The individual fiber of a peripheral nerve is composed of an axon or neurite, which is usually encased in a myelin sheath. Surrounding this is a protoplasmic envelope, the sheath of Schwann. These elements, the neurite, the myelin sheath, and sheath of Schwann, are neurogenic in origin (Fig. 1). The neurite is a prolongation of an individual nerve cell, while the sheath of Schwann is composed of a syncytium of cells which migrate out from the neural crest in early embryonic life (Harrison). The myelin sheath is supposedly a product of the nerve cell. The individual nerve fibers are embedded in connective tissue, the endoneurium, and are gathered into bundles enclosed by fibrous tissue, the perineurium. The entire nerve, consisting of these bundles of individual fibers, is overlaid by connective tissue, referred to as epineurium (Fig. 2).

Tumors of the peripheral nerves were divided by Virchow, in 1863, into false neuromas, which include tumors of the nerve sheath, and true neuromas including growths arising from nerve fibers or nerve cells. Among the true neuromas are ganglioneuromas of the peripheral, spinal, and sympathetic nerves, and amputation neuromas, which are a combination of nerve fiber and sheath regeneration following the severing of a nerve trunk. Sporadic examples of neuro-epitheliomas of the peripheral nerves have been reported.

The false neuromas or tumors of the nerve sheath are far more common than tumors derived from nerve fibers. Tumors of the nerve sheath occur on both spinal and sympathetic nerves, on both sensory and motor nerves, centrally at their roots, peripherally on the deep nerve trunks, and superficially near the terminal ramifications, particularly in the subepidermal tissues. According to one school these tumors are derived from the sheath of Schwann, i.e., are of neuro-ectodermal derivation; another seeks their origin in the connective tissue of the endoneurium and perineurium.

Clinical-anatomical classifications of nerve sheath tumors have been attempted, the best defined clinical group being the multiple variety described by von Recklinghausen. These tumors are sometimes hereditary and are extremely varied in their manifestations. Melanotic plaques in the epidermis, subcutaneous multiple fibrous tumors, plexiform involvement of the nerves of an extremity with or without elephantiasis, and solitary nodules on the deep nerves, both benign and malignant, are among the varied findings.

Two varieties of solitary benign nerve sheath tumors are recognized, a differentiated and undifferentiated group. The more highly

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1 Aided by a grant from The Anna Fuller Fund.
differentiated tumors are rich in collagen and fibrous tissue and in one or more zones of the tumor a clumping of the nuclei in a characteristic palisade arrangement can be seen under the microscope. These tumors are surrounded by the perineurium except at the point of attachment to the nerve and rarely undergo malignant change. They have been variously termed perineural fibroblastomas, neurinomas, Schwannomas, neurilemomas, and lemmomas. They occur most frequently in the subcutaneous tissues or centrally along the roots of the cranial or spinal nerves in adults.

The tumors of the undifferentiated group may or may not be encapsulated and are prone to recur and to undergo malignant change. These tumors occur most frequently on the deep nerve trunks of the upper or lower extremities and also superficially beneath the epidermis. Both children and adults may be affected. The combination of multiple superficial and deep tumors of this type is part of the clinical picture of von Recklinghausen's disease. Histologically these growths are composed of reticulated myxomatous tissue often arranged in bundles and sometimes extremely cellular. These tumors have been variously referred to as fibromyxomas, fibroneuromas, and myxoid neurinomas.

Sarcoma of the nerve sheath may arise in either type of solitary nerve tumor just mentioned. It is the most common form of sarcoma of the soft parts. Usually this malignant change affects the deep nerve trunks of the extremities, and it may complicate von Recklinghausen's disease.

The following table shows the classification and the incidence of these tumors recorded in the Johns Hopkins Surgical Pathological Laboratory.

<table>
<thead>
<tr>
<th>Tumors of the Nerve Sheath (False Neuromas)</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palisaded neurinomas (Neurilemomas)</td>
<td>150 cases</td>
</tr>
<tr>
<td>Peripheral (55 cases)</td>
<td></td>
</tr>
<tr>
<td>Spinal (25 cases)</td>
<td></td>
</tr>
<tr>
<td>Acoustic (70 cases)</td>
<td></td>
</tr>
<tr>
<td>Myxoid neurinomas (Neurilemoblastomas)</td>
<td>350 cases</td>
</tr>
<tr>
<td>Subepidermal (240 cases)</td>
<td></td>
</tr>
<tr>
<td>Deep (70 cases)</td>
<td></td>
</tr>
<tr>
<td>von Recklinghausen's, multiple (40 cases)</td>
<td></td>
</tr>
<tr>
<td>Sarcoma of the nerve sheath</td>
<td>350 cases</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumors of Nerve Fibers (True Neuromas)</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amputation neuromas</td>
<td>40 cases</td>
</tr>
<tr>
<td>Ganglioneuromas</td>
<td>8 cases</td>
</tr>
<tr>
<td>Peripheral neuro-epitheliomas</td>
<td>2 cases</td>
</tr>
<tr>
<td>Total</td>
<td>900 cases</td>
</tr>
</tbody>
</table>

**Tumors of the Nerve Sheath: False Neuromas**

**Palisaded Neurinomas (Neurilemomas)**

The palisaded neurinomas arise from the sheaths of the subcutaneous nerves or the roots of the spinal or cranial nerves. They are encapsulated by the perineurium, are solitary, and do not implicate an entire nerve trunk. With the peripheral tumors a tender lump
Fig. 1. Photomicrograph of a normal medullated nerve fiber occurring in an amputation neuroma on the sciatic nerve

The axon courses through the center of the myelin, which stains in the form of small droplets. The nucleated sheath of Schwann is seen above the fiber. Above and below are the anastomosing columns and fibers of the Schwannian synctium. Masson’s trichrome stain. Path. No. 56853.

