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ATLAS OF TUMOR PATHOLOGY

Section II - Fascicle 6

TUMORS OF THE PERIPHERAL NERVOUS SYSTEM

by

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I record with pleasure my special thanks to Mr. Walter I. O'Neill for all of the excellent photomicrographs of this fascicle.

Arthur Purdy Stout.

TUMORS OF THE PERIPHERAL NERVOUS SYSTEM

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TUMORS OF THE PERIPHERAL NERVOUS SYSTEM

INTRODUCTION

The tumors of the peripheral nervous system are relatively few in number but richly varied in appearance and nature. Apparently, this is due to the remarkable versatility of the cells composing them. In the main these are derived from the neural crest, and include the Schwann cells which sheathe all of the nerve fibers outside of the central nervous system, the sympathetic ganglion cells, and the paraganglionic cells. The Schwann cells are very active and multiply easily. When originally they come from the neural crest it is possible and even probable that they bring with them melanoblasts which account for the pigmented moles and the malignant melanomas of the skin and certain ectodermally derived mucosae. This can also account for the presence of melanoblasts in some neurofibromas (see fig. 27). Tissue culture studies show that the Schwann cells can produce connective tissue fibers and, indeed, many believe that the endoneurium and perhaps the perineurium are formed by the Schwann cells instead of being mesodermal structures. This probably accounts for the connective tissue content of the common growths such as neuroma, neurofibroma, and neurilemoma. A minority of writers, however, believe all of these are basically fibrous mesodermal growths. In addition to connective tissue fibers, the Schwann cells of tumors are seemingly able to produce bone, cartilage, fat, and striated muscle, a phenomenon not demonstrated in normal humans but known to be a function of derivatives of the neural crest (mesectoderm) in certain amphibia. Finally, cell derivatives of the neural crest can form tumors in the peripheral nerves which imitate the morphological characteristics of central nervous system cells, producing rare malignant neoplasms that caricature the appearance of central nervous system tumors. These neuroepithelial tumors, however, are exceedingly rare.

The more common malignant tumor derived from the sheaths of peripheral nerves has long been subject for debate because of the uncertainty as to whether it is a Schwannian growth (i. e., a malignant Schwannoma) or a fibrosarcoma derived from connective tissue cells (neurogenic sarcoma). Because of the great confusion and misunderstanding occasioned by the words "neurogenic sarcoma," the term "malignant Schwannoma" is preferred for those tumors showing certain characteristic histological features to be later described. The term "neurogenic sarcoma" should be abandoned because the word "sarcoma" has come to be associated with malignant tumors of mesodermal origin and it is uncertain whether or not the mesodermal elements of the nerve sheath can produce malignant fibrous tumors.

Reference to the table (p.11) will show that possibly the only primary tumors of mesodermal origin found in nerve sheaths are vascular and include the benign hemangioma and the malignant hemangiosarcoma . Lipomas can be attached to nerve sheaths, but whether or not they are derived from them is uncertain. Ganglions comparable to those found attached to tendon sheaths, neuroxanthomas, and pure fibromas have all been described, but are not generally accepted as primary tumors of the nerve sheaths.

Multiple neurofibromatosis (von Recklinghausen's disease) produces a number of nerve sheath proliferations and occasionally malignant tumors. These are largely Schwannian, but they differ in certain respects from the solitary nerve sheath tumors (neurilemoma) and so deserve a separate name (neurofibroma). This disease sometimes induces the formation of certain tumors and lesions which are not in themselves composed of nervous elements, but are mentioned because of their association with this particular disease. Mention is also made of two tumor forms in which nerve fibers form an important component element, namely, the glomus tumor and the skin leiomyoma. They will be described in detail in the fascicle on "Tumors of the Soft Tissues."

The tumors composed of cells which imitate the appearance of adult and embryonal sympathetic ganglion cells (ganglioneuroma and sympathicoblastoma) are highly specific and relatively easy to recognize as are the tumors composed of caricatures of the paraganglionic cells. These last are generally called pheochromocytomas if hormonally active in producing epinephrine, and paragangliomas if hormonally inert. Finally, there occur proliferations in the nose and orbit of heterotopic central nervous system tissue with the formation of both benign and malignant tumors.

TUMORS OF THE PERIPHERAL NERVOUS SYSTEM

A. TUMORS OF PERIPHERAL NERVES

Non-neoplastic Neurectodermal Tumors
- Traumatic and Amputation Neuroma
- Appendiceal Neuroma

Neurectodermal Neoplasms

Supportive Tissue Type

Benign	Malignant
Neurilemoma	Malignant Schwannoma
Neurofibroma	
Multiple Neurofibromatosis (von Recklinghausen's Disease)	

Ganglionic Cell Type

Benign	Malignant
Ganglioneuroma (fully differentiated)	Neuroepithelioma
	Medulloblastoma
	Medulloepithelioma

Melanoblastic Type

Benign	Malignant
Pigmented Mole	Malignant Melanoma

Neoplasms Composed of Multiple Tissues of Which Nerves Form Part

Benign
Glomus Tumor
Leiomyoma (cutaneous)

Mesodermal Tumors

Benign	Malignant
Hemangioma	Hemangiosarcoma
(Lipoma?)	(Fibrosarcoma?)
(Ganglion?)	(Neurogenic Sarcoma?)
(Fibroma?)	

Secondary Neoplasms
- Direct Invasion into Nerve Sheath
- Intraneural Metastasis
- Tumors of Ganglia Lying Within Nerves

B. NEOPLASMS OF SYMPATHETIC GANGLIA

- Ganglioneuroma
  - (a) Differentiated (benign)
  - (b) Partly Differentiated (malignant)
- Sympathicoblastoma (Neuroblastoma) (malignant)

C. NEOPLASMS OF PARAGANGLIONIC CELLS

Pheochromocytoma (benign and malignant)
Paraganglioma (benign and malignant)

D. COMPLEX MALIGNANT NEOPLASMS

E. NEOPLASMS OF HETEROTOPIC CENTRAL NERVOUS SYSTEM TISSUES

Benign	Malignant
Glioma (Astrocytoma)	Olfactory Neuroepithelioma
Ganglioglioma (Ganglioblastoma)	

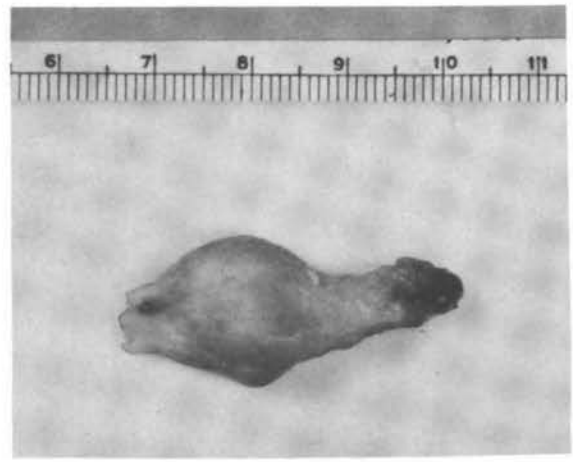
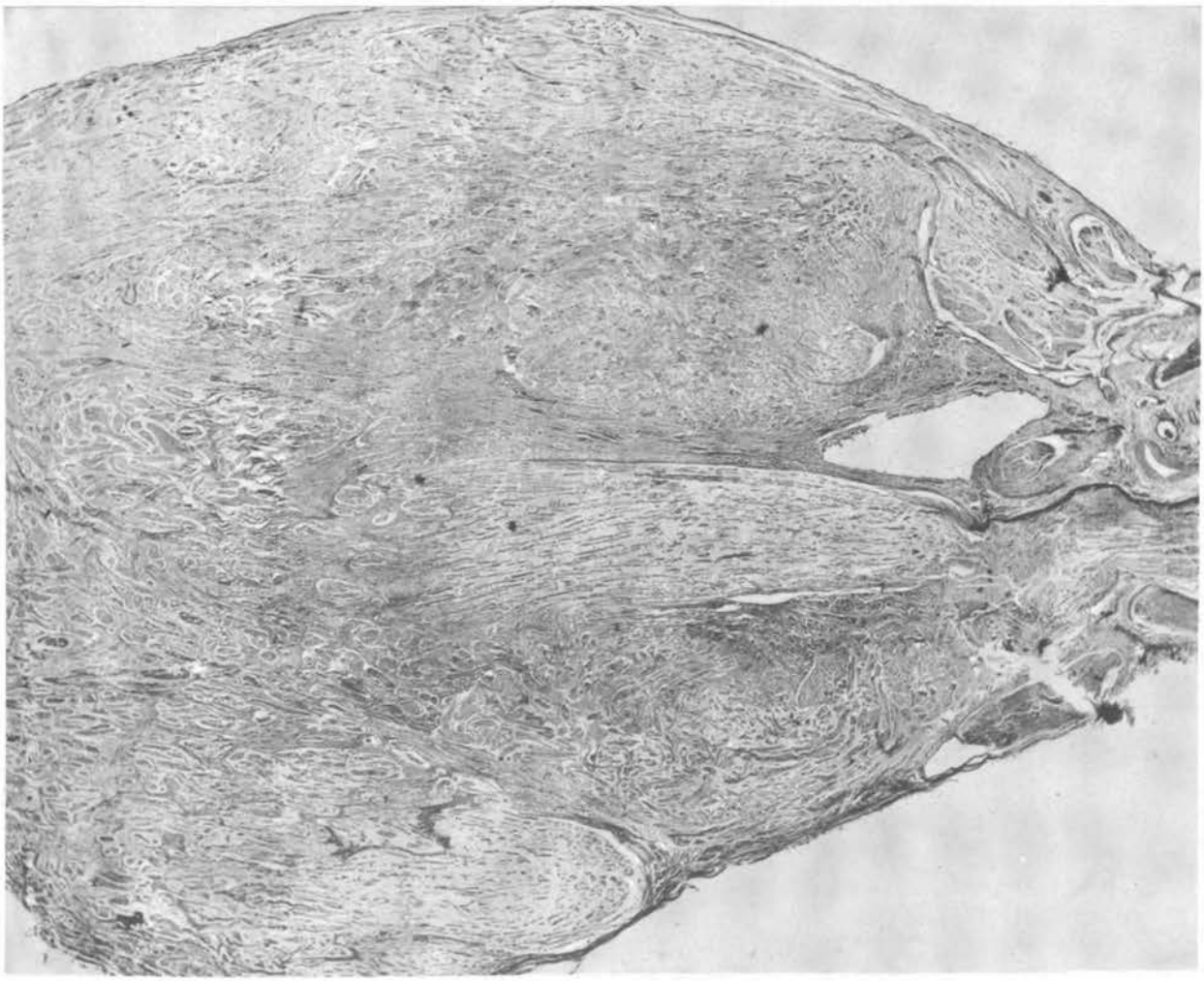


Figure 1. Neuroma from proximal segment of ulnar nerve 9 years after traumatic division. Proliferative mass is confined by the perineurium. A. F. I. P. Neg. Ac. No. 218564–49.

Figure 2. Neuroma of ulnar nerve. The swollen bundles of fasciculi plunge into the neuroma where they are lost in a tangle of sheathed nerves running in every direction. A. F. I. P. Neg. Ac. No. 218564–34.



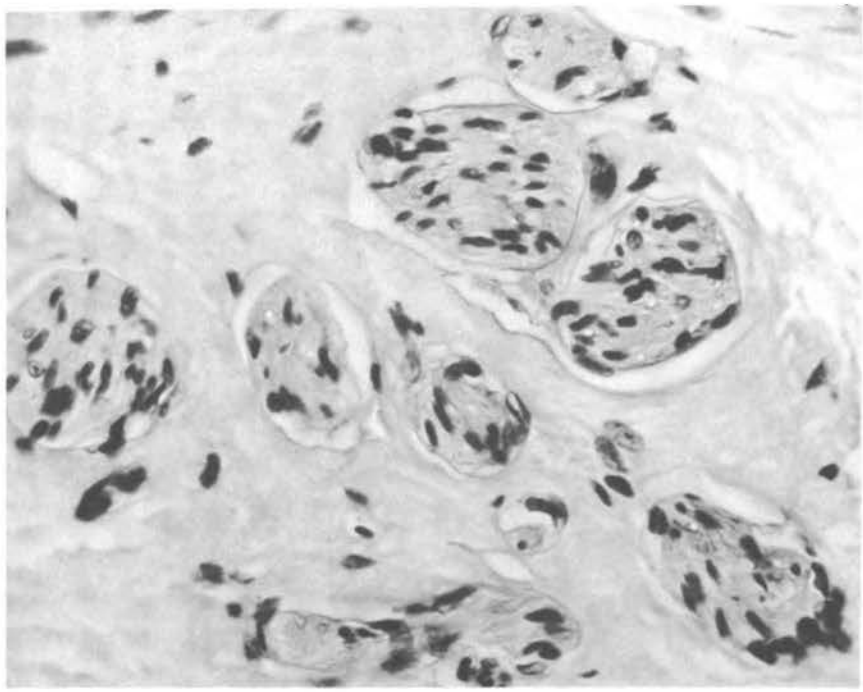


Figure 3. Neuroma of ulnar nerve. Bundles of Schwannian cells sheathing invisible nerve fibers are embedded in scar tissue. A. F. I. P. Neg. Ac. No. 218564–41.

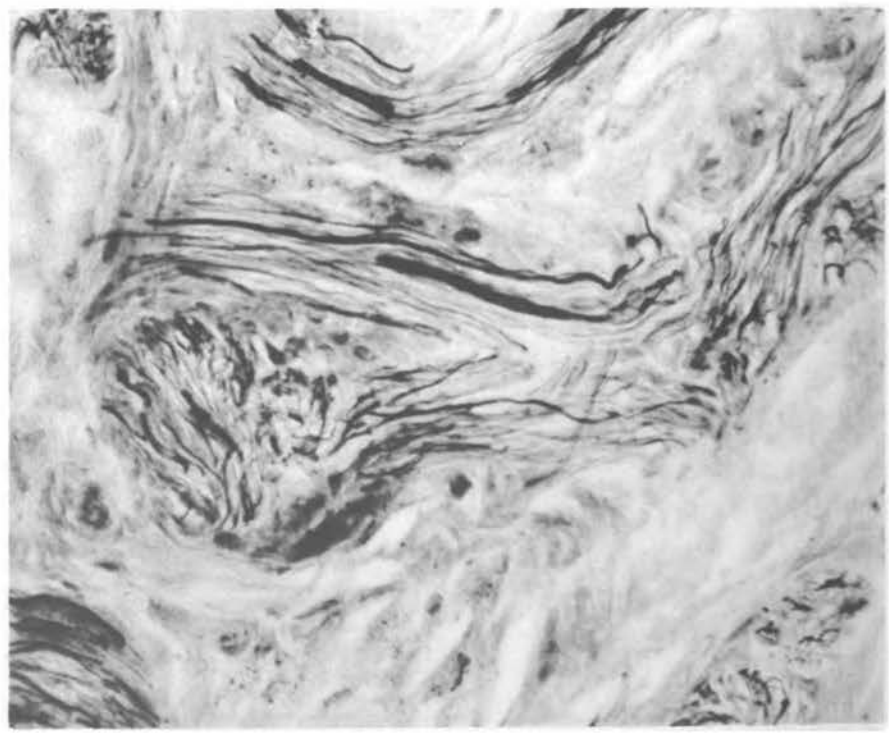


Figure 4. Neuroma of ulnar nerve. Cajal silver impregnation showing the neurites which inhabit the Schwannian sheaths illustrated in figure 3. A. F. I. P. Neg. Ac. No. 218564–14.

A. TUMORS OF PERIPHERAL NERVES

NON-NEOPLASTIC NEURECTODERMAL TUMORS

Neuroma. Synonyms and Related Terms: Neuroma (Lat.)* amputation; appendiceal; spontaneous; traumatic. In the older literature an enormous number of qualifying adjectives were applied to neuroma to designate almost any kind of neurogenic tumor. These have been replaced by more definite histogenic terms.

The term neuroma with qualifying adjectives "traumatic" and "amputation" applies to the proliferative mass of Schwann cells with mesodermal elements and neurites that may develop at the proximal end of an injured nerve. It is a proliferative response and not a true neoplasm.

When nerves are divided and the cut ends become separated, there occurs an active proliferation of the Schwann cells first and later of the mesodermal elements. This causes a bulbous enlargement of the cut nerve ends which is inconspicuous on the distal fragment but may attain macroscopic proportions on the proximal end (fig. 1). After Wallerian degeneration is completed and new axis cylinders grow out, they follow the potential sheaths formed by the sprouted Schwann cells which, if they do not unite with the distal fragment or some other nerve, form a tangled mass of sheathed axis cylinders running in various directions in a matrix of scar tissues (figs. 2, 3, and 4). If the scar tissue is fixed, dense and unyielding, the proximal neuroma may be painful. While neuromas are generally found in connection with peripheral nerves, they may occasionally be observed in nerves of the autonomic system, as for instance, in the gastrointestinal tract. Masson has described a special form of neuroma in the appendix which is dealt with in the section devoted to that organ. The development of a true neoplasm from a neuroma has not been recorded.

NEURECTODERMAL NEOPLASMS

SUPPORTIVE TISSUE TYPE

BENIGN

Neurilemoma (from νευρον-nerve, ειλημα—a closely adhering sheath and ωμα—a tumor). **Synonyms and Related Terms:** neurilemoma (Lat.); acoustic nerve tumor; acoustic neuroma; angioneurofibroma; false neuroma (Virchow); fibroglioma; fibromyxoma; glioma; myoschwannoma; neurilemoblastoma (Geschickter); neurinoma; neurofibromyxoma; neurolemmoma; neuroma fibrillare; peripheral glioma; perineural fibroblastoma; perineural glioma; Schwannoglioma; Schwannoma; specific nerve sheath tumor.

This is the characteristic solitary encapsulated benign tumor occurring in the peripheral, cranial, and sympathetic nerves; and arising from the sheath of Schwann. When the nerve of origin is small, it will be found, if at all, in the capsule of the tumor. If large, the tumor generally forms inside the epineurial sheath and as growth proceeds

* Latin incorporates words from other languages as all languages have done.

by expansion the component nerve fascicules become spread out over the surface of the tumor attached to its capsule (fig. 7). When small, the tumors are relatively solid (figs. 6 and 12), but as they grow larger, degeneration is very apt to occur and they often become partly cystic (fig. 7). When found peripherally they rarely attain a size greater than 6 cm. but in deeper regions, such as the mediastinum and retroperitoneal area, they may attain a much greater size. While usually solitary and spontaneous, neurilemomas may be multiple, and can be found in von Recklinghausen's disease. They may arise at any age, in both sexes, and probably in all races from any nerve or nerve root that has a Schwannian sheath. They enlarge slowly and usually without symptoms although when a large nerve trunk is expanded pain, paresthesia, or other symptoms due to pressure may occur. These tumors are benign and always encapsulated. They rarely recur after removal even if the capsule is left behind. It is questionable whether or not a malignant tumor ever develops from them.

HISTOLOGICALLY, the picture is characteristic. Inside the sheath, the tumor tissue is composed of two parts intermingled but quite sharply defined one from the other. A more solid portion consists of Schwann cells generally arranged in sinuously twisted bands or cords and accompanied by delicate connective tissue (reticulum) fibers (fig. 10). The nuclei often show a tendency to be aligned in rows with intervening spaces without nuclei. This is often called palisading of nuclei (figs. 9, 10, 12). This phenomenon is not limited to Schwannian growths but can also be found in smooth muscle tumors. In the neurilemoma this arrangement of cells, nuclei, and fibers often assumes an organoid appearance suggesting an exaggerated tactile corpuscle sometimes called a Verocay body. The whole solid complex is designated as Antoni type A tissue. Between the masses of type A tissue is the type B tissue composed of very loosely arranged Schwann cells set haphazardly in a kind of meshwork composed of microcysts and delicate reticulum fibers. The microcysts may coalesce to form gross cystic spaces (fig. 8). This degeneration is of a serous type and no mucin, hyaluronic acid, or epithelium is present. Tissue culture studies have shown that the cells from these two areas are all Schwannian although each kind has different growth characteristics (figs. 13 and 14). Another feature of these tumors is the presence of thick collagen sheaths around many of the blood vessels (fig. 8). The bulk of the neurilemoma contains no neurites. However, expansile growth of the tumor inside the epineurial sheath of a large nerve may injure its nerve fibers, so that sprouts from them enter the periphery of a tumor and may be detected there by appropriate technical methods (fig. 11). Mast cells are often present in considerable numbers just as they are in neurofibromas. Phagocytes loaded with lipoid in tiny cytoplasmic vacuoles are found sometimes in deeply situated neurilemomas, especially those attached to the acousticus, the posterior nerve roots, and in the mediastinum but rarely elsewhere.

