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Different Types of Benign Nerve Sheath Tumors

Light Microscopy, Electron Microscopy and Autoradiography

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Summary. In a light-, electronmicroscopic and autoradiographic study different types of nerve sheath tumors were classified. Their cellular population was quantitatively evaluated in the electron microscope.

In the neurinoma the predominant cell was found to be the Schwann cell, but in the different types of neurofibromata a variable content of connective tissue cells was noted. The diffuse neurofibromata showed a quantitative cellular composition similar to normal peripheral nerves. In the plexiform neurofibroma a large number of fibroblasts were present and in the argyrophilic neurofibroma high content of perineurial cells was found. In autoradiographic sections the tumors showed in general a low proliferation rate (L.i. 1–3.6%). In the argyrophilic neurofibrom a higher labelling index (9.5%) was found.

Key words: Neuroma – Neurofibroma – Ultrastructure – Cell-kinetic.

Zusammenfassung. Verschiedene Typen von Nervenscheidentumoren wurden lichtmikroskopisch, elektronenmikroskopisch und autoradiographisch untersucht. Die elektronenmikroskopische quantitative Bestimmung der verschiedenen Zelltypen in den Tumoren ergab bei den Neurinomen eine überwiegende Beteiligung von Schwannschen Zellen (87,1%). Bei den Neurofibromen konnte eine unterschiedlich große Anzahl von Bindegewebszellen nachgewiesen werden. Die diffusen Neurofibrome wiesen im allgemeinen eine Zellpopulation auf, wie man sie auch in normalen peripheren Nerven finden kann. Bei den plexiformen Neurofibromen überwogen die Fibroblasten und bei den argyrophilen Neurofibromen wurde eine hohe Perineuralzellbeteiligung gefunden. Die Proliferationsrate der Tumore in der Autoradiographie war im allgemeinen relativ gering, nur das argyrophile Neurofibrom wies einen deutlich höheren Markierungsindex (9,5%) auf.

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Introduction

Light microscopic classification of nerve sheath tumors has always been controversial because of the difficulty of identifying individual cell types in peripheral nerves by the light microscope. A summary of the different nomenclatures is given in Table 1.

When the electron microscope was introduced into the investigation of nerve sheath tumors (Luse, 1960; Gruner, 1960) it was hoped to eliminate the discrepancies of nomenclature because of the better cell identification then possible. However, once again controversial results were obtained, firstly because few light microscopical types of peripheral nerve tumors had been investigated (Neurinoma: Pineda, 1964; Wechsler and Hossmann, 1965; Waggener, 1966; Cervos Navarro and Matakas, 1968; Fisher and Vuzevski, 1968; Cravioto, 1969. Diffuse Neurofibroma: Pineda, 1966; Poirier et al., 1968; Fisher and Vuzevski, 1968; Weber and Braun-Falco, 1972; Kimura et al., 1974. Neurofibroma with tactile corpuscles: Weiser, 1975) and secondly many different cell types (Schwann cells, fibroblasts, perineurial cells etc.) have been found in the tumors (e.g. Poirier et al., 1968; Raimondi and Beckman, 1967; Fisher and Vuzevski, 1968; Cravioto, 1969). The aim of this investigation was to select different types of nerve sheath tumors with the light microscope and to study their cell population, quantitatively, in the electron microscope. In addition an attempt was made to evaluate the proliferation kinetics of these tumors, using an in vitro autoradiographic method.

Table 1. Review of the different nomenclatures of benign nerve sheath tumors

Virchow, 1863	Zülch, 1962	Haferkamp, 1960	Stochdorph, 1965	Harkin, Reed, 1968	Russel, Rubinstein, 1971	Krücke, 1974	Lever, 1975
False Neuroma	Neurinoma	Neurinoma	Neuroma with different structural organization	Schwannoma	Schwannoma	Neurinoma	Neurilemmoma
		Encapsulated Neurofibroma		Plexiform Neurofibroma	Neurofibroma	Typ I (Plexiform Neurofibroma)	Neurofibroma
		Diffuse Neurofibroma Plexiform Neurofibroma		Diffuse Neurofibroma		Typ II Diffuse Neurofibroma	
						Typ III Neurofibroma with tactile corpuscles	
		Argyrophilic Neurinoma					
				Myxoma		Myxoma	

Materials and Methods

The clinical data of the patients are summarized in Table 2. The material investigated represented either biopsy specimens or tissue gained from surgical intervention. Immediately after resection the material was divided into small tissue blocks, which were prepared in the following ways:

a) Frozen material was used for the demonstration of Acetylcholinesterase (Karnovsky and Roots, 1964).

b) Formalin fixed material was treated for the demonstration of biogenic amines (Sakharowa and Sakharow, 1971) or embedded in paraffin. The sections were stained with HE, Alcian blue, van Gieson Elastic, Cauna silver technique.

c) Thin tissue slices were incubated in tissue culture medium (Trowells T 8) containing 20 μ Ci H^3-Thymidine/ml for one hour at 37° C and afterwards fixed in Glutaraldehyde and Osmiumtetroxide Palade and embedded in Epon 812.

The autoradiographic procedure on semithin sections was performed as described earlier (Jurecka et al., 1975).

Ultrathin sections were examined in a Philips EM 200 after staining with Uranylacetate and lead citrate.

For quantitative evaluation in the electron microscope at least 1000 cells of each specimen were classified. Cells were counted only when their nucleus was cut in the plane of section. Determination of the labelling index was performed by evaluating the relativ amount of labelled cells of at least 4000 cells counted in light microscopic autoradiographic sections.