Fig. 2. Photomicrograph showing the connective-tissue sheaths of a normal nerve

may be palpated in the subcutaneous region, and pressure may provoke pain referred along the distribution of the affected nerve. About one-third of these tumors lie immediately beneath the epidermis (Fig. 5).

Stout has reviewed the literature on the peripheral tumors of this type, collecting 194 cases and adding 50 of his own. He has suggested

![Diagram showing distribution of subepidermal and central palisaded neurinomas]

The location of the tumors was as follows:

Peripheral tumors
- Head and neck, including face, scalp, and eyelids: 18
- Upper extremities: 14
- Trunk: 12
- Lower extremities: 6

Central tumors
- Acoustic nerve: 70
- Spinal cord and cauda equina: 25

the term neurilemoma for these growths. In the central tumors involvement of the cranial nerves or compression of the spinal cord is the outstanding feature. Whether these tumors are central or peripheral in distribution the upper portion of the body and the upper extremities are affected more often than the lower. With the central tumors the cranial nerves are involved more frequently than the spinal roots,
and in the subcutaneous regions the head and neck and upper extremities more frequently than the trunk and lower extremities (Fig. 3). On the extremities the flexor surfaces are usually affected. Eighty per cent of all cases occur in adults between the ages of thirty and fifty years (Fig. 4).

**FIG. 4. AGE DISTRIBUTION OF NERVE SHEATH TUMORS**

Histologically these are benign, well differentiated tumors showing varying degrees of fibrosis, which is maximal in the region of the capsule. A few degenerating axons with myelin sheaths may be demonstrated by special stains but these are persisting normal structures and not part of the new growth. The major portion of the tumor is composed of wavy bands of collagen interspersed with elongated parallel fibrils (Fig. 6). Whorls of fibers may occur and in these zones clumping of the nuclei to produce so-called palisades may be seen (Fig. 7A). This is referred to by Antoni as Type A tissue. Interspersed with the collagenous and palisaded structures there is a loose reticulated tissue containing cells with small nuclei, many fine radiating fibrils, and minute cystic spaces. These reticulated or loose-meshed areas, termed by Antoni Type B, can be found in all of these growths, but the palisading is a more helpful finding from the standpoint of diagnosis (Fig. 7B).

Masson has studied in detail the cytological characteristics of the predominating cells in these tumors, which he believes are sheath of Schwann cells or lemmocytes. The nuclei are fairly large with moderate amounts of chromatin arranged at the periphery. The cytoplasm of the cell is abundant and forms syncytial columns of protoplasm marked by numerous delicate fibrils arranged both longitudinally and circularly. This syncytium stains pink with Masson’s trichrome stain; it is encased in a reticulum of fibers which stain blue by this same method. We have been able to confirm Masson’s findings in the present study. When a reticulum stain is used the entire tumor is seen to be
crowded with many fine fibrils, which Masson believes are derived from the lemmocytes of the sheath of Schwann rather than from the connective tissue of the endoneurium.

These subcutaneous or peripheral neurilemomas may be treated by simple excision. Sacrifice of an important nerve is not necessary, since the deep peripheral nerves are rarely involved and recurrence after excision is extremely uncommon. Malignant change has occasionally been reported (Stewart and Copeland; Peers) in tumors in the deeper tissues but not in those in the subcutaneous regions.

*Acoustic Nerve Tumors:* Tumors occupying the cerebellopontine angle and involving the acoustic nerve comprise about 10 per cent of all intracranial neoplasms. In the present series 105 cases were placed in this group, on the basis of operative findings. Of this group 70 were selected as typical after microscopic study. The majority of these cases were from the surgical service of Dr. Walter E. Dandy, although 10 of the cases had been previously reported by Cushing.

The acoustic tumors in the present series, with two exceptions, occurred in adults beyond the age of twenty years. The two younger patients were eighteen and nineteen years of age. The duration of symptoms is prolonged, extending beyond a five-year period in many instances. A characteristic syndrome is usually present, beginning with a roaring in the ears or dizziness, after which the hearing is gradually lost on the affected side. There is loss of sensation over the affected side of the face and occasionally in the anterior two-thirds of the tongue. The voice may become thick and the patient becomes
ataxic, with a staggering gait. The symptoms relate to the eighth, fifth, seventh, and ninth cranial nerves on the affected side and to the cerebellum. They are followed by signs of intracranial pressure including headache, impairment of vision, and vomiting.

The findings on examination include impairment of hearing, loss of vestibular response on caloric test (absence of nystagmus when the ear is irrigated with hot or cold water), and absence of the corneal reflex on the affected side. Facial asymmetry and anesthesia, nystagmus, ataxia, paralysis of the vocal cords, dysphagia, and hemiatrophy of the tongue are among the other findings.

