of the von Recklinghausen type, Schwann cells were clearly impregnated along nerve fibers which passed through the tumor, whereas the tumor cells themselves proved to be of a totally different type (Figs. 4 and 5). The Schwann cells were rectangular, with large, clear oval nuclei containing scant chromatin particles and with considerable spongy cytoplasm which was often vacuolated; the tumor cells, on the other hand, similar to those in the solitary perineural fibroblastomas, were narrow and elongated with deeply staining nuclei and cytoplasm which ended in tapering processes, one at each pole of the cell, the entire cell presenting the appearance of the fibroblast. In some areas where degenerative changes had occurred the cells were round or irregular in shape with several straight or wavy processes radiating from the cell body. Similar cells were disclosed in the loose reticular areas of the soli-

tary perineural fibroblastoma. In no respect, however, did any of the tumor cells present the morphological appearance suggestive of the clearly impregnated Schwann cells, which occurred along normal nerve fibers or in traumatic neuromas (Figs. 7, 8 and 9). Around the nuclei of the Schwann cells which occurred along nerve fibers in the neurofibroma of the von Recklinghausen type, the toluidine blue technic of Reich, which requires fixation in Müller's fluid, revealed numerous purple granules (protagon-like or  $\pi$  granules of Reich), so characteristic of Schwann cells (Fig. 6). Such granules did not occur within the tumor cells.

Both tumors of the vagus nerve roots were found during the course of routine autopsies on adults. One was from a male aged 60 years, who died from carcinoma of the prostate gland with extensive metastases. The other tumor was from a patient who died from a non-neoplastic disease, the exact nature of which is not known. No symptoms which might be attributed to the presence of the tumor occurred in either case.

The tumor in each case occurred on one of the cephalic, smaller ventral roots of the vagus nerve. The larger tumor (Figs. 10, 11 and 12) measured 2 mm. in diameter, the other tumor being about one-half this size. Both tumors were well encapsulated and arose from the peripheral non-glial segment of the nerve root about 5 mm. from the site of origin of the nerve from the brain stem. It will be recalled that at this point the arachnoid has not yet become applied to the nerve root as the perineurium; this occurs more peripherally along the course of the nerve root in the vicinity of the jugular foramen (Text-Fig. 1).

Microscopically in each case the tissue presented the appearance of interlacing bundles of cells (Figs. 13 and 14) and reticulum fibers which were cut across at various angles so that certain groups of nuclei appeared round and others oval or elongated. The nuclei contained moderate amounts of evenly dispersed chromatin granules without nucleoli. They were surrounded by a vaguely fibrillar cytoplasm which usually ended in two long processes, one at either pole of the cell. There was some tendency toward palisading of nuclei. An occasional nucleus was large and bizarre in shape, containing a nuclear inclusion body. Mitotic figures did not occur. Preparations stained by Laidlaw's method for connective tissue revealed an abundant connective tissue stroma which consisted of



## DISCUSSION

There is considerable evidence that Schwann cells are homologous with oligodendroglia, and the fact that the Dockrill technic brings out both types of cells quite clearly is a point rather in favor of this. Of more importance in favoring this homology is the fact that the cells possess a morphological resemblance to each other, and along the course of the nerve fibers from the central to the peripheral nervous system cells are observed which appear to be transitional between oligodendroglia and Schwann cells. Oligodendrogliomas are not associated with reticulum of the type noted in the tumors under consideration and, on the basis of this homology, one would not expect real schwannomas to be associated with such reticulum. This is a bit of indirect evidence against the schwannian origin of perineural fibroblastoma. In this study, however, it is the direct evidence against the schwannian hypothesis that is stressed.

