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An Electron Microscope Study of "Pacinian Neurofibroma"

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Summary. An electron microscope study has been made of the "Pacinian neurofibroma". Unlike the usual neurofibroma the "Pacinian neurofibroma" is characterized by a proliferation of the so-called perineurial cells. Groups of surface vesicles, the absence of mesoaxons and a fragmented basallamina differentiate these perineurial cells from Schwann cells. The formation of the perineurial cells can be traced continuously from small and wide submicroscopic cell-bands and clubshaped thickenings to ribbonlike cell complexes as well as to tactile-like structures. The most developed complexes and structures are visible with the light microscope. These formations do not correspond with real tactile corpuscles, rather they can be considered as neoplastic structures of the perineurium.

Introduction

Neurofibromas occur singly or manifoldly in Recklinghausen's disease. Studies with the light microscope have shown that neurofibromas involve a distinct proliferation of all the cell components of the peripheral nerve, whereby it is assumed that the perineurium is also present (Stochdorph, 1965; Ackerman and Rosai, 1974). Observed with the electron microscope cells of the Schwann cell type, which are characteristic for this tumor and distinguish its form, are visible in the neurofibroma, fibroblasts, collagen fibres, vessels, mast cells and macrophages, all of which are a part of the proliferated endoneurium, together with processes of the Ganglion cells, i.e. the axons are also visible (Gruner, 1960; Pineda, 1966, 1970; Waggener, 1966; Fisher and Vuzevski, 1968; Poirier *et al.*, 1968; Nürnberger *et al.*, 1970; Weber and Braun-Falco, 1972). Another particular cell type of the peripheral nerve is the so-called perineurial cell; cells of this type are found within the perineurium. Feyrter (1938) considered them as endothelial cells and Denny-Brown (1946) regarded them as specialized mesothelial cells. On the basis of electron microscope studies Lehman (1957, 1959) termed them "neurothel"; Shanthaveerappa and Burne (1962, 1963, 1964) used the expression perineurial epithelium. In general this cell type is considered to be a so-called perineurial cell. (Röhlich and Knoop, 1961; Thomas, 1963, 1967; Gamble, 1964; Gamble and Eams, 1964; Waggener *et al.*, 1965; Gamble and Breathnach, 1965; Thomas and Jones, 1967; Lassmann and Ammerer, 1974); its participation in the formation of neurofibromas has not yet been established.

The ultrastructure of "distorted organoid structures" (Ackerman and Rosai, 1974), which are found in some neurofibroma, is also unknown. Observed with a light microscope they remind one partly of tactile corpuscles (pseudo-Meissnerian corpuscles: Stout, 1949; Mikuz and Propst, 1972); for this reason such neurofibromas were also described as plexiform neuroma with tactile corpuscles (Brögli, 1931), Corpusculo-Schwannoma (Jordan, 1933), tumors of tactile end-organs

(Saxen, 1948), neuroma of Wagner-Meissner tactile corpuscles (Hill, 1951), Pacinian neurofibroma (Prichard and Custer, 1952), as well as neurofibroma with aberrant tactile corpuscles (Schochet and Barrett, 1974).

Case Report

Recently we were provided the opportunity to study such a tumor with the electron microscope. We obtained information regarding the formation of the tactile-like structures in the neurofibroma, on the one hand, and regarding the participation of the so-called perineurial cells in proliferations, on the other hand.

Material and Methods

The tissue samples were taken from an eleven day old male infant. A neurofibroma approximately as large as the palm of a hand, which was clinically considered to be a lymphangioma, was removed surgically from the right flank area. The materials obtained during the operation for the electron microscope study were prepared using the usual methods. The tissue blocks were fixed with phosphate buffered (0.15 M, pH 7), 6.5% glutaraldehyde followed by post-fixation with Dalton's chrome-osmium tetroxide. Thin sections (Reichert OM UII) stained with uranyl acetate and lead citrate were examined in a Zeiss electron microscope EM 9A.

Results

Light Microscopy

In the cutaneous and subcutaneous tissue a typical neurofibroma is found. It consists of cells with markedly elongated nuclei, a typical disorderly array of fibres and vessels, innumerable tactile-like structures, as well as nerve bundles located on the lower edge of the tumor. The tactile-like structures vary in size; they are oval or elongated and are found singly or in groups (Fig. 1a and b). These structures in the semi-thin sections are closely related to the ribbonlike cell complexes (Fig. 1c). Furthermore it becomes clear that they show a palisading of the cells or have a whirling configuration with eccentrically located nuclei (Fig. 1d). All of these formations are found in the fibromatous section of the tumor.