Grossly these tumors are encapsulated and vary in color from a grayish white to a yellow or red. They are usually fibrous but may be quite vascular. They range in size from one to several centimeters in diameter. At operation they are found just beneath the cerebellum, which must either be lifted or uncapped before the tumor presents. Dandy prefers a complete enucleation of the tumor with the curette, followed by removal of the capsule, whereas Cushing is often content with intracapsular enucleation, awaiting the possibility of recurrence before more radical removal. The operative mortality is between 15 and 25 per cent. Paralysis of the facial nerve follows surgical removal of these lesions and anastomosis is usually performed at a second stage between the peripheral portion of the seventh nerve and the central portion of the eleventh.

\[1\] In rare instances the hearing may be retained.
These tumors show varying degrees of vascularity and fibrosis. The more cellular growths resemble spongioblastomas or glioblastomas of the brain and the more fibrous lesions resemble meningiomas. In one or more portions the tumors show typical reticulated tissue and elsewhere collagenous areas with clumping of the nuclei. They do not differ as a group from the palisaded neurinomas found on the peripheral nerves (Fig. 8).

There have been various theories as to the nature and origin of these tumors. The frequency of their occurrence in the region of the cerebellopontine angle has led Sternberg, Verocay and others to refer them to embryonic rests occurring in the complex development of this region. These tumors, however, have been reported, also, on the seventh nerve by Raymond, Huet and Alquier and on the fifth nerve by Cohen and by Glaser. Cooper has reported two neurinomas invading the Gasserian ganglion. He was able to collect from the literature records of 76 tumors affecting this structure. One of the cases in the present series involved the tenth and another the twelfth cranial nerve. A series of six tumors ranging from 1 to 3 mm, in diameter has been collected in Dr. Crowe's laboratory for otological research at the Johns Hopkins Hospital, on the distal portion of the eighth nerve within the internal auditory canal. The histology of these minute tumors on the distal portion of the nerve, is identical with that of the larger tumors at the cerebellopontine angle and of the tumors on the peripheral spinal nerves. This substantiates the origin of these tumors from the sheath of the acoustic nerve.

_Extramedullary Neurilemomas of the Spinal Cord:_ Tumors of the palisaded neurinomatous type occur on the spinal cord in an extra-medullary location. They may be intradural or extradural and occur on the roots of the spinal nerves within the vertebral canal anywhere
from the cervical region to the cauda equina. They are sometimes multiple or associated with meningeal tumors in the presence of von Recklinghausen's disease. The symptoms produced vary with the level of the tumor. The onset is usually insidious, indicating cord compression with unilateral sensory and motor disturbances. Root pains exacerbated by coughing or sneezing occur. Girdle pains, weakness of the legs, progressive paralysis (at first spastic) below the painful area, and disturbance of the bladder and rectal functions, are common findings. Diagnosis is much aided by the injection, in the subarachnoid space above the lesion, of lipiodol and roentgenographic demonstration of a block in its downward course.

Tumors in the anterior portion of the cord are more difficult to locate and to excise. The tumors are usually encapsulated and do not invade the cord, but in one case in the present series associated with von Recklinghausen's disease there was definite invasion and a portion of the tumor was left behind at the operation (Fig. 9). In other cases the growth may form an anterior extension (so-called hour-glass tumor), the major portion being found in the neck, mediastinum, or in the retroperitoneal spaces.

Tumors of the cauda equina present certain diagnostic difficulties. The majority of tumors in this region are sheath tumors, the neurinomas being more common than the meningiomas. The pain, which may be very prolonged, is frequently attributed to sacro-iliac arthritis or sciatica. There is flaccid paralysis with loss of reflexes and marked disturbance of the bladder and rectal functions. An area of "saddle"
anesthesia is present in the perineum. The exposure of these tumors at operation is more difficult than those of the spinal cord, but the prognosis is better. The distribution of these sheath tumors in the spinal cord and in the cauda equina is as follows:

<table>
<thead>
<tr>
<th>Region</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical region</td>
<td>6</td>
</tr>
<tr>
<td>Thoracic region</td>
<td>7</td>
</tr>
<tr>
<td>Lumbar region</td>
<td>2</td>
</tr>
<tr>
<td>Cauda equina</td>
<td>10</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>25</strong></td>
</tr>
</tbody>
</table>

![Photomicrograph of an Extramedullary Neurilemoma of the Spinal Cord Complicating a Case of von Recklinghausen's Disease](image)

A portion of the tumor invaded the cord. Path. No. 53373.

**Myxoid Neurinomas or Neurilemoblastomas**

The myxoid neurinomas of the nerve sheath differ from the palisaded neurinomas both clinically and pathologically. The distribution of these tumors is subepidermal and along the deeper nerve trunks, in contrast to the subcutaneous and central location of the palisaded neurinomas. These myxoid tumors also have a wider age distribution and occur more frequently in children. The majority of the tumors are not encapsulated. Histologically they are more undifferen-
tiated and particularly in the deeper locations are prone to undergo malignant change. Multiple nodules are not an unusual finding and both the subepidermal and deep lying nerves may be diffusely involved by such tumors in von Recklinghausen's disease. The accompanying table contrasts the myxomatous neurinomas with the palisaded neurinomas.