Neurofibroma and Multiple Neurofibromatosis. Synonyms and Related Terms: neurofibroma (Lat.); dumb bell tumor; elephantiasis neuromatosa; fibroma molluscum; hour glass tumors of the spine; multiple neurofibromatosis; multiple neuroma; neurinomatosis; neuroblastomatosis; neurofibromatosis;

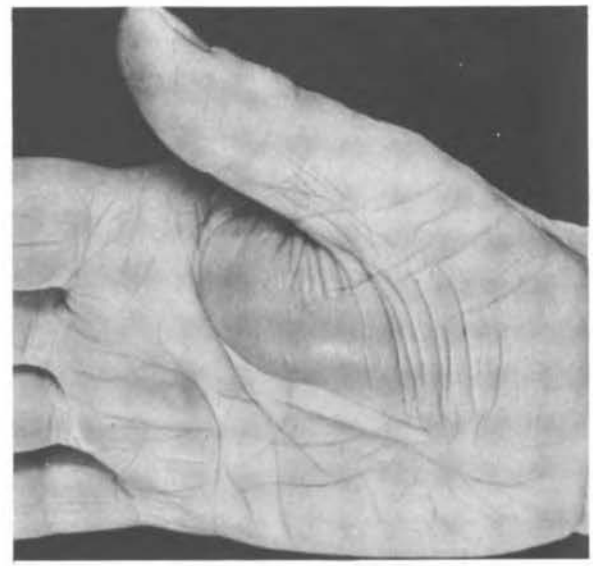


Figure 5. Neurilemoma. Appearance of a subcutaneous 3 x 2 cm. encapsulated tumor present 20 years in the subcutaneous tissue of the palm of a female 53 years old. The overlying skin was purplish, the tumor fluctuated and was slightly tender. A. F. I. P. Neg. Ac. No. 218564–20.

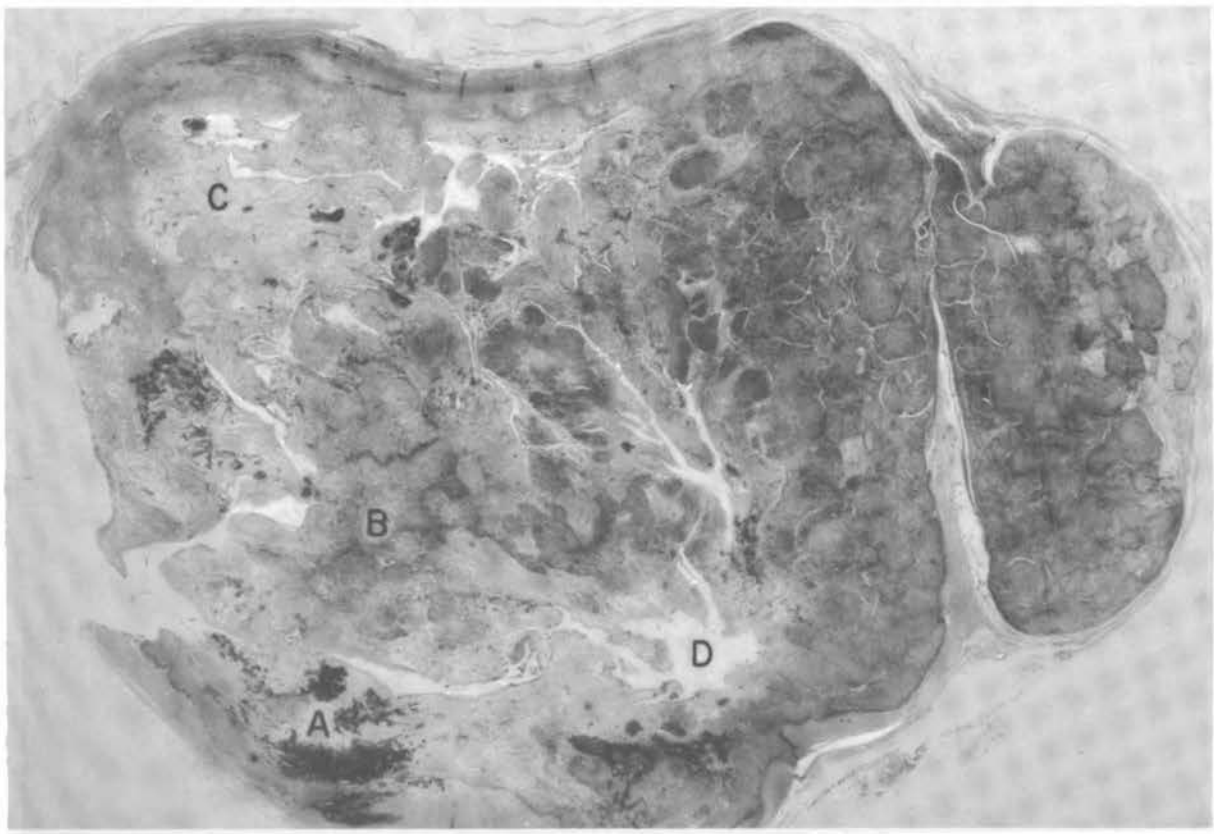


Figure 6. Section through the entire tumor shown in figure 5. It is encapsulated. A: The black stippling is caused by blood pigment. B. The dark solid areas are the Antoni type A formations. C: The lighter zones represent Antoni type B tissue. D: The empty spaces are areas of degeneration. A. F. I. P. Neg. Ac. No. 218564–30.

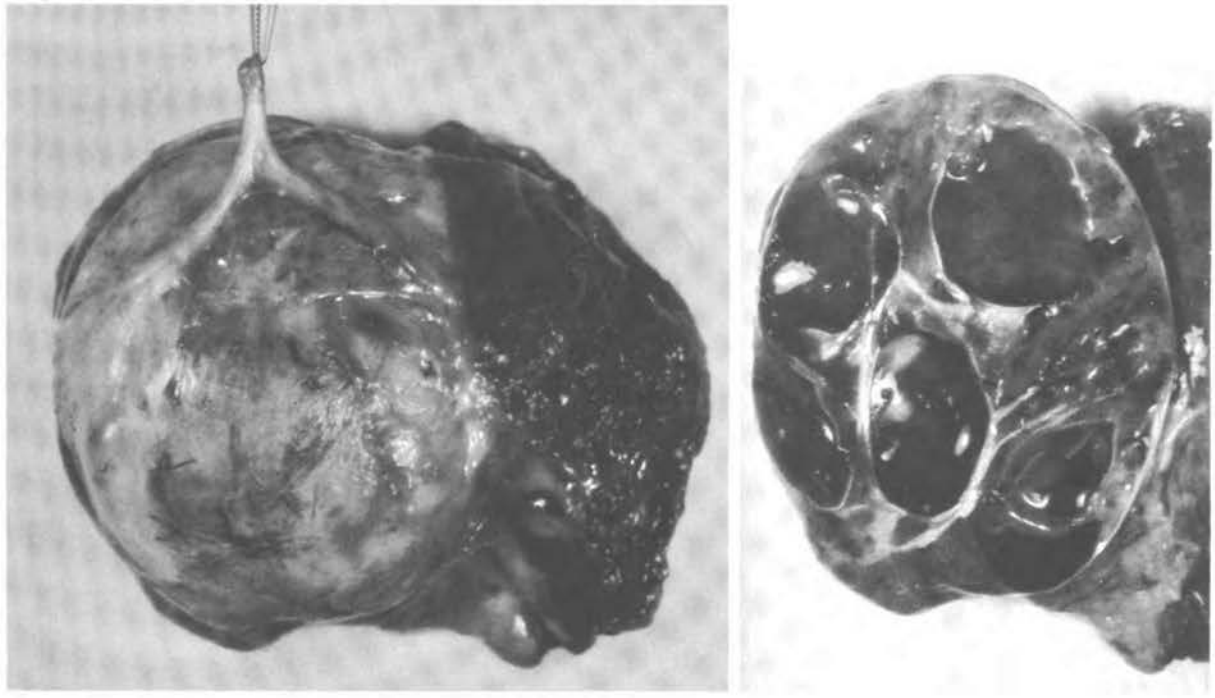


Figure 7. Neurilemoma of the sural nerve showing separation of the component fascicles of the nerve which are spread out over the capsule of the tumor that has developed within the epineurium. At the right a cross section shows the large degeneration cavities within the tumor. A. F. I. P. Neg. Ac. No. 218564–50.

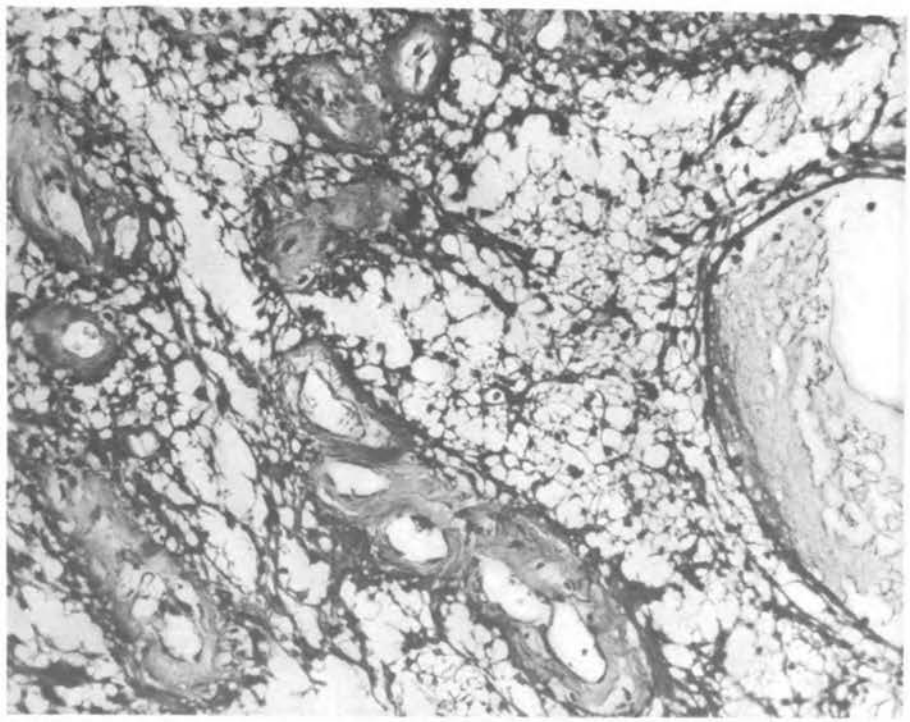


Figure 8. Antoni type B tissue in a neurilemoma with microcystic degeneration, part of a degeneration cyst at the right and several blood vessels with thick collagen sheaths; a special feature of this tumor. A. F. I. P. Neg. Ac. No. 218564–23.

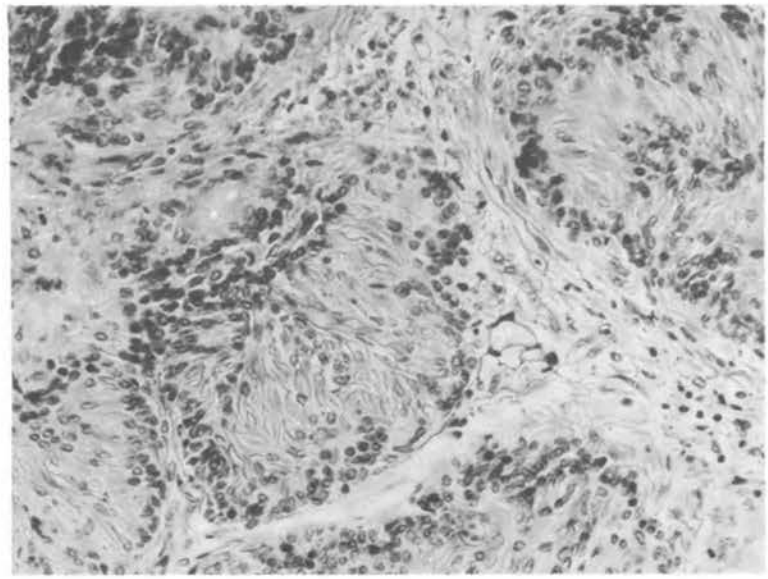


Figure 9. Verocay bodies in a neurilemoma. The twisted formations with palisaded nuclei caricature the appearance of tactile corpuscles. A. F. I. P. Neg. Ac. No. 218564–52.

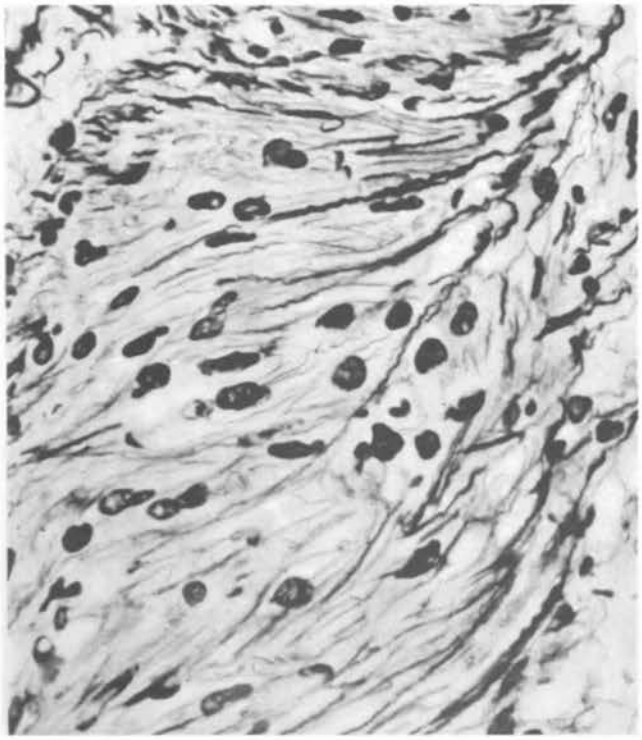


Figure 10. Verocay body in a neurilemoma. Laidlaw silver connective tissue stain showing the arrangement of the delicate reticulum fibers in the twisted organoid structure. A. F. I. P. Neg. Ac. No. 218564–53.

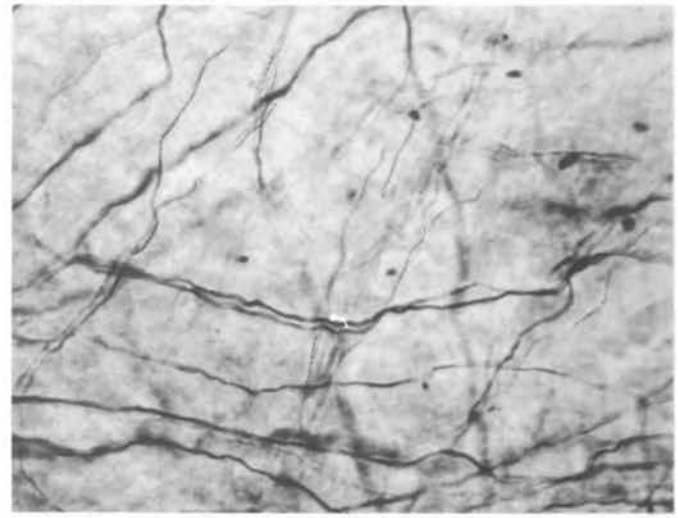


Figure 11. Neurites in the periphery of a neurilemoma. Gros silver technique modified by Laidlaw. Frozen section. A. F. I. P. Neg. Ac. No. 218564-15.

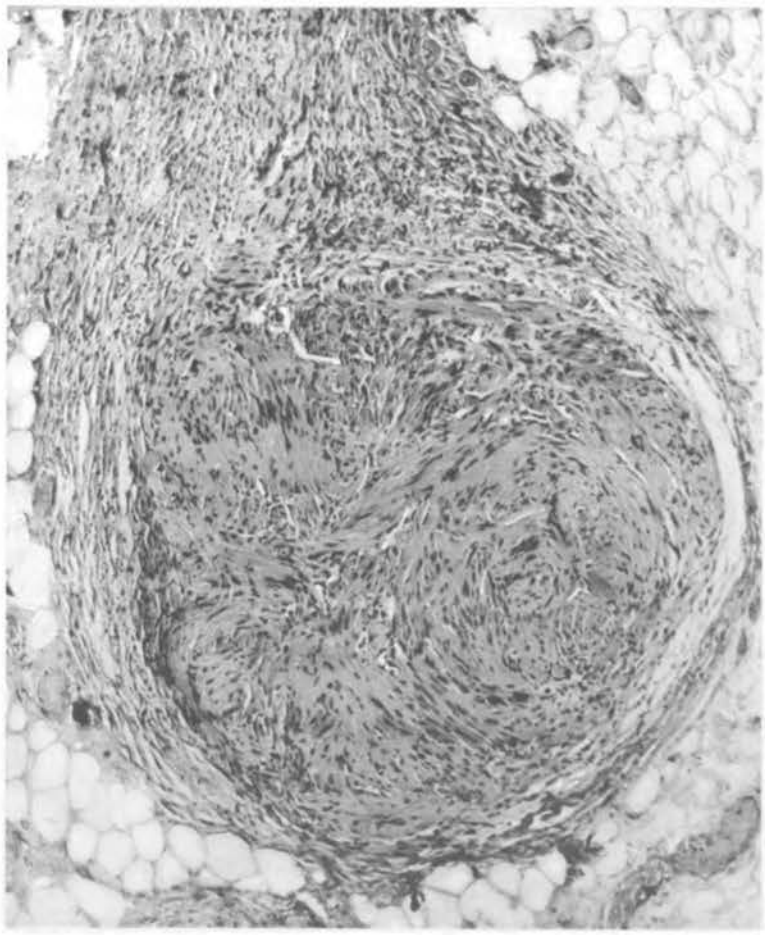


Figure 12. Incipient neurilemoma. It consists largely of Antoni type A tissue. A. F. I. P. Neg. Ac. No. 218564-4.

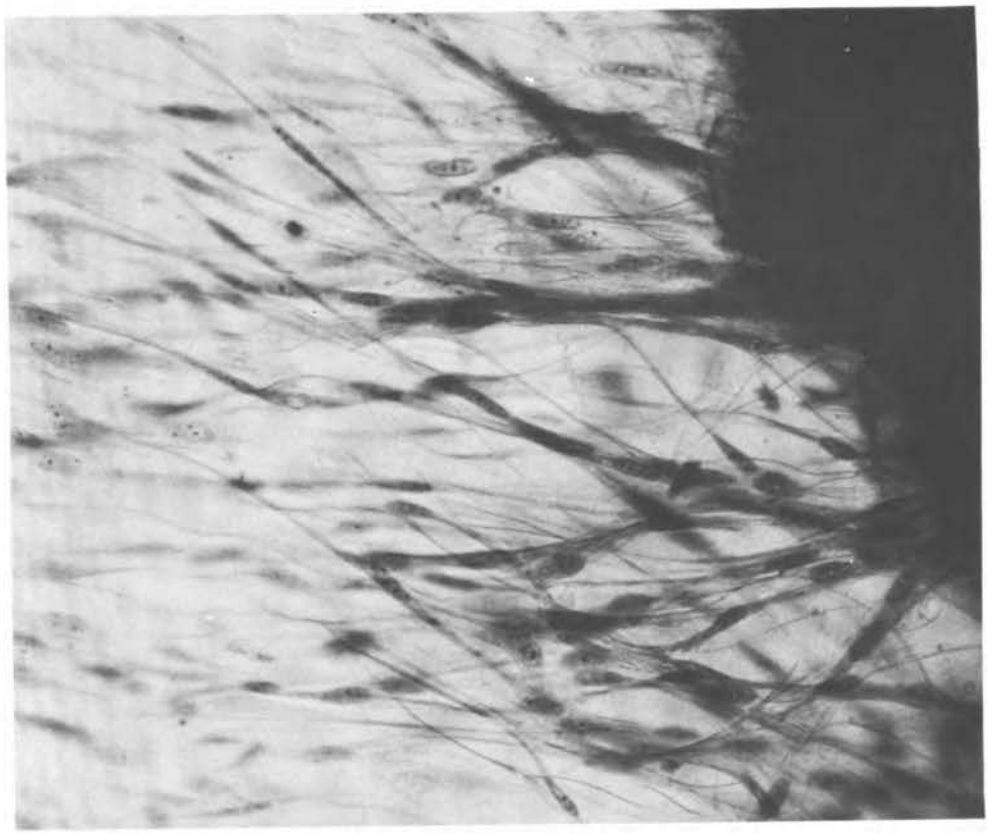


Figure 13. Explant of a neurilemoma in vitro. Characteristic outgrowths of Schwann cells in tufts from Antoni type A area (x 450). (Preparation by Dr. M. R. Murray.) A. F. I. P. Neg. Ac. No. 218564–5.