Electron Microscopy

The characteristic ultrastructural features of the neurofibroma are shown in Fig. 2–4.

Examined under the electron microscope the tactile-like structures are shown to have distinct differences in size and various forms, however they always consist of groups of the same kind of elongated cells (Fig. 2).

They are distinguished by flattened cell bodies, which branch out into narrow cytoplasmic processes; the latter are often found, as a result of sectioning, isolated from the mother cell. Mitochondria, the endoplasmic reticulum and Golgi apparatus are situated predominantly in the perinuclear area. Large groups of surface vesicles, as well as a fragmented circumferential basallamina are very typical. The narrow cell bodies are arranged in wavelike or spirallike patterns, whereby the central nuclear area is eccentric. Intercellular contact is inferred by a slight overlapping of the long cytoplasmic processes (Fig. 3). Isolated axons

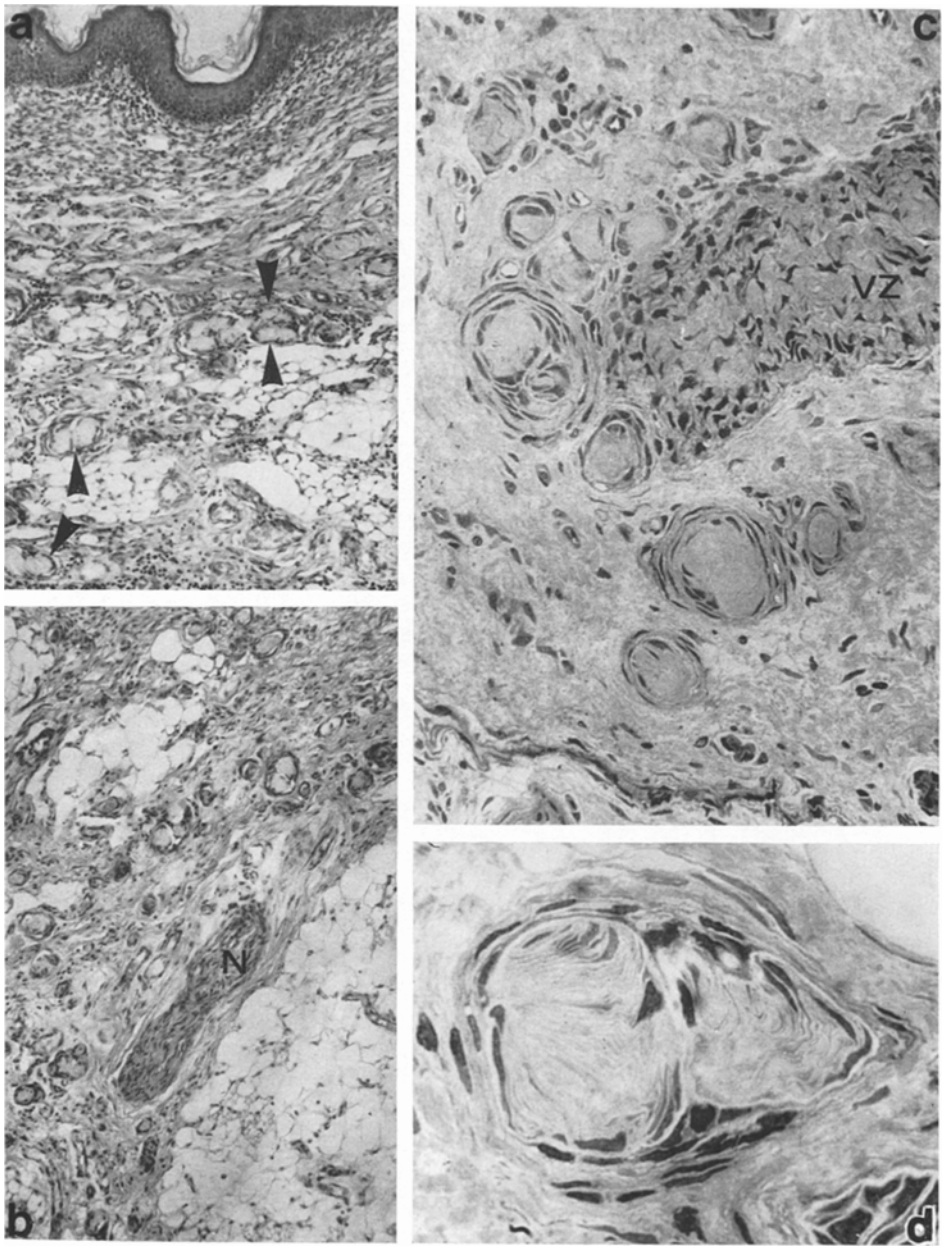

Fig. 1. (a and b) So-called "Pacinian neurofibroma" with typical nerve bundles (*N*) and innumerable tactile-like structures, which are found singly or in groups (indicated by arrows). Note the difference in size. HE×40. (c) Ribbonlike cell complexes (*VZ*) closely related to the tactile-like structures. Semi-thin section. Methylene blue, ×400. (d) Tactile-like structures with a palisading of the cells or a whirling configuration; eccentrically located nuclei. Semi-thin section. Methylene blue, ×1000