**Table I: Comparison of Palisaded and Myxoid Neurinomas**

<table>
<thead>
<tr>
<th></th>
<th>Neurilemomas</th>
<th>Neurilemoblastomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>150</td>
<td>350</td>
</tr>
<tr>
<td>Age peak</td>
<td>40-50</td>
<td>20-30</td>
</tr>
<tr>
<td>Children affected</td>
<td>None</td>
<td>20 per cent</td>
</tr>
<tr>
<td>Most frequent locations</td>
<td>Roots of eighth cranial and spinal nerves, subcutaneous fibers, head and neck, arm, hand</td>
<td>Subepidermal fibers, deep nerve trunks of upper and lower extremities, visceral sympathetics</td>
</tr>
<tr>
<td>Encapsulation</td>
<td>Majority encapsulated</td>
<td>Majority not encapsulated</td>
</tr>
<tr>
<td>Microscopic findings</td>
<td>Palisading and fibrous tissue</td>
<td>Reticulation and myxomatous tissue</td>
</tr>
<tr>
<td>Behavior after treatment</td>
<td>No recurrence after simple excision</td>
<td>Tendency to recur after simple excision</td>
</tr>
<tr>
<td>Malignant change</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Association with von Recklinghausen's disease</td>
<td>Rare</td>
<td>Common</td>
</tr>
</tbody>
</table>

*Subepidermal Myxoid Neurinomas (So-called Neurofibromas):* Subepidermal nodules associated with the sheaths of the peripheral nerves are among the most common tumors. Nearly every patient examined will be found to have one or two of these pedunculated lesions several millimeters in diameter. They differ from the lesions found in typical von Recklinghausen's disease in the absence of symptoms produced, their small size, their restricted numbers, and their failure to follow the entire cutaneous distribution of the nerve. In the present series of cases there were 240 tumors of appreciable size which had been excised and classed as neurofibromas after microscopic study. These growths were usually removed for cosmetic reasons, although rarely increase in size or deepening pigmentation was the indication for excision. In some cases the nodules had become increasingly painful or tender. With few exceptions only a single tumor was removed from an individual. The nodules were more frequently situated on the extremities than on the head, neck or trunk (Fig. 10).

Microscopic study discloses three types of subepidermal nodules associated with the nerve sheath. The most common form is characterized by an increase in adult connective tissue and is often considered, erroneously, a simple fibroma (so-called fibroma molluscum). Another form is composed of bundles or fasciculae of elongated cells which may
be arranged in whorls, some of which display marked cellularity. A third type is composed of a diffuse proliferation of small spindle cells without any characteristic arrangement. Any of these three histologic types may be associated with melanin pigment (Figs. 11-13), and none of them shows complete encapsulation. They represent three stages of differentiation in the same pathologic process. The essential pathologic change is apparently a proliferation of sheath cells about one or more bundles of nerve fibers entering the subepidermal region. The nodules composed of undifferentiated spindle cells represent the earlier phase of a process which terminates with fibrosis after passing through a stage characterized by bundles of elongated sheath cells.

Multiple nodules of this character are the outstanding feature of von Recklinghausen’s disease. Penfield was able to stain axons of nerve fibers entering the subcutaneous nodules, and interpreted the nodules as a reactionary fibrosis of probable neurotrophic origin. He retained the term neurofibroma for these lesions, because of the axon
found in the tumor area. From the present study no special significance can be attached to the demonstration of axonal fibers in these nodules. They can be demonstrated in the normal skin and subcutaneous regions and their persistence in the affected area is not neces-

FIG. 11. LOW-POWER AND HIGH-POWER PHOTOMICROGRAPHS OF A SUBEPIDERMAL NEURILEMOBLASTOMA
Mature collagenous fibers predominate. Path. No. 31502.

FIGS. 12 AND 13. SUBEPIDERMAL NEURILEMOBLASTOMAS
The tumor in Fig. 12 (left), occurring in a child of seven months, is composed of interlacing bundles of collagenous fibrils (Foot's reticulum stain). The tumor in Fig. 13 (right) is composed of undifferentiated spindle cells; a small deposit of melanin is seen in the lower right hand corner. Path. Nos. 54726 and 32725.

sarily related to the pathologic changes (Figs. 14 and 15), but merely indicates proximity to neural structures. In general neither axons nor myelin are found as part of the neoplastic process in tumors of the nerve sheath.

Subepidermal Nerve Sheath Sarcoma, Grade I.: In the present series there was a group of 30 very cellular spindle-cell tumors oc-
Fig. 14. **Photomicrograph of a Subepidermal Nodule Occurring on the Nerve Sheath**
A large nerve fiber is seen entering the tumor. Path. No. 32414.

Fig. 15. **Photomicrograph of Axonal Fibers Entering a Subepidermal Nodule**
(Hielschowsky's Stain). Path. No. 54958
occurring immediately beneath the epidermis and apparently of nerve sheath origin (Figs. 16 and 17). These cases were formerly classed in the laboratory as sarcomas of the skin. With few exceptions they occurred about the head and face and on the upper extremities. All of them had been treated by simple excision, including a margin of healthy skin and the subcutaneous tissues down to the underlying fascia.

**Fig. 16.** Photomicrograph of Subepidermal Spindle-cell Nodule (Grade I Sarcoma) Cured by Local Excision. Path. No. 36073

**Fig. 17.** Photograph and Photomicrograph of a Subepidermal Spindle-cell Sarcoma of the Nerve Sheath Recurrent after Excision and Irradiation

The characteristic cells of Schwann are shown in the photomicrograph, with large amount of collagen. Path. No. 53380.
Histologically the majority of these tumors are Grade I, when compared with sarcoma of the deep nerve trunks, although some of them are Grade II, III or IV in malignancy. This group of tumors is singled out because of the results following treatment. Of 18 patients followed for more than five years after excision of the tumor, 16 remained well and only two died of metastasis (Fig. 18). The curability of these subepidermal nodules is far higher than that of sarcoma affecting the sheaths of the deeper nerves, and they warrant a better prognosis than they are usually accorded.

