# Ultrastructural Study of the Human Pineal Gland in Aged Patients Including a Centenarian

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**An ultrastructural study of human pineal glands obtained at autopsy from 7 patients older than 70 years was conducted in order to clarify the functional anatomy of the pineal in the aged. By light microscopy, the pineal glands from aged patients were parenchymatous and almost indistinguishable from those of younger controls. Electron microscopy of the pineal parenchymal cells revealed deep nuclear indentations, synaptic ribbons and ribbon fields, Golgi apparatus, lipofuscin granules and microtubular sheaves in all subjects, cilia with a 9+0 pattern in a few, and lamellated structures suggestive of the outer segment of photoreceptor cells very rarely. Microtubules were numerous in the cytoplasmic processes and bulbous endings. Fibrous astrocytes located between the pinealocytes showed long and thin cytoplasmic processes containing numerous glial filaments. Two types of nerve bouton were present in the pineal parenchyma, one of which contained clear vesicles forming synapse-like contacts with pinealocytes. There were no significant age-related changes in these features in a qualitative comparison with pineal glands from 5 adult patients younger than 70 years. These findings indicate that even in advanced age, the human pineal gland maintains some functions, such as intercellular communication and photoreception, in common with the pineal in lower vertebrates. Acta Pathol Jpn 40: 30-40, 1990.**

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## INTRODUCTION

The human pineal gland is widely regarded as a phylogenetically rudimentary organ and has not been studied in detail in the neuroendocrinological field in comparison with its counterpart in other mammals. As many workers have better characterized the functional and morphological aspects of the pineal gland in many vertebrates through comprehensive investigations (1), a basic and clearer understanding of the human pineal is now required in order to evaluate the clinical importance of various biological substances secreted by this organ, especially melatonin, which could be a possible diagnostic marker of neoplasms and biological rhythms and a future therapeutic tool for certain diseases.

Our recent study on age-related changes in the human pineal gland (2), based on gravimetry and quantitative morphology, showed that in individuals older than 49 years, the weight of the pineal does not necessarily decrease progressively in proportion to age and that the pineal parenchymal cells in patients with senility do not show remarkable atrophy or degeneration as observed by light microscopy. As a further step forward, it remains to be elucidated from an ultrastructural viewpoint whether human pinealocytes lose the basic cytological architecture necessary for neuroendocrine function with aging. Although there seem to be no serious technical limitations in determining this aspect, such studies have been exceedingly rare to our knowledge. The objective of this study was therefore to clarify the detailed electron microscopic features of the human pineal gland in aged individuals, about which very little is still known, and to discuss the possible function of this enigmatic organ in humans.

## MATERIALS AND METHODS

Pineal glands were obtained at autopsy from 7 aged

patients (aged 71–100 years, mean 79 years) and 5 younger adult patients as a control group (aged 36–68 years, mean 49 years). Specimens from the aged individuals were taken within 3 h of death (mean 1.5 h) at the Department of Pathology, Tokyo Metropolitan Geriatric Hospital, and those from the control group were removed within 5 h of death (mean 4 h) at the Departments of Pathology of Tokyo University and Odawara Municipal Hospital.

The pineal glands were resected from the brain during autopsy and the arachnoid tissue covering the gland was removed carefully. Each gland was immediately fixed by immersion in ice-cold 2.0% paraformaldehyde-2.5% glutaraldehyde in 0.1 M Na-cacodylate buffer (pH 7.3). About 15 min later, the gland was weighed on a direct reading balance (Mettler H 20, sensitivity 0.01 mg), and the length, width and thickness were also measured using a slide caliper (accuracy 0.1 mm). Each gland was then divided longitudinally into two halves with a clean blade, one half for light microscopy and the other for transmission electron microscopy. The half used for light microscopy was re-fixed in 10% formalin solution for routine processing including paraffin embedding, sectioning and conventional staining (hematoxylin and eosin, Watanabe's silver impregnation and Azan-Mallory). The other half of the gland was minced into 1-$mm^3$ cubes and placed in a container filled with above-mentioned paraformaldehyde-glutaraldehyde fixative. The tissue was washed with 0.1 M Na-cacodylate-buffer (pH 7.3) and post-fixed in 2.0% osmium tetroxide for 1.5 h. After embedding in a single Poly/Bed 812 block, thick sections, cut into 1-$\mu$m slices, were prepared and stained with toluidine blue and examined to exclude severely calcified areas. Ultrathin sections 50–70 nm thick were cut with a diamond knife, stained with uranyl acetate and lead citrate, and then examined and photographed with a H-600 transmission electron microscope (Hitachi Ltd.) or a JEM-1200EX (JEOL Ltd.) operated at 80 kV.

## RESULTS

### General structure

There were areas of mild to severe calcification and glial cyst formation in the pineal glands, but in all the specimens from aged patients the pineal parenchyma was retained with preserved cellularity in some parts, making electron microscopic observation feasible.