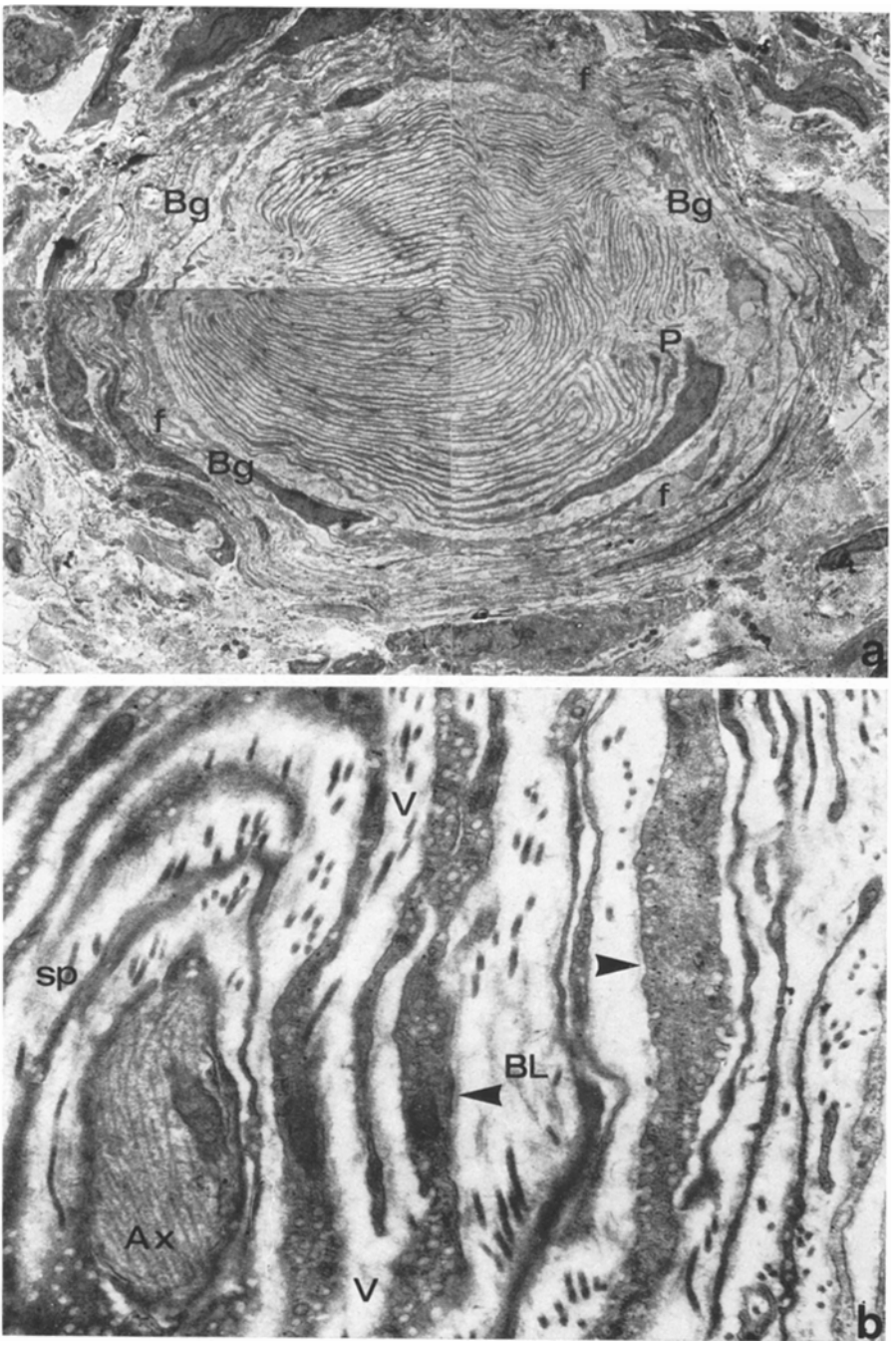

Fig. 2. (a) An electron microscope view of a tactile-like structure consisting of groups of proliferated perineurial cells (*P*). Directly next to it the concentric structure of the connective tissue (*BG*) of the neurofibroma with fibroblasts (*f*). Original magnification, ×1800. (b) A tactile-like structure with an axon which is in close contact with perineurial cells. Note the characteristic grouping of surface vesicles (*V*) and the fragmented basallamina (*BL*). Original magnification, ×11100