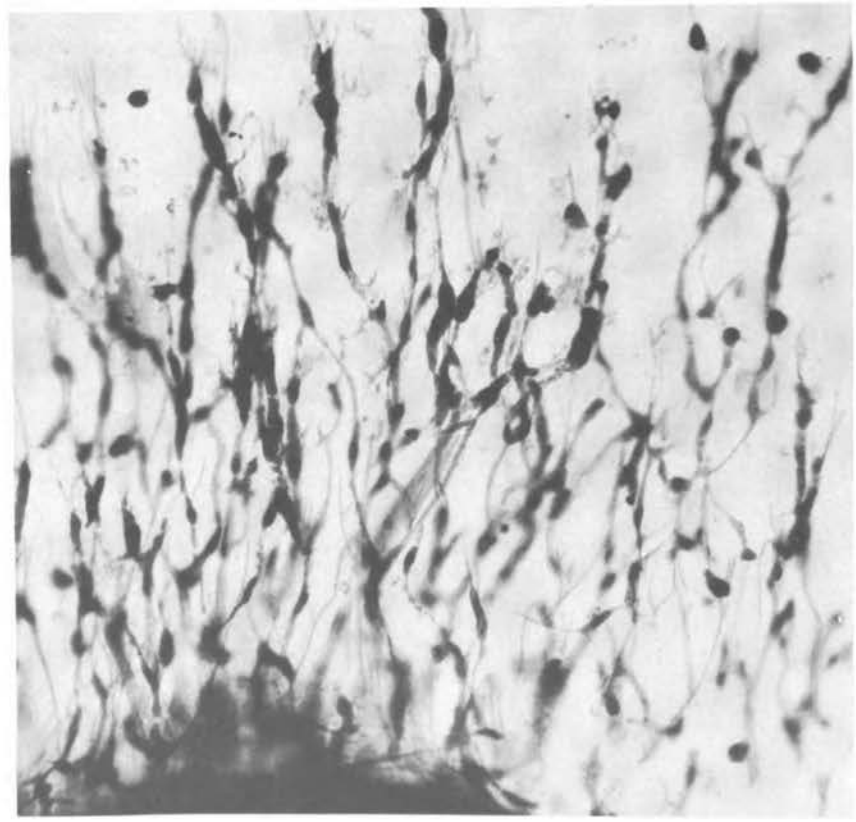


Figure 14. Explant of neurilemoma in vitro. Sinuously twisted sprouts of Schwann cells characterizing outgrowth from Antoni type B area (x 375). (Preparation by Dr. M. R. Murray.) A. F. I. P. Neg. Ac. No. 218564–8.

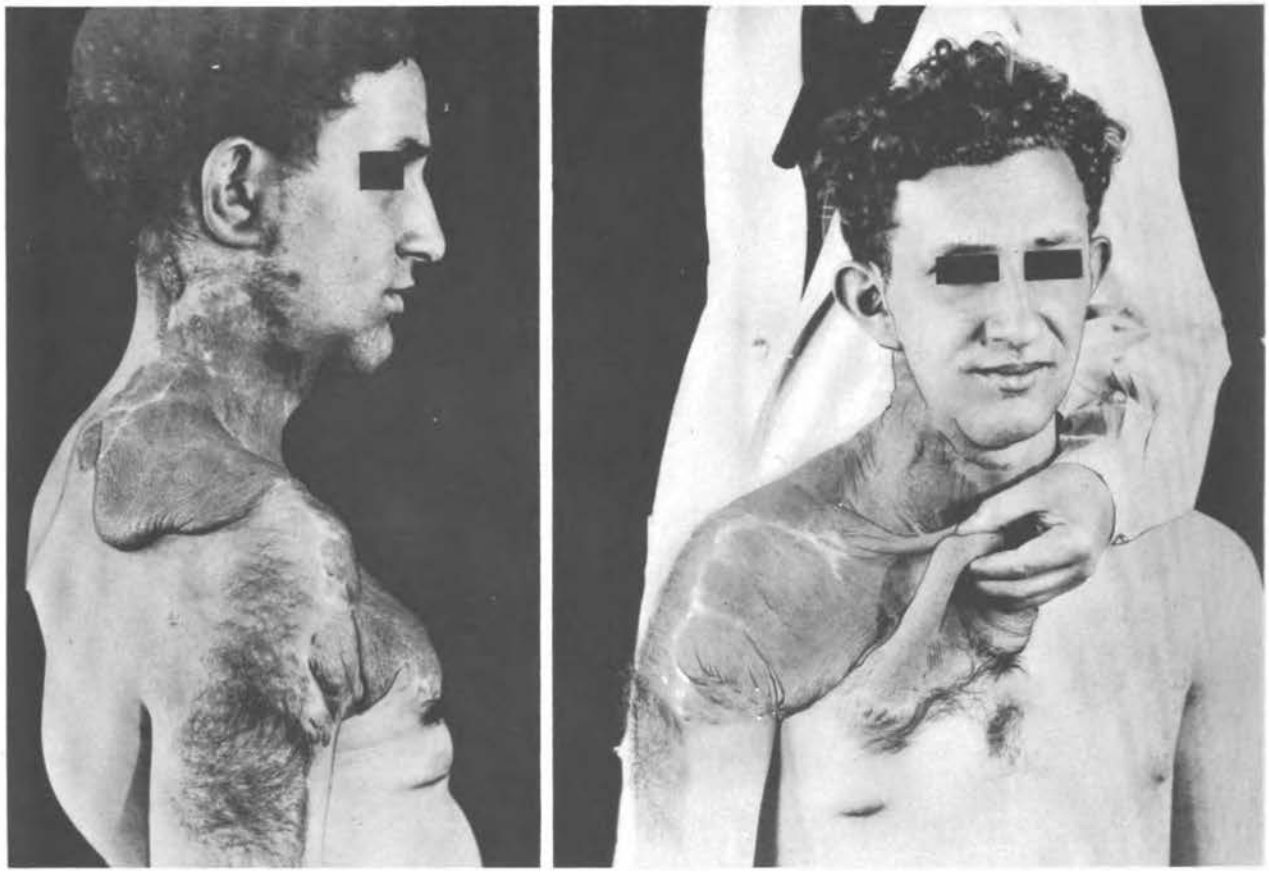


Figure 15. Von Recklinghausen's disease in a19-year-old boy showing right sided elephantiasis neuromatosa of neck, shoulder and chest and right sided hirsutism of chest and arm. A. F. I. P. Neg. Ac. No. 218564–43.

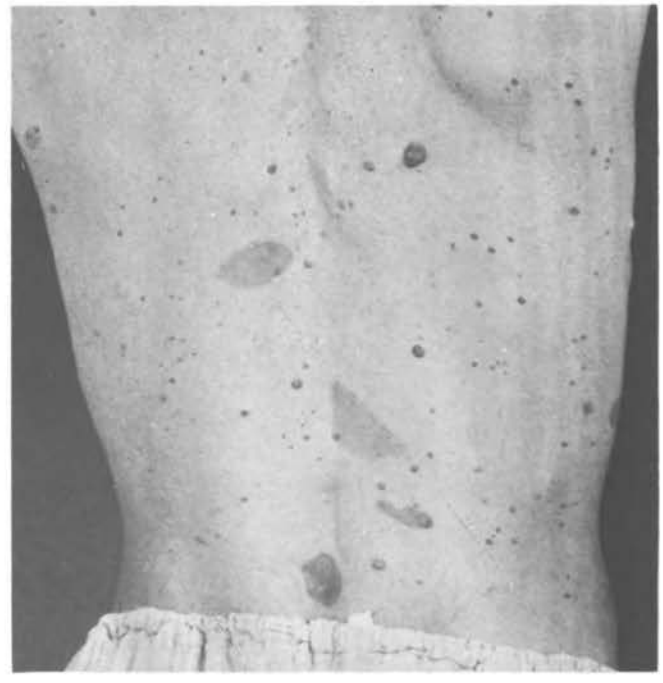


Figure 16. Von Recklinghausen's disease with café-au-lait spots and pigmented neurofibromas of the back. A. F. I. P. Neg. Ac. No. 218564-46.

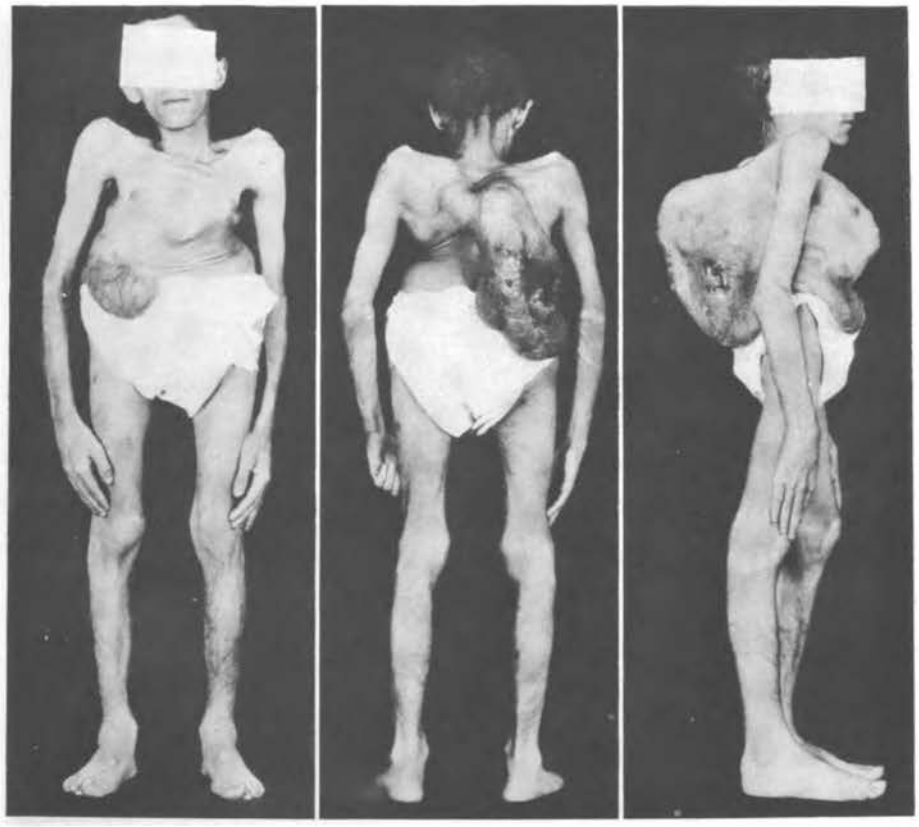


Figure 17. Von Recklinghausen's disease with marked destruction of the vertebrae producing hairpin kyphos, and elephantiasis neuromatosa of back, side, and abdomen. A. F. I. P. Neg. Ac. No. 218564–36.

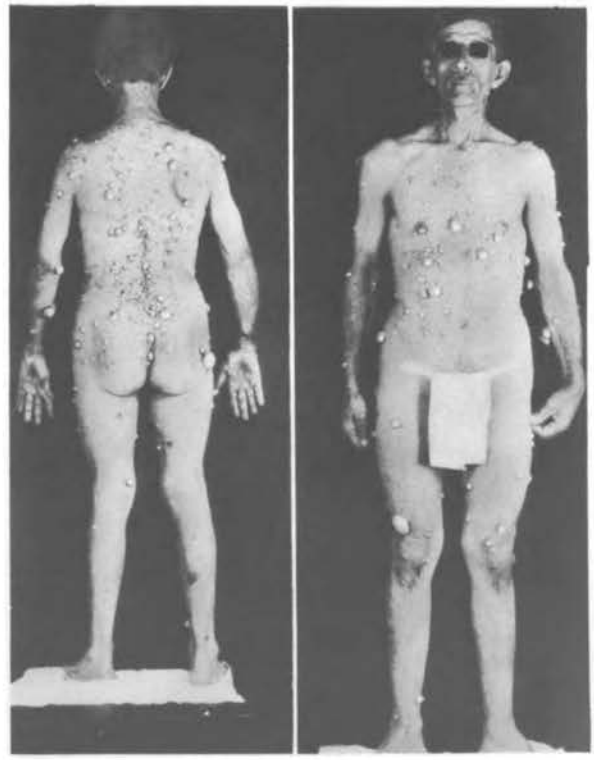


Figure 18. Von Recklinghausen's disease with extensive fibromata mollusca. A. F. I. P. Neg. Ac. No. 218564–28.

Figure 19. Von Recklinghausen's disease. Neurofibroma of the left orbit displacing the globe downward and destroying part of the bony roof of the orbit. A. F. I. P. Neg. Ac. No. 218564–27.

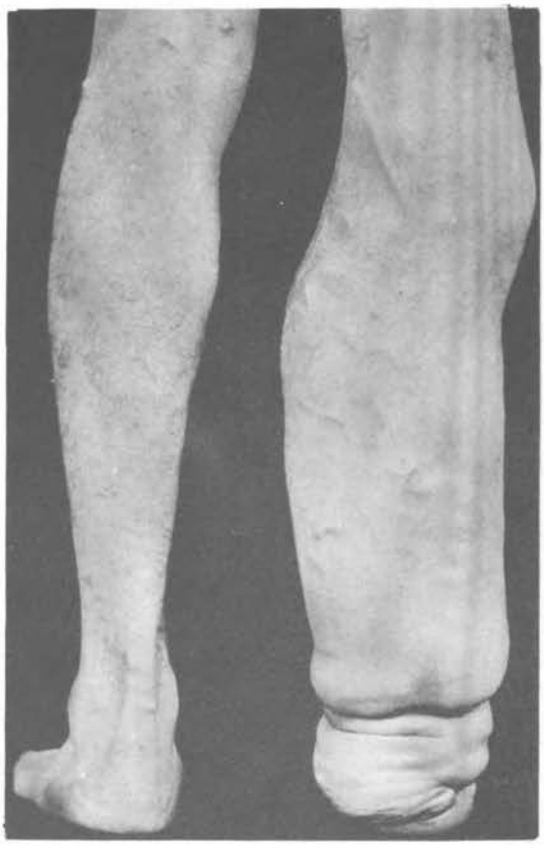


Figure 20. Same case as figure 19. Elephantiac hypertrophy causing marked thickening of the leg and foot with thickening and lengthening of the tibia. A. F. I. P. Neg. Ac. No. 218564–37.

Figure 21. Elephantiasis neuromatosa showing the tremendous thickening of the skin due to Schwann cell proliferation both within and outside of the nerves. A. F. I. P. Neg. Ac. No. 218564–39.

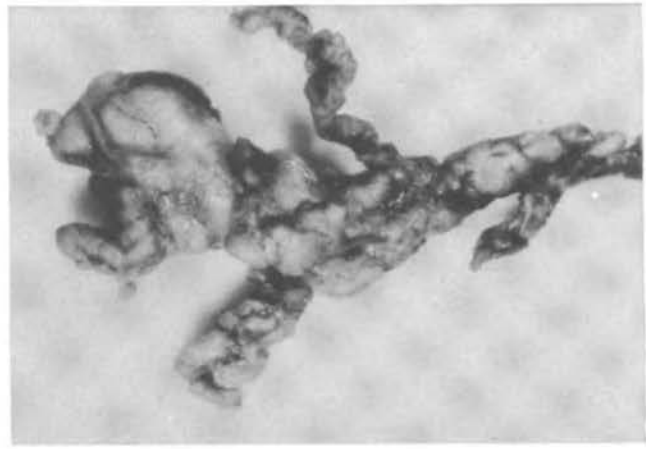


Figure 22. Plexiform neurofibroma from a case of von Recklinghausen's disease. A. F. I. P. Neg. Ac. No. 218564–19.

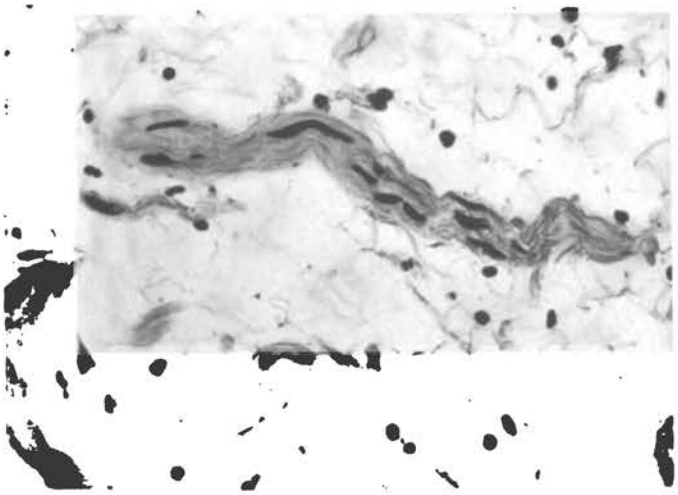


Figure 23. Neurofibroma. The basic unit is a thickening of the Schwann cells forming the sheath of a single nerve fiber with marked edema of the tissues between fibers. A. F. I. P. Neg. Ac. No. 218564–40.

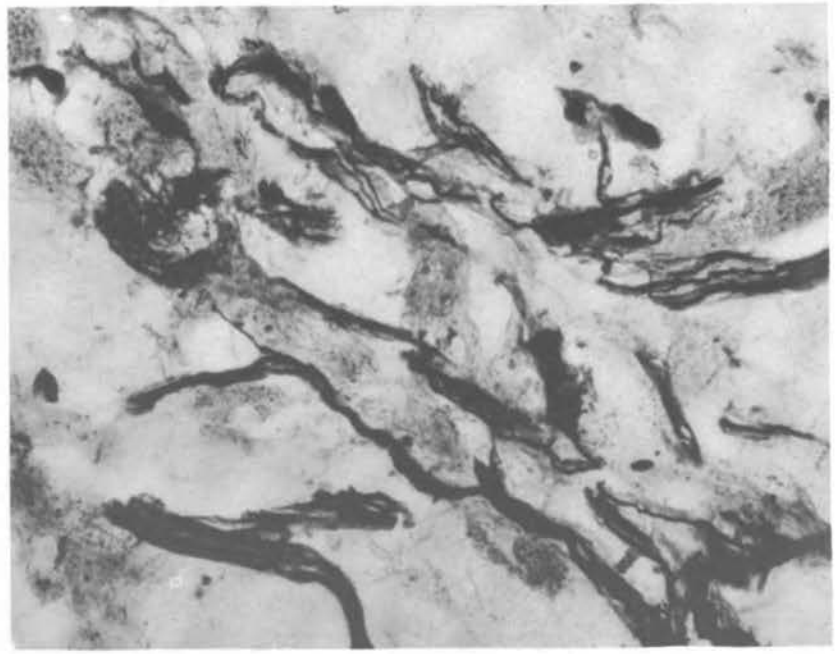


Figure 24. Neurofibroma. Cajal silver impregnation of the neurites within the thickened sheaths. A. F. I. P. Neg. Ac. No. 218564–26.

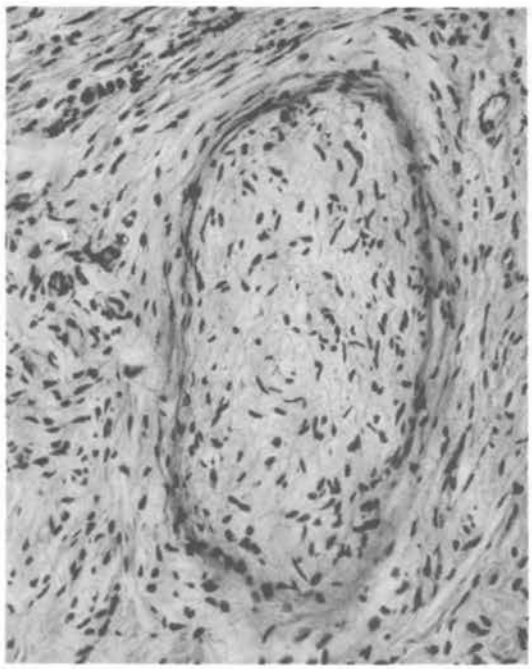


Figure 25. Neurofibroma in the skin showing the thickening of a nerve twig inside of its sheath due to edema and Schwann cell proliferation and the proliferation of Schwann cells in the corium outside the nerve sheath. A. F. I. P. Neg. Ac. No. 218564–52.

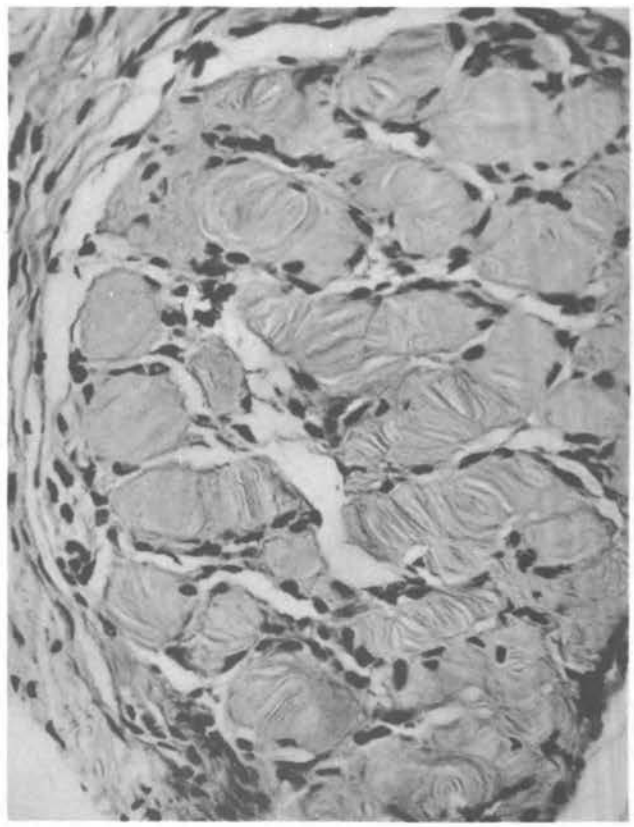


Figure 26. Neurofibroma. Caricatures of Wagner-Meissner tactile corpuscles formed within a nerve in an area of elephantiasis neuromatosa. A. F. I. P. Neg. Ac. No. 218564–25.