One-micronmeter-thick sections of the pineal gland from aged individuals showed a parenchymatous architecture divided into lobular structures by connective tissue septa composed of capillaries and perivascular spaces. Electron microscopy revealed that each peri-

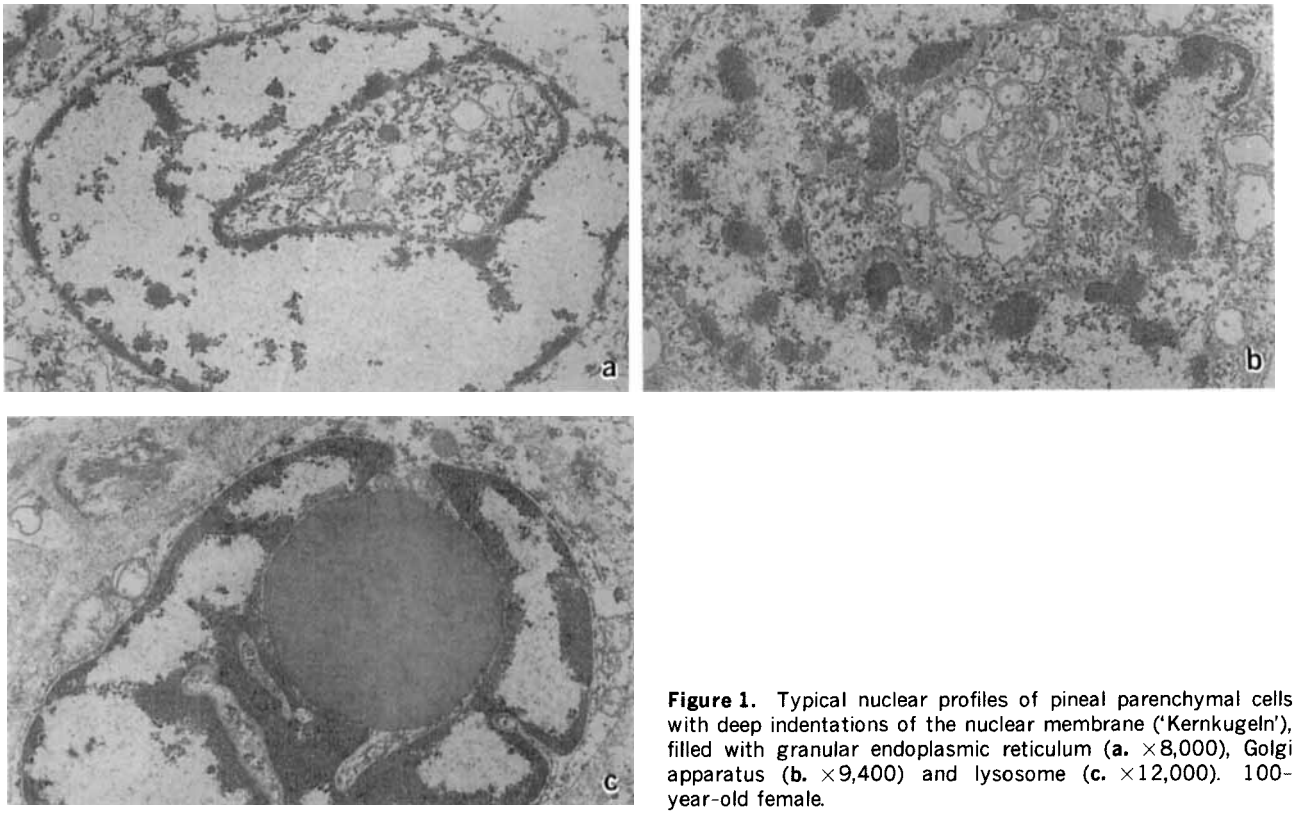


**Figure 1.** Typical nuclear profiles of pineal parenchymal cells with deep indentations of the nuclear membrane ('Kernkugeln'), filled with granular endoplasmic reticulum (**a.** ×8,000), Golgi apparatus (**b.** ×9,400) and lysosome (**c.** ×12,000). 100-year-old female.

vascular space had two boundaries, an inner one consisting of the capillary basal lamina and an outer one formed from the basal lamina of the pineal parenchyma.

## Pineal parenchymal cells

By light microscopy, pinealocytes showed round to oval nuclei each with a prominent nucleolus, and an ill-defined cytoplasm. It was rather difficult to differentiate these cells from interstitial cells or astrocytes on the basis of photomicroscopic findings alone. The extent of the intercellular space formation, probably due to a fixation artefact and/or post-mortem change rather than aging, varied from case to case. In some specimens, the pineal parenchymal cells tended to possess a rich perikaryon, showing a close cell-to-cell interface, whereas in others they showed a rather slender cytoplasm with electron-lucent open intercellular spaces.