Table 2. Clinical diagnosis of the patients. Localization of the biopsy and light microscopic classification of the tumors investigated

No.	Name	Age	Clin. Diag.	Localisation of biopsy	Light microscopic diagnosis
1	St.R.	49a	Acoustic neurinoma	Acoustic nerve	Neurinoma
2	P.W.	$1\,^1/_2$a	Neurofibromatosis	Face	Plexiform neurofibroma
3	W.A.	15a	Neurofibromatosis	Neck	Plexiform neurofibroma
4	K.H.	26a	Neurofibromatosis	Trunk	Diffuse neurofibroma
5	H.K.	28a	Neurofibromatosis	Face	Diffuse neurofibroma + Tactile corpuscles
6	T.E.	33a	Neurofibromatosis	Arm	Diffuse neurofibroma
7	T.E.	33a	Neurofibromatosis	Thigh	Diffuse neurofibroma
8	N.C.	51a	Neurofibromatosis	Leg	Diffuse neurofibroma
9	L.M.	52a	Neurofibromatosis	Breast	Diffuse neurofibroma
10	S.F.	52a	Neurofibromatosis	Trunk	Diffuse neurofibroma
11	W.A.	52a	Neurofibromatosis	Neck	Diffuse neurofibroma
12	V.E.	53a	Neurofibromatosis	Trunk	Diffuse neurofibroma
13	P.M.	13a	Neurofibromatosis	Arm	Argyrophilic neurofibroma

Results

1. Common Features in Different Types of Peripheral Nerve Tumors

a) Cells. In all types of nerve sheath tumors cells characteristic of normal peripheral nerves were observed in the light and electron microscope. However

distinct differences in the quantitative relationships of the individual cell types were found (Table 3).

Schwann cells were covered by a continuous basement membrane. The cells themselves contained a rounded or ovoid nucleus, a variable amount of cytoplasm and often long slender cell processes. Among the few cytoplasmic organelles, mitochondria predominated. Sometimes bundles of tiny intracytoplasmic filaments were found (Fig. 1a).

During the process of tumor formation the Schwann cells had mostly lost their characteristic relationship to the axons. However in all nerve sheath tumors except the Neurinoma myelinated and unmyelinated nerve fibers were found, if selected areas were examined (Fig. 1a, Fig. 2).

Occasionally, the Schwann cells of myelinated nerve fibers contained some myelin figures which could be interpreted as signs of myelin destruction (Fig. 2a). In one case some π-Granules were observed in the cytoplasm of Schwann cells of these fibers (Fig. 2b).

Regenerative phenomena (cluster formation of Schwann cells around myelinated and unmyelinated nerve fibers, basement membrane duplications around nerve fibers) were sometimes detected. Tumorous Schwann cells often formed onion bulb like formations around central myelinated fibers (Fig. 2c) as described by Ohnishi and Nada (1972).

Fibroblasts lacked a basement membrane (Fig. 1a). The elongated sometimes spindle shaped nucleus showed a more dense arrangement of chromatin. The

Table 3. Electron microscopic cell counts and labelling indices in the tumors investigated

No.	SC	F	PC	Mast cell	Vessels		Ly mono-nucl. C.	LI	C/SU
					EC	Peri-cytes			
1 NN	87.1	1.9			2.4	0.2	8.4		
2 PNE	42.6	48.0	2.7	0	5.4	0.2	1.1	1.0	69.0
3 PNF	30.4	45.1	2.5	1.5	13.5	3.3	3.7	2.0	16.8
4 DNF	52.5	31.2	7.6	3.0	5.4	0.3		3.6	55.1
5 DNF+T	25.9	34.2	1.1	12.9	16.9	2.9	6.1	1.2	35.7
6 DNF	50.9	30.8	8.6	3.3	5.8	0.6		1.0	43.4
7 DNF	53.0	30.3	4.2	3.2	7.0	2.2	0.1	1.0	42.0
8 DNF	55.6	27.8	0.9	8.7	4.8	0.4	1.8	1.1	67.5
9 DNF	74.8	15.9	0.9	3.1	4.1	0.3	0.9	3.6	61.5
10 DNF	59.1	30.4	1.2	1.4	7.2	0.7			
11 DNF+T	58.3	27.6	1.0	2.7	7.7	1.7	1.0	3.4	66.9
12 DNF	61.6	26.7	0.7	4.9	5.8	0.3	0.1		
13 ANF	37.1	17.3	30.7	2.2	11.0	1.2	0.5	EN	EN
								7.4	20.7
								EP	EP
								9.5	42.7

NN = Neurinoma, PNF = Plexiform Neurofibroma, DNF = Diffuse Neurofibroma, ANF = Argyrophilic Neurofibroma, T = Tactile Corpuscles, SC = Schwann Cells, F = Fibroblasts, PC = Perineurial Cells, EC = Endothelial Cells, Ly = Lymphocytes, LI = Labelling index, C/SU = Cell/Square Unit, EN = Endoneurial, EP = Epineurial