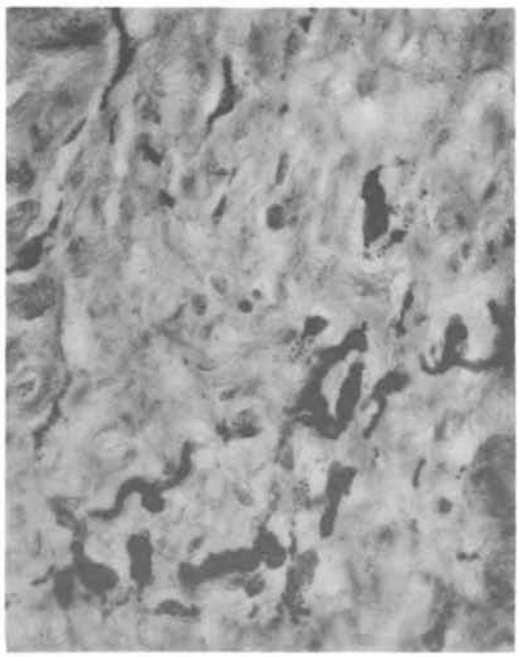


Figure 27. Neurofibroma. Fontana silver stain showing the presence of melanoblasts in a neurofibroma deep in the corium. A. F. I. P. Neg. Ac. No. 218564–24.

neuromatosis; plexiform neuroma; von Recklinghausen's disease.

The neurofibroma is characterized by diffuse proliferation of the peripheral nerve elements in contradistinction to the neurilemoma which is the encapsulated tumor. While it may occur as a solitary and localized phenomenon, it is much more common to observe it as part of the complex affection known as multiple neurofibromatosis or von Recklinghausen's disease. This is one variety of misdevelopment of the entire nervous system or any of its component parts, with a strong hereditary background. It can manifest itself by producing a wide variety of lesions, the most spectacular of which concern the peripheral nervous system. These are of two varieties: (1) those lesions which are due to a proliferation of sheath cells and nerve fibers producing the various forms of neurofibroma; and (2) secondary or associated lesions induced directly or indirectly by the neurofibromatous proliferations or observed merely to occur in patients suffering from the disease.

The neurofibroma grows in a number of different ways. A common one is at the end of a nerve, especially in the skin. This can produce isolated small non-encapsulated nodules with pigmentation in the overlying epidermis (fig. 16). It may also occur diffusely, causing a tremendous degree of thickening called elephantiasis neuromatosa (figs. 15, 17, 20, and 21), so that the thickened, loose, heavily pigmented skin may hang in folds. Elephantiac hypertrophy also occurs in bones (fig. 19), in the appendix, and other portions of the intestinal tract. The proliferations frequently occur inside of nerve sheaths which thereby become greatly thickened and extremely tortuous. The term plexiform neurofibroma is usually applied to such nerves (fig. 22). Plexiform neurofibromas may occur alone or as components of elephantiasis neuromatosa. A plexiform neurofibroma may progress continuously up a nerve or group of nerves toward the spinal roots until finally the spinal cord itself is involved (hour glass tumor), resulting in death. No metastases occur. Histologically, the plexiform neurofibroma maintains the general pattern of the neurofibroma, but the Schwann cells become hyperchromatic, with bizarre forms.

Neurofibromas can affect bones in two different ways. They may develop inside the bone producing extensive destruction and leading to marked deformity (fig. 17), or they may induce an elephantiac hypertrophy of a bone which thereby becomes thickened and lengthened (fig. 20). A relaxation of spinal ligaments resulting in scoliosis is also observed.

The commonest associated stigma of von Recklinghausen's disease is the café-au-lait spot of pigmentation (fig. 16). As the name implies, the spot has the color of coffee diluted with milk. The spots vary greatly in relative size and are always irregularly shaped with finely jagged borders. The pigment is melanin. It is found in the deeper layers of the epidermis and sometimes in phagocytes in the papillary layers. Pigmented moles are quite frequent. Less common is the fibroma mollusum (fig. 18), a simple proliferation of fibrous tissue in the superficial layers of the corium forming a projecting and sometimes pedunculatod growth. A few such fibromas are often formed without evidence of von Recklinghausen's disease. Growths sometimes associated with this disease are lipomas, sebaceous adenomas, an excessive growth of hair, melano-

blasts (fig. 27), adult sympathetic ganglion cells, and immature striated muscle cells. In the deeper portion of some pigmented moles neurofibromatous proliferations can sometimes be detected.

HISTOLOGICALLY, the neurofibroma consists essentially of a proliferation of Schwannian cells often accompanied by neurites in a diffuse and haphazard fashion (figs. 23 and 24), instead of in the more orderly arrangement shown in the traumatic neuroma (figs. 2, 3, and 4). This may occur inside of the perineurium or outside of it, or both may occur in the same lesion (fig. 25). The neurofibroma does not form the twisted Verocay bodies of the neurilemoma but sometimes it forms very exact replicas of the Wagner-Meissner tactile corpuscle both inside (fig. 26) and outside the perineurial sheath.

The lesions of von Recklinghausen's disease generally appear first in childhood or adolescence and may cease when full maturity is attained. On the other hand, growth may recommence at any time during life and progress in an alarming and sometimes fatal fashion. It may do this in either one of two different ways: by the centripetal growth of a plexiform neurofibroma; or by the development of a malignant and metastasizing Schwannoma.

MALIGNANT

Malignant Schwannoma. Synonyms and Related Terms: Schwannoma malignum (Lat.); fibromyxosarcoma of nerve; fibrosarcoma myxomatodes; fibrosarcoma of nerve sheath (Schwannosarcoma); malignant neurilemoma; malignant neurioma; malignant peripheral glioma; myxosarcoma of nerve sheath; neurilemosarcoma; neurofibrosarcoma; neurogenic or neurogenous sarcoma; sarcoma of peripheral nerve; secondary malignant neuroma.

This is a malignant tumor of peripheral nerves derived from Schwann cells. It is not associated with benign neurilemoma but may be associated with neurofibromatosis. About half of the malignant Schwannomas arise in individuals with von Recklinghausen's disease. Hosoi estimates that 13 percent of the cases of von Recklinghausen's disease develop malignant tumors. This figure is probably much too high since it applies only to reported cases. Many mild cases of multiple neurofibromatosis are unrecorded and indeed unrecognized.

The malignant Schwannoma may occur at any age but is more common in the later years of life. It rarely causes local symptoms other than those due to its mass. Occasionally, when a large nerve is involved, there are symptoms of pain and paresthesia due to pressure upon the nerve or to interruption of its fibers. It infiltrates insidiously, metastasizes freely through the blood stream but rarely through lymphatics, and is frequently fatal.

GROSSLY, it may produce a fusiform enlargement of a recognized nerve trunk or it may develop from tiny unrecognized nerve twigs. In this case, the tumor has no specific gross characteristics (figs. 28 and 29).

In vivo and in vitro, like Schwann cells, the cells of malignant neurilemoma grow in cords with the nuclei in tandem formation and tending to palisade. The delicate intercellular connective tissue (reticulum) fibers are like long straight wires parallel to the long axis of the cells (figs. 30, 31 and 32. Malignant Schwannomas do not always retain clearly defined histological characteristics, espe-

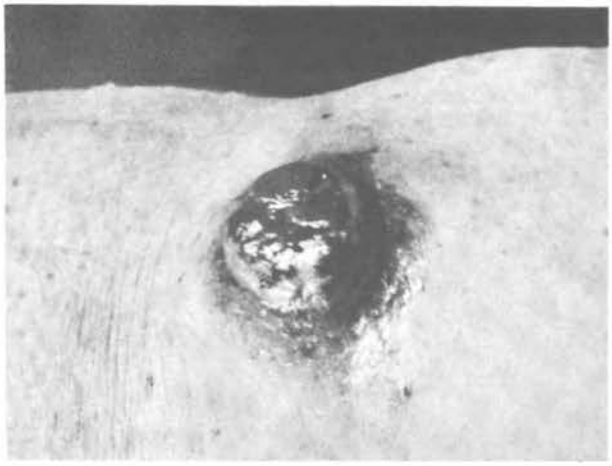


Figure 28. Ulcerated malignant Schwannoma of the loin which recurred locally and metastasized to the lungs. A. F. I. P. Neg. Ac. No. 218564–33.

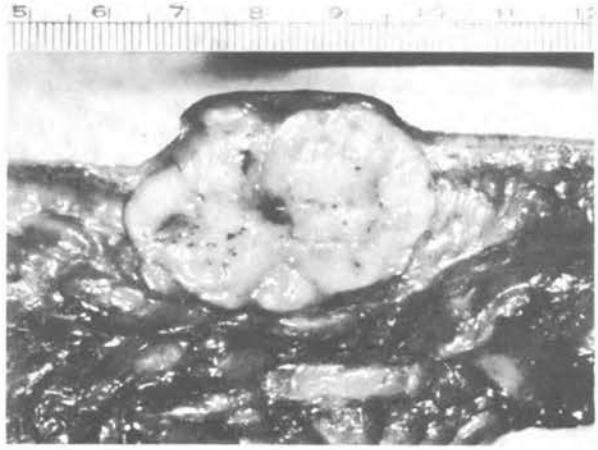


Figure 29. Cut surface of figure 28 shows wide excision of the circumscribed fine textured tumor. Figures 30, 31, and 32 are from the same case. A. F. I. P. Neg. Ac. No. 218564–51.

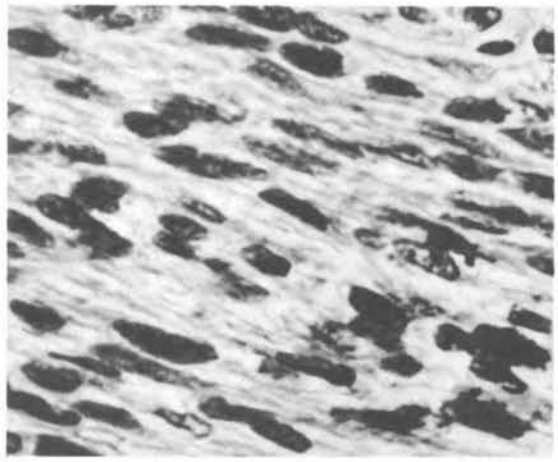


Figure 30. Malignant Schwannoma. The tendency of the elongated cells to grow in cords with palisaded nuclei suggested the diagnosis. When the explanted tumor grew Schwann cells in vitro, the diagnosis was established. (See fig. 32.) A. F. I. P. Neg. Ac. No. 218564–35.

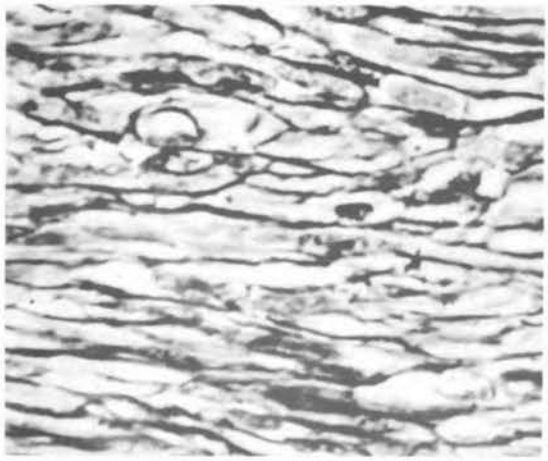


Figure 31. Malignant Schwannoma. Laidlaw silver connective tissue stain showing the straight wire reticulum fibers characteristic of Schwann cell tumors. A. F. I. P. Neg. Ac. No. 218564–29.

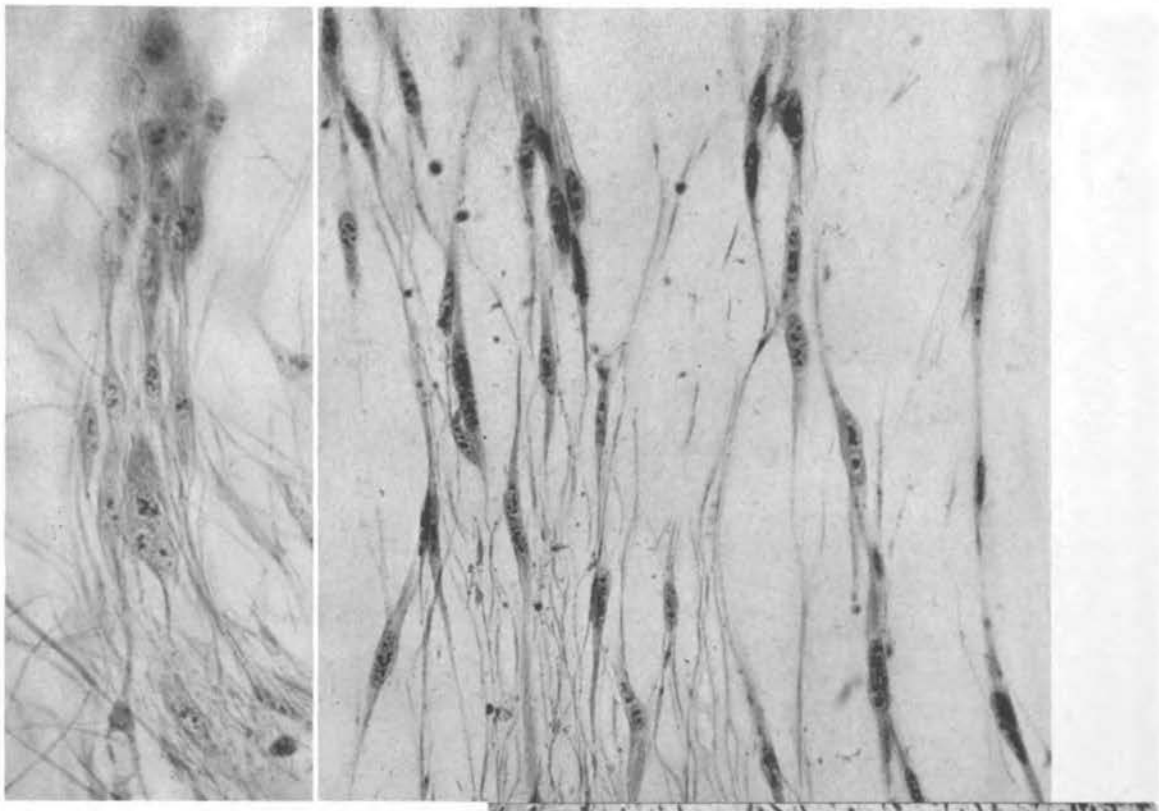


Figure 32. Explant of tissue from tumor illustrated in figures 28, 29, 30, and 31. Outgrowth of cells showing some variation in size and nuclear hyperchromatism but otherwise having the characteristics of Schwann cells (X375). On the left is an outgrowth of a group of cells with close packed parallel arrangement and a tendency toward nuclear palisading (X450). (Preparation by Dr. M. R. Murray.) A. F. I. P. Neg. Ac. No. 218564–9.

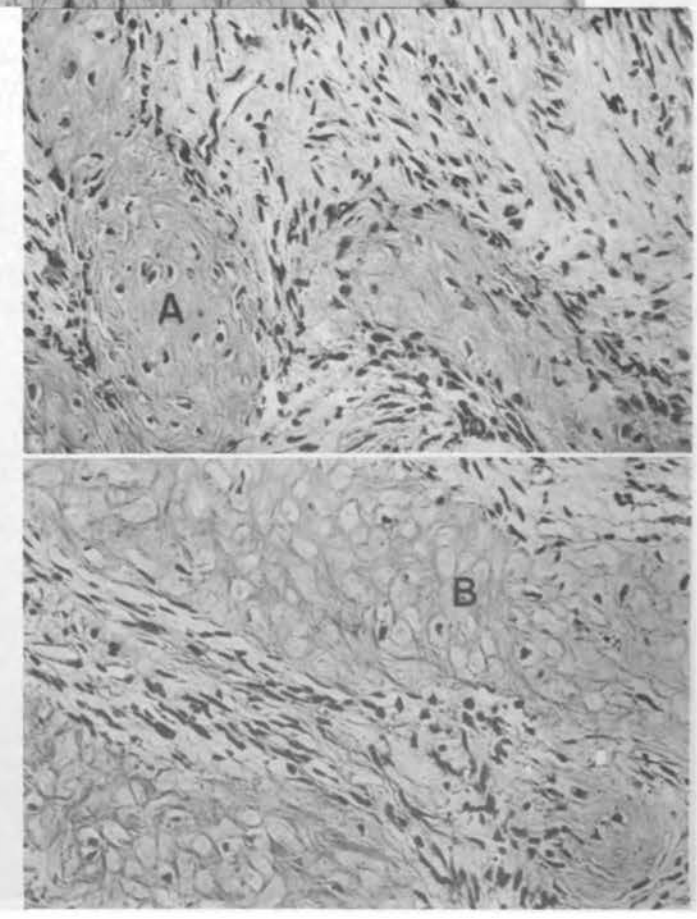


Figure 33. A malignant Schwannoma of the brachial plexus in an 18-year-old girl with invasion of the chest wall and lung resulting in death. A: Osteoid, and B: Cartilage were formed by the Schwann cells in the primary tumor. A. F. I. P. Neg. Ac. No. 218564–7.

cially in the late stages when metastasis has occurred. Yet, it is unsafe to classify a tumor as a malignant Schwannoma unless some identifying features can be recognized, especially in patients whose tumors do not enlarge and violate a recognizable nerve sheath. Just because a nerve is found disappearing into a tumor mass is, in itself, no proof that the tumor arose from that nerve. There are many soft-part sarcomas which by progressive infiltrative growth surround and engulf nerves which they happen to encounter. There is also a tendency on the part of some pathologists erroneously to call benign and malignant smooth muscle tumors Schwannian growths because of the presence of palisaded nuclei. This has led to many mistaken reports of such tumors, especially in the gastrointestinal tract, where, in fact, Schwannian tumors are very rare while smooth muscle tumors are relatively common. It may be that the Schwann cells can produce tumors which cannot be distinguished from malignant fibrosarcomas, or that the mesodermal fibroblasts of the nerve sheath can develop fibrosarcomas, but as yet proof of this is lacking. It is better to call tumors that have only the characteristics of fibrosarcomas by that name and abandon the debatable term "neurogenic sarcoma."

Various metaplastic tissues are occasionally found associated with Schwannian cells in these tumors. Figure 33 illustrates the presence of cartilage and osteoid in a malignant Schwannoma of the brachial plexus. Other tissues reported include rhabdomyoblasts and fat.

GANGLIONIC CELL TYPE

BENIGN

Ganglioneuroma. (See page 25—Neoplasms of Sympathetic Ganglia). Neurofibromas containing ganglion cells have occasionally been reported in von Recklinghausen's disease but this is an exceedingly rare occurrence.

MALIGNANT

Malignant Neuroepithelial Tumors. Synonyms and Related Terms: neuroepithelioma malignum (Lat.); glioblastoma; glioblastoma with metaplasia; malignant glioma; medulloblastoma; medulloepithelioma; neuroepithelioma; neuroepithelioma with rosettes; peripheral ependymoma; peripheral glioblastoma; sympathicoblastoma. These are exceedingly rare. They develop in peripheral nerves and reproduce in their growth the appearance of certain developmental stages of cells of the neural crest which normally are found in the central nervous system and are never seen in the peripheral nerves. For this reason, it has been necessary to turn to the nomenclature in use for corresponding tumors in the central nervous system. While these tumors in the peripheral nervous system histologically resemble their central nervous system congeners, biologically they differ in one very important respect: they are capable of metastasizing generally through the blood stream and are often fatal.

Neuroepithelioma. A malignant tumor of the radial nerve has been described by Stout and Murray and is illustrated in figures 34, 35, and 38. It was composed of completely undifferentiated neuroepithelial cells which, when

explanted in vitro, showed an epithelial habit of growth without any neurite formation. This is, of course, quite different from the undifferentiated sympathicoblastoma, the cells of which regularly develop neurites in vitro.