In electron micrographs, the nuclei of the pineal parenchymal cells were round to oval-shaped, 7-10 $\mu$m in diameter, sometimes accompanied by deep indentations of the nuclear membrane, so-called 'Kernkugeln'. These invaginations were filled with organelles such as granular endoplasmic reticulum (Fig. 1a) and, at times, Golgi apparatus (Fig. 1b) and lysosomes (Fig. 1c). The nuclear envelope consisted of two nuclear membranes enclosing a narrow perinuclear space, measuring 10-30 nm in thickness. The nuclear pores were 60-70 nm in diameter, each with an accompanying diaphragm (Fig. 2). The nucleoli were prominent and heterochromatin

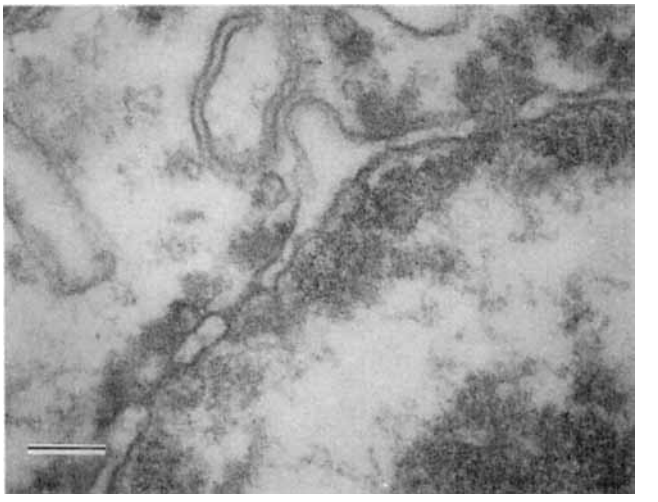

**Figure 2.** Nuclear envelope of a pineal parenchymal cell with nuclear pores and an accompanying diaphragm (×100,000). Bar=100 nm. 76-year-old male.

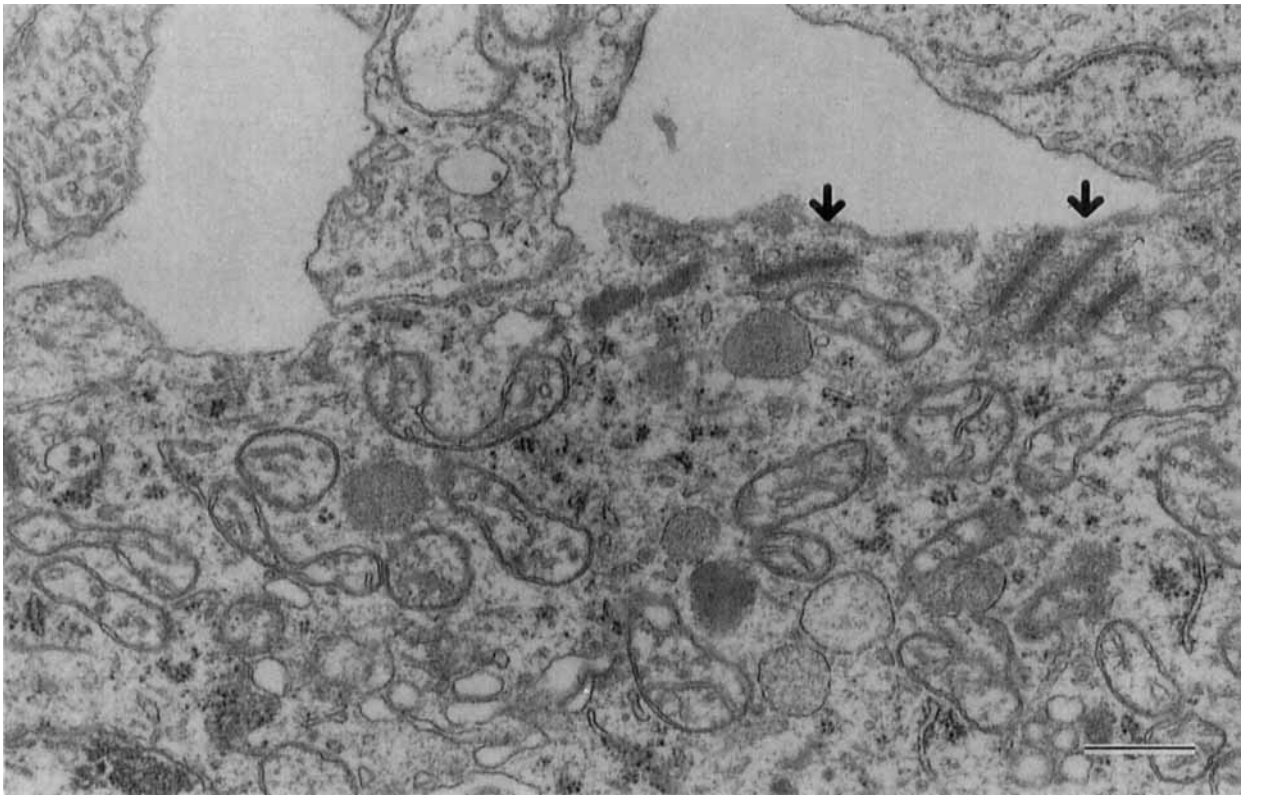

**Figure 3.** Cytoplasm of pinealocyte containing mitochondria, polysomes and synaptic ribbons (arrow) (×29,000). Bar=0.5 $\mu$m. 73-year-old male.

