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Fine Structure of the Pick and Hirano Bodies in a Case of Pick's Disease

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Summary. Brain tissue from an autopsied case of Pick's disease was studied by light and electron microscopy. Intraneuronal argentophilic Pick bodies were most numerous in the pyramidal cells of the hippocampus. By electron microscopy, these inclusions consisted of a conglomeration of granules enmeshed in an irregular network of proliferated neurofilaments. There were also multiple eosinophilic juxtaneuronal structures (Hirano bodies). By electron microscopy these consisted of interwoven sheaves of beaded and continuous filaments. The possible location of the Hirano bodies within degenerating axonal terminals is discussed.

Zusammenfassung. Hirngewebe eines Falles von Pickscher Krankheit wurde licht-und elektronenmikroskopisch untersucht. Intraneuronale argentophile Picksche Körper wurden am zahlreichsten in den Pyramidenzellen des Hippocampus gefunden. Elektronenoptisch bestanden die Einschlußkörper aus einer Zusammenballung von körnigen Gebilden, die in einem unregelmäßigen Netz von vermehrten Neurofilamenten verstreut lagen. Viele eosinophile Hiranosche Körper fanden sich in nächster Nachbarschaft von Nervenzellen. Diese Körper bestanden aus verflochtenen Schichten von geperlten oder glatten Filamenten. Die mögliche Lokalisation der Hiranoschen Körper innerhalb von degenerierenden Axonendigungen wird diskutiert.

Key-Words: Pick's Disease — Pick Bodies — Hirano Bodies — Electron Microscopy.

In 1892 Pick published a clinical description of a progressive nonarteriosclerotic dementia, which subsequently became known as Pick's disease. Alzheimer in 1911 provided the first histologic study of this rare condition, including a description of enlarged neurons that contained globular argentophilic inclusions, or Pick bodies. The nerve cells affected in this manner were most often found in regions of the cerebral cortex undergoing early degeneration.

Recently HIRANO (1965, 1966, 1968) has observed spindle-shaped bodies in the hippocampi from cases of Pick's disease and amyotrophic lateral sclerosis from Guam. These inclusions were distinguished from the Pick bodies by their eosinophilic staining and juxtaneuronal position.

In this report we compare the fine structure of the Pick bodies to that of the juxtaneuronal bodies (Hirano bodies) as observed in a case of Pick's disease.

Material and Methods

The material used in this study is from the brain of a 69-year-old man who had been confined to a mental institution for the last 5 months of his life because of severe dementia. The disease started at the age of 61 with aphasia. He was found aimlessly wandering around,

lost and confused. During the last months of life he was bedridden, mute, stared into space, and could not recognize anyone.

For light microscopy, blocks of the formalin-fixed tissue from the left cerebral hemisphere were embedded in paraffin. The sections were stained with hematoxylin-eosin, Kluver-Barrera, Masson's trichrome, phosphotungstic acid-hematoxylin (PTAH), periodic acid-Schiff, Holmes silver, Hirano silver, and Congo red stains.

For electron microscopy, blocks of tissue from the left hippocampus were postfixed in osmic acid and embedded in Epon. After sections 2 microns thick were screeened, thin sections were stained with uranyl acetate and lead citrate. The material was examined in a Siemens IA electron microscope.

Results

Gross Observations

At autopsy the brain displayed symmetric atrophy of the cerebral convolutions with a distribution pattern characteristic of Pick's disease (Fig. 1). The frontal, orbital, and anterior temporal convolutions showed severe knife-edge atrophy. The lower parietal lobe was

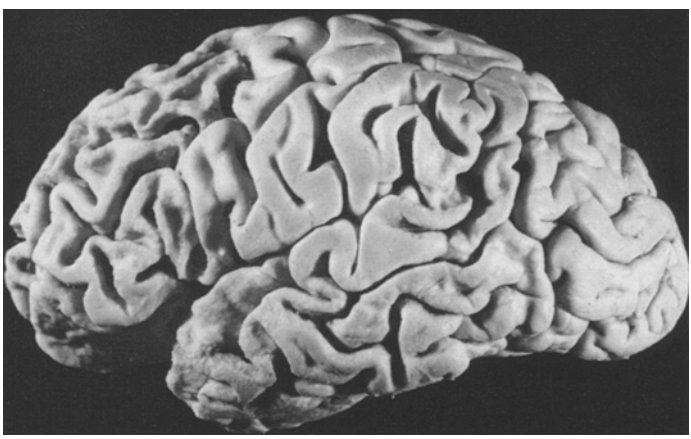

Fig. 1. Lateral view of the left cerebral hemisphere showing knife-edge atrophy of the frontal, orbital, and anterior temporal convolutions. The parietal lobe shows milder involvement. AFIP Neg. 66-13050