Neuroepithelioma with Rosettes. A malignant tumor of the ulnar nerve reported by Stout consisted of masses of rounded cells in the main undifferentiated but at times forming true rosettes (figs. 36, 37, and 38). Such structures are not known to form during the development of the sympathetic nervous system. Their resemblance to the rosettes of the embryonal central nervous system justified calling this tumor a neuroepithelioma.

Medulloblastoma. A primary malignant tumor of the sciatic nerve was given to the writer by Hawksley, pathologist of the Royal Cancer Hospital, Free, of London. It closely resembles the histological appearance of a sympathicoblastoma with the formation of pseudo-rosettes (fig. 38), but because of its undoubted origin in the sciatic nerve, it seemed more proper to classify it as a medulloblastoma, the central nervous system counterpart of the sympathicoblastoma.

Medulloepithelioma. A small number of recurring tumors of peripheral nerves have been described containing epithelial-like structures resembling the embryonal medullary canal of the cord, embedded in Schwann cells. The tumor illustrated in figure 38 shows one of those structures with a few of the surrounding Schwann cells. It was reported by Lanford and Cohn, and by Cohn. These authors called it an ependymoma. It was also studied by Penfield who called it a neuroepithelioma. Other similar cases have been described by Foraker, Garré, and Hackel. It is a recurring tumor but apparently does not metastasize.

Those who prefer to regard the Schwann cells as peripheral glial cells take exception to these various terms, preferring to designate all of the malignant peripheral nerve tumors with epithelial formations as malignant gliomas or glioblastomas with metaplasia.

Melanoblastic Type. Since Masson and others have suggested a derivation from neurectoderm for pigmented moles and malignant melanomas, they must be mentioned here. They will not be further described because Fascicle 3, "Melanotic Tumors of the Skin," has been devoted to them.

NEOPLASMS COMPOSED OF MULTIPLE TISSUES OF WHICH NERVES FORM PART

BENIGN

Glomus Tumor. This is primarily a vascular tumor, but unlike other vascular tumors it has a definite and rich component nervous element. It is described in the fascicle dealing with "Tumors of the Soft Tissues."

Cutaneous Leiomyoma. This tumor differs from ordinary leiomyomas because it is richly supplied with nerves. It is described in the fascicle dealing with "Tumors of the Soft Tissues."

Mesodermal Tumors. It has already been indicated that the writer doubts whether lipomas, ganglions (cysts of tendon sheaths), xanthomas and fibromas ever arise from the tissues forming the nerve sheath. He is uncertain about fibrosarcomas since he has never seen one to recognize it but acknowledges that

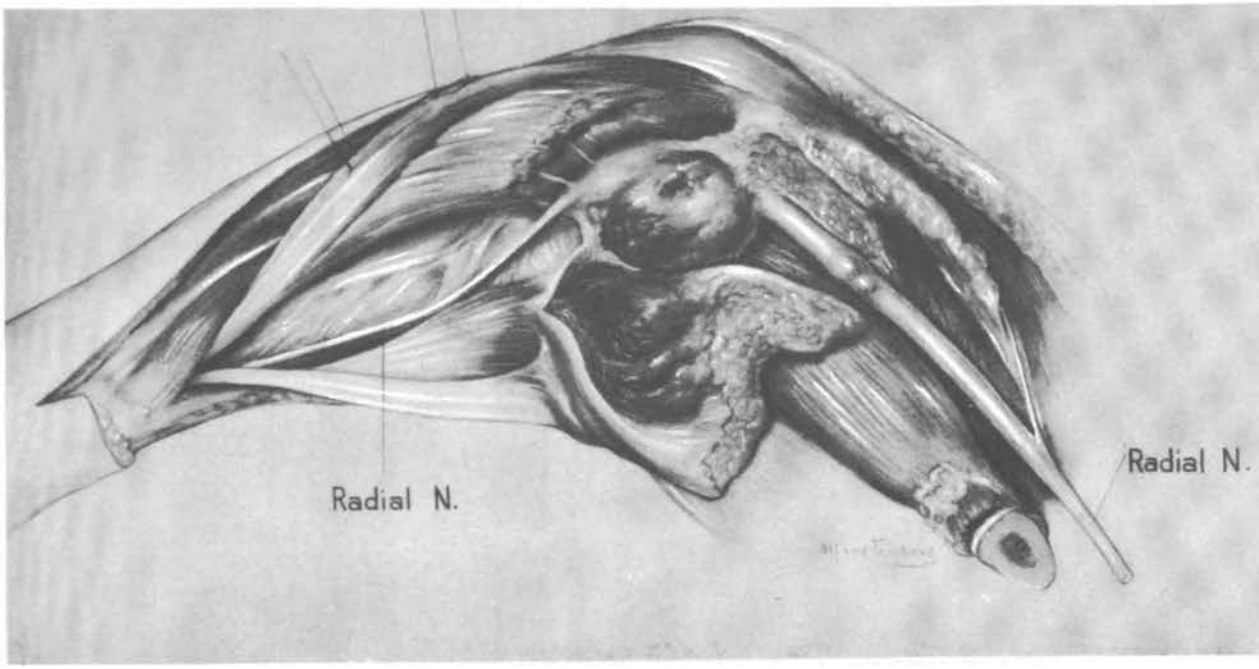


Figure 34. Undifferentiated malignant neuroepithelioma of the radial nerve. The growth has spread widely within the epineural sheath and has emerged to form a palpable mass outside the nerve at the elbow. The 35-year-old patient died of pulmonary metastases. A. F. I. P. Neg. Ac. No. 218564–55.

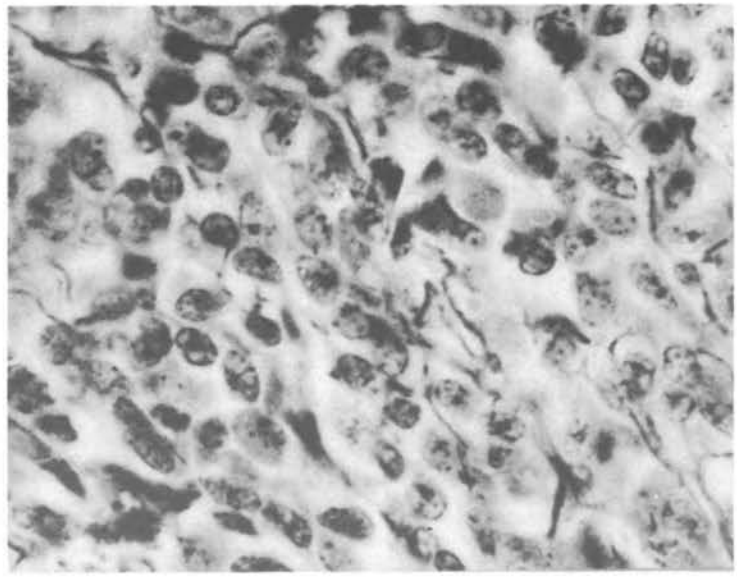


Figure 35. Undifferentiated malignant neuropithelioma of the radial nerve. Laidlaw silver reticulum stain showing the undifferentiated neuroblasts supported by a minimum of reticulum fibers. (See also fig. 38.) A. F. I. P. Neg. Ac. No. 218564–17.

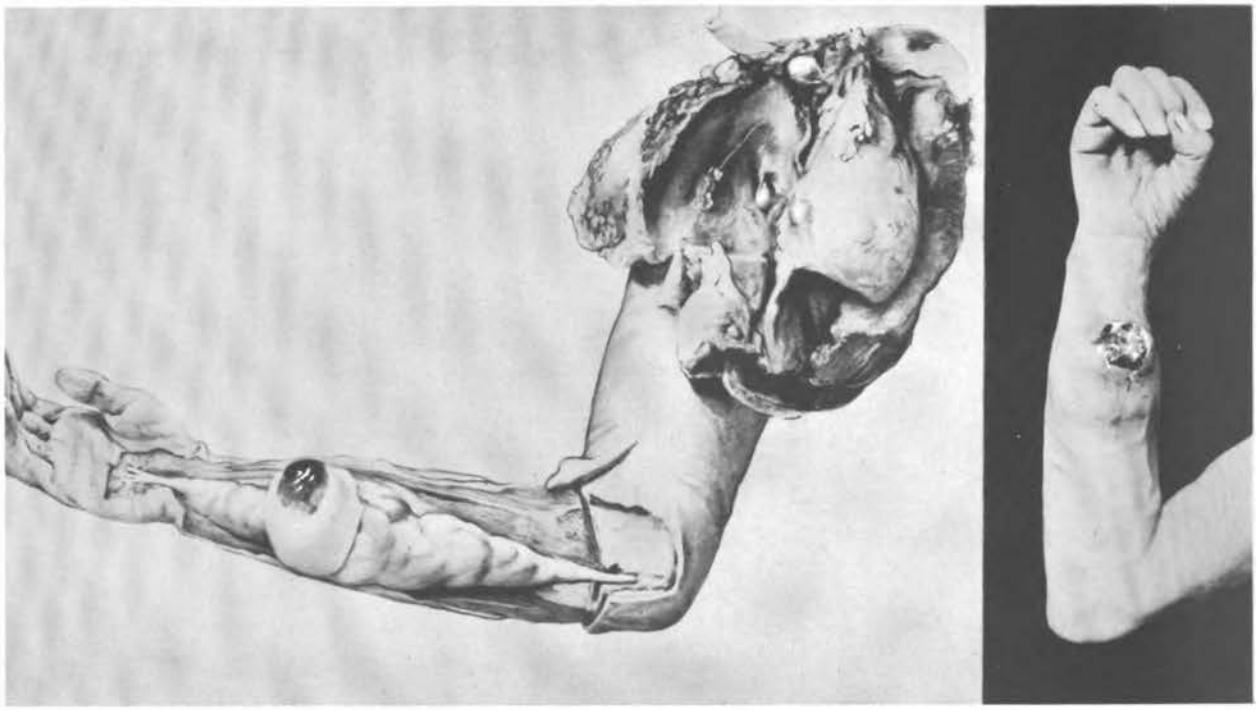


Figure 36. Malignant neuroepithelioma with rosettes of the ulnar nerve in a 42 year old male. The entire length of the ulnar nerve in the forearm has become enlarged by tumor tissue expanding its sheath. Ulceration has occurred at the site of biopsy. Metastases are present in the axillary nodes. Interscapulothoracic amputation was followed by local recurrence in the scar. A. F. I. P. Neg. Ac. No. 218564-44.

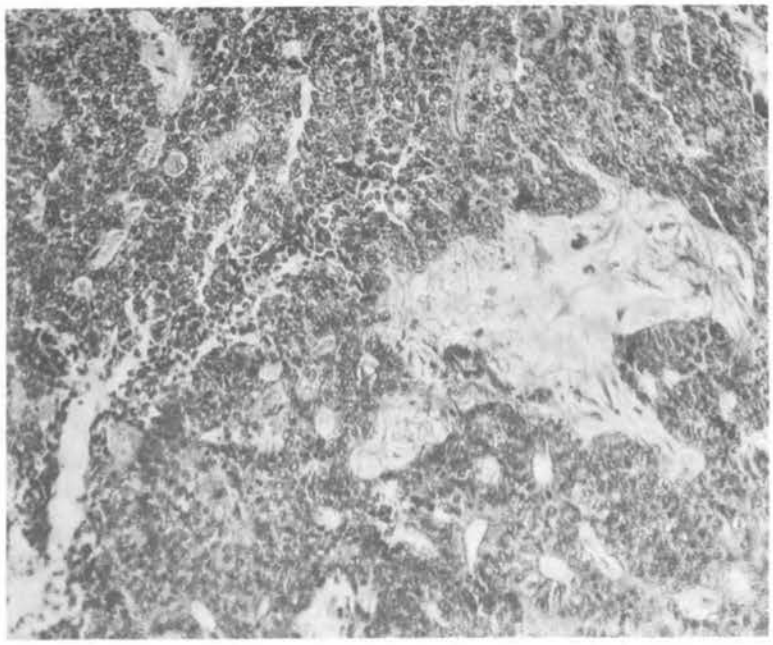


Figure 37. Malignant neuroepithelioma of the ulnar nerve. The rounded tumor cells grow in masses. Some of them assume a cylindrical shape and form rosettes which in this picture appear as small rounded holes. (For higher magnification see fig. 38.) A. F. I. P. Neg. Ac. No. 218564-38.

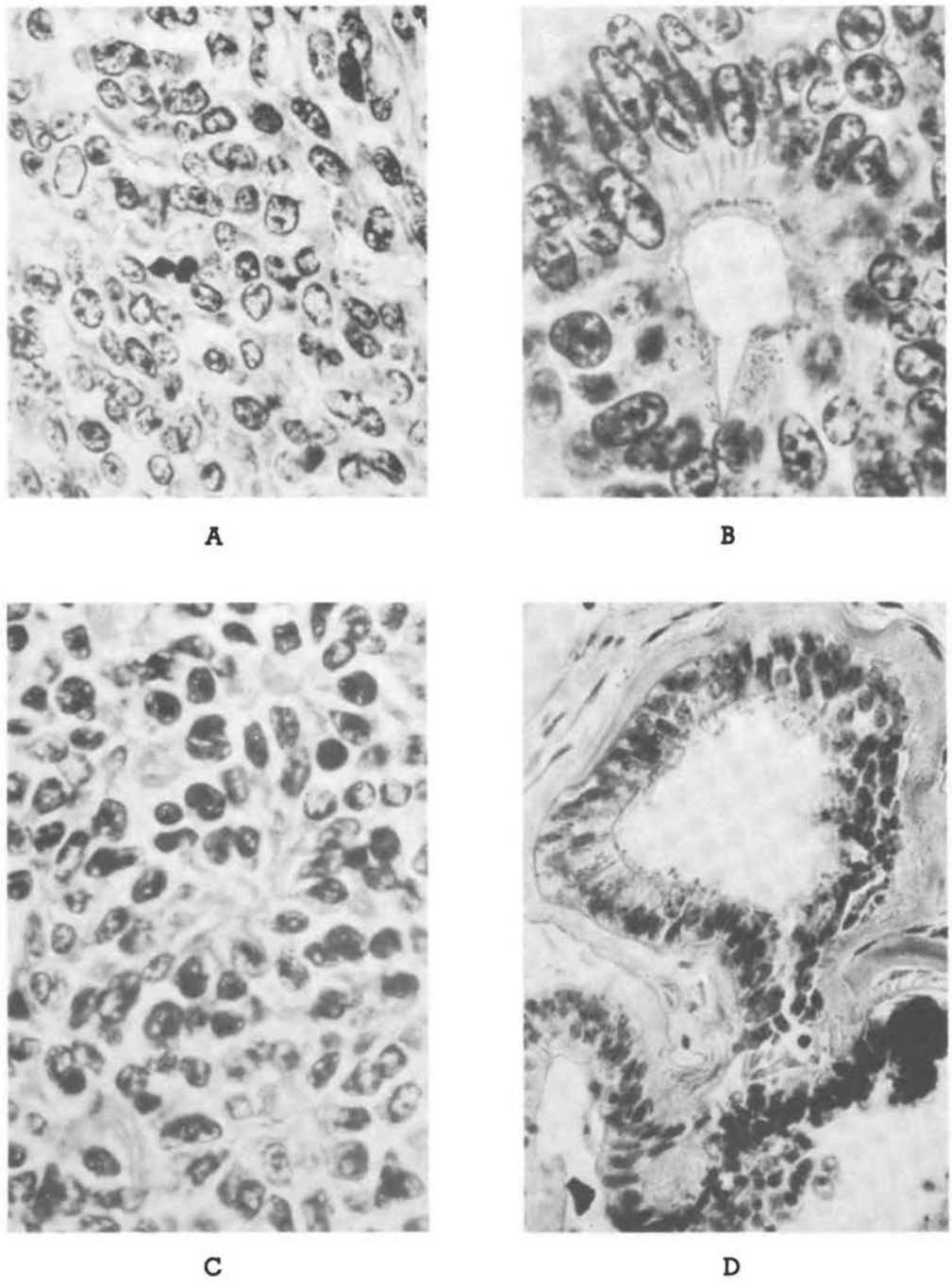


Figure 38. A composite picture showing four different varieties of malignant peripheral nerve tumors featuring structures ordinarily found in the Central Nervous System. A: Undifferentiated neuroepithelioma of radial nerve. B: Neuroepithelioma with rosettes of ulnar nerve. C: Medulloblastoma with pseudorosettes of sciatic nerve. D: Medulloepithelioma of median nerve with structures resembling the embryonal medullary canal. A. F. I. P. Neg. Ac. No. 218564-16.

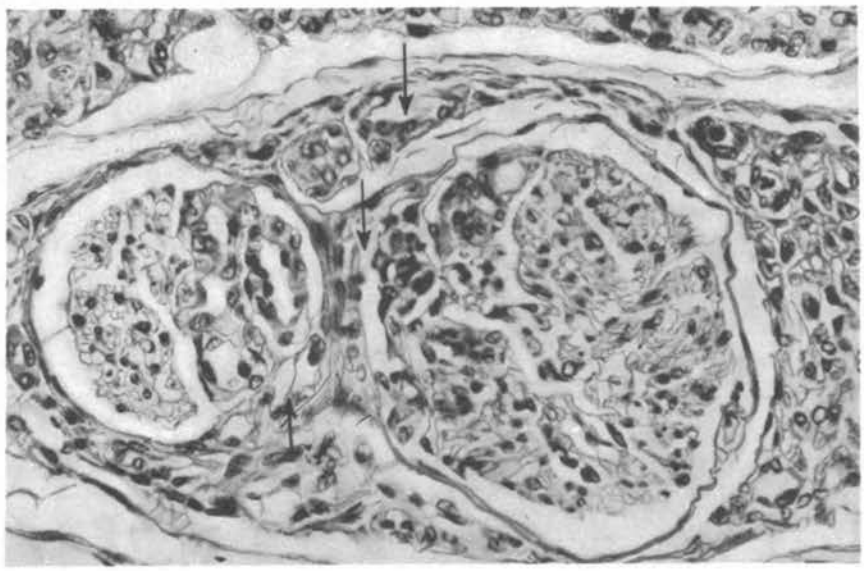


Figure 39. Hemangioma involving a nerve from the scalp of a young child. Capillaries are found both inside and outside of the perineural sheath. A. F. I. P. Neg. Ac. No. 218564–18.

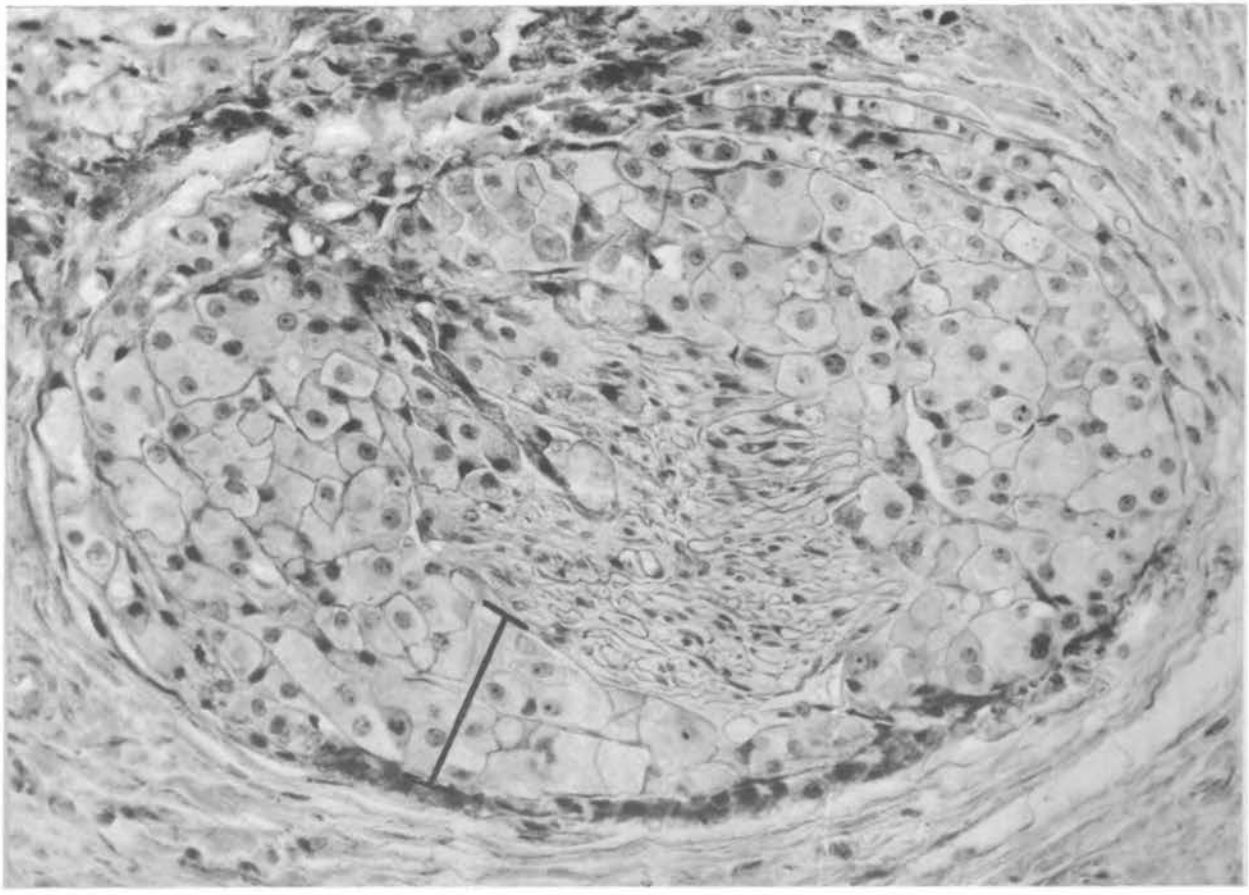


Figure 40. Extension of carcinoma along a nerve inside of the perineural sheath. A. F. I. P. Neg. Ac. No. 218564–42.

it might exist. If so, it would be a better and more accurate term than neurogenic sarcoma.