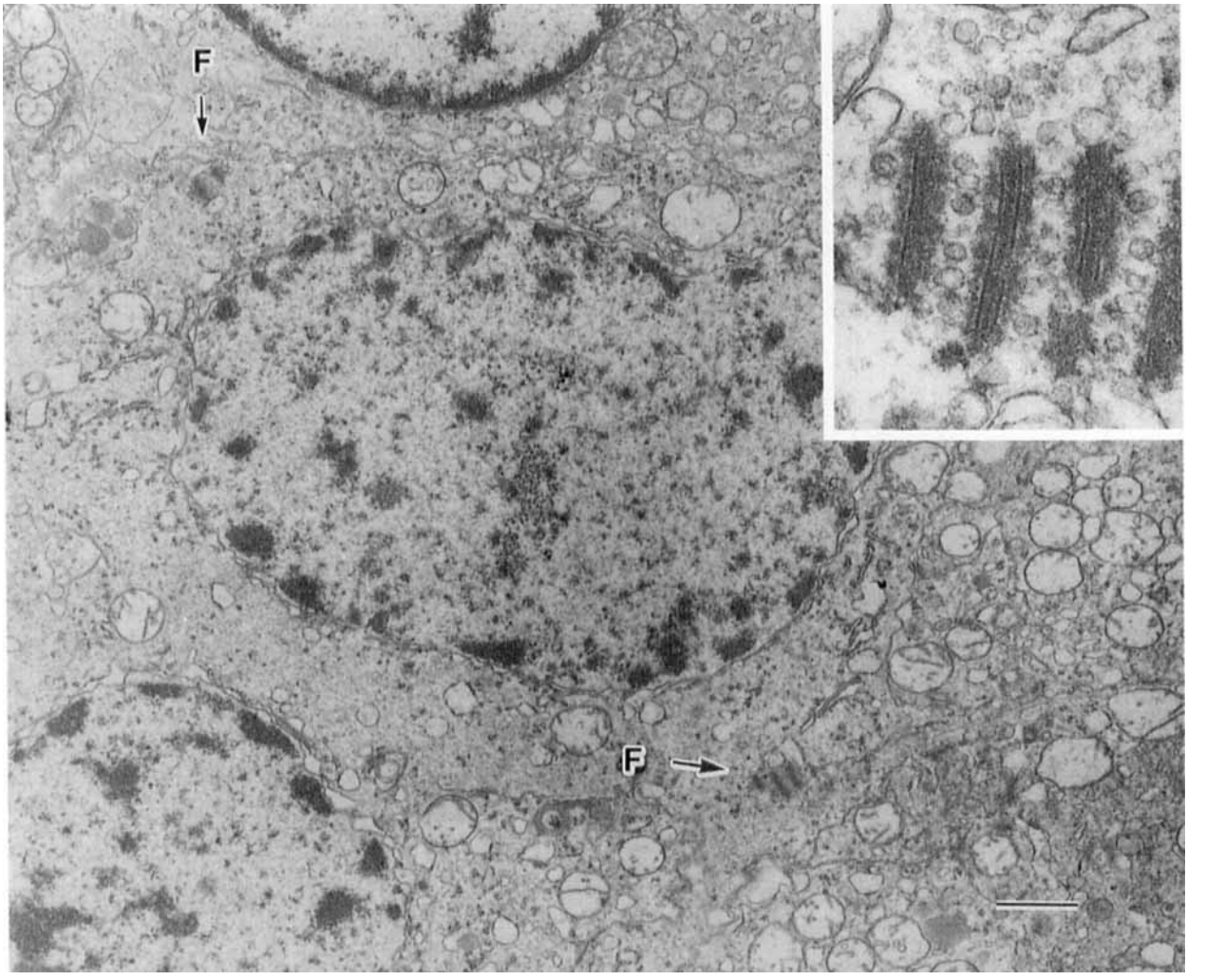


**Figure 4.** Electron microscopy of pineal parenchymal cells containing two synaptic fields (F) on opposite sides of the nucleus (×11,000). Bar=1 μm. 80-year-old female. Inset: High-power view of synaptic ribbons consisting of electron-dense plates surrounded by numerous vesicles (×56,000). 72-year-old male.

was poor in well preserved materials.

The perikaryon of the pinealocytes contained mostly round and occasionally elongated mitochondria, 0.7-1.2 μm in diameter (Fig. 3), and a Golgi apparatus about 1 μm in size, although there was no distinct sign of dense-core vesicle formation resembling secretory granules in this series or in the control group. Rough endoplasmic reticulum was present in moderate amount and polyribosomes were abundant. Occasionally, lysosomes and lipid droplets, up to 2.5 μm in greatest dimension, were observed.