The occurrence of  $\pi$  or protagon granules within Schwann cells, and their absence within the type cells of the tumor, do not exclude a Schwann cell origin for these tumors. The granules have been found to be related to the presence of myelin along nerve fibers, and hence their absence might merely indicate the absence of myelination. However, the inability to impregnate Schwann cells in solitary perineural fibroblastomas, while under the same conditions Schwann cells have been impregnated along peripheral nerve fibers, constitutes evidence against the schwannian origin of these tumors. Further convincing evidence is to be found in the clear impregnation of Schwann cells along the course of a nerve fiber within an encapsulated tumor in a case of von Recklinghausen's neurofibromatosis in which the tumor cells proved to be of a totally different type, presenting the characteristics of fibroblasts. Since the type cell of the solitary perineural fibroblastoma and the neurofibroma of the von Recklinghausen type are doubtless the same, the totally different character of the tumor cells and the Schwann cell, as seen in a single microscopic field in a case of neurofibromatosis, seems to be valid evidence against a schwannian origin for the tumors in each instance.

One might argue that the tumor cells might still represent proliferating Schwann cells and yet not be impregnated by the Dock-

rill technic. It has been possible to answer this objection effectively by impregnating proliferating Schwann cells in a traumatic neuroma of the ulnar nerve of 7½ months duration by this technic. The Schwann cells thus stained occurred both along nerve fibers and independent of nerve fibers, at times in groups of two or three nuclei within the same cytoplasm (Fig. 8). They possess large, round or oval nuclei with perinuclear spongy cytoplasm which usually becomes attenuated a relatively short distance from the nuclei. The Schwann cells even in proliferation possess distinctive characteristics and stained by the Dockrill technic they may be quite clearly differentiated from the elongated fibroblasts (Fig. 9). The type cell of the perineural fibroblastoma, or of the neurofibroma of the von Recklinghausen type, possesses no features even remotely suggestive of normal or of proliferating Schwann cells.

The occurrence of cells resembling neuroglial cells within the loose reticular areas of perineural fibroblastoma (particularly noticeable in preparations stained by Dockrill's technic) makes it understandable that these tumors were formerly thought to contain neuroglial elements. However, these cells possess no gliosomes and present no vascular or connective tissue attachments. Moreover, they occur within an abundant reticulum stroma which is not associated with neuroglia. Their appearance is only superficially similar to neuroglial cells. They occur only in areas where the tissue structure is lax. Transitions may frequently be traced from the elongated fibroblasts to these multipolar cells, some of which are bizarre in shape. These cells arise as a result of degenerative changes affecting the tumor cells (fibroblasts).

The fibroblastic nature of perineural fibroblastoma seems evident on the basis of the cell type and the stroma of the tumor. The rich reticulum stroma recalls that of endoneurium. Attempts have been made to demonstrate that reticulum is not necessarily related to fibroblasts but may be formed by other types of cells, for example Schwann cells, but these attempts have not been convincing. Masson, as evidence to support the view that Schwann cells may provoke the formation of reticulum without the intervention of fibroblasts, cites Nageotte's demonstration that reticulum occurs along the central prolongations of nerve fibers through the pial ring in the same distribution as the mem-

brane of Schwann. Nageotte <sup>7</sup> was of the opinion that fibroblasts did not occur in this region and hence were not essential for the formation of reticulum. However, this argument is not valid (Tarlov <sup>8</sup>) since I was able to demonstrate fibroblasts central to the pial ring, along the same distribution as reticulum (Figs. 17 and 18). The fibroblast is constantly found in association with reticulum of the endoneurium.

The structure of the tumors of the vagus nerve roots was characteristically that of perineural fibroblastoma. The occurrence of the two tumors on portions of nerve roots which were unaccompanied by perineurium indicates that the endoneurium must have given rise to the tumors. Therefore, the term endoneurial fibroblastoma would appear to be a more accurate designation for these tumors. If such tumors arose from perineurium, one might expect to find them on the optic nerve which contains perineurium but not endoneurium. To my knowledge, however, no such tumor, arising unmistakably from the optic nerve, has ever been reported. It has been stated, however, that such tumors may arise from the perineurium (Bailey and Herrmann <sup>9</sup>). If one accepts this view and is inclined to use a term that is exact in its connotation, then endoperineural fibroblastoma would appear to be the best designation for these tumors. The term perineural fibroblastoma should be retained for these tumors although it must be understood that they commonly arise from the endoneurium.