involved to a lesser extent. The posterior portion of the superior temporal gyrus, the transverse gyrus, the precentral and postcentral gyri, and those of the occipital lobe were spared. Grossly the hippocampal gyrus and Ammon's horn showed only moderate atrophy. The vessels at the base of the brain were strikingly free of arteriosclerosis.

Light Microscopic Observations

The atrophic cerebral cortex showed loss of neurons without predilection for any particular layers. The residual gray matter was spongy and revealed a striking astrogliosis, as did the underlying white matter. The basal ganglia were similarly involved.

Many of the remaining neurons were enlarged and had a globular configuration. Some of these cells contained typical Pick bodies within their cytoplasm. Most of the bodies were homogeneous, but some contained minute vacuoles and/or lipochrome granules. They were most numerous in the pyramidal cells of the subiculum. They stained pale blue with hematoxylin-eosin. With both the Holmes (Fig. 2a) and Hirano silver stains they were strongly argentophilic. Neither Masson's trichrome nor PTAH stained the inclusions. They were neither congophilic nor birefringent.

In addition to the Pick bodies, the sections from the hippocampus also contained numerous eosinophilic spheroidal or spindle-shaped structures similar to those described by

Hirano (1965, 1968). These were most often immediately adjacent to the perikarya of the pyramidal cells (Fig. 2b). They were not stained by our Holmes silver technique but were stained dark purple with PTAH and dark red with Masson's trichrome stains. They were neither congophilic nor birefringent.

Abundant lipochrome pigment and granulovacuolar changes were evident in many of the neurons within the subiculum. Rare neurofibrillary tangles were present in Sommer's sector. Numerous corpora amylacea were found beneath the pia, under the ependyma, and about blood vessels.

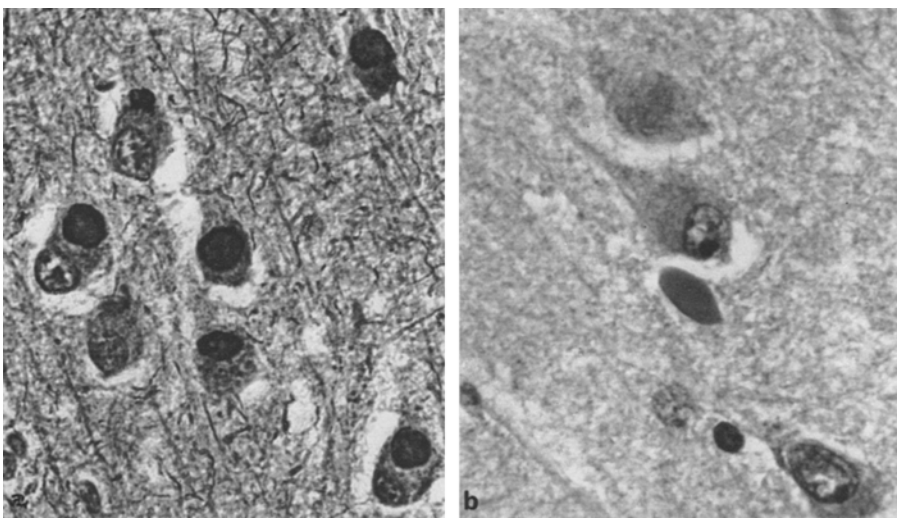

Fig. 2a and b. Light microscopic appearance of the inclusion bodies in the hippocampus. a Argentophilic intraneuronal Pick bodies. Holmes stain. × 500. b Eosinophilic juxtaneuronal Hirano body. Hematoxylin-eosin. × 660. AFIP Neg. 67-1006

Electron Microscopic Observations

Many of the hippocampal neurons were enlarged and contained abundant lipochrome pigment. The Pick bodies corresponded to poorly demarcated osmophilic masses that displaced the nucleus and cytoplasmic organelles. Many of the inclusions were uniformly granular, while others contained minute vacuoles and/or lipochrome granules (Figs. 3a and b). Higher magnification disclosed that the inclusions were actually a conglomeration of fine osmophilic particles enmeshed within the interstices of a loose, randomly arranged network of neurofilaments. The particles were morphologically similar to the granules attached to the rough endoplasmic reticulum and were thus considered to be ribonucleoprotein particles (RNP) or ribosomes. The individual filaments measured approximately 200 Å in diameter and were periodically constricted (Fig. 3c). Some of the filaments tended to swirl about the periphery of the body, but no limiting membrane could be discerned.