Vascular Tumors. Hemangioma and Hemangioendothelioma. The presence of a hemangioma in a nerve without any associated hemangioma outside of the sheath is extremely rare. Only one such case has been recorded in the laboratory of Surgical Pathology, Columbia University. More often in cases of locally diffuse hemangiomatosis, capillaries may proliferate both inside and outside of the perineural sheath (fig. 39). This is a benign process and does not harm the nerve. The writer has also seen sections of a large neurilemoma of the sciatic nerve within which a hemangioendothelioma had developed and invaded its capsule.

SECONDARY NEOPLASMS IN PERIPHERAL NERVES

Metastases coming from a distance and lodging in peripheral nerves are so rare as to be curiosities. However, a nerve sheath is not infrequently invaded by tumor cells which may extend diffusely inside of it or extend along its lymphatics. Because these lymphatics have few external connections, they may provide a pathway for easy distant spread (fig. 40). Some nerves, particularly the cranial nerves, harbor ganglia and paraganglionic cells. Tumors characteristic of these structures can therefore develop inside of these nerves as, for instance, a paraganglioma can develop from the ganglion nodosum lodged within the vagus nerve near its point of exit from the skull through the foramen lacerum.

B. NEOPLASMS OF SYMPATHETIC GANGLIA

BENIGN

Differentiated Ganglioneuroma. Synonyms and Related Terms: ganglioneuroma (Lat.); differentiated and undifferentiated; gangliocytoneuroma; ganglioneuroma; ganglioma; ganglion cell tumor; ganglioneuroblastoma; ganglioneuroblastoma sympathicum; ganglioneuroma simplex; ganglionueroma telangiectaticum cysticum; ganglionic neuroma; myelinated neuroma gangliocellulare; neurofibroma ganglionare; neuroganglioma myelinicum verum; neuroma gangliocellulare (Virchow); neuroma gangliocellulare amyelinicum; neuroma gangliocellulare benignum; neuroma verum amyelinicum gangliosum; neuroma verum gangliosum amyelinicum; sympathicocytoma (Rio-Hortega); true neuroma (Virchow); unmyelinated neuroma gangliocellulare.

This is a tumor composed of sympathetic ganglion cells and vast numbers of sheathed nerve fibers. It is relatively uncommon, and is found in both sexes with a slight preponderance in females. Although it may be found at any age, most of the patients are young and 60 percent are below the age of 20 years. The vast majority of these tumors develop in the chain of sympathetic ganglia, extending from the base of the skull to the coccyx and in the adrenal medulla. Sporadic cases have been found in other situations. The most frequent site of involvement is the posterior mediastinum. They are encapsulated and may attain a weight of over 6 kilos. The majority of these tumors are made up of

fully differentiated ganglion cells, often accompanied by their satellites, set in a dense stroma of sheathed neurites running in every direction (figs. 41, 42, and 43.) When explanted in vitro the ganglion cells grow readily and reproduce themselves by mitoses (fig. 44). While this differentiated variety is always localized and does not metastasize, its situation may make it impossible to eradicate by surgery. This is especially true if the tumor extends through an intervetebral foramen to ramify extradurally within the spinal canal, compressing the cord and producing paraplegia.

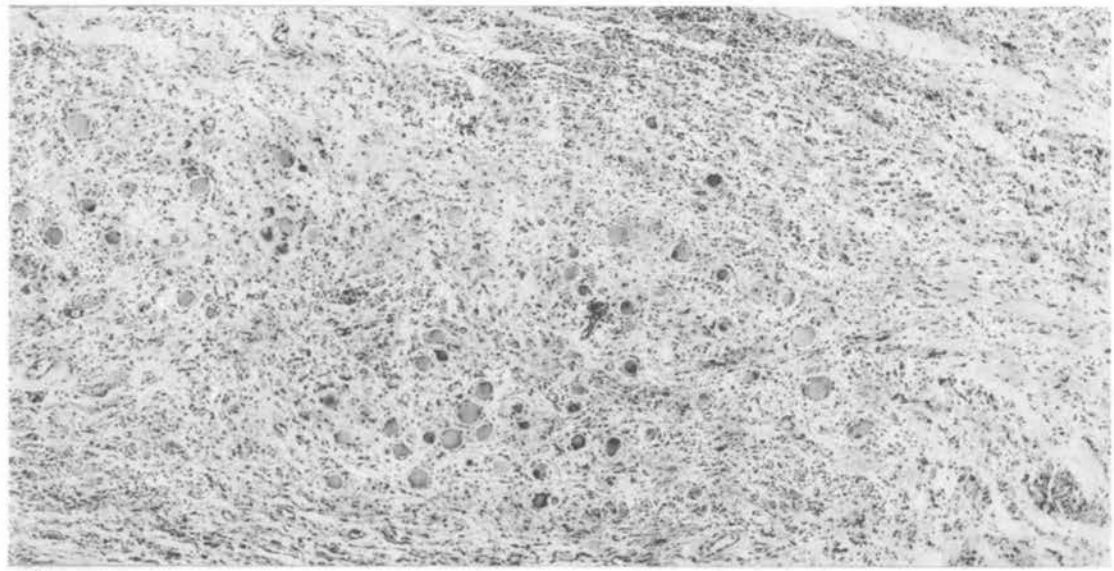
MALIGNANT

Partly Differentiated Ganglioneuroma. Synonyms and Related Terms: gangliocytoma; ganglioneuroblastoma; ganglioneuroma immaturum; immature ganglioneuroma; malignant ganglioneuroma; metastasizing ganglioneuroma; neuroma gangliocellulare malignum; sympathetic neuroma; sympathoblastoma.

About one-fourth of the ganglioneuromas are incompletely differentiated. These occur in two different forms. In one, the ganglion cells of the entire tumor show a mixture of cells varying from undifferentiated sympathicoblasts up to fully or incompletely differentiated ganglion cells (figs. 41–B and 42). Eighteen percent of these tumors metastasize. In another variant, one part of a tumor may be a completely differentiated ganglioneuroma while another contiguous portion will be a characteristic sympathicoblastoma. Of this type, 65 percent produce metastases.

Sympathicoblastoma. Synonyms and Related Terms: Sympathicoblastoma (Lat.); atypical, and typical; with pseudorosettes (Río-Hortega); ganglio-sympathicoblastoma; lymphosarcoma (obs.); neuroblastoma; neurocytoma; sympathetic neuroblastoma (N. C. Foot); sympathicogonioma—differentiated and undifferentiated; sympathoblastoma (Standard); sympathogonioma; sympathoma; sympathoma embryonale (Willis.)

This is the characteristic malignant tumor composed of embryonal sympathicoblasts. It has very much the same distribution as the mature benign ganglioneuroma but with a much greater number of primary tumors originating in the adrenal medulla (See "Tumors of the Adrenal Glands," fascicle number 29), and the retroperitoneal ganglia than in the other sympathetic stations, and with an even greater preponderance in infants and young children. The characteristic tumor grows rapidly to a relatively large size and metastasizes freely by all routes, but especially through the blood stream. While some concentrate their metastases in the lymph nodes and the liver which organ may increase rapidly to a large size (Pepper type), other cases seem to specialize in bone metastases, particularly to the cranium, sometimes resulting in orbital tumors which displace the globe (Hutchinson type). A bone metastasis manifesting itself suddenly and without warning may long precede the discovery of the primary focus which can escape attention until autopsy. If undifferentiated, such solitary bone metastases may be mistaken for primary Ewing's tumor of the bone marrow. Ordinary stains will not distinguish surely between the two; this can only be done with certainty either by explantation in vitro when neurites will be rapidly formed if the tumor cells are sympathicoblasts (figs. 48 and 49), or with less certainty by special fixation



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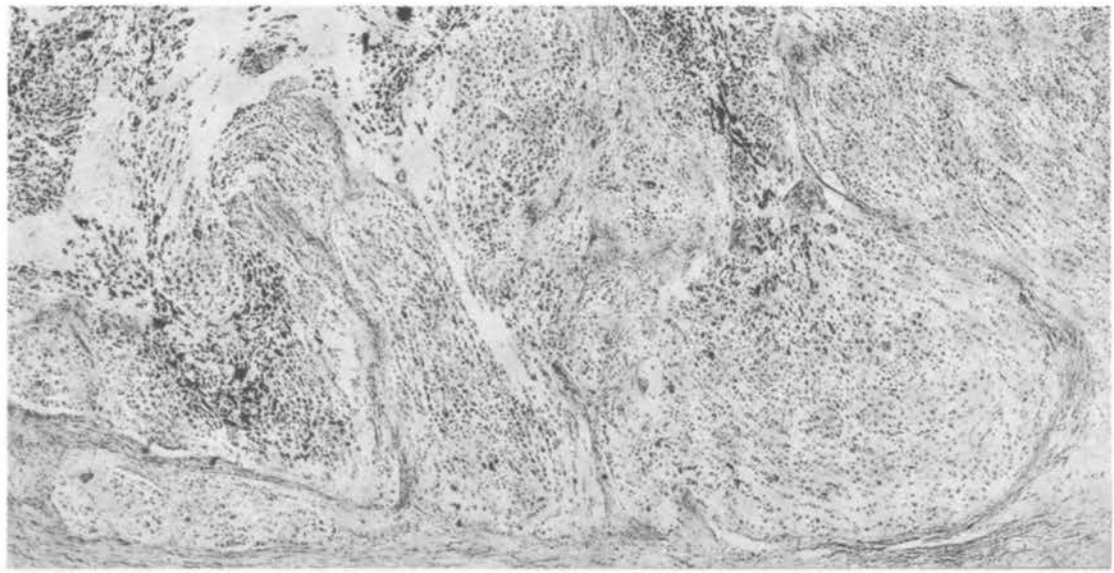

B

Figure 41. Ganglioneuroma. A: The fully differentiated variety with adult sympathetic ganglion cells and neurofibromatous stroma containing many neurites sheathed by Schwann cells. B: The partly differentiated variety composed of incompletely differentiated sympathicoblasts and ganglion cells. A. F. I. P. Neg. Ac. No. 218564–48.

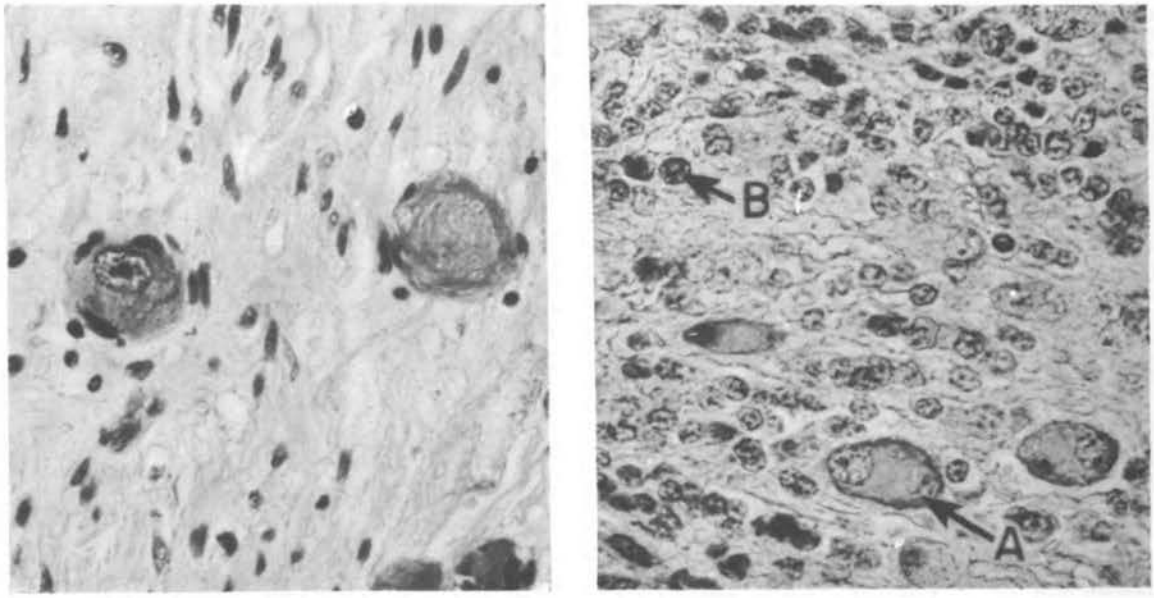

Figure 42. Ganglioneuroma. A: Characteristic area with fully adult ganglion cells sheathed by satellites and with Schwann cells between them. B: (a) Immature ganglion cells, and (b) Sympathicoblasts in a partly differentiated tumor. A. F. I. P. Neg. Ac. No. 218564–45.

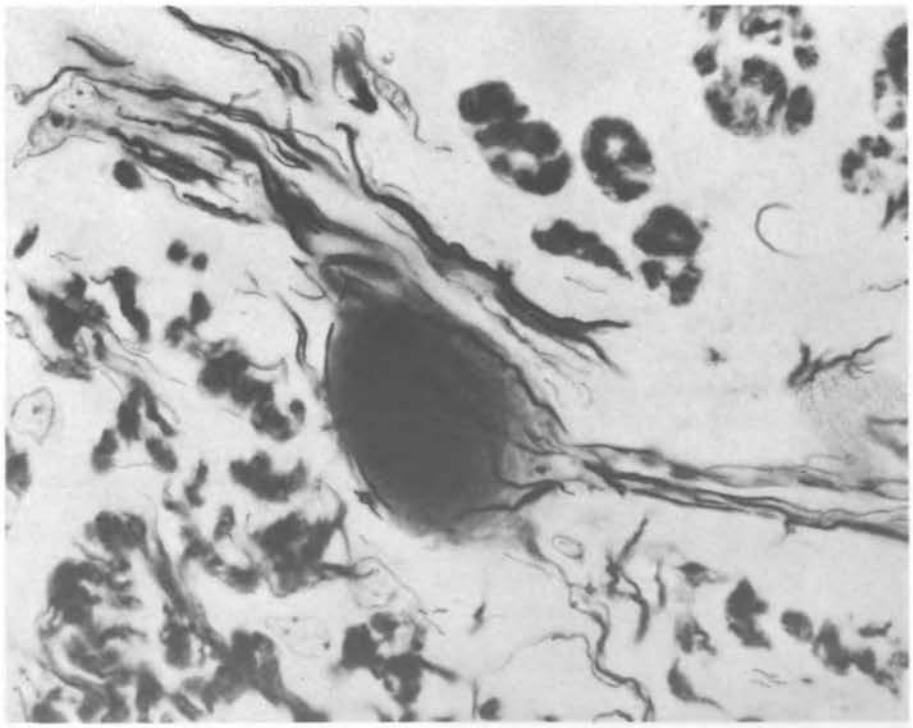

Figure 43. Ganglioneuroma. Cajal silver impregnation showing a multipolar ganglion cell with its nerve fibers. A. F. I. P. Neg. Ac. No. 218564-22.

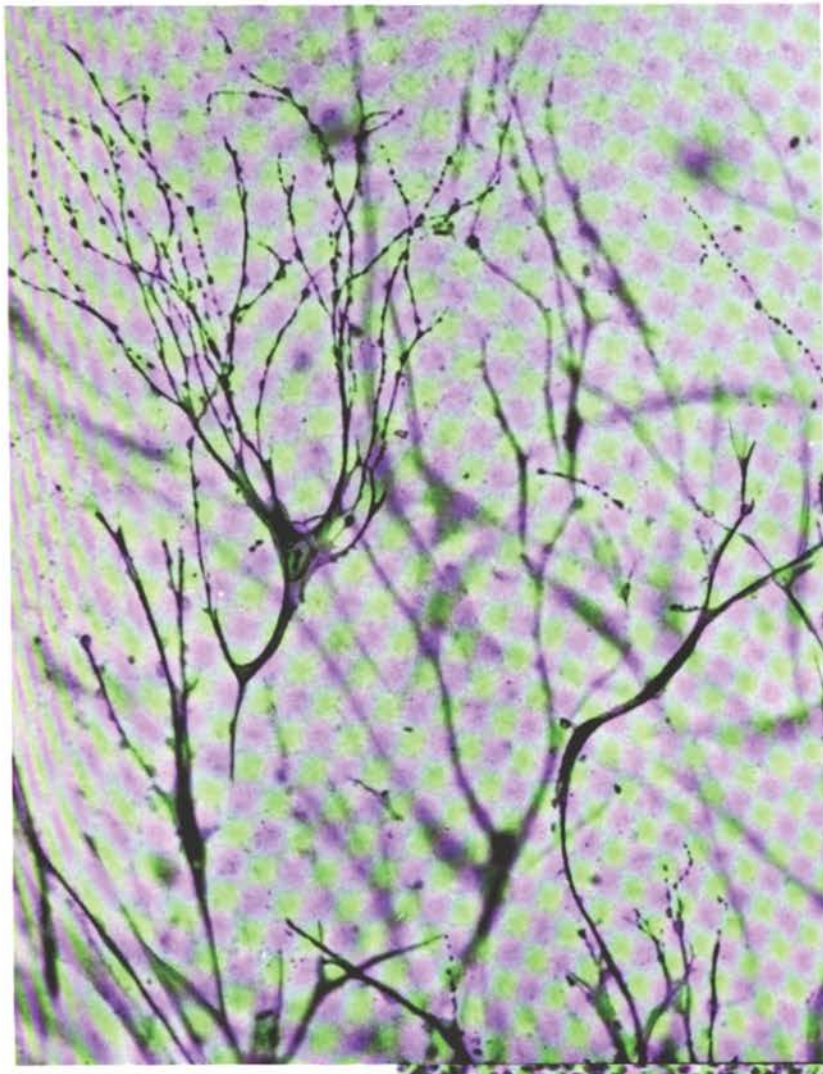

Figure 44. Formation in vitro of an adult sympathetic ganglion cell with many branched dendritic processes from an explanted fragment of a fully differentiated ganglioneuroma (X450). (Preparation By Dr. M. R. Murray.) A. F. I. P. Neg. Ac. No. 218564–6.

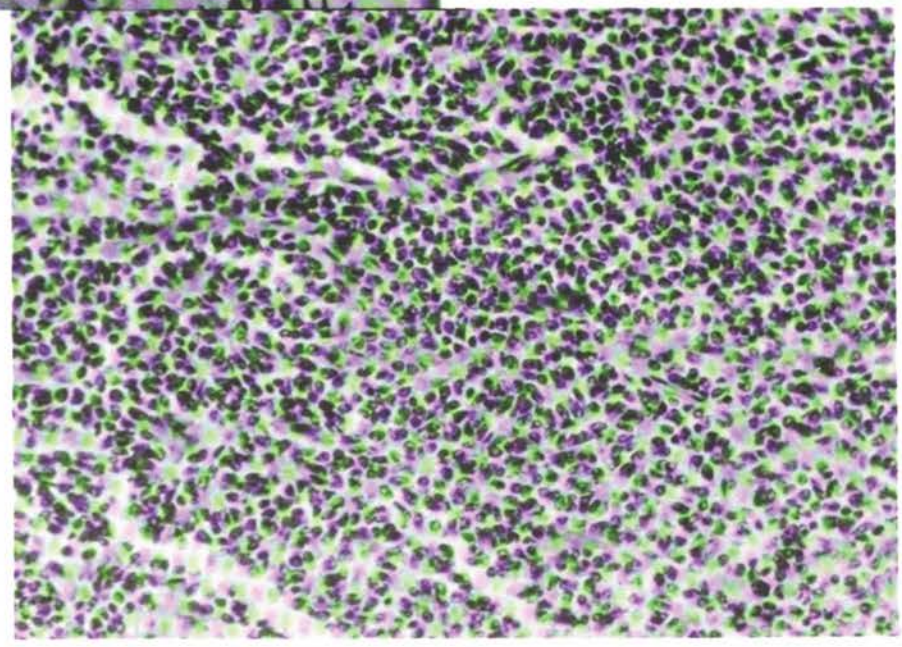

Figure 45. Sympathicoblastoma (Neuroblastoma). Topographical photomicrograph showing the cells grouped without formation in some areas and in pseudorosettes in others. A. F. I. P. Neg. Ac. No. 218564–11.