A distinctive feature of the pinealocyte cytoplasm was the presence of synaptic ribbons and/or ribbon fields in all the subjects studied (Figs. 3-5), lying freely in the perikaryon, in the vicinity of the plasma membrane arranged perpendicular to the above-mentioned intercellular gap, and also in the cytoplasmic processes and endings. Each ribbon appeared as an electron-dense rod or plate, measuring 100 nm in average diameter or width and up to 600nm in length, comprising three electron-dense lines, and surrounded by numerous electron-lucent vesicles, about 50 nm in diameter (Fig. 4). The ribbon fields consisted of as many as 30 synaptic ribbons in this series (Fig. 5). Pineal synaptic ribbons with their vesicles, compared with other organelles such as mitochondria, appeared to endure post-mortem autolytic changes rather well and were almost always found in electron micrographs of human autopsy materials.

Centrioles of human pinealocytes, as well as those in pinealocytes of other mammals, showed several unusual characteristics suggesting some implications regarding

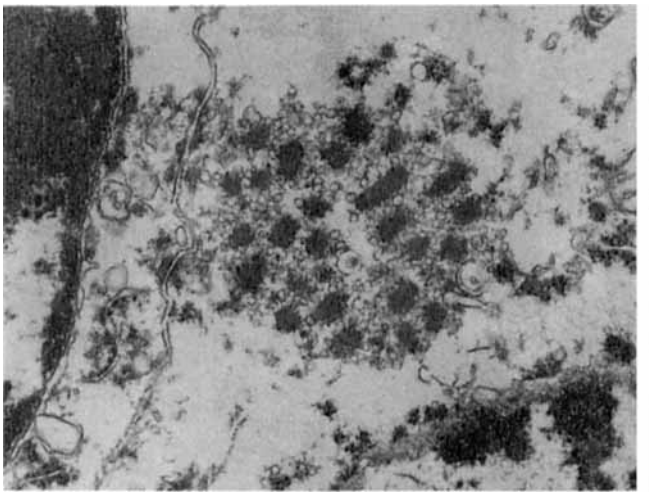

**Figure 5.** Synaptic field in the vicinity of the plasma membrane consisting of many synaptic ribbons (×25,000). 100-year-old female.

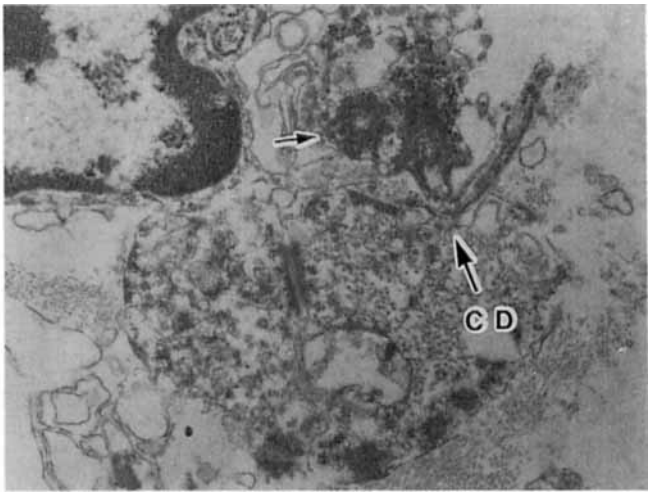


**Figure 6.** Ciliary derivative (CD) with a cilium of the 9+0 pattern (×20,000) and a centriole (arrow). 100-year-old female.