Myxoid Neurinomas of the Deep Nerves: Benign nerve sheath tumors of the non-encapsulated myxoid variety (neurilemoblastomas) apparently affect the major nerve trunks less frequently than the superficial fibers. When allowance is made for the probability that small asymptomatic nodules escape detection because of their deep location, and for the fact that those tumors undergoing malignant change are grouped with the sarcomas, the incidence of these tumors on the deep nerves may be said to approach that of the subepidermal nodules.

In the present series of cases the sciatic nerve, in the thigh or popliteal space, was affected more frequently than any of the other nerve trunks. The femoral, median, and ulnar nerves were next in frequency. The nerve sheath tumors of the sympathetic system supplying the internal viscera are usually of this myxoid type, as determined from the present study (Fig. 19). At operation the tumors may
TUMORS OF THE PERIPHERAL NERVES

give the impression of being encapsulated, but they frequently extend without any definite boundary above or below, up and down the nerve trunk. These tumors are usually larger at the time of their clinical recognition than the other varieties of nerve sheath tumor, varying from the size of a walnut to that of a grapefruit. They tend to have a somewhat gelatinous consistency and a gray, translucent appearance. Although pain and tingling along the distribution of the nerve may be complained of by the patient, the fairly rapid growth of the swelling is often the only significant finding in the history.

Fig. 19. Low-power and High-power Photomicrographs of a Myxoid Neurinoma in the Wall of the Stomach

The tumor is undergoing malignant change. Path. No. 55320.

The outstanding clinical feature in this group of tumors is the tendency to recurrence. Thirty per cent of the tumors in the present series recurred, and of the recurrent growths slightly more than half underwent malignant change, resulting in the death of the patient. Whereas simple excision suffices in the treatment of the subepidermal nodules and the palisaded neurinomas, the myxoid neurinomas should without exception be excised with a margin of healthy tissue. If a major nerve trunk must be sacrificed, this should be done with an attempt at subsequent nerve suture. These tumors in our experience have not proved radiosensitive.

Histologically, these growths are composed of interlacing strands of elongated or short spindle cells with varying amounts of collagenous and myxomatous intercellular substance. Reticulated areas in which small branching cells lie free in a translucent matrix are a prominent feature. Marked fibrosis and definite palisading were not present in the sections examined. From the standpoint of treatment any nerve
sheath tumor occurring on the deeper nerve trunks or on the sympathetic nerves of the viscera should be resected rather than excised on the presumptive evidence that it belongs to this group (Figs. 20–22). Tumors of this type exceeding 2 cm. in diameter are usually malignant.

**Neurofibromatosis:** Von Recklinghausen's disease or neurofibromatosis is a congenital disturbance of the nerve sheaths resulting in multiple subepidermal nodules along the distribution of the peripheral nerves, tumors of the deeper nerve trunks and roots, and disturbances in pigmentation. Meningeal tumors, angiomas, lipomas, and trophic disturbances, such as hypertrophy of a limb or spina bifida, are often associated conditions. Typical cases in which tumor nodules are widely distributed over the body are not common, but atypical cases (so-called

![Fig. 20. Benign Mynoid Neurinoma](image)

The tumor occurred on the radial nerve just above the periosteum on the lower end of the radius. The patient was reported well four years later. Path. No. 40346.

*forme fruste*, in which one or more areas of the body show pigmentation and tumor nodules, are seen more frequently. The present study is based upon 40 typical cases in which tissue was available for study following surgical excision or autopsy.

Although cases in which the disease shows hereditary or familial features are not rare in the literature (Stalmann), in the present series of 40 cases no instance is recorded in which members of the patient's family were known to be affected. The disease pursues a slow, insidious course, approximately one-third of the patients being in the third decade before disability or disfigurement brings them to the physician. Although the majority of the patients were between the ages of twenty and fifty years, 11 of the 40 cases were congenital in onset, 7 began in childhood, and in 5 nodules had been observed more than ten years previously. Presumably all cases are congenital in origin. Multiple nodules (0.5
Fig. 21. Photomicrograph of a Benign Neurinoma (Neurilemoblastoma) Excised from the Forearm

The patient was reported well four years later. Path. No. 40592.

Fig. 22. High-power Photomicrograph of an Edematous Myxoid Neurinoma

The cells are arranged in parallel rows. Path. No. 47077.
to 1 cm. in diameter), freely movable and tender to pressure, situated on the trunk and extremities and accompanied by pigmentation were the outstanding features in most cases (Figs. 23 and 24). Involvement of the head and face was prominent in 6 cases, and in an equal number nodules were found on the feet and hands. The tumors follow the distribution of the peripheral nerves and are often pedunculated. In one or more locations larger nodules, from 3 to 5 cm. in diameter, may be palpated. The tumors along deeper nerves may give rise to rheumatic pains for many years before becoming palpable. Thirty of the 40 patients in the present series had demonstrable involvement of the deep nerves or central tumors within the skull or along the spinal cord. Subcutaneous angiomatous lesions were present in 4 cases, spina bifida in 2 instances, curvature of both wrists in one, congenital club foot in another, and hypertrophy of an extremity with plexiform neuromas three times.

Nine of the 40 patients with von Recklinghausen's disease in the present series had sarcoma of a deep nerve trunk, proving fatal in each case. In 6 other patients tumors of the acoustic nerve, of the meninges, of the spinal roots within the vertebral canal, or tumors within the mediastinum resulted in death.

Histologically the superficial tumors are similar to the solitary subepidermal nodules of the nerve sheath (Figs. 25-27). The deeper tumors are myxoid neurinomas or sarcomas of the nerve sheath. Typical palisaded neurinomas, however, were not observed in von Recklinghausen's disease in this series except within the cranial cavity or along the spinal cord.