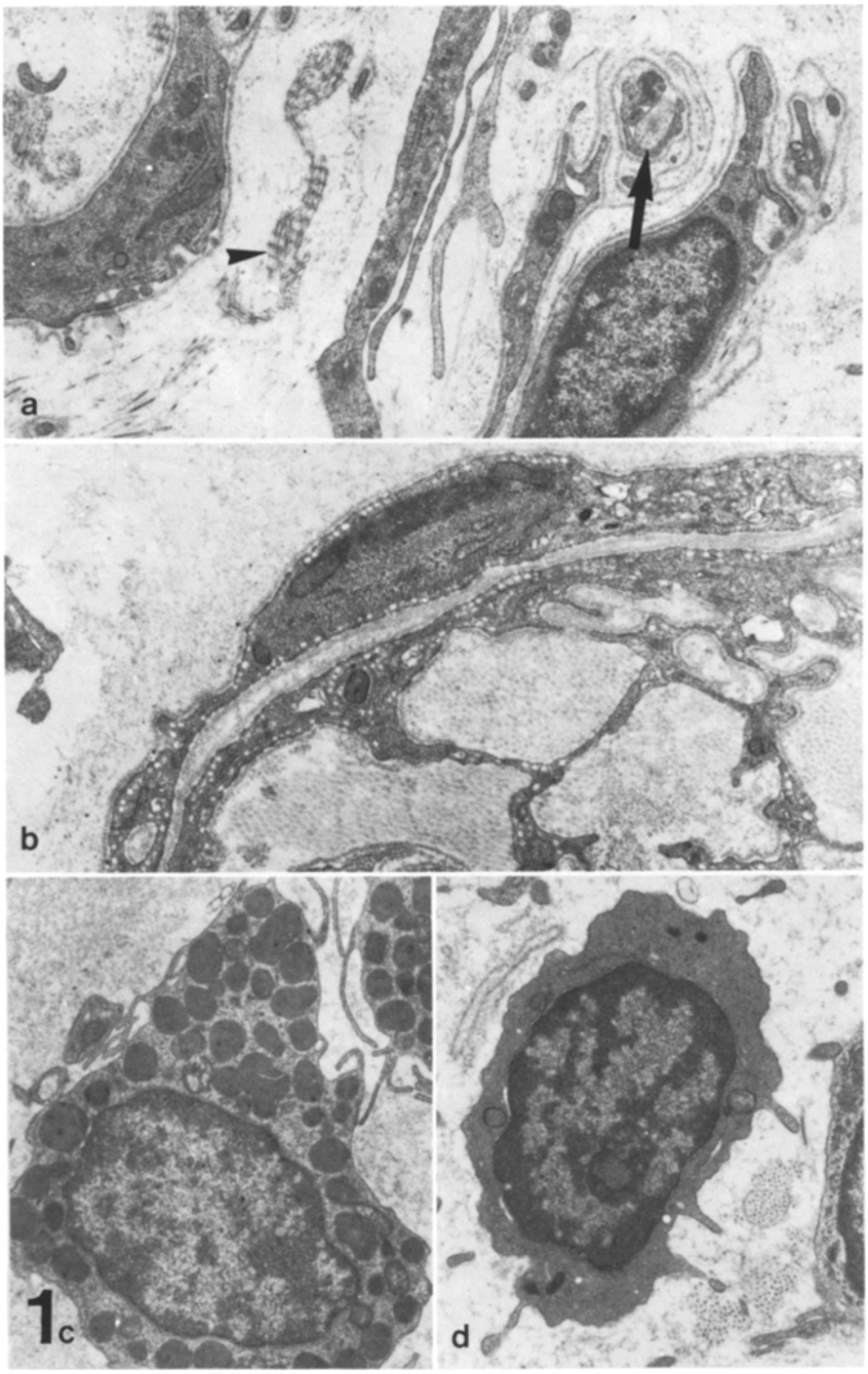


Fig. 1. a No. 11 Diffuse Neurofibroma. Schwann cells and their processes can be recognized by their continuous basement membrane. An axon (↑) is surrounded by multiple layers of basement membranes. In the middle of the figure a process of a connective tissue cell. (▲) Long spacing collagen. ×12,000. **b** No. 4 Diffuse Neurofibroma. Numerous perineurial cell processes covered by a basement membrane and numerous surface vesicels. ×12,000. **c** No. 5. Typical mast cell in a diffuse Neurofibroma. ×9000. **d** No. 2. Lymphocyte in a plexiform Neurofibroma. ×9000