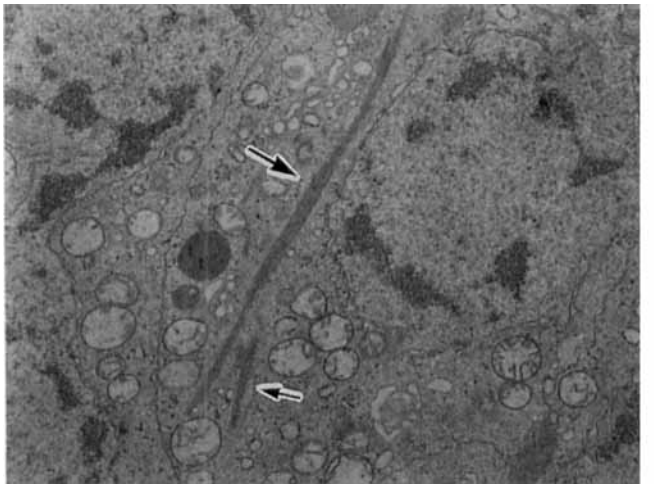

**Figure 7.** Microtubular sheaves (arrow) in pinealocyte cytoplasm (×8,000). 71-year-old female.

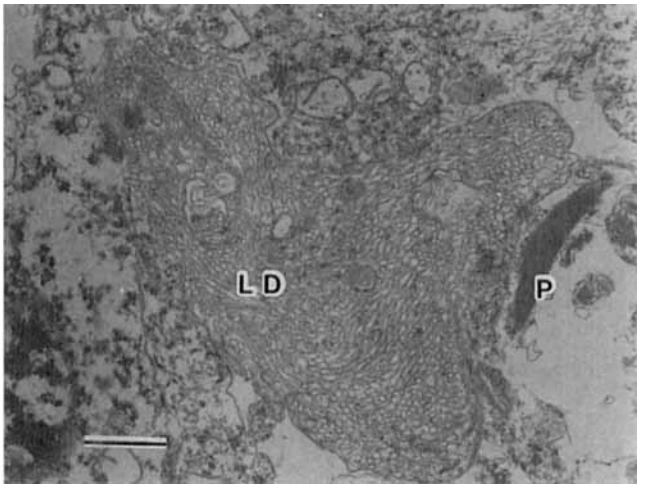


**Figure 8.** A lamellar disc structure (LD) suggestive of the outer segment of photoreceptor cells (×10,000). P: process of a fibrous astrocyte. Bar=1 $\mu$m. 100-year-old female.

pineal phylogenesis. In some Golgi areas and perikarya, a field with modified centrioles and microtubular sheaves comprising as many as 10 centrioles were seen. Rarely, one of a pair of centrioles extended distally to the intercellular space to form a ciliary derivative, i.e. cilia with a 9+0 pattern, measuring 400 nm in diameter (Fig. 6). An elongated and modified centriole (microtubular sheaf) was also observed in the cytoplasm, measuring as much as 10 $\mu$m in length (Fig. 7). Very rarely, lamellar disc structures suggestive of the outer segments of photoreceptor cells were found, each measuring 6×5 $\mu$m in external dimension (Fig. 8). Microtubules with a diameter of about 25 nm were distributed in the processes in a parallel manner and in the perikarya randomly (Fig. 9). The quantity of microtubules in the cytoplasm varied from one pinealocyte to another and among sites within the cytoplasm.

## Interstitial cells

The second cell type in the pineal parenchyma was interstitial cells occurring between the pinealocytes. In electron micrographs, these cells had long and thin cytoplasmic processes containing bundles of numerous parallel glial microfilaments, less than 10 nm in diameter (Fig. 10), coursing through the intercellular spaces between the pinealocytes, and forming a dense network in the vicinity of the outer basal lamina of the perivascular space. Each bundle of glial filaments measured 0.4-0.8 $\mu$m in diameter. The main cell bodies (perikar-

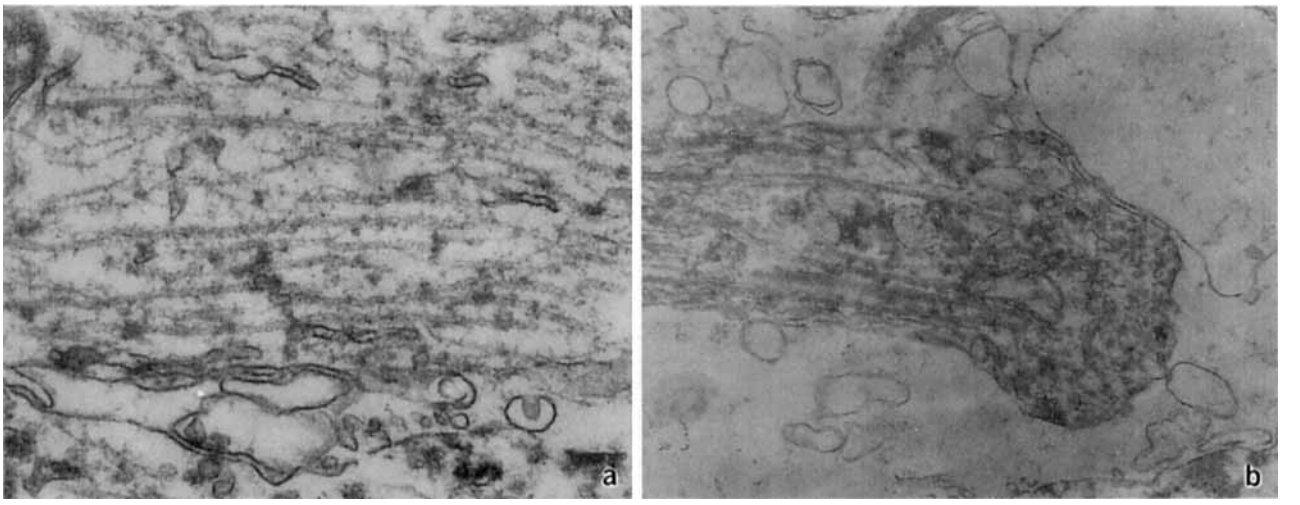


**Figure 9.** Microtubules with a diameter of about 25 nm in pinealocytic processes.
**a.** Proximal part of a process (×40,000). 76-year-old male. **b.** Bulbous ending (×30,000). 68-year-old female.