Plexiform neuroma or elephantiasis nervorum is considered a form of congenital elephantiasis, since in the region affected the nerves, connective tissue, and vessels may all show enlargement. In this type of
Fig. 24. Patient with von Recklinghausen's Disease. Path. No. 37818

Fig. 25. Photomicrographs showing melanotic (left) and neurinomatous (right) portions of a subepidermal nodule in von Recklinghausen's Disease.
Path. No. 20339

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nerve involvement, usually seen in von Recklinghausen's disease, a limited part of the nerve is thickened and elongated as the result of an overgrowth of the sheath and connective tissue along the tortuous and beaded course of the fibers. Lewis has reviewed the literature and discussed in detail this phase of the disease under the heading "Elephantiasis Nervorum." Bruns was the first to analyze a series of these cases, collecting 42 from the literature and adding 8 of his own. Lewis described 5 cases and stressed the enlargement of the part (Fig.
and the association of vascular and connective-tissue disturbances and a tendency for malignant tumors to develop on the involved nerve. These plexiform neuromas are essentially a *forme fruste* of von Recklinghausen's disease, since similar enlargements of the spinal nerves at their roots are often an outstanding feature in the more generalized form. The following case is characteristic:

A colored male, aged seventeen, was admitted to the hospital in August 1933, having noticed multiple nodules beneath the skin over the surface of the body for a little more than one year. He complained of pain in the left chest accompanied by increasing shortness of breath. A decided right scoliosis was present, with drooping of the left shoulder. The skin nodules, the largest of which were about 4 cm. in diameter, followed the distribution of the superficial nerves about the body and down the extremities. The face, palms of the hands, and soles of the feet were the only portions of the body free from these nodules. All of them were tender to pressure. The main physical findings pertained to consolidation in the left chest. X-ray revealed a large tumor in the mediastinum compressing the left lung. The neurological examination was essentially negative. In January 1934 death occurred from respiratory embarrassment.

Autopsy revealed in addition to the superficial nodules a lobulated tumor mass 18 × 12 × 12 cm. in the left chest. Numerous tumor nodules 1 cm. in diameter followed the distribution of the nerves along the trachea and esophagus. The sympathetic nerve chains anterior to the abdominal spine were thickened and beaded by tumor formation. Both the brachial plexus and the sciatic nerves were markedly thickened and beaded by numerous tumors. The roots of the thoracic and lumbar nerves showed bilateral tumor nodules. Nearly every spinal nerve at the intervertebral angle contained a tumor nodule slightly in excess of five mm. in diameter. Microscopic examination showed the nerve fibers of the various spinal nerves separated by loose myxomatous tissue. The axis cylinders and myelin sheaths were visible in specially stained preparations in scattered fibers only. The mediastinal mass showed two types of tumor, one of these was typical nerve sheath sarcoma composed of interlacing strands of spindle cells, the other portion was epithelial in appearance and resembled a paraganglioma of the adrenal or, in places, parathyroid tissue (Fig. 29).
Sarcoma of the Nerve Sheath

Sarcoma of the nerve sheath arises most commonly along the deep nerve trunks of the upper and lower extremities. The sites of occurrence correspond very closely to the distribution of the benign deep myxoid neurinomas previously described. The lower extremity is more often affected than the upper, and the region of the popliteal space and the anterior and posterior portion of the thigh are the most common sites (Fig. 30). The incidence of these tumors reaches its peak in the decade between thirty and forty years with approximately 10 per cent of the patients under twenty years (Fig. 4). The average duration of symptoms was slightly under one year in 75 per cent of the cases; the remainder of the patients had known of a swelling or pain from five to fifteen years. The results of both the clinical and pathological study of the cases in the present series indicate that a large percentage of these sarcomas represent malignant change in pre-existing benign myxoid neurinomas.

Histologically there is a remarkable degree of uniformity in the majority of these tumors. They are composed of tightly interlacing strands of plump spindle cells which may occasionally be elongated with wavy fibrils and at other times show enlarged nuclei with mitotic figures and tumor giant cell formation. From this typical picture, which can be considered Grade II or III sarcoma (Figs. 32 and 33), the tumors vary on the one hand toward the benign myxoid neurinomas, merging imperceptibly with the histological forms of this benign group.
(Fig. 31), which may be termed the Grade I sarcomas, and on the other hand a group showing numerous tumor giant cells and epithelioid forms, representing Grade IV in malignancy (Fig. 34). In 9 of the cases of this series, the malignancy complicated von Recklinghausen’s disease. In an equal number of cases the malignant change occurred in palisaded neurinomas (Fig. 35).

These tumors recur after excision and extend along the perineural lymphatic spaces. Transplantation by this route, rather than the for-
Fig. 31. Photomicrograph of Grade I Sarcoma of the Nerve Sheath Developing in a Pre-existing Benign Myxoid Neurinoma. Path. No. 31968

Fig. 32. Photomicrograph of Grade II Sarcoma of the Nerve Sheath. Path. No. 31775
Fig. 33. Photomicrograph of Grade III Sarcoma of the Nerve Sheath. Path. No. 39696

Fig. 34. Photomicrograph of Grade IV Sarcoma of the Nerve Sheath. Path. No. 15152
Second, irradiation did not produce a permanent cure when used alone, but in the recurrent tumors apparently delayed metastasis or the spread of the disease in a small percentage of cases. Third, where the tumors had invaded bone, or deeper structures such as the pelvis, no cures were effected. The prognosis of this form of sarcoma of the soft parts, arising from the nerve sheath, is far worse than that of fibrospindle-cell sarcoma of fascial origin, with which it is easily confused histologically.