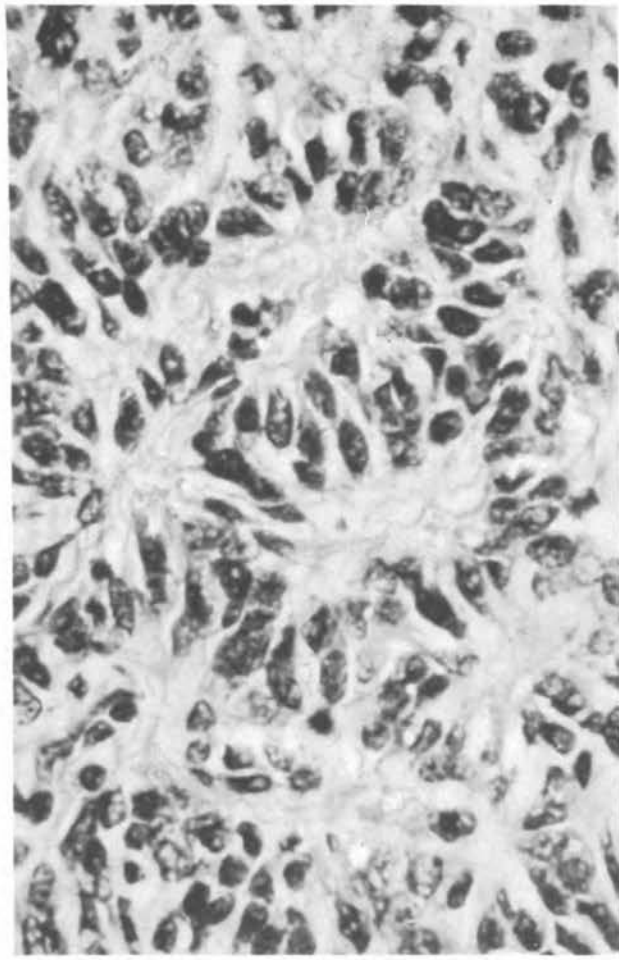

Figure 46. Sympathicoblastoma. Pseudorosette formation. The cells form spheres with the nuclei oriented peripherally and the central zone filled with their cytoplasmic processes. A. F. I. P. Neg. Ac. No. 218564–12.

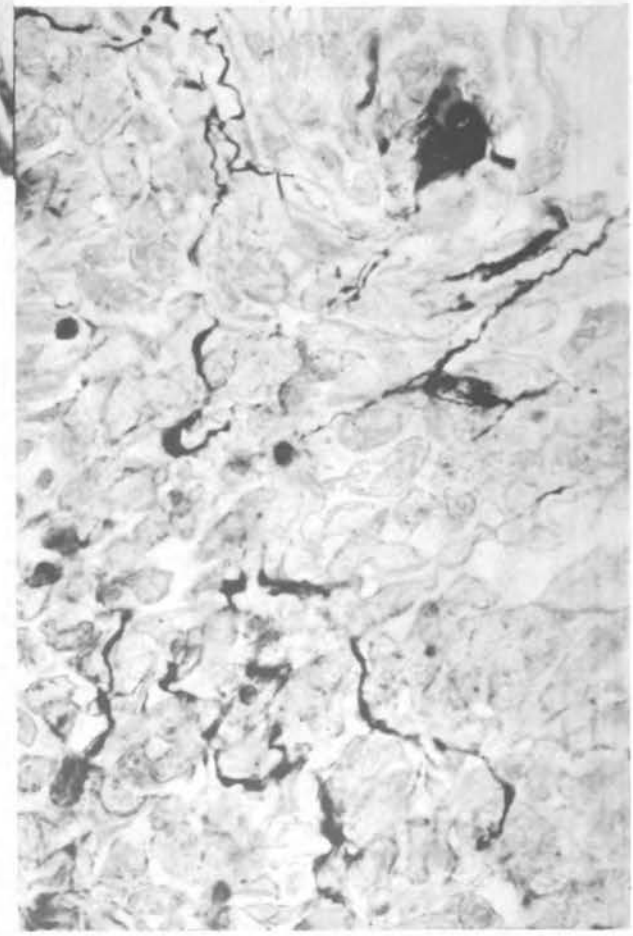

Figure 47. Sympathicoblastoma. Cajal silver impregnation showing the short delicate neurites formed by some of the sympathicoblasts. When explanted in vitro these tumor sympathicoblasts will grow neurites which serve to identify them. (See figs. 48 and 49.) A. F. I. P. Neg. Ac. No. 218564–3.

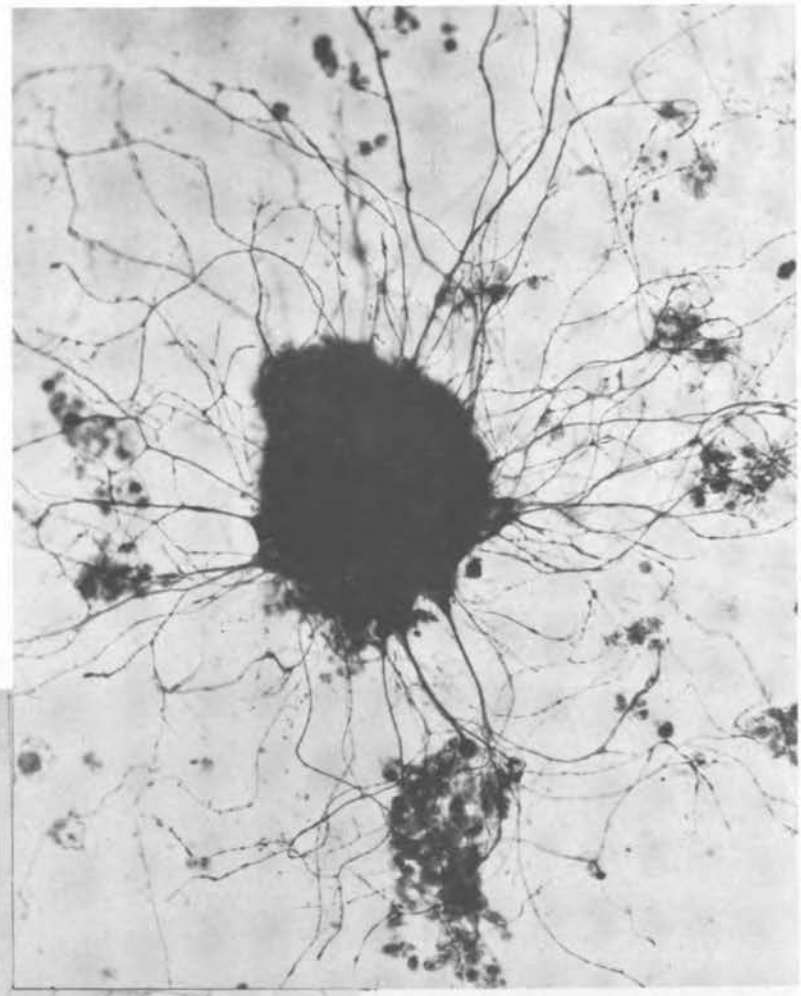

Figure 48. An isolated fragment of explanted cells from a sympathicoblastoma. Many delicate neurites have sprouted from it (x 200). (Preparation by Dr. M. R. Murray.) A. F. I. P. Neg. Ac. No. 218564–13.

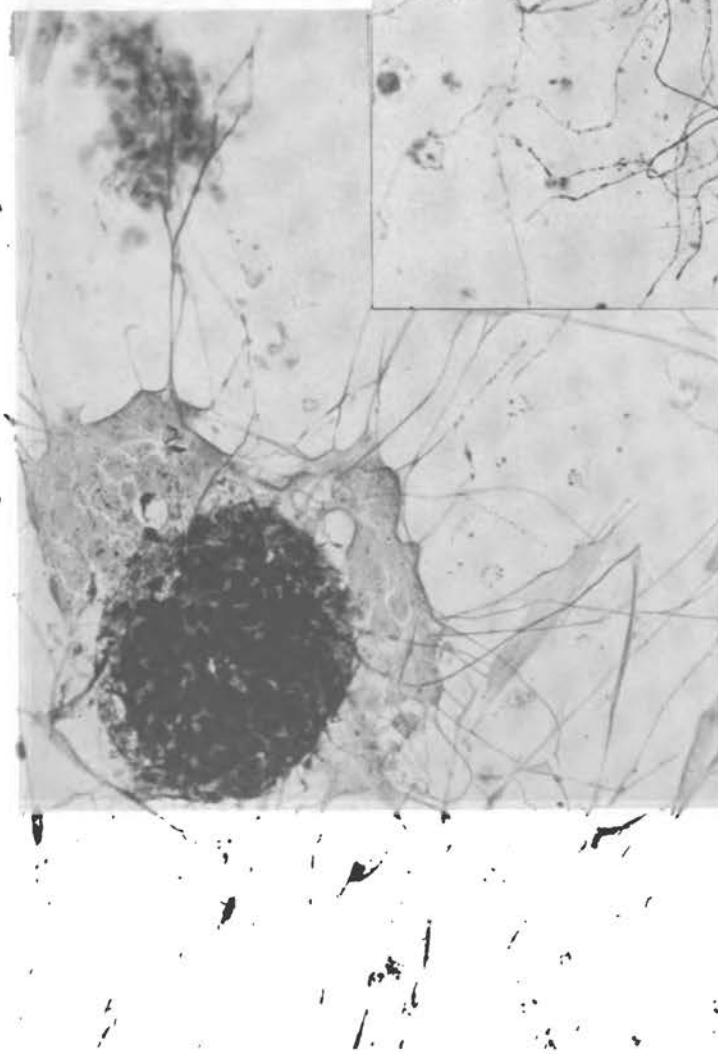

Figure 49. Sympathicoblasts growing as a flat neuroepithelium with sprouting neurites surrounding an isolated ball of necrotic tumor (x 250). (Preparation by Dr. M. R. Murray.) A. F. I. P. Neg. Ac. No. 218564–10.

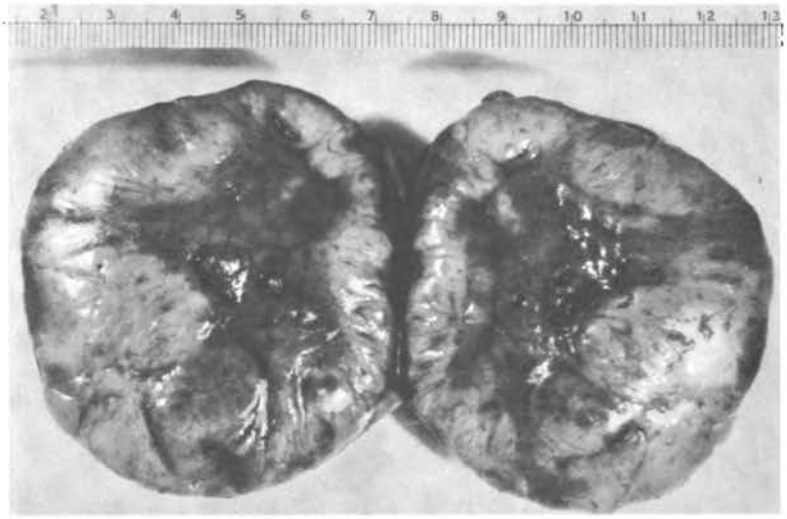

Figure 50. Pheochromocytoma. Bisected. The soft consistency and marked vascularity are characteristic. A. F. I. P. Neg. Ac. No. 218564-31.

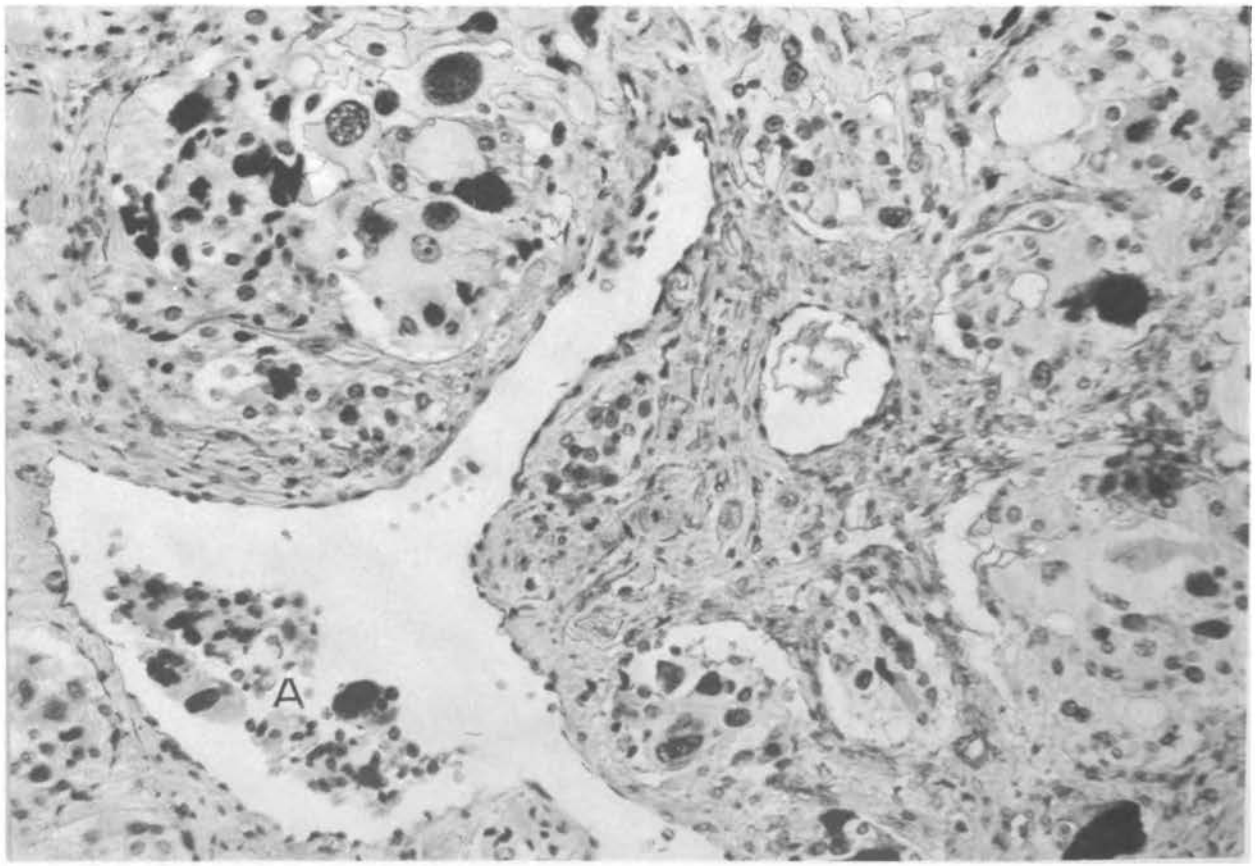

Figure 51. Pheochromocytoma. The tumor cells are arranged in small groups with the blood vessels passing between the majority of them. This photomicrograph indicates the marked variation in the relative size and shape of the tumor cells and their nuclei. The presence of tumor cells in a blood vessel as shown here (A) occurs frequently in tumors of endocrine organs but is seldom an indicator of metastasis; it was not in this case. A. F. I. P. Neg. Ac. No. 218564-21.

(preferably in 25% chloral hydrate) and silver impregnation (best by the Cajal method) which will demonstrate neurites (fig. 47), if the tumor cells have formed them. The tissue culture diagnostic method has permitted the recognition of several sympathicoblastomas in adults, indicating that they are not quite as rare as was formerly supposed. Moreover, these tumors in adults do not appear to grow as rapidly or metastasize as surely as they do in infants.

HISTOLOGICALLY, the sympathicoblastoma is composed of rounded cells collected into groups without connective tissue fiber formation between the individual cells but with a fibrous framework supporting the groups. The cells vary in shape from round to elongated and in size from somewhat larger than a lymphocyte to considerably larger. There is a marked tendency for the tumor to become necrotic. Most of the tumors do not show any other characterizing differential features in ordinary stains, although if Cajal impregnation is used after chloral hydrate fixation one can sometimes demonstrate delicate neurites stemming from some of the neuroblasts. Occasionally, pseudorosettes are formed (figs. 45 and 46). These consist of groups of cells in ball formation with the cell nucleus oriented toward the periphery, and most of the cell body extended toward the center in the form of a cytoplasmic process. Silver nerve fiber stains will sometimes demonstrate neurites coiled up in the center of a pseudorosette. Various names have been proposed for these variations. Del Río-Hortega called the undifferentiated variety sympathogonioma, the form with pseudorosettes, typical sympathicoblastoma, and all other variations are called atypical sympathicoblastoma. Differentiated ganglioneuromas he called sympathicocytomas. It seems hardly necessary to distinguish the tumors which form pseudorosettes from those which do not, because both are apparently equally malignant and almost always fatal in young children, although not so in adults. Most of the reported cures of sympathicoblastomas in children have in fact been partly differentiated ganglioneuromas and not pure sympathicoblastomas.

C. NEOPLASMS OF PARAGANGLIONIC CELLS

Pheochromocytoma, Paraganglioma. There are two sets of paraganglionic cells; those connected with the sympathetic nervous system found especially in the adrenal medulla and the chain of ganglia extending from the base of the skull to the coccyx; and those connected with the parasympathetic system found especially in the carotid body, the cardioaortic body and certain cranial nerves such as the vagus and the glossopharyngeal nerve and its branches in the middle ear. Some of the paraganglionic cells of the sympathetic system contain chromaffin granules and are concerned in the secretion of epinephrine and norepinephrine. They are found particularly in the adrenal medulla, in some of the retroperitoneal, and occasionally in the posterior mediastinal sympathetic ganglia. The rest of the paraganglionic cells of the sympathetic system as well as all of the paraganglionic cells of the parasympathetic system are hormonally inert so far as is known.

Tumors occasionally arise from all of these cells. Microscopically they have a similar structure and cannot be distinguished one from the other except in the case of those tumors the cells of which contain chromaffin granules. The diverse sites of origin of tumors of the sympathetic, parasympathetic, and related structures, together with the cytological variations in this group of tumors has given rise to confusion in their terminology. For example, the paraganglionic cell tumors of the sympathetic system when hormonally active have been called pheochromocytomas, chromaffinomas, and paragangliomas; and when inactive the name paraganglioma has been used. When malignant, this adjective has been placed before the diagnostic term. For the tumors arising from the cells of the parasympathetic system or associated with it, the term paraganglioma has been used or the tumor has simply been called after the structure in which it arose. The writer has preferred the simplification gained by the use of the fewest possible terms, and has been accustomed to call hormonally active tumors of the paraganglionic group pheochromocytomas, and all inactive ones paragangliomas, in each instance naming the region or tissue of origin. The use of the term paraganglioma for the characteristic tumors of the carotid and aortic bodies, the ganglion nodosum in the vagus nerve, the ganglia in sheath of the glossopharyngeal nerve in the middle ear, and for tumors of the ciliary ganglion, when they are observed, is based not only upon the morphological similarities with corresponding hormonally inactive tumors of the sympathetic nervous system, but also upon phylogenetic and embryological studies. Benoit, Watzka and many others offer evidence satisfactory to this author of the common origin of these specific cells in the above named localities with that of the ganglia of the cranial nerves. The rejection of the term paraganglioma for these hormonally inactive tumors is based upon the desire of certain other students of the subject to reserve the names paraganglionic cells and paraganglionic tumors for those which are hormonally active. Since hormonally active cells are not found in the above mentioned sites, these writers prefer to reject or ignore the probable common embryological origin of both cell types, and consign these hormonally inactive cells, and the tumors derived from them to the limbo of bastards of undetermined parentage and without name, except for that of the locality in which they are found. (See Fascicle 16, "Tumors of the Carotid Body".)

Pheochromocytoma. Synonyms and Related Terms: pheochromocytoma (Lat.): chromaffin tumor, chromaffinoblastoma; chromaffinoma, cystic medullary struma of adrenal; functionally active paraganglioma; medullary adenoma of adrenal; pheochromoblastoma.