The Hirano bodies were also intracytoplasmic but apparently not within neural perikarya. Most were immediately adjacent to neurons, including ones that contained Pick bodies. The Hirano bodies had a variable configuration ranging from spheroidal to spindle-shaped (Fig. 4a). They were composed of interwoven sheaves of parallel filaments. Occasionally they appeared splintered,

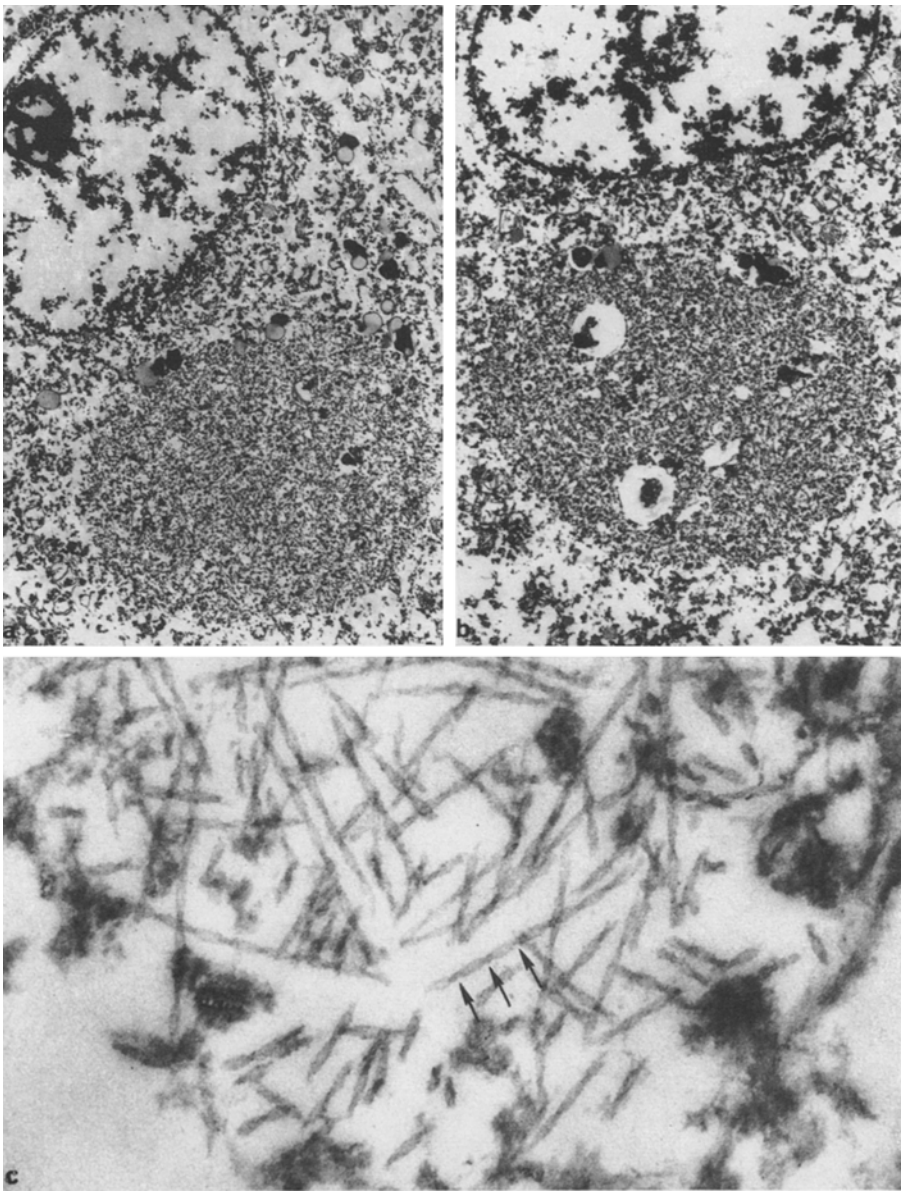

Fig. 3 a—c. Electron microscopic appearance of the Pick bodies. a Note the poor demarcation and the presence of occasional lipochrome granules. × 3500. b Another inclusion, containing vacuoles. × 3500. c Higher magnification of the Pick body showing that it is composed of a conglomeration of osmophilic granules enmeshed in a loose network of neurofilaments. Note the periodic constrictions of the filaments (arrows). × 70000