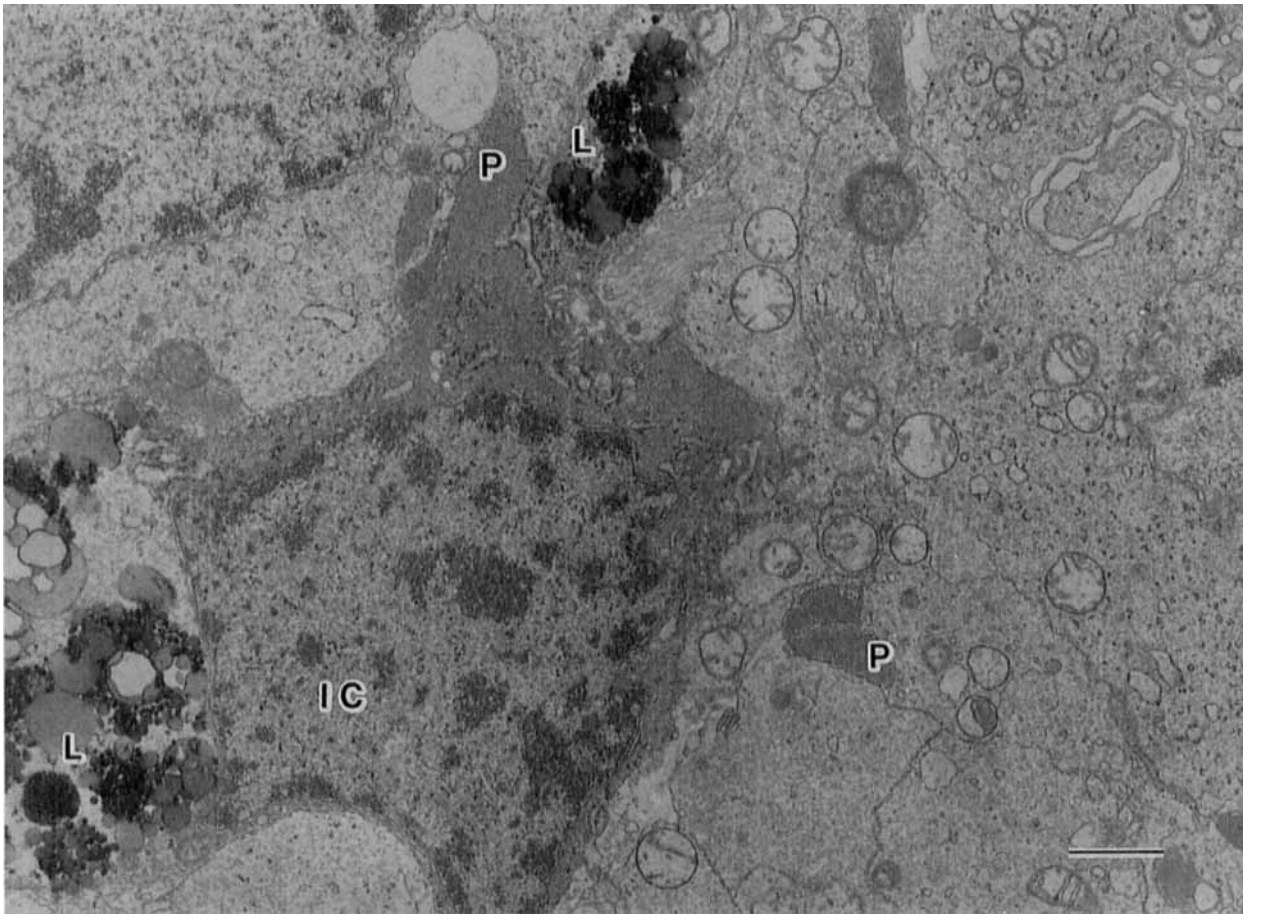


**Figure 10.** Electron microscopy of an interstitial cell (IC) with electron-dense cytoplasm projecting long processes (P). Bundles of numerous glial microfilaments are evident in them. L: lipofuscin granules (×12,000). Bar=1 μm. 71-year-old female.

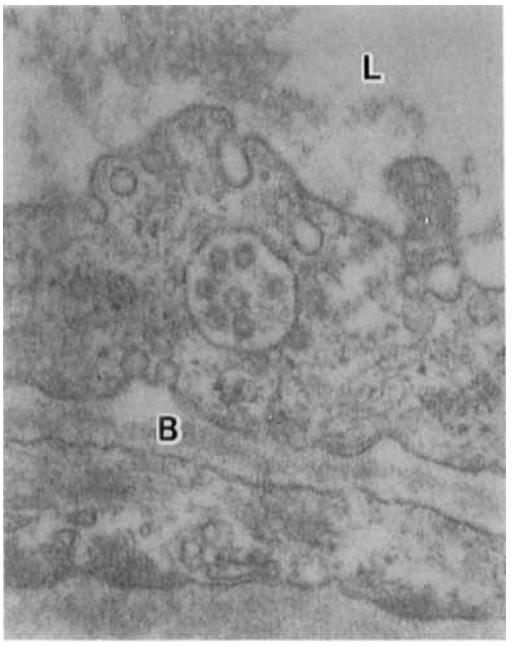


**Figure 11.** Pinocytotic vesicles of an endothelial cell (×60,000). L: lumen of capillary. B: basal lamina. 73-year-old male.

yon) projecting these processes, which are designated as 'dark cells' by some authors, did not seem to be so numerous judging from the electron micrographs, although it may be nearly impossible to differentiate all of the interstitial cells from pinealocytes only by the electron density of the cytoplasm and questionable presence of glial filaments within the perikaryon.