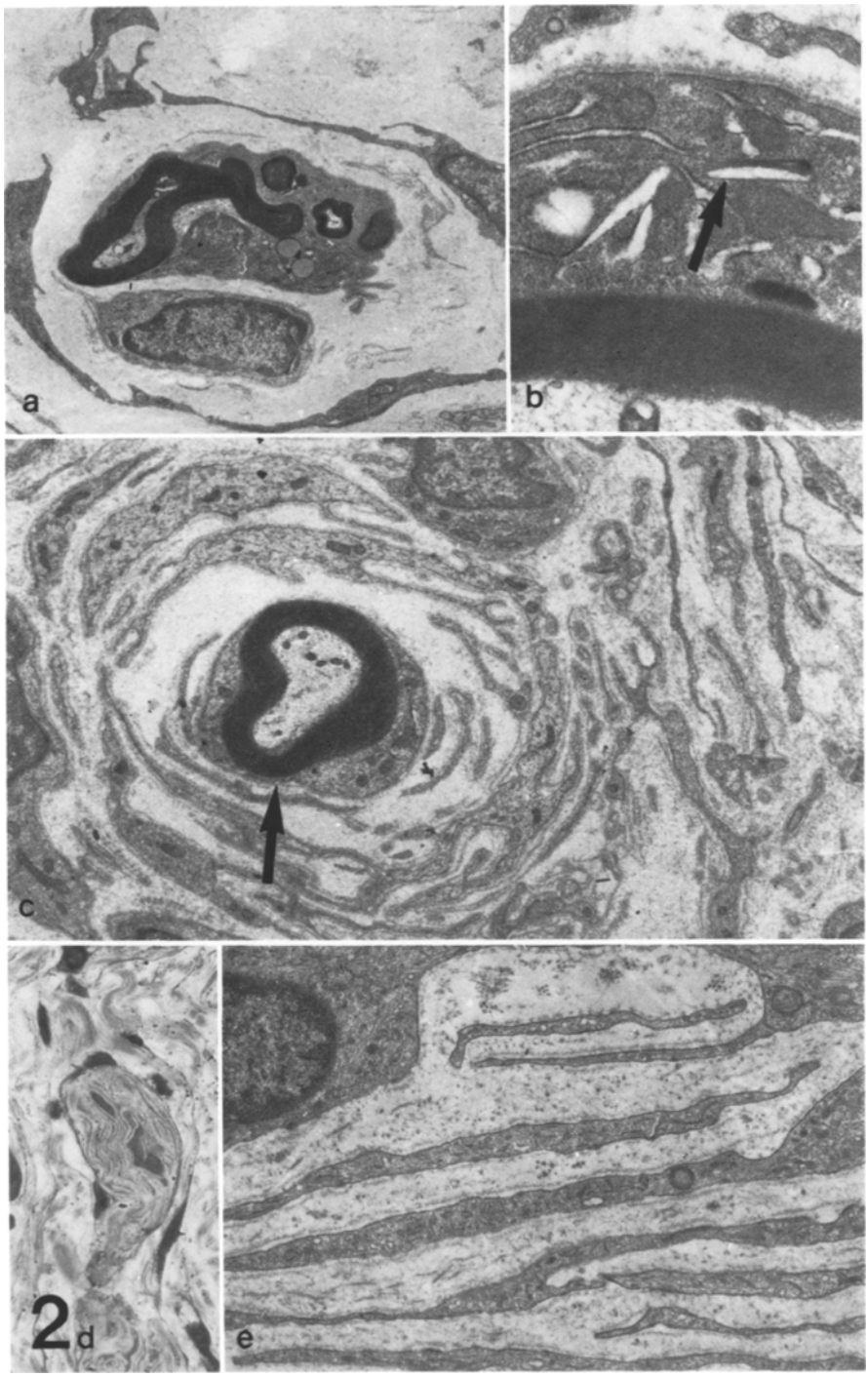


Fig. 2. a No. 5. Myelinated nerve fiber in a diffuse Neurofibroma. The Schwann cell cytoplasma contains some myelin figures and pigment. ×4800. **b** No. 2. Myelinated nerve fiber in a plexiform Neurofibroma. In the Schwann cell cytoplasm sometimes π-Granules could be found (↑). ×18,000. **c** No. 9. Myelinated nerve fiber in a diffuse Neurofibroma. The nerve fiber (↑) is surrounded by numerous concentric Schwann cell processes, forming an onion bulb like structure. ×6000. **d** No. 5. Tactile corpuscle like formation in a diffuse Neurofibroma. Semithin section. ×500. **e** No. 5. The same structure as in Figure 2d in the electron microscope. The cell processes are covered by a basement membrane and contain no surface vesicles. ×14,500

cytoplasm contained more cell organelles, including smooth and rough endoplasmic reticulum, a Golgi apparatus and mitochondria.

The typical perineurial cell was a spindle shaped cell with a chromatin dense, elongated nucleus and long slender overlapping and sometimes ramifying cell processes. The surface of the cells was covered by a basement membrane and numerous surface vesicles. There were few organelles and cytoplasmic fibrils were sometimes found (Fig. 1 b). Cells probably representing a transition between fibroblasts and perineurial cells were sometimes found. Apart from these typical cells a variable number of other cell types were present. These included mast cells (Fig. 1 c) lymphocytes and mononuclear cells mostly in a perivascular position (Fig. 1 d), capillary endothelial cells, pericytes and smooth muscle cells.

b) Blood Vessels. The blood vessels of the tumors sometimes contained multiple layers of basement membranes but otherwise showed normal ultrastructure. Vascularity varied in the different types of tumors; this is quantitatively reflected by the number of endothelial cells in Table 3.

c) Connective Tissue Fibers. A detailed description of the structure of connective tissue fibers has been given in a previous report (Lassmann et al., 1975). In tumor tissue a variable amount of collagenous fibers of endo- and epineurial type as well as long-spacing collagen (Fig. 1 a) and some elastic fibers are found.

d) Mucoid Degeneration. A common feature of the peripheral nerve sheath tumors is the so-called mucoid degeneration (Krücke, 1942). This is characterized by an increase of Alcian blue positive ground substance in the endoneurium combined with a diminution of endoneurial cellular structures and the occurrence of socalled "Körnchenzellen" (Krücke, 1939) (Fig. 3 b). In the electron microscope this mucoid material was not visible, but large vacuolated fibroblast-like cells were often found in these areas (Asbury et al., 1971). The vacuoles often contained microfibrillary or filamentous material (Fig. 3 b). Sometimes bundles of collagenous fibrils were found within the vacuoles, and it was sometimes also possible to demonstrate communication between the vacuoles and the extracellular space.

2. Specific Features of Individual Types of Peripheral Nerve Sheath Tumors

a) Neurinoma. This tumor type was predominately composed of Schwann cells (Table 3). In Antoni Typ A areas (Fig. 4 e) often numerous Schwann cells and their processes were bundeled together and surrounded by a common basement membrane (Fig. 4 g), whereas in Antoni Typ B areas Schwann cells were more isolated and often contained cytoplasmic inclusions.

b) Plexiform Neurofibroma. In light microscopic sections of plexiform Neurofibroma large areas of the nerve fascicles showed signs of mucoid degeneration while other areas revealed normal endoneurial structure containing numerous

myelinated and unmyelinated nerve fibers (Fig. 3a–c). Besides of the demonstration of nerve fibers by the Cauna silver technique and acetylcholinesterase reaction, in one case (No. 3) numerous adrenergic nerve fibers were recognized with the aim of formalin induced fluorescence.

In the electron microscope the tumor cell population revealed a predominance of connective tissue cells.