with one or more small bundles separated from the main mass by amorphous osmophilic material (Fig. 4 b). The majority of the individual filaments were 100 Å in width and consisted of a series of minute osmophilic densities with a periodicity of 100 to 150 Å. When arranged in register, they produced a para-

crystalline or herringbone pattern (Fig. 5). Other filaments were less osmophilic and uniform. These occurred individually and in small bundles.

The Hirano bodies were usually solid, with the center appearing as a point or a line, depending upon the plane of section. Occasional bodies contained a conglomeration of filaments, dense particles, and clumped vesicular structures in their centers (Fig. 6a and b). No continuity could be demonstrated between the filaments and the chains of osmophilic densities.

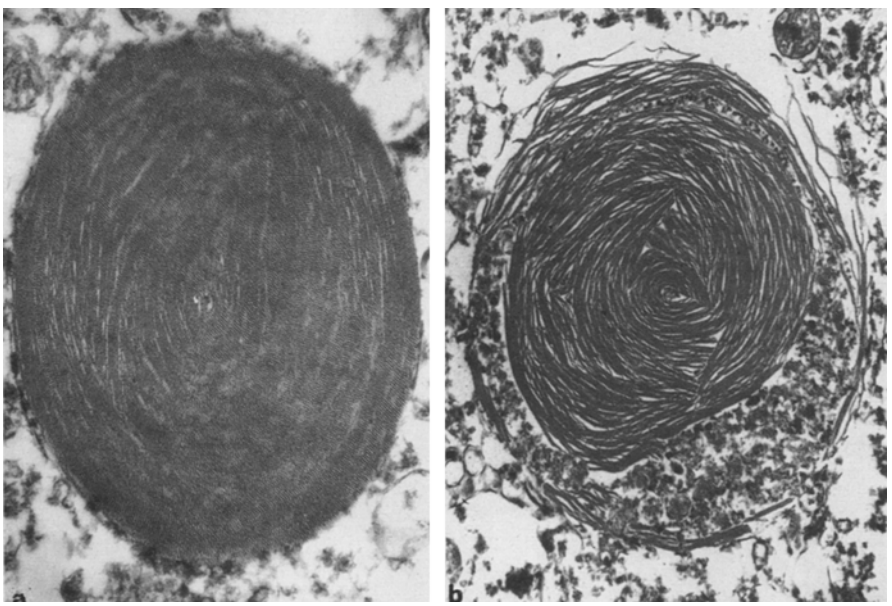

Fig. 4a and b. Electron microscopic appearance of the Hirano bodies. a Hirano bodies showing the interwoven sheaves of beaded filaments, forming a paracrystalline pattern. × 15000. b Hirano body showing separation of the sheaves by amorphous osmophilic material. × 15000

Elsewhere in the hippocampus, neurofibrillary tangles and corpora amylacea were encountered. These had the same appearance as described by others (Terry, 1963; Ramsey, 1965).

Discussion

By electron microscopy, the argentophilic intraneuronal Pick bodies consisted of a conglomeration of fine osmophilic particles enmeshed in the interstices of a loose network of neurofilaments. The osmophilic particles had the same appearance as the granules attached to the rough endoplasmic reticulum and were thus considered to be ribosomes. The irregular arrangement of the filaments and the intimate association with the RNP particles distinguish the Pick bodies from neurofibrillary tangles, which are compact bundles of parallel neurofilaments that displace other cytoplasmic organelles (Terry, 1963). The random orientation of the filaments in the Pick bodies also explains the absence of birefringence.