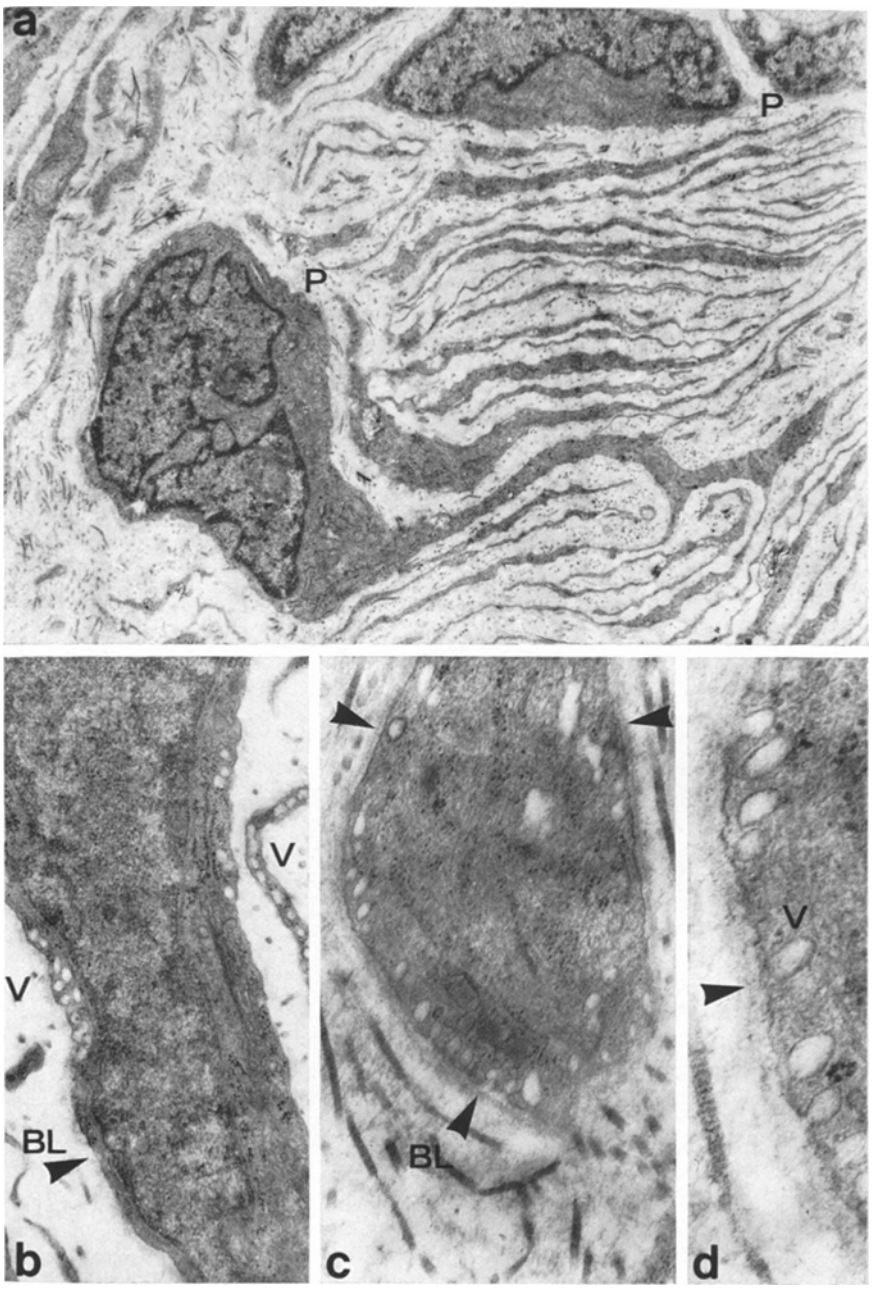

Fig. 3. (a) Proliferated so-called perineurial cells (*P*) with eccentric perinuclear area and elongated cell bodies branching out into narrow cytoplasmic processes. The collagen fibres are more dense within the intercellular spaces. Original magnification, ×4000. (b) Characteristic groups of vesicles (*V*) on the cell surface. Golgi apparatus, endoplasmic reticulum and mitochondria are prominent in the perinuclear area. Basallamina (*BL*). Original