This rare tumor is found in connection with the sympathetic ganglia in the adrenal medulla, the retroperitoneal ganglia between the adrenals, and rarely in other retroperitoneal and mediastinal ganglia. Its cells secrete epinephrine and nor-epinephrine and the tumor growth is associated with attacks of either paroxysmal or continuous hypertension. There is some times an associated hyperinsulinism and hyperthroidism but this is not common. It is rarely possible to palpate the tumor. Its presence may be demonstrated sometimes by roentgenograms after air injections. Since the functionally active tumors often have increased epinephrine in the blood, its presence in cases of

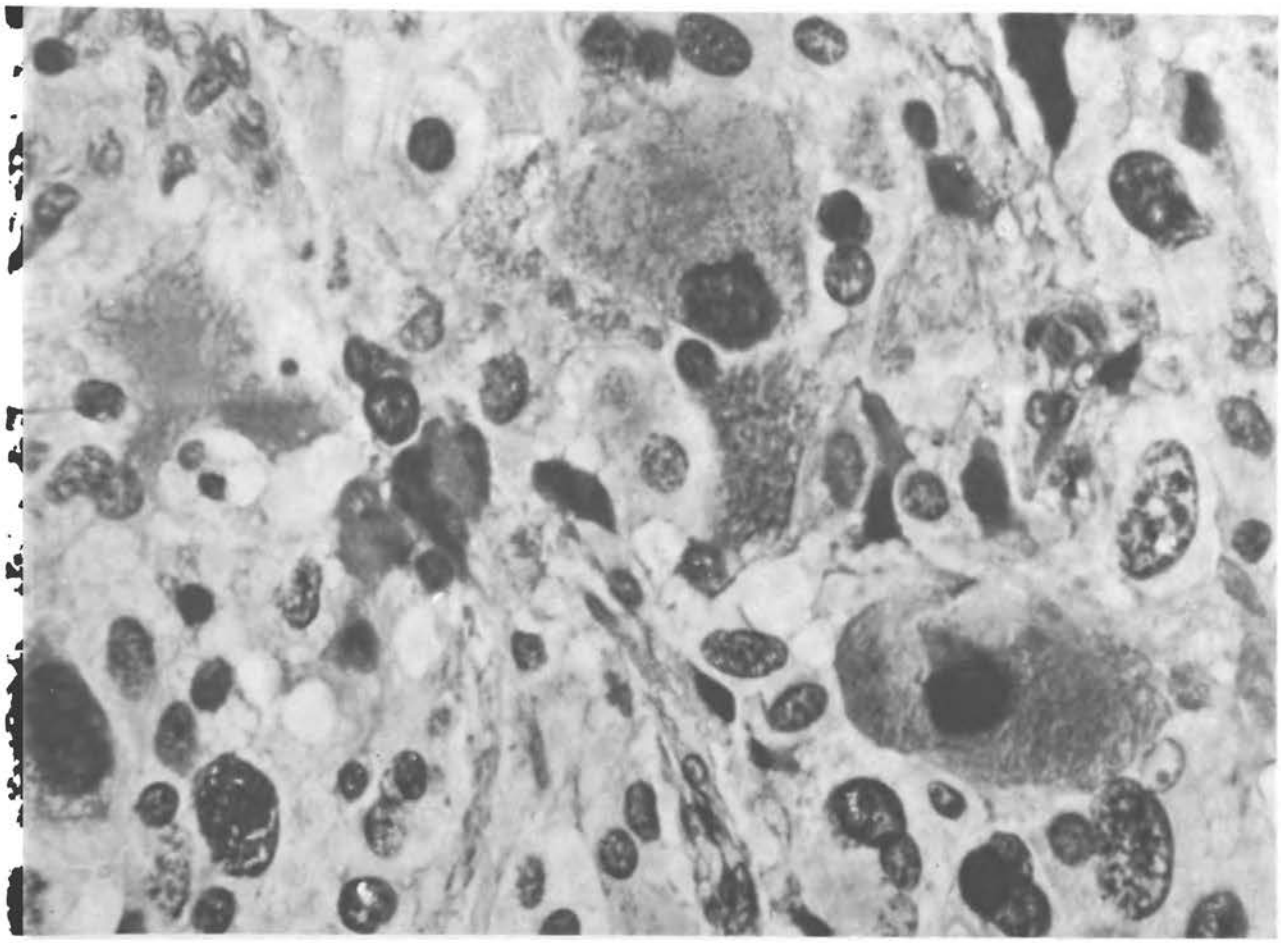

Figure 52. Pheochromocytoma. Schmorl stain after fixation in Orth's fluid. Chromaffin granules in the cells. These are found only in hormonally active tumors (x 1225). A. F. I. P. Neg. Ac. No. 218564–54.

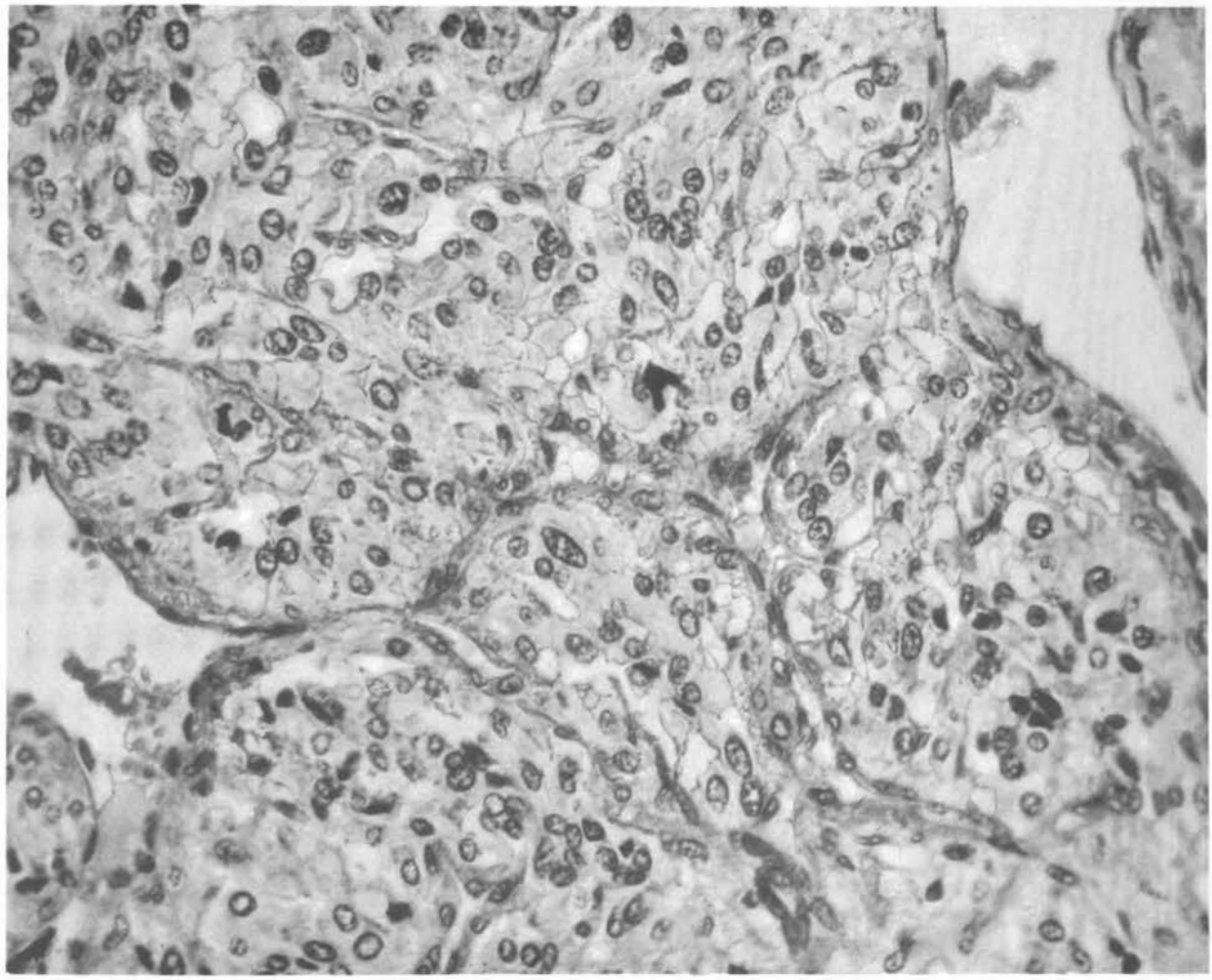

Figure 53. Paraganglioma of the carotid body. The tumor is formed of enlarged caricatures of the normal paraganglionic cells which are arranged in masses with capillaries coursing between each small mass. The tumors are not hormonally active and the cells show no chromaffin granules. A. F. I. P. Neg. Ac. No. 218564–47.

hypertension can be demonstrated by the use of adrenolytic benzodioxane. This is regarded as a relatively reliable method of distinguishing hypertension due to hypersecretion of epinephrine from other forms of hypertension. Extreme care is required in the removal of these tumors because squeezing tends to force the epinephrine into the circulation, sometimes resulting in sudden and fatal elevation of an already high blood pressure. Although these tumors will persist and continue to grow if incompletely excised, very few of them metastasize.

GROSSLY, the tumors do not reach a very large size. They may be multiple. They are apt to be reddish and very vascular (fig. 50).

MICROSCOPICALLY, the cells are arranged in small groups separated by slender connective tissue septa bearing blood vessels. This is a characteristic endocrine arrangement best calculated to facilitate the passage of cellular secretion directly into the circulation. The cells are often but not always bizarre, of polygonal shape and large size with extremely misshapen nuclei that show pyknotic hyperchromatism. Like their progenitors in the adrenal medulla, the functioning pheochromocytomas contain in their cytoplasm granules which are stained brown by chrome salts. This is an oxidation which may be produced by hydroquinones, polyphenols, and other substances. It is not specific for epinephrine but is biologically and diagnostically useful. The chromaffin granules are not present in all cells nor in all parts of the cytoplasm of the same cell; the arrangement seems capricious and haphazard. These granules can best be demonstrated by fixation in Orth's fluid after which they appear brown in hematoxylin and eosin preparations and green if Schmorl's stain is used (fig. 51). Most of the tumors are benign and do not metastasize in spite of the fact that they are very vascular and masses of tumor cells are frequently found in their veins (fig. 52). (See Fascicle 29, "Tumors of the Adrenal".)

Paraganglioma. Synonyms and Related Terms: Paraganglioma (Lat.); carotid body sarcoma; carotid body tumor; glomus jugulare tumor; glomus jugularis tumor; inactive paraganglioma; paraganglion caroticum sarcoma;paraganglion caroticus tumor.

These are the tumors which arise from the paraganglionic cells of the sympathetic and parasympathetic systems. These tumors are found arising in the same areas as the pheochromocytomas, namely in the adrenal medulla, in the retroperitoneal and mediastinal ganglia, in the carotid body, in connection with the glossopharyngeal nerve and its branches in the middle ear, and in the ganglion nodosum within the vagus nerve just after it emerges from the foramen lacerum. Cases reported from the organ of Zuckerkandl are questionable. Bloom has reported cardioaortic body tumors in dogs. No human cases of tumors of the cardioaortic bodies have been published. The writer has seen sections of two paragangliomas in the upper anterior mediastinum intimately associated with the aortic arch which he believes arose from the cells in the cardioaortic body. Since nonfunctioning paraganglionic cells have been reported in the region of the ciliary ganglion, this tumor may also be looked for in the orbit. These tumors are sometimes multiple. They regularly show persistent growth after incomplete removal. (See Fascicle 16, "Tumors of the Carotid Body".)

HISTOLOGICALLY, they all have the same structure like that of the pheochromocytoma but with cells of less bizarre appearance and without any

chromaffin granules in the cytoplasm. The tumors seem encapsulated and very vascular. It is often possible to find tumor cells in blood vessels (fig. 53). This is by no means evidence that these tumors will metastasize, although occasionally a malignant paraganglioma will be encountered.

D. COMPLEX MALIGNANT NEOPLASMS

Occasionally, tumors arise in the sympathetic ganglionic system in which all varieties of the above described tumor forms are represented, such as, the adrenal tumor reported by Wahl in which there were found areas of differentiated ganglioneuroma, chromaffin cell groups, and sympathicoblastoma. Only the latter metastasized.

E. NEOPLASMS OF HETEROTOPIC CENTRAL NERVOUS SYSTEM TISSUES

BENIGN

Ganglioglioma. Synonyms and Related Terms: ganglioglioma (Lat.); astrocytoma; fibroglioma; ganglioblastoma; ganglioneuroschwannospongioblastoma (Montpellier); glioma, nasal glioma.

There are two areas in the body where, as the result of congenital malformations, tumors composed of elements of the brain are found. These are the root of the nose and the orbit. Such growths are rare and usually develop in infants but occasionally in older children and adults. Cogenital cysts of the mucosa of nose, encephalocele and neurofibromas have to be considered in clinical differential diagnosis. The tissue generally consists of masses of fibrous astrocytes (fig. 54), occasionally with the admixture of ganglion cells. In the nose, Davis favors the hypothesis of Schmidt that they result from the formation of an encephalocele during later embryonal development with or without the cutting off of the stalk. This would account for the fact that a few of the tumors are still attached to the brain when removed. He rejects the hypothesis of Süssenguth that some of them come from the olfactory bulb rather than the brain. Most of them are small and form subcutaneous nodules over the bridge of the nose or else intranasal tumors attached to the upper part of the nasal cavity. The intranasal growths appear like polyps; and no harm comes from their removal unless they are attached to the brain, when meningitis and death may result. Most of these tumors are small, but one which was brought to the writer's attention by Dr. Maurice Rice formed a huge subcutaneous cyst extending from the root of the nose to the occiput of a new born infant.

Gliomas composed of fibrous astrocytes are also found in the orbit outside of the optic nerve, which is the more common site of origin for these tumors. A complex variant, called a ganglioneuroschwannospongioblastoma, has been described by Montpellier (et al.).

MALIGNANT

Olfactory Neuroepithelioma. Synonyms and Related Terms: epithelioma nervi olfactorii (Lat.); esthésio-neuroblastome des fosses nasales (Portmann, Bonnard, and Moreau; esthésioneuroepithélioma olfactif (Berger, Luc, and Rich-

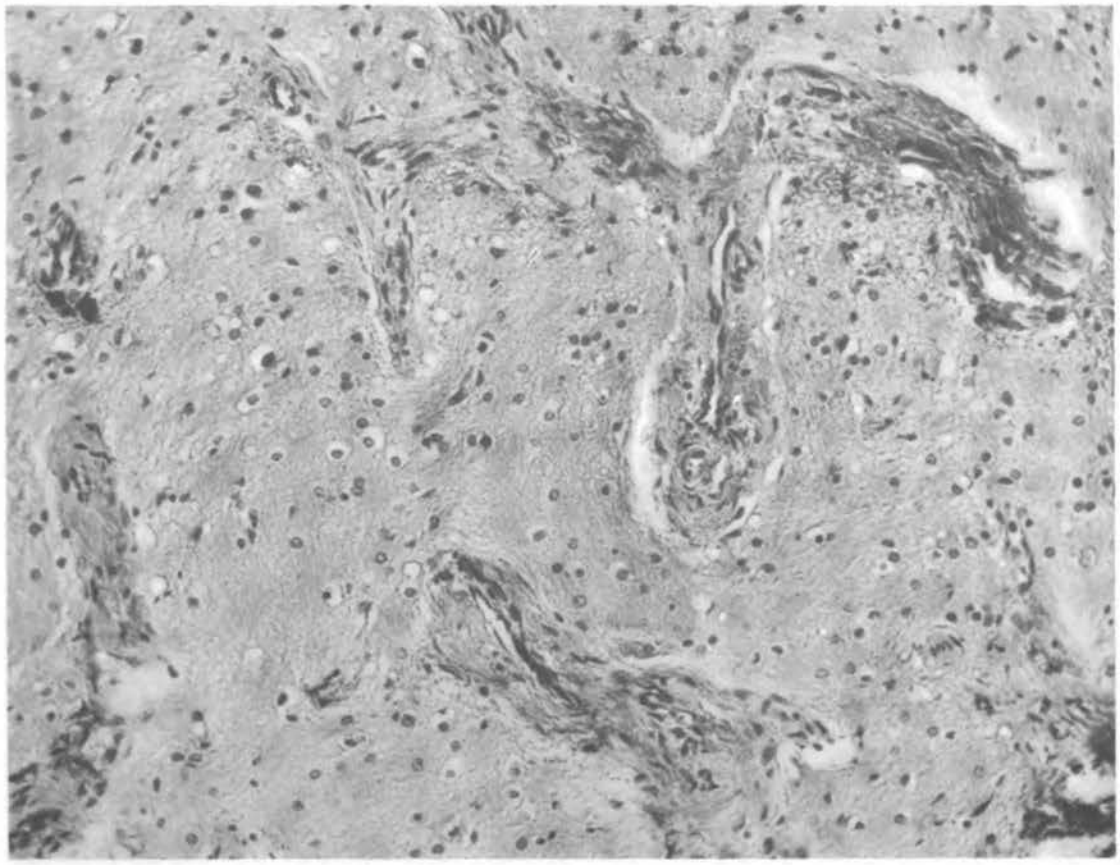

Figure 54. Glioma (Astrocytoma) of the nasal mucosa. Anastomosing cords of astrocytes set in a tangle of glial fibers are supported by slender strands of fibrous tissue and capillaries. A. F. I. P. Neg. Ac. No. 218584–2.

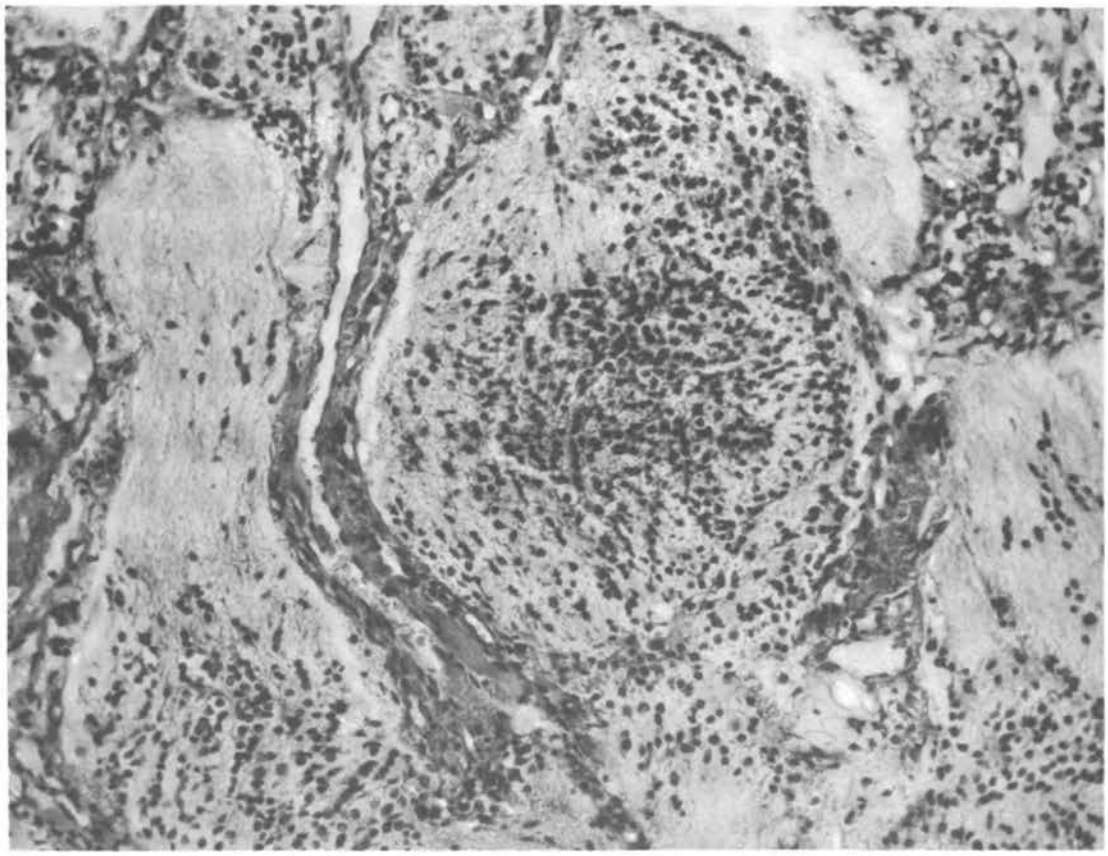

Figure 55. Olfactory neuroepithelioma in the nasal mucosa. The neuroepithelial cells and glial framework are supported by slender bands of vascular fibrous tissue. A. F. I. P. Neg. Ac. No. 218584-1.

Figure 56. Nasal glioma. (Case of Edward W. Davis, M. D. Copyright from: Journal of Neuropathology and Experimental Neurology, 1:312–319, 1942.)

ard); malignant glioma; olfactory esthesioneuroepithelioma; esthesioneuroblastoma.

This is a rare and peculiar tumor which seemingly arises from the olfactory placode in the nasal cavity of adults. It grows slowly by infiltration and may invade the adjacent sinuses. It does not metastasize. In spite of a tendency to recur after incomplete excision, cases have been cured by a combination of surgical excision and radiotherapy. The tumor is seemingly made up of neuroblasts set in a gliomatous stroma. The neuroblasts are small rounded cells and are generally gathered into irregular masses with gliomatous tissue between them (fig. 55). Berger et al. described rosettes and neurofibrillated bands but these have not been found by the writer.

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