**Histogenesis**

An interpretation of the histogenesis of these neoplasms of the peripheral nerves should account for the histologic differences between the palisaded neurinomas and the myxoid form. It should also account for the peripheral and central distribution of the tumors showing palisading, for their differentiation and fibrosis, for their encapsulation, their occurrence in adults, and their benign clinical course. It should likewise explain the distribution of the myxoid neurinomas subepidermally and on the deep nerve trunks, their non-encapsulation, their tendency to be multiple and congenital in von Recklinghausen’s disease, their recurrence after excision, and frequent malignant change.

These fundamental differences in behavior in the two groups of tumors of the nerve sheath are apparently related to the presence or absence of a myelin sheath on the nerve fibers affected. According to Nageotte, the myelin exerts a physiological control over the character of the sheath of Schwann. In the presence of myelin individual tubular sheaths are formed about each nerve fiber, and small bundles of fibers are surrounded by perineurium. In non-myelinated nerves in the sympathetic system, in the skin, and in the cornea, the sheath of Schwann is multitubular, enclosing a community of fibers in a syncytial network. This is well illustrated in the nerves of the corneal plexus. In the chick embryo the nerves invade the cornea in the form of a syncytial arborization. The network lying outside of the cornea at the time of myelinization becomes medullated and is provided with individual sheaths. On the other hand, the neurites of the cornea, in order to maintain the transparency of that organ, do not become medullated, and a syncytial network or collective sheath remains about the corneal plexus of fibers.

This intimate relationship which exists between the myelin and the sheath of Schwann also exists between the myelin and the perineurium. Not only is the re-arrangement of the sheath of Schwann concurrent with the appearance of myelin, but the perineurium also forms at the time that myelin appears. In the absence of myelinization a community of nerve fibers within a syncytium of Schwann cells persists without a definite perineurial envelope, the connective-tissue sheath of these fibers remaining incomplete.

The palisaded neurinomas apparently arise in connection with medullated nerves, the sheath of Schwann forming definite columns within the tumor at its inception and being encased by perineurium. The fibrous reaction of the perineurium accounts for the encapsulation.
and relatively benign character of these growths. The contact of the
tumor at its periphery with myelinated nerve fibers accounts for the
palisaded effect. As the tumor grows, neither axons nor myelin par-
ticipate; hence, the invariable presence of syncytial or reticulated areas

within the center of the tumor. This relationship of the palisaded
neurinomas to myelinated nerves accounts for their distribution in the
subcutaneous peripheral nerves and on the roots of the cranial and
spinal nerves.
The myxoid neurinomas, on the other hand, tend to form in the subepidermal nerve fibers which are normally non-myelinated at their terminal ramifications. These tumors also occur on the non-medullated visceral sympathetics, and on the deep nerve trunks at the site of the larger nerve plexuses of the arm and leg. These plexuses during embryonic life and early childhood represent a syncytial network of sheath cells and fibers, where myelinization is delayed. The origin of these tumors in a syncytium of Schwann cells accounts for their reticulated and non-palisaded arrangement, for their failure to be encapsulated by perineurium, and for their tendency to invade the more definite tubular structures in the nerve above and below the site of origin when they occur on the deep nerves. In the subepidermal tissue the connective tissue of the corium reacts to surround the tumor, acting as a form of encapsulation.

The association of the myxoid neurinomas with childhood is probably related to delayed myelinization of the nerves. The occurrence of multiple nodules of this type in the superficial and deep nerves in cases of von Recklinghausen’s disease is likewise probably related to a congenital disturbance in myelinization at the sites of tumor formation. That such abnormalities in myelinization occur in von Recklinghausen’s disease is demonstrated by the finding of demyelinated nerve fibers in the retina (Copeland, et al).

The interpretation just presented accepts the origin of these tumors from the cells of the sheath of Schwann. Masson’s cytological studies have shown that the cells in these tumors are identical with the cells of the sheath of Schwann which proliferate in the so-called experimental schwannomas, first studied by Nageotte. If the sciatic nerve of a rabbit is cut there is observed by the fourth day degeneration of the distal fibers with mitotic proliferation of the Schwann cells. If the proximal end of the nerve is removed, so that it cannot innervate the distal segment and if a second cut is made in this distal segment, hypertrophy and mitotic proliferation continue in the sheath of Schwann. These aneuritic bundles of regeneration in the distal segment are termed experimental schwannomas, and the individual cells resemble those seen in the neurinomas of both the palisaded and non-palisaded varieties. Masson believes the collagen present to be a product of the Schwann sheath rather than of fibroblasts. He has suggested that palisading occurs in the tumors forming on sensory nerves (simulating Wagner-Meissner tactile corpuscles) and that non-palisaded neurinomas occur on motor nerves.

In the Tissue Culture Laboratory of the Surgical Pathological Laboratory Dr. G. O. Gey has maintained for months cultures of malignant nerve sheath tumors removed at operation. These cultures behave entirely differently and are histologically easily distinguished from cultures of normal human fibroblasts (Figs. 36 and 37).

Besides the histological features of these tumors there are other grounds for believing them of neurogenic rather than of connective-tissue origin. The association of both benign and malignant tumors
FIG. 36. TISSUE CULTURE FROM A SARCOMA OF THE NERVE SHEATH
The cells are growing out in a syncytium. Note the large vesicular nuclei. Compare with Figure 37. Path. No. 45016.