magnification, ×19000. (c and d) Cell process with circumferential basallamina (*BL*) and surface vesicles (*V*). Original magnification, ×19000 and ×42000 resp.

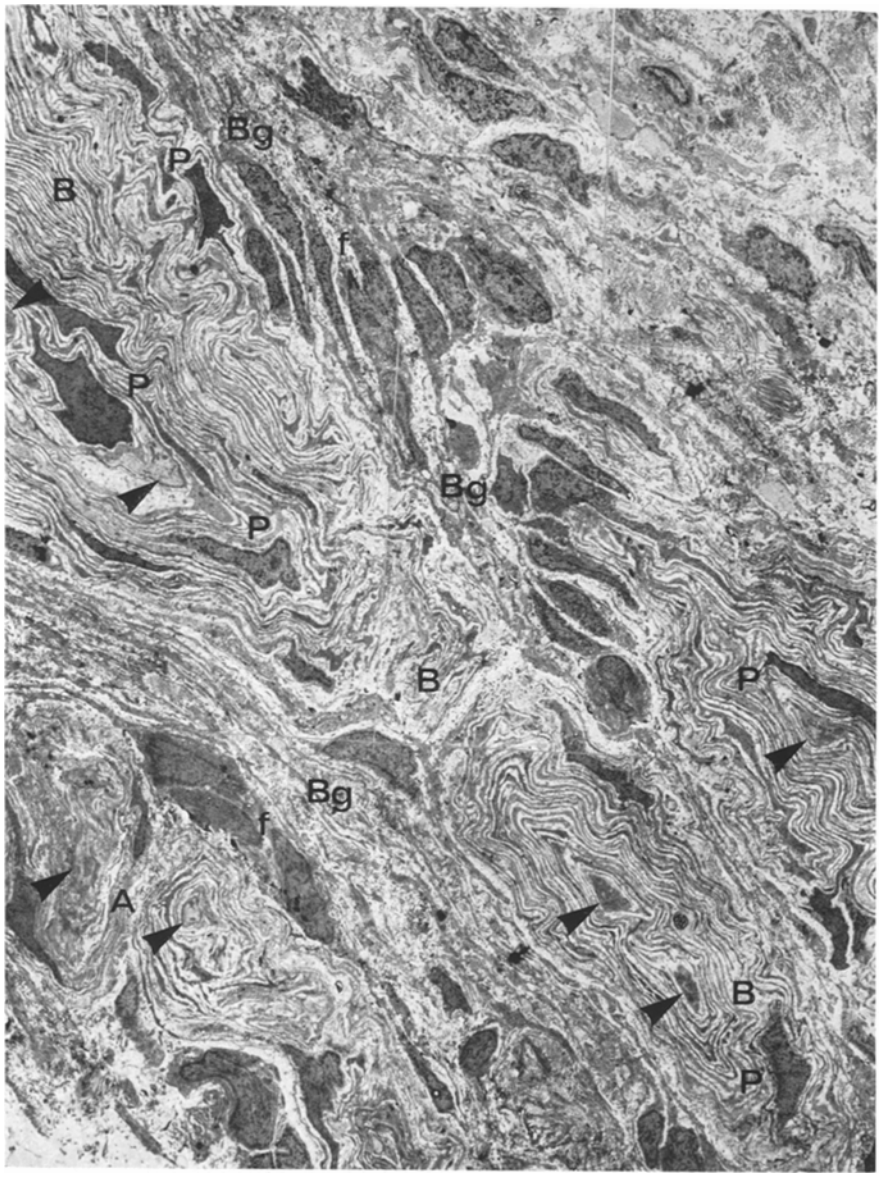

Fig. 4. Wide cell bands (*B*) and clubshaped thickenings (*A*) of the perineurial cells (*P*). Between them isolated axons (indicated by arrows) are found as in the tactile-like structures (see Fig. 2b). Connective tissue (*BG*) and fibroblasts (*f*) of the neurofibroma. Original magnification, ×1800