It has been stated <sup>2</sup> that the solitary perineural fibroblastoma may be differentiated from the neurofibroma of the von Recklinghausen type by the fact that the former tumor has nerve fibers about its capsule but not within the tumor itself, the occurrence of nerve fibers within the tumor being considered characteristic of the multiple neurofibromas. While this view would seem to be true in general, the observation of an occasional nerve fiber within one of the solitary tumors, which is reported, would indicate that exceptions to the rule may occur.

#### SUMMARY AND CONCLUSIONS

1. Direct staining evidence by a technic that brings out normal and proliferating Schwann cells excludes the Schwann cell as

the type cell of the common encapsulated tumor of peripheral nerves.

2. The type cell of these tumors presents the morphological characteristics of the fibroblast.

3. The term perineural fibroblastoma should be retained for these tumors although it must be realized that they may arise from endoneurium, as in the case of the tumors of the vagus nerve roots which are herein reported.

4. Although the occurrence of nerve fibers within an encapsulated tumor of the peripheral nerves is usually characteristic of multiple neurofibromatosis, an occasional nerve fiber may occur within the solitary perineural fibroblastoma.

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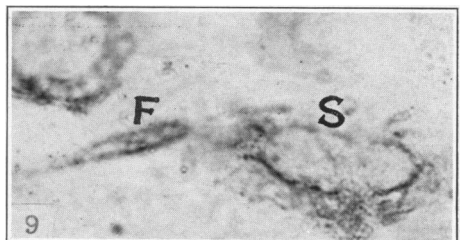
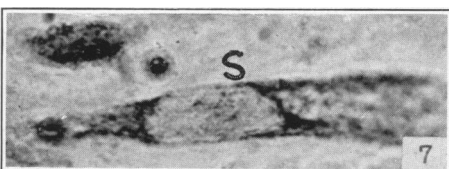
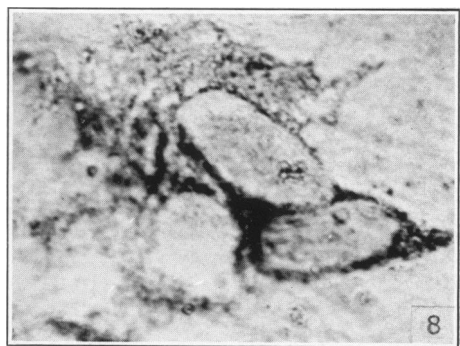
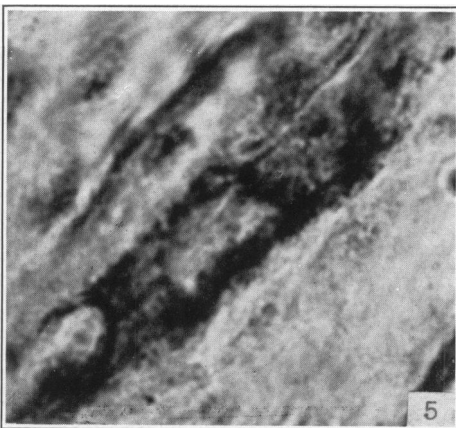
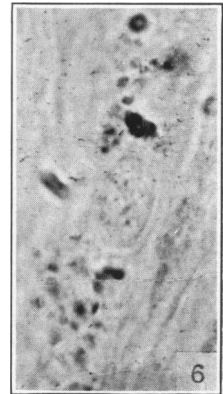
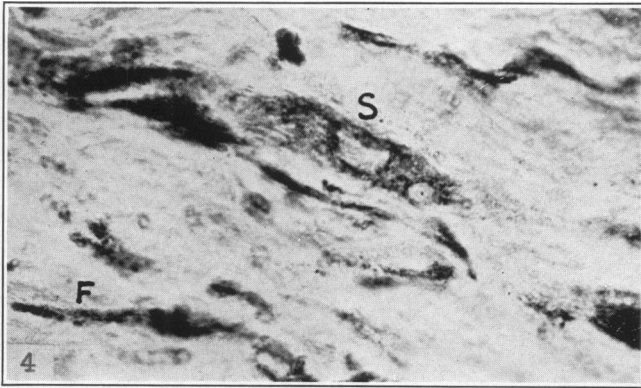
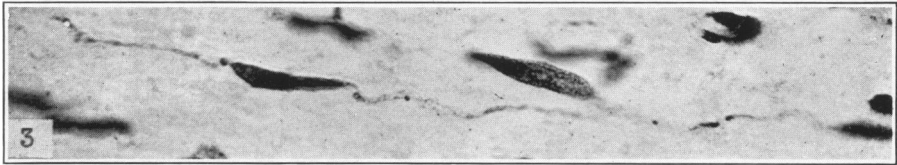
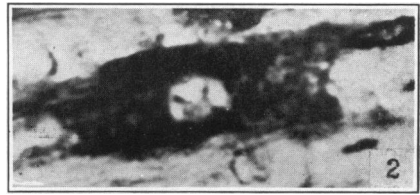
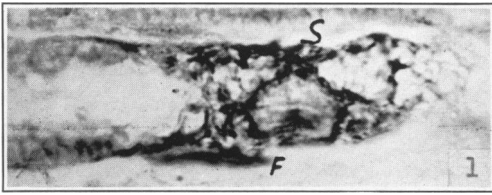