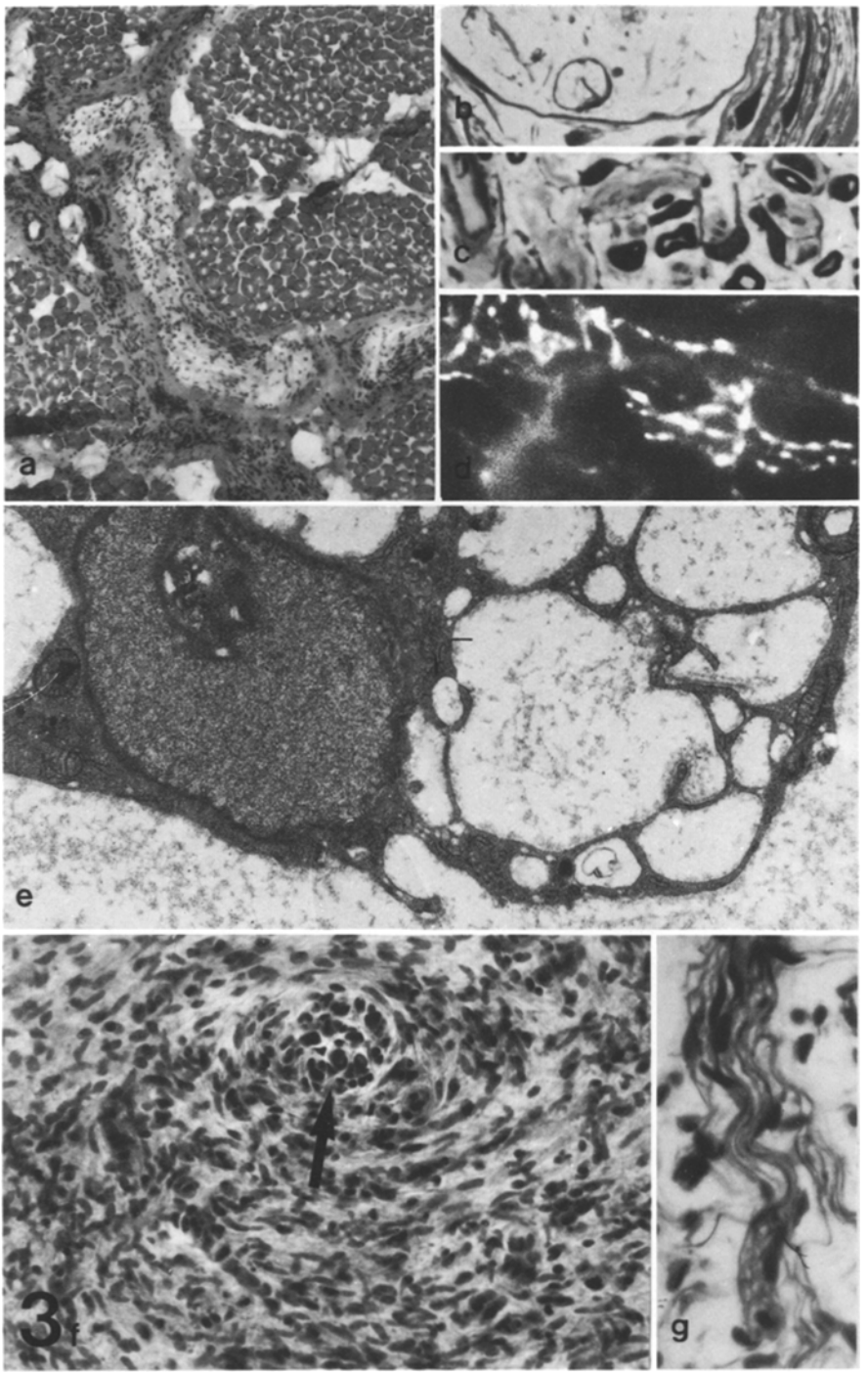
c) Diffuse Neurofibroma. Diffuse Neurofibroma (Fig. 3f, g) was mostly built up by Schwann cells and connective tissue cells. The quantitative evaluation of the different cell types revealed an average of 50–60% Schwann cells, 20–30% connective tissue cells and a variable amount of perineurial cells (Table 3). These values are comparable with the cellular composition of normal peripheral nerves (Thomas, 1963; Ochoa and Mair, 1969). This quantitative relation was relatively constant with the exception of two tumors, one with an amount of 75% Schwann cells, the other with 26% Schwann cells.

In two cases of diffuse neurofibromata tactile corpuscle like formations (Verocay Bodies) were found. In the electron microscope, these structures were built up entirely by Schwann cells (Fig. 2d, e).

d) Argyrophilic Neurofibroma. In the argyrophilic neurofibroma areas of endoneurial tumor formation like plexiform neurofibroma were found together with areas of diffuse tumor growth (Fig. 4a–c). In the silver impregnation (Cauna) numerous argyrophilic cells and cell processes were noted (Fig. 4d). The nerve fascicles in the plexiform part of the tumor were characterized by a largely increased thickness of the perineurium. In the endoneurium large areas showed signs of mucoid degeneration. In between some myelinated and unmyelinated nerve fibers were found. The quantitative evaluation of the cell population in this tumor type revealed a high amount of perineurial cells (31%, Table 3) in the plexiform as well as in the diffuse areas of the tumor.

Comparing the sections treated with the Cauna silver impregnation technique with the structure in the electron microscope it seemed that the argyrophilic cell processes belonged to perineurial cells as well as to Schwann cells.