are also found in these tactile-like structures. The small cytoplasmic processes of the described cells lie close to the axons, however mesoaxon formations typical for the Schwann cells are never present (Fig. 2b). Within the intercellular spaces of the tactile-like structures the collagen bundles are more dense than in the

remaining connective tissue of the neurofibroma (Fig. 2 and 3). Under the electron microscope the ribbonlike cell complexes, which are also observed with the light microscope, vary considerably in size and form. Like the tactile-like structures they consist submicroscopically of the same elongated cells with eccentric perinuclear areas. These cells also form various lamellar bands and clubshaped thickenings; collagen fibre bundles and sometimes occasional axons are found between them (Fig. 4). Vessels are only found in the pure fibromatous part of the tumor and are inconspicuous.

Discussion

Grossly and microscopically the tumor has all the typical characteristics of a surface neurofibroma. Grossly, it has a soft consistency and typical changes of elephantiasis in this skin region are evident. Microscopically, it is formed by a combined proliferation of all the elements of a peripheral nerve. We would like to point out that tactile-like structures and ribbonlike cell concentrations are also found in the tumor. Electron microscopically the proliferated cells of the Schwann cell type and fibroblasts are prominant in the usual neurofibroma (Gruner, 1960; Pineda, 1966, 1970; Fisher and Vuzevski, 1968; Poirier *et al.*, 1968; Nürnberger *et al.*, 1970; Weber and Braun-Falco, 1972). In the neurilemoma and the granular cell myoblastoma (Abriskossoff, 1926, 1931; Feyrter, 1935, 1949, 1952 etc.) proliferated cells of the Schwann cell type alone are prominant (Luse, 1960, 1962; Pineda, 1964a, 1964b, 1965; Wechsler and Hossmann, 1965; Cervos-Navarro *et al.*, 1968; Fisher and Vuzevski, 1968; Fisher and Wechsler, 1962; Garancis *et al.*, 1970; Sobel *et al.*, 1971; Weiser and Propst, 1973; etc.). In the present neurofibroma a different cell type corresponding to the tactile-like structures and the ribbonlike cell complexes is prominant. This cell type is characterized by a narrow elongated cell body with an eccentric perinuclear area, a fragmented circumferential basallamina and groups of innumerable surface vesicles. The latter and the absence of mesoaxons distinguish this cell type from proliferated Schwann cells of the neurofibroma. Moreover it has many parallels with the perineurial cells of the peripheral nerve, which likewise have elongated cell bodies with central cytoplasm, numerous surface vesicles and a fragmented circumferential basallamina (Röhlich and Knoop, 1961; Thomas, 1963; Waggener *et al.*, 1965; etc.); in this respect they are identical. In our opinion the type mentioned above can be considered as a proliferated perineurial cell.

The perineurial cells of the peripheral nerve lie in the perineurial lamellar sheath. This sheath consists of at least one or more cell layers and surrounds the individual nerve bundles. In our opinion this formation in the present neurofibroma is imitated by the proliferated perineurial cells in the form of tactile-like structures and ribbonlike cell complexes. The axons found in these formations help clarify the structure of the regular perineurium. The formation of the proliferated perineurial cells can be traced from submicroscopic narrow cell bands to cell complexes which are visible with the light microscope. Accordingly the ribbonlike cell complexes and tactile-like structures, which consist of proliferated perineurial cells, represent the most distorted forms of the perineurium. These structures in the tumor, despite certain similarities with the nervous end-organs of the Wagner-Meissner (Cauna and Ross, 1960) or the Vater-Pacinian type

(Pease and Quilliam, 1957; Polacek and Mazanec, 1966; Nishi *et al.*, 1969; Spencer and Schaumburg, 1973) should therefore not be characterized as tactile corpuscles, which based on the results of light microscope studies was the case until now (Brögli, 1931; Jordan, 1933; Saxen, 1948; Hill, 1951; Prichard and Custer, 1952; Schochet and Barrett, 1974).

Based on the findings of electron microscope studies, the so-called "Pacinian neurofibroma" should therefore be considered as a neurofibroma with a dominant proliferation of perineurial cells.