## DESCRIPTION OF PLATES

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### PLATE 7

- FIG. 1. Schwann cell (S) along the oculomotor nerve with fibroblast (F) just out of focus. Note the clear contrast between these cells. Silver carbonate impregnation (Dockrill's modification of Hortega's technic).  $\times 1400$ .
- FIG. 2. Schwann cell along the oculomotor nerve showing less vacuolization than in Figure 1. Silver carbonate impregnation (Dockrill's modification of Hortega's technic).  $\times 1200$ .
- FIG. 3. Type cell (fibroblasts) of perineural fibroblastoma. Note the clear contrast between these cells and the Schwann cells in Figures 1 and 2. Silver carbonate impregnation (Dockrill's modification of Hortega's technic).  $\times 1200$ .
- FIG. 4. Schwann cell (S) along a nerve fiber within a tumor of the von Recklinghausen type. Note the contrast between the Schwann cell and the elongated cells (fibroblasts, F) which form the type cell of this tumor as well as of the perineural fibroblastoma. Silver carbonate impregnation (Dockrill's modification of the Hortega's technic).  $\times 1470$ .
- FIG. 5. Same as in Figure 4. Silver carbonate impregnation (Dockrill's modification of Hortega's technic).  $\times 2000$ .
- FIG. 6. Proton ( $\pi$ ) granules along a nerve fiber within a neurofibroma of the von Recklinghausen type. Reich's toluidine blue stain.  $\times 1850$ .
- FIG. 7. Schwann cell (S) occurring along a nerve fiber in a traumatic neuroma of the ulnar nerve. Silver carbonate impregnation (Dockrill's modification of Hortega's technic).  $\times 1600$ .
- FIG. 8. A group of proliferating Schwann cells occurring in a traumatic neuroma of the ulnar nerve. Silver carbonate impregnation (Dockrill's modification of Hortega's technic).  $\times 1600$ .
- FIG. 9. Schwann cells (S) and fibroblast (F) in a traumatic neuroma of the ulnar nerve. Note the clear contrast in cell types. Silver carbonate impregnation (Dockrill's modification of Hortega's technic).  $\times 1600$ .



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Perineural Fibroblastoma

PLATE 8

FIG. 10. Photograph showing a perineural fibroblastoma along one of the roots of the vagus nerve in a 60 year old male.

FIGS. 11 and 12. Drawings of the tumor shown in Figure 10.

FIG. 13. Microphotograph of the same tumor shown in Figure 10. The appearance is characteristic of perineural fibroblastoma. Hematoxylin-eosin stain.  $\times 100$ .

FIG. 14. Higher power of tumor shown in Figure 13. Hematoxylin-eosin stain.  $\times 925$ .