Fig. 3. a No. 2. Thickened nerve fascicle in a plexiform Neurofibroma embedded in muscle tissue. Only in a small part in the center of the fascicle normal endoneurial structure can be found. Paraffin section, H.E. ×100. **b** No. 2. Marginal zone of a nerve fascicle in plexiform Neurofibroma showing signs of mucoid degeneration with a so called "Körnchenzelle". Semithin section, ×640. **c** No. 2. Central part of a nerve fascicle in plexiform Neurofibroma. Scattered myelinated nerve fibers are surrounded by an increased amount of ground substance and some connective tissue cells. Semithin section, ×640. **d** No. 3. Adrenergic nerve fibers in the central part of a nerve fascicle in plexiform Neurofibroma. Formalin induced Fluorescence (Sakharov). ×480. **e** No. 2. Electron micrograph of a so called "Körnchenzelle" (Giant vacuolated fibroblast). The content of the vacuoles is similar to the content of the extracellular space. ×8700. **f** No. 5. Diffuse Neurofibroma. In the center the transition of a nerve fascicle in the tumor tissue can be seen (↑). Paraffin section, HE. ×125. **g** No. 5. Nerve fibers in a diffuse Neurofibroma. Cauna silver technique. ×400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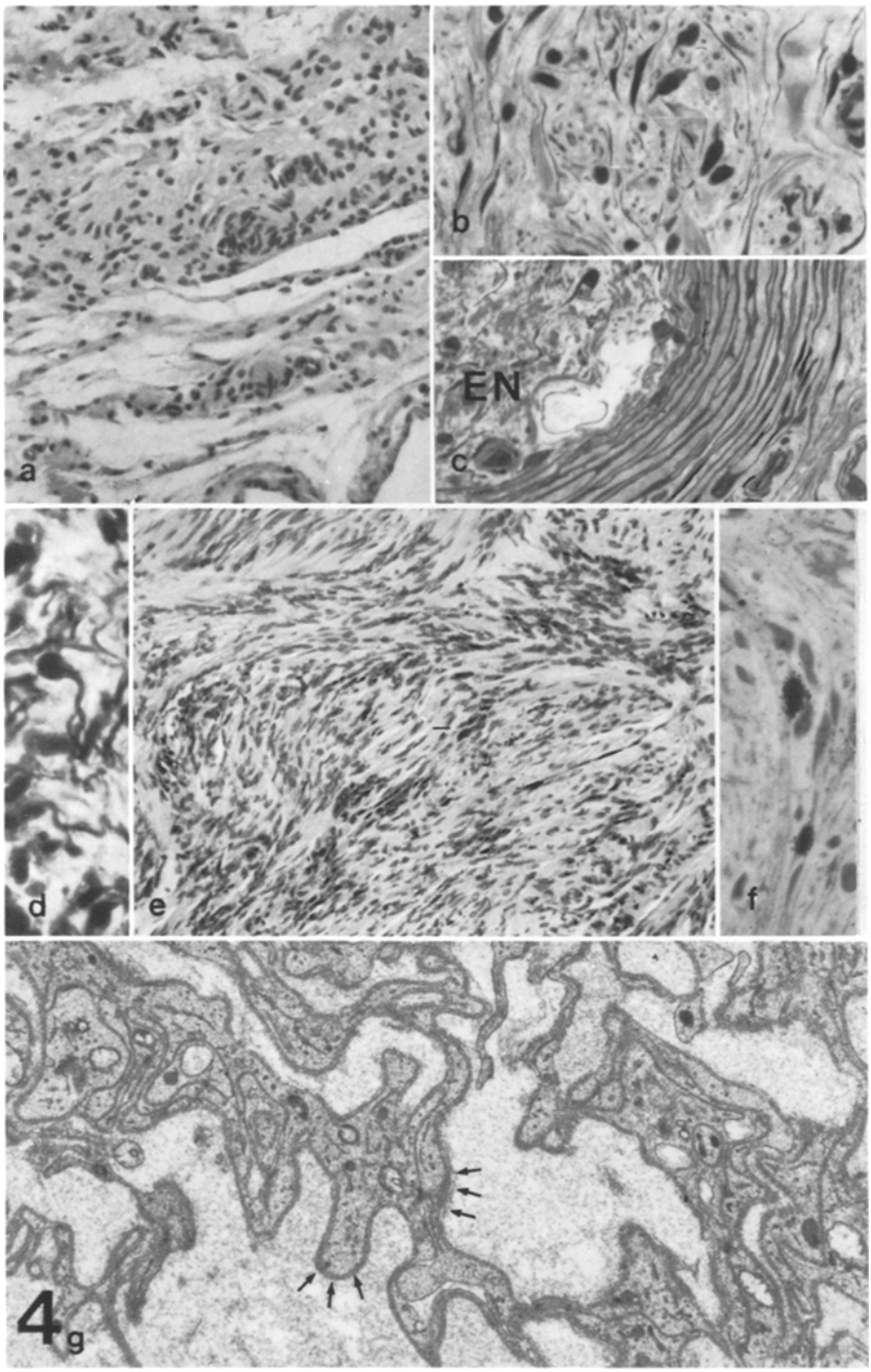

Fig. 4. **a** No. 13. Rows of tumor tissue in the diffuse part of argyrophilic Neurofibroma. Paraffin section, HE. ×200. **b** No. 13. Diffuse part of an argyrophilic Neurofibroma. The cell population consists of rounded and spindle shaped cells. Semithin section. ×400. **c** No. 13. Plexiform part of an argyrophilic Neurofibroma. The Perineurium of the fascicles is markedly increased in thickness. In the Endoneurium (*EN*) signs of mucoid degeneration can be demonstrated. Semithin section. ×320. **d** No. 13. Argyrophilic Neurofibroma. In the sections treated with the Cauna silver technique numerous argyrophilic cells and cell processes can be demonstrated. Cauna silver technique. ×800. **e** No. 1. Fibrillary portion of a Neurinoma. Paraffin section, HE. ×120. **f** No. 13. Autoradiography of an argyrophilic Neurofibroma. Two cells with ovoid nuclei are labelled. Semithin section. ×400. **g** No. 1. Fibrillary portion of Neurinoma. Numerous Schwann cell processes are covered by a common basement membrane (↑). ×8400

3. Autoradiography

All nerve sheath tumors investigated with autoradiography had a low labelling index (Table 3). As far as could be determined from light microscopic sections, Schwann cells, connective tissue cells and perineurial cells were all labelled. The labelling indices of diffuse neurofibromata ranged from 1‰ to 3.4‰. Argyrophilic neurofibroma had a higher labelling index (9.5‰). The plexiform Neurofibroma revealed a very low proliferation rate (1–2‰ Table 3).

Discussion

Our identification of the individual cell types in nerve sheath tumors was based on the characteristic appearances of these cells in normal peripheral nerves (Gamble, 1964; Thomas, 1963; Röhlich and Knoop, 1961). In general, discrimination of the different cell types was simple. Nevertheless the characterization of an individual cell sometimes proved difficult, especially regarding the transitional forms between perineural cells and fibroblasts. The main characteristic of Schwann cells – their relationship to axons – is mostly lost in peripheral nerve tumors and can only be found in the vicinity of nerve bundles entering the tumor. Previous light microscopic observations have suggested that de- and regenerative phenomena of myelinated and unmyelinated nerve fibers are very rare (Verocay, 1910; Thies, 1954; Lassmann, 1967), a finding supported by our present investigation. The nature of the cell responsible for the formation of nerve sheath tumors has been a matter of controversy since the first descriptions by Virchow (1859), Verneul (1861), Recklinghausen (1882) and Bruns (1908). Whereas in Neurinoma most electron microscopic descriptions claim the Schwann cell to be the tumor forming cell (Gruner, 1960; Luse, 1960; Wechsler and Hossmann, 1965; Poirier et al., 1968; Cervos-Navarro and Matakas, 1968; Cravioto, 1969), in Neurofibromata a variable content of other cell types has always been found. This observation is also confirmed by our investigation. We have quantified these differences in cell population and our results in various tumors ranged from a predominantly Schwann cell type, to predominantly fibroblastic tumors or tumors with a high content of perineurial cells.