References

Abrikossoff, A.: Über Myome ausgehend von der quergestreiften willkürliche Muskulatur. Virchows Arch. path. Anat. **260**, 245–238 (1926)

Abrikossoff, A.: Weitere Untersuchungen über Myoblastenmyome. Virchows Arch. path. Anat. **280**, 723–740 (1931)

Ackerman, L. V., Rosai, J.: Surgical pathology, 1128 pp. St. Louis, Mo.: C. V. Mosby Co. 1974

Brögli, M.: Ein Fall von Rankenneurom mit Tastkörperchen. Frankfurt. Z. Path. **41**, 595–610 (1931)

Cauna, N., Ross, L. L.: The fine structure of Meissner's touch corpuscles of human fingers. J. biophys. biochem. Cytol. **8**, 467–482 (1960)

Cervos-Navarro, J., Matakas, F., Lazaro, M. C.: Das Bauprinzip der Neurinome. Ein Beitrag zur Histogenese der Nerventumoren. Virchows Arch. Abt. A **345**, 276–291 (1968)

Denny-Brown, D.: Importance of neural fibroblasts in the regeneration of nerve. Arch. Neurol. Psychiat. (Chic.) **55**, 171–215 (1946)

Feyrter, F.: Über eine eigenartige Geschwulstform des Nervengewebes im menschlichen Verdauungsschlauch. Virchows Arch. path. Anat. **295**, 480–501 (1935)

Feyrter, F.: Über den Naevus. Virchows Arch. path. Anat. **301**, 417–469 (1938)

Feyrter, F.: Über die granulären neurogenen Gewächse. Beitr. path. Anat. **110**, 181–208 (1949)

Feyrter, F.: Über die granulären Neurome (sog. Myoblastenmyome). Virchows Arch. path. Anat. **322**, 66–72 (1952)

Fisher, E. R., Vuzevski, V. D.: Cytogenesis of Schwannoma (Neurilemoma), Neurofibroma, Dermatofibroma, and Dermatofibrosarcoma as revealed by electron microscopy. Amer. J. clin. Path. **49**, 141–154 (1968)

Fisher, E. R., Wechsler, H.: Granular cell myoblastoma—a misnomer. Cancer (Philad.) **15**, 936–954 (1962)

Gamble, H. J.: Comparative electron-microscopic observations on the connective tissues of a peripheral nerve and a spinal nerve root in the rat. J. Anat. (Lond.) **98**, 17–25 (1964)

Gamble, H. J., Breathnach, A. S.: An electron-microscope study of human foetal peripheral nerves. J. Anat. (Lond.) **99**, 573–584 (1965)

Gamble, H. J., Eames, R. A.: An electron microscope study of the connective tissues of human foetal peripheral nerves. J. Anat. (Lond.) **98**, 655–633 (1964)

Garancis, J. C., Komorowski, R. A., Kuzma, J. F.: Granular all myoblastoma. Cancer (Philad.) **25**, 542–550 (1970)

Gruner, J. E.: Les lésions élémentaires de la neurofibromatose de Recklinghausen. Etude au microscope electronique. Rev. neurol. **102**, 525–529 (1960)

Hill, R. P.: Neuroma of Wagner-Meissner Tactile corpuscles. Cancer (Philad.) **4**, 879–882 (1951)

Jordan, P.: Tastkörperartige Bildungen in einem zelligen Naevus der behaarten Kopfhaut. Zur Kenntnis des Neuronaevus, des Neurinoms, des Psammoms, der Cutis und Pseudo-Cutis verticis gyrata und der Recklinghausenschen Krankheit. Arch. Derm. Syph. (Berl.) **169**, 105–126 (1933)

Lassmann, H., Ammerer, H. P.: Schwann Cells and Perineurium in Neuroma. Virchows Arch. Abt. B **15**, 313–321 (1974)

Lehman, H. J.: Über Struktur und Funktion der perineuralen Diffusionsbarriere. Z. Zellforsch. **46**, 232–241 (1957)

Lehman, H. J.: Die Nervenfaser. In: Handbuch der mikroskopischen Anatomie des Menschen, Bd. IV/I. Ed. W. Bargman. Berlin-Heidelberg-New York: Springer 1959

Luse, S. A.: Electron microscopic studies of brain tumors. Neurology (Minneap.) **10**, 881–905 (1960)

Luse, S. A.: Electron microscopy of brain tumors. In: W. S. Fields and P. C. Sharkey, The biology and treatment of intercranial tumors. Springfield: Ch. C. Thomas 1962

Mikuz, G., Propst, A.: Über vasculäre Neurofibromatose. Virchows Arch. Abt. A **356**, 173–185 (1972)