Swelling of the perikarya, with proliferation of both RNP particles and neurofilaments, has been observed in nerve cells following section of their axons

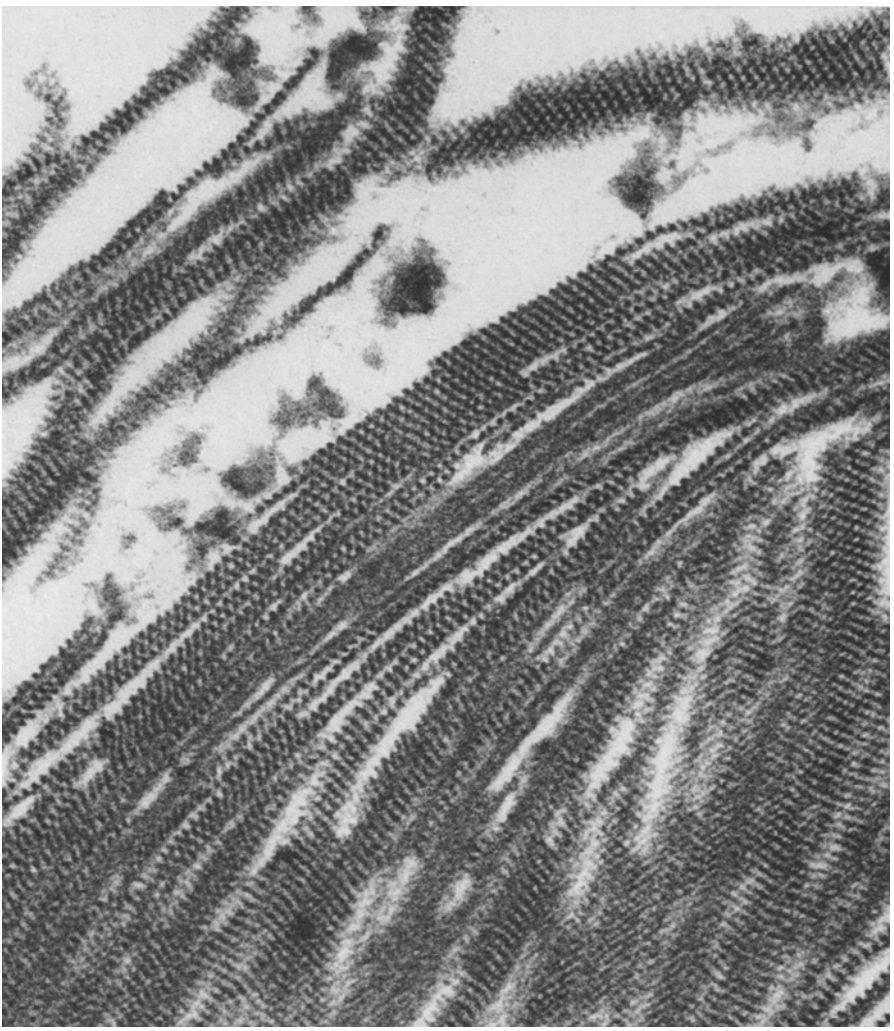

Fig. 5. Higher magnification of a Hirano body showing the chains of strongly osmophilic densities and the continuous, less osmophilic filaments. × 80000

(Takano, 1964; Pannese, 1963). The similarity of the Pick cells to neurons undergoing reactive changes secondary to axonal injury had been emphasized by Onari and Spatz (1926), who suggested that Pick's disease may primarily affect the axon. Williams (1935) has shown that the Pick bodies are nonspecific and may occur in a wide variety of diseases that affect the proximal portion of the axon. Attempts to reproduce these changes experimentally by undercutting the cerebral cortex have failed, however (Ramon y Cajal, 1928).

The Hirano bodies encountered in the present case were composed of interwoven sheaves of filaments. Most of the filaments consisted of chains of osmophilic densities with a periodicity of 100 to 150 Å. Others were less osmophilic and continuous. These bodies were identical to those described in cases of amyo-