The occurrence of cells without basement membrane has been explained in various ways, either by an incorporation of connective tissue cells from the primary tissue by the proliferating Schwann cells (Gruner, 1960; Waggener, 1966; Cravioto, 1969), an explaination that would not explain the high content of connective tissue cells in the plexiform neurofibromata or by dedifferentiation of Schwann cells into cells similar to connective tissue cells in the course of tumor formation (Heine et al., 1976). Alternatively Schwann cells, connective tissue cells and perineurial cells might all differentiate from a pluripotent mesenchymal stem cell (Feigin, 1971). We were not able to find convincing evidence from our material to support these views.

It has been suggested that all elements of normal peripheral nerves are involved in the formation of neurofibromata (Poirier et al., 1968; Chino and

Tsuruhara, 1968; Kimura et al., 1974; Lassmann et al., 1976). This hypothesis seems to agree with our observations in diffuse neurofibromata, which with two exceptions have a cellular composition similar to that of normal peripheral nerves.

The formation of tactile corpuscle like structures in nerve sheath tumors is a rare observation (Flörken and Steinbiss, 1921; Scherer, 1933; Schochet and Barrett, 1974; Krücke, 1974). Weiser (1975) reported a case of Paccinian neurofibroma, built up almost entirely of perineurial cells. In contrast, we found two cases in which so-called Verocay bodies were found, imitating Meissner corpuscles. These structures were composed of Schwann cells.

Comparing the light and electronmicroscopic sections of the argyrophilic neurofibroma, it was evident that Schwann cells and perineurial cells showed argyrophilia in the light microscope. It seems evident that a functional state of the cells is responsible for the argyrophilia, rather than a particular morphology. A characteristic of neurofibromata is their high content of mast cells (Greggio, 1911; Cornil and Michon, 1924). It is interesting that in one case of plexiform neurofibroma and in the neurinoma, no mast cells were found. In this connection the youth of the patient with plexiform neurofibroma has to be considered; in early life very few mast cells are found in the tissues (Rosenheim, 1886).

The absence of mast cells in our case of neurinoma might be explained by the fact that in these tumors 95% of mast cells are localized in the capsular or subcapsular region (Justich, 1973), regions which may have been missed in our investigation. In general the nerve sheath tumors investigated showed a low proliferation rate in autoradiographic preparations. Nevertheless, marked differences between the individual tumors were observed, the labelling index ranging from less than $1^0/_{00}$ to nearly $10^0/_{00}$. Further studies will be necessary to determine whether these differences can be correlated with the prognosis.

Much controversy surrounds the nomenclature of nerve sheath tumors (Table 1). The best classification would be an aetiologic one, based on the cell type responsible for tumor formation, but from our results it is evident that a classification of this type would be very difficult. Another possibility is a classification following the histological picture of the tumors, including their demarcation from the surrounding tissues and their content of connective tissue fibers. Thus the classifications introduced by Harkin and Reed (1968) or Krücke (1974) seems to be the best avaliable, since they are useful in routine pathology without being unduly complex.

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References

Asbury, A.K., Cox, S.C., Baringer, J.R.: The significance of giant vacuolation of endoneurial fibroblasts. Acta Neuropath. **18**, 123–131 (1971)

Bruns, L.: Die Geschwülste des Nervensystems. III. Die Geschwülste des extrakraniellen Anteils der Hirnnerven, der peripheren spinalen Nerven und des Plexus. Neurome und paraneurale Geschwülste. S. 419–473. Berlin: S. Karger 1908

Cervós-Navarro, J., Matakas, F.: Elektronenmikroskopischer Beitrag zur Histogenese der Neurinome. Verh. dtsch. Ges. Path. **52**, 391–395 (1968)
Chino, F., Tsuruhara, T.: Electron microscopic study of Recklinghausens disease. Jap. J. Med. Sci. Biol. **21**, 249–257 (1968)
Cornil, L., Michon, P.: Sur la présence de mastocytes dans les tumeurs cutanées de la maladie de Recklinhausen. C.R. Soc. Biol. (Paris) **91**, 787 (1924)
Cravioto, H.: The ultrastructure of acoustic nerve tumors. Acta Neuropath. **12**, 116–140 (1969)
Feigin, I.: The nerve sheath tumor, solitary and in von Recklinghausen's disease; a unitary mesenchymal concept. Acta Neuropath. **17**, 188–200 (1971)
Fisher, E.R., Vuzevski, V.D.: Cytogenesis of Schwannoma (neurilemmoma), neurofibroma, dermatofibroma and dermatofibrosarcoma as revealed by electron microscopy. Amer. J. clin. Path. **49**, 141–154 (1968)
Flörcken, H., Steinbiss, W.: Ein elephantiastisches Neurofibrom der Kopfschwarte. Bruns Beitr. klin. Chir. **124**, 451–458 (1921)
Gamble, H.C.: Comparative electron microscopic observations on the connective tissues of a peripheral nerve and a spinal nerve root in the rat. J. Anat. **98**, 17–25 (1964)
Greggio, H.: Les cellules granuleuses (Mastzellen) dans les tissus hormaux et dans certaines maladies chirurgicales. Arch. Med. exp. **23**, 323 (1911)
Gruner, J.: The elementary lesions of Recklinghausen's neurofibromatosis; Electron microscopic study. Rev. Neurol. **102**, 525–529 (1960)
Haferkamp, O.: Über die Neurome. Z. f. Krebsforsch. **63**, 378–408 (1960)
Harkin, J.C., Reed, R.J.: Tumors of the peripheral nervous system. AFIP Atlas Tumor Pathology II Ser., Fasc. 3 Washington, DC: AFIP 1968
Heine, H., Schaeg, G., Nasemann, Th.: Licht- und elektronenmikroskopische Untersuchungen zur Pathogenese der Neurofibromatose. Arch. Derm. Res. **256**, 85–95 (1976)
Jurecka, W., Ammerer, H.P., Lassmann, H.: The regeneration of a dissected peripheral nerve. An autoradiographic and electron microscopic study. Acta neuropath. (Berl.) **32**, 299–312 (1975)
Justich, E.: Über den Mastzellgehalt in Tumoren des peripheren Nervensystems. Acta Neuropath. **25**, 271–280 (1973)
Karnovsky, M.J., Roots, L.: Direct-colouring thiocholine technique for cholinesterases. J. histochem. Cytochem. **12**, 219–221 (1964)
Kimura, M., Kamata, Y., Matsumoto, K., Takaya, H.: Electron microscopical study on the tumor of von Recklinghausen's neurofibromatosis. Arch. Path. Jap. **24**, 79–91 (1974)
Krücke, W.: Die mucoide Degeneration der peripheren Nerven. Virchows Arch. path. Anat. **304**, 442–463 (1939)
Krücke, W.: Zur Histopathologie der neuralen Muskelatrophie, der hypertrophischen Neuritis und Neurofibromatose. Arch. Psychiat. Nervenkr. **115**, 180–236 (1942)
Krücke, W.: Pathologie der peripheren Nerven. In Handbuch der Neurochirurgie, bearbeitet v. W. Krücke. Bd. 7/3 Berlin-Heidelberg-New York: Springer 1974
Lassmann, G.: Neurofibromatose Recklinghausen. Untersuchungen bei 2 Fällen von cutaner Neurofibromatose und einem Neurofibrome encapsulée der Gebärmutter. Dt. Zeitschr. f. Nervenheilkunde **190**, 241–266 (1967)
Lassmann, H., Gebhart, W., Stockinger, L.: The reaction of connective tissue fibers in the tumor of Recklinghausen's disease. Virchows Arch. B Cell Path. **19**, 167–177 (1975)
Lassmann, H., Jurecka, W., Gebhart, W.: Some electron microscopic and autoradiographic results concerning cutaneous neurofibromas in von Recklinghausen's disease. Arch. Derm. Res. **255**, 69–81 (1976)
Lever, W.F.: Histopathology of the skin. pp. 684–685, Philadelphia: J.B. Lippincott Co. 1975
Luse, S.A.: Electron microscopic studies of brain tumors. Neurology **10**, 881–905 (1960)
Ochoa, J., Mair, W.G.P.: The normal sural nerve in man. I. Ultrastructure and numbers of fibers and cells. Acta Neuropath. (Berl.) **13**, 197–216 (1969)
Ohnishi, A., Nada, O.: Ultrastructure of the onion bulb like lamellated structures observed in the sural nerve of a case of von Recklinghausen's disease. Acta Neuropath. **20**, 258–263 (1972)
Pineda, A.: Submicroscopic structure of acoustic tumors. Neurology **14**, 171–184 (1964)
Pineda, A.: Electron microscopy of the tumor cells in neurofibromas. J. Neuropath. exp. Neurol. **25**, 158–159 (1966)
Poirier, J., Escourolle, R., Castaigne, P.: Les neurofibromes de la maladie de Recklinghausen. Etude ultrastructurale et place nosologique par rapport aux neurinomes. Acta Neuropath. **10**, 279–297 (1968)