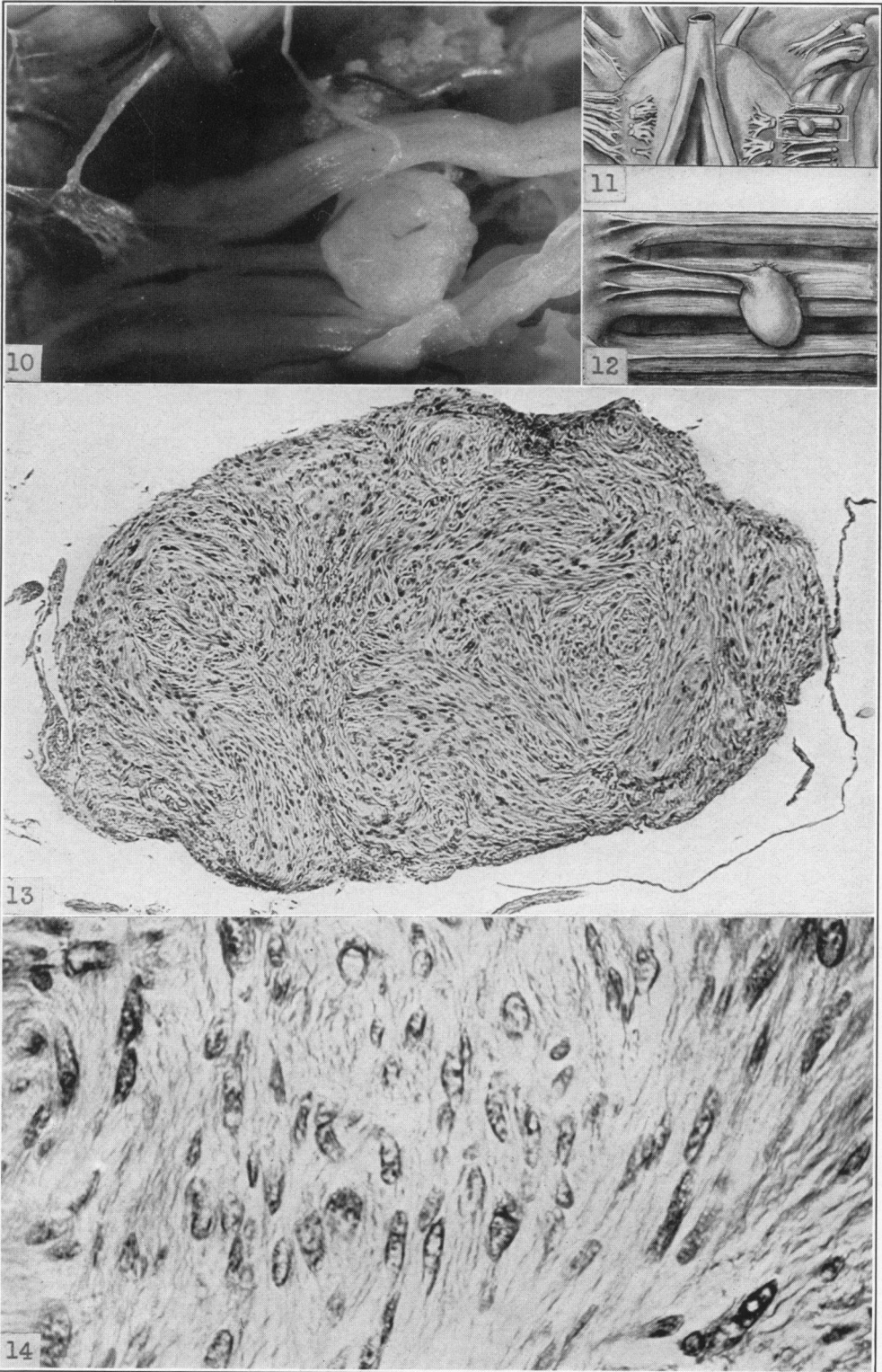


PLATE 9

- FIG. 15. Reticulum stroma of the tumor shown in Figure 13. Laidlaw's modification of Hortega's technic.  $\times 800$ .
- FIG. 16. Nerve fiber (n) coursing through the tumor shown in Figure 15. Loyez' myelin sheath stain.  $\times 1000$ .
- FIG. 17. Reticulum occurring along nerve fibers central to the pial ring. Laidlaw's modification of Hortega's technic.  $\times 750$ .
- FIG. 18. Fibroblast (F) occurring just central to the pial ring (indicated by dotted line) in the same region of distribution as the reticulum tubules shown in Figure 17. Hematoxylin-eosin stain.  $\times 1000$ .