FIG. 37. TISSUE CULTURE OF NORMAL FIBROBLASTS
Note the interlacing network of cells and the dense elongate nuclei. Compare with Figure 36. Magnification same as in Fig. 36.
of this group with melanoma, the fact that they are associated anatomically with the nerves and that similar tumors do not occur in the fascial structures, and their malignant behavior clinically, which exceeds that of fascial tumors, are in favor of a neurogenic origin. Ferguson (cited by Copeland) has reported the finding of intermedin in the blood of patients with malignant melanomas, with von Recklinghausen’s disease, and with nerve sheath sarcoma. The finding of this melanophore-expanding hormone of the pituitary in these patients is in keeping with the neurogenic origin of the tumors.

In the present series of cases no sharp dividing line exists between the palisaded and myxoid neurinomas and between the benign and malignant tumors, all of them representing various phases of neoplastic growth in the sheath of Schwann. The contention of Penfield and others that the subepidermal nodules are true neurofibromas and different in origin from the palisaded neurinomas does not seem justifiable. In several instances in this series a single nodule in the subepidermal and subcutaneous regions contained both types of tissue. Furthermore, the conception of a separate group of tumors as axonal and fibromatosus in nature (neurofibroma) is contradicted by tissue culture experiments. It is well recognized that cultures are easily made of the cells of the sheath of Schwann, but that without the presence of such cells the neurites will not grow and cannot be maintained in culture. The proliferation of such neurites, therefore, in the presence of connective tissue only is highly hypothetical. It is doubtful whether any neurites in the peripheral nervous system exist without an accompanying sheath of Schwann (Nageotte).

Tumors Containing Nerve Fibers: True Neuromas

Amputation Neuromas: Following the division of a main nerve by amputation or injury a neuroma forms on the proximal end of the divided nerve. This mass of regenerating tissue differs from tumors of the nerve sheath, containing regenerating neurites as well as sheath of Schwann cells and fibrous tissue. The physiological details of nerve regeneration leading to neuroma formation have been studied in great detail. The following description is based largely on the studies of Nageotte.

When a peripheral nerve trunk is severed, new collateral sprouts proceeding from the neurites (axons) above the lesion appear a few hours after the injury. They soon form a plexus of non-medullated fibers encircled by a syncytium of proliferating cells of the sheaths of Schwann on the proximal side of the division. Newly formed connective tissue from the endoneurium and perineurium supplies a stroma and a fibrous capsule envelops the regenerating mass, which is termed a neuroma (Fig. 1). The growth of the neuroma is rapid and disorderly at first but gradually a normal organization is resumed when the down-growing neurites enter the proliferating sheaths of Schwann proceeding from the distal portion of the severed trunk. Eventually the ordered neurites become myelinated. If, as in amputations, the
neuroma forming on the proximal stump fails to find the channels of the sheath elements of the distal fragments and encounters instead resistant scar tissue, the proliferation of neurites, Schwann cells, and connective tissue of the neuroma continue without myelination to form a typical painful “amputation neuroma.” Similar neuromas follow nerve injuries where scar tissue forms an impediment to the regenerating fibers. The painful masses are treated by excision. In performing amputation, injection of the nerve stump with alcohol prevents the formation of these neuromas.

Neuro-epithelial Tumors of the Peripheral Nerves: Tumors showing a primitive neuroblastic structure, while not uncommon in the neural structures of the sympathetic system, are extremely rare on the peripheral spinal nerves. Cohn reported a recurrent neuro-epithelial tumor on the median nerve in a case of von Recklinghausen’s disease in a man of thirty-five. Penfield has illustrated a case of Stout’s involving the ulnar nerve and showing definite rosette formation. These tumors may represent undifferentiated forms of ganglioneuroma, to which they are undoubtedly related. They do not warrant a separate classification in view of the fact that the majority of all sheath tumors arising from the Schwann cells of the peripheral nerves are likewise neuro-ectodermal in origin. Sarcomas of the nerve sheath, which are highly malignant tumors, are not infrequently seen in which cells have an epithelial-like form or arrangement (Fig. 29). These epithelioid features of neurogenic sarcoma were noted in approximately 10 percent of the cases of sarcoma in the present series. Stewart and Cope-land found similar microscopic variants in their cases of sarcoma of the nerve sheath. These epithelioid features in sarcoma of the nerve sheath are additional evidence in favor of the origin of these tumors from the sheath of Schwann.

Ganglioneuromas: These are among the rarest tumors of the nervous system. The majority of the 150 tumors recorded in the literature have occurred on the sympathetic nerves, most frequently in the region of the suprarenal glands. The 8 cases in the present series have been previously reported (Lewis and Geschickter). They occurred in the acoustic nerve, mid-brain, cervical region (2), adrenal, thigh, and finger.

McFarland and Sappington have recently reported a case and made a complete survey of the literature. They were able to collect 143 cases, of which 41 were retroperitoneal or within the adrenals, 18 were in the cervical, and 10 in the mediastinal region. Fifteen cases were intracranial and 13 occurred on the cranial nerves. Six cases showed multiple subcutaneous tumors, the maximum number of a single patient being 160. One of the cases was associated with von Recklinghausen’s disease. Many of the cases showed immature neuroblasts or neurocytes, 10 of such cases being recorded as malignant.

These tumors are embedded in a stroma of Schwann cells, and palisading may occasionally be seen. The ganglion cells vary from small to large mature forms and occasional neurites are found.

\[<sup>2</sup> These do not include the cases previously reported by Lewis and Geschickter.\]
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