Raimondi, A.J., Beckman, F.: Perineurial fibroblastomas. Their fine structure and biology. Acta Neuropath. **8**, 1–23 (1967)
Recklinghausen, F.v.: Über die multiplen Fibrome der Haut und ihre Beziehung zu den multiplen Neuromen. Virchows Festschrift. Berlin: A. Hirschwald 1882
Röhlich, P., Knoop, A.: Elektronenmikroskopische Untersuchungen von den Hüllen des Nervus ischiadicus der Ratte. Z. Zellforsch. **53**, 299–312 (1961)
Rosenheim, T.: Über das Vorkommen und die Bedeutung der Mastzellen im Nervensystem des Menschen. Arch. Psychiat. Nervenkr. **17**, 820 (1886)
Russel, P.S., Rubinstein, L.J.: Pathology of tumors of the nervous system. 2nd Ed. London: Edward Arnolds 1971
Sakharova, A.V., Sakharov, D.A.: Visualization of intraneuronal monoamines by treatment with formalin solutions. Histochemistry of Neurol. Transmission. Amsterdam: Elsevier, Prof. Brain Res. **34**, 11–25 (1971)
Scherrer, H.J.: Zur Frage des Zusammenhanges zwischen Neurofibromatosis und umschriebenem Riesenwuchs. Virchows Arch. path. Anat. **289**, 127–150 (1933)
Schochet, S.S.Jr., Barrett, D.A.: Neurofibroma with Aberrant Tactile Corpuscles. Acta neuropath. (Berl.) **28**, 161–165 (1974)
Stochdorph, O.: Über Gewebsbilder von Tumoren der peripheren Nerven. Acta Neuropath. **4**, 245–266 (1965)
Thies, W.: Beitrag zur Histogenese der von Recklinghausenschen Neurofibromatose der Haut unter besonderer Berücksichtigung des vegetativen Nervensystems. Arch. Derm. Syph. (Berl.) **198**, 619–623 (1954)
Thomas, P.K.: The connective tissue of peripheral nerve, an electron microscopic study. J. Anat. **97**, 35–44 (1963)
Thomas, P.K.: The cellular response to nerve injury. 1. The cellular outgrowth from the distal stump of transected nerve. J. Anat. (Lond.) **100**, 287–303 (1966)
Verneul, A.A.S.: Observations pour servir à l'histoire des alterations locales des Nerves (Nevr. plexiforme). Arch. gén. Med. **II**, 537–552 (1861)
Verocay, I.: Zur Kenntnis der Neurofibrome. Beitr. Path. Anat. **48**, 1–69 (1910)
Virchow, R.: Die Cellularpathologie. Berlin: August Hirschwald 1859
Virchow, R.: Die krankhaften Geschwülste. Bd. 3. Berlin: August Hirschwald 1863
Waggener, J.D.: Ultrastructure of benign peripheral nerve sheath tumors. Cancer **19**, 699–709 (1966)
Weber, K., Braun-Falco, O.: Zur Ultrastruktur der Neurofibromatose. Hautarzt **23**, 116–122 (1972)
Wechsler, W., Hossmann, K.A.: Zur Feinstruktur menschlicher Akustikusneurinome. Beitr. path. Anat. **132**, 319–343 (1965)
Weiser, G.: An electron microscope study of "Pacinian Neurofibroma". Virchows Arch. A. Path. Anat. and Histol. **366**, 331–340 (1975)
Zülch, K.I.: Brain tumors: their biology and pathology. New York: Springer 1962

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