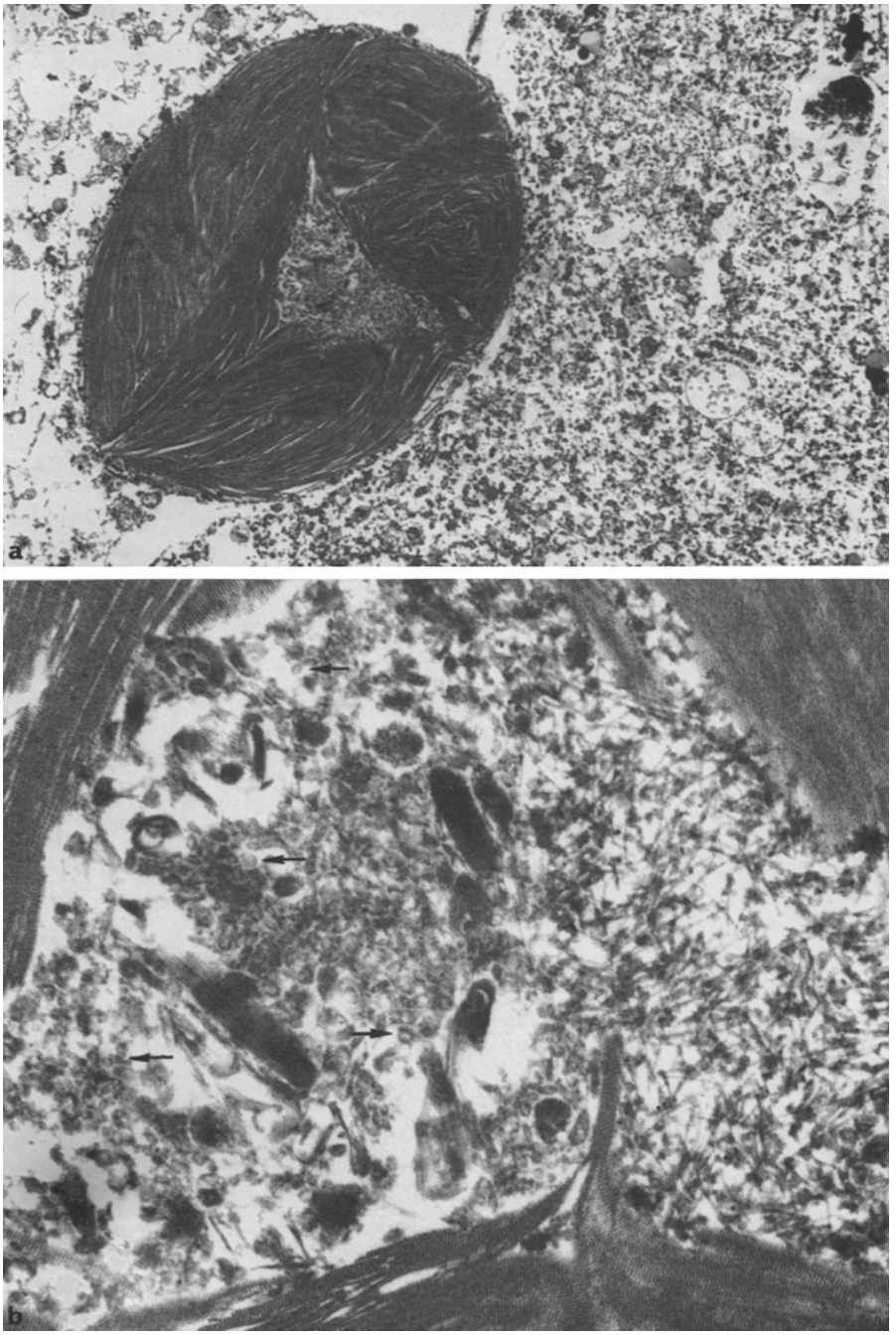

Fig. 6. a A Hirano body adjacent to a neuron. × 6000. b Higher magnification of the center of the Hirano body shows a conglomeration of neurofilaments (at right), dense particles, and clumped vesicular structures (arrows). × 40000

trophic lateral sclerosis from Guam (HIRANO, 1965). It is of interest that the simultaneous occurrence of Picks's disease and amyotrophic lateral sclerosis has been described previously (VON BRAUNMÜHL, 1932; VAN MANSVELT, 1954).

By light microscopy the Hirano bodies appeared juxtaneuronal, but by electron microscopy they were clearly intracytoplasmic. Occasionally the bodies were hollow and their centers contained a conglomeration of filaments, dense particles, and clumped vesicular structures. This closely resembled the proliferation of neurofilaments and granular degeneration of vesicles observed in synaptic endings following axonal degeneration (GRAY and HAMLYN, 1962). Furthermore, lamellated whorls with a periodic substructure similar to that of the Hirano body have been described within presynaptic terminals adjacent to tumors (RAMSEY, 1967). For these reasons, we suggest that the Hirano bodies are probably located in abnormal axonal endings.

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