Nishi, K., Oura, C., Pallie, W.: Fine structure of Pacinian corpuscles in the mesentery of the cat. J. Cell Biol. **43**, 539–552 (1969)

Nürnberger, F., Müller, G., Rockert, H.: Zur Ultrastruktur des Neurofibroms. Arch. klin. exp. Derm. **237**, 796–799 (1970)

Pineda, A.: Submicroscopic structure of acoustic tumors. Neurology (Minneap.) **14**, 171–184 (1964a)

Pineda, A.: Neurolemmomas. Trans. Amer. neurol. **89**, 241–242 (1964b)

Pineda, A.: Collagen formation by principal cells of acoustic tumors. Neurology (Minneap.) **15**, 536–547 (1965)

Pineda, A.: Electron microscopy of the tumor cells in "neurofibromas". J. Neuropath. exp. Neurol. **25**, 158–159 (1966)

Pineda, A.: The fine structure of peripheral nerve tumors, current concepts. At the VI. Int. Congr. Neuropath. 1970

Poirier, J., Escourolle, R., Casthigne, P.: Les neurofibromes de la maladie de Recklinghausen. Etude ultrastructurale et place nosologique par rapport aux neurinomes. Acta neuropath. (Berl.) **10**, 279–294 (1968)

Polacek, P., Mazanec, L.: Ultrastructure of mature Pacinian corpuscles from the mesentery of adult cat. Z. mikr.-anat. Forsch. **75**, 343–354 (1966)

Prichard, R. W., Custer, R. Ph.: Pacinian-neurofibroma. Cancer (Philad.) **5**, 297–301 (1952)

Röhlich, P., Knoop, A.: Elektronenmikroskopische Untersuchungen an den Hüllen des N. Ischiadicus der Ratte. Z. Zellforsch. **53**, 299–312 (1961)

Saxen, E.: Tumours of tactile end-organs. Acta path. microbiol. scand. **25**, 66–79 (1948)

Schochet, S. S., Barrett, D. A.: Neurofibroma with aberrant tactile corpuscles. Acta neuropath. (Berl.) **28**, 161–165 (1974)

Shanthaveerappa, T. R., Bourne, G. H.: The "perineurial epithelium", a metabolically active, continuous, protoplasmic cell barrier sourrounding peripheral nerve fasciculi. J. Anat. (Lond.) **96**, 527–537 (1962)

Shanthaveerappa, T. R., Bourne, G. H.: The perineurial epithelium: nature and significance. Nature (Lond.) **199**, 577–579 (1963)

Shanthaveerappa, T. R., Bourne, G. H.: The perineurial epithelium of sympathetic nerves and ganglion and its relation to the pia-arachnoid mater of the central nervous system and perineurial epithelium of peripheral nerves. Z. Zellforsch. **61**, 742–753 (1964)

Sobel, H. J., Marquet, E., Avrin, E., Schwarz, R.: Granular cell Myoblastoma. Amer. J. Path. **65**, 69–71 (1971)

Spencer, P. S., Schaumburg, H. H.: An ultrastructural study of the inner core of the Pacinian corpuscle. J. Neurocytol. **2**, 217–235 (1973)

Stochdorph, O.: Über Gewebsbilder von Tumoren der peripheren Nerven. Acta neuropath. (Berl.) **4**, 245–266 (1965)

Stout, A. P.: Tumors of the peripheral nervous system. Atlas of tumor pathology, sect. II, fasc. 6. Washington, D. C.: Armed Forces Institute of Pathology 1949

Thomas, P. K., Jones, O. G.: The cellular response to nerve section. J. Anat. (Lond.) **101**, 45–55 (1967)

Waggener, J. D.: Ultrastructure of benign peripheral nerve sheat tumors. Cancer (Philad.) **19**, 699–709 (1966)

Waggener, J. D., Bunn, S. M., Beggs, J.: Diffusion of ferritin within the peripheral nerve sheat. J. Neuropath. exp. Neurol. **24**, 430–454 (1965)

Weber, K., Braun-Falco, O.: Zur Ultrastruktur der Neurofibromatose. Hautarzt **23**, 116–122 (1972)

Wechsler, W., Hossmann, K. A.: Zur Feinstruktur menschlicher Acusticusneurinome. Beitr. path. Anat. **132**, 319–343 (1965)
Weiser, G., Propst, A.: Elektronenoptische Untersuchung zur Histogenese des Granulären Neuroms. Virchows Arch. Abt. A **358**, 193–204 (1973)

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