## Blood supply

As mentioned above, the vascular network consisted of capillaries accompanying the perivascular spaces. The endothelial cells possessed cytoplasmic processes on the luminal surface and showed common organelles such as mitochondria, rough endoplasmic reticulum and ribosomes. Pinocytotic vesicles were numerous, measuring between 50 and 80 nm in diameter (Fig. 11).

An interesting feature of the perivascular space was that it contained a small number of notched elongated structures made of numerous delicate protofibrils, fibrous long-spacing collagen (FLSC), showing a transverse periodicity of 120-140 nm instead of the classic 64-nm banding (Fig. 12).

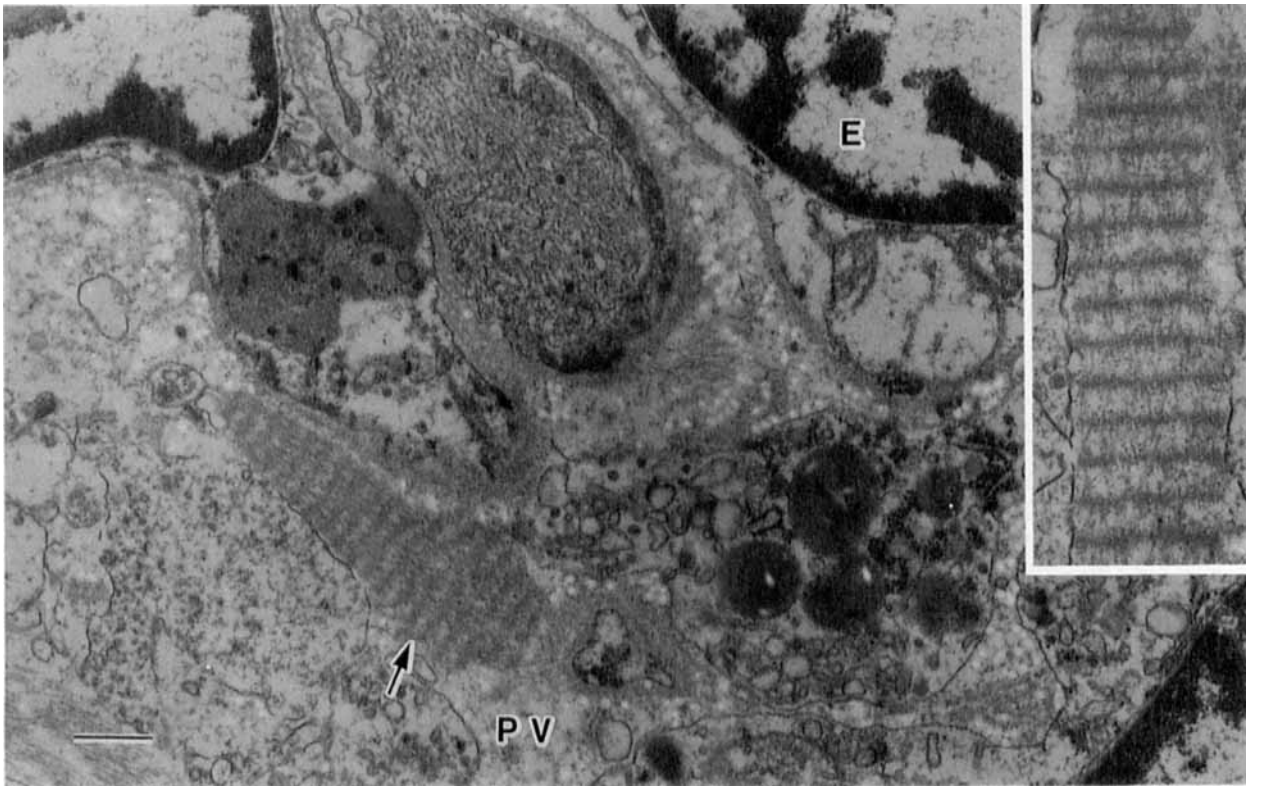


**Figure 12.** Fibrous long-spacing collagen (FLSC, arrow) in the perivascular space (PV) of the pineal (×19,000). E: endothelial cell, Bar=0.5 $\mu$m. 72-year-old male. Inset: High-power view of FLSC with a periodicity of 120-140 nm (×40,000). 80-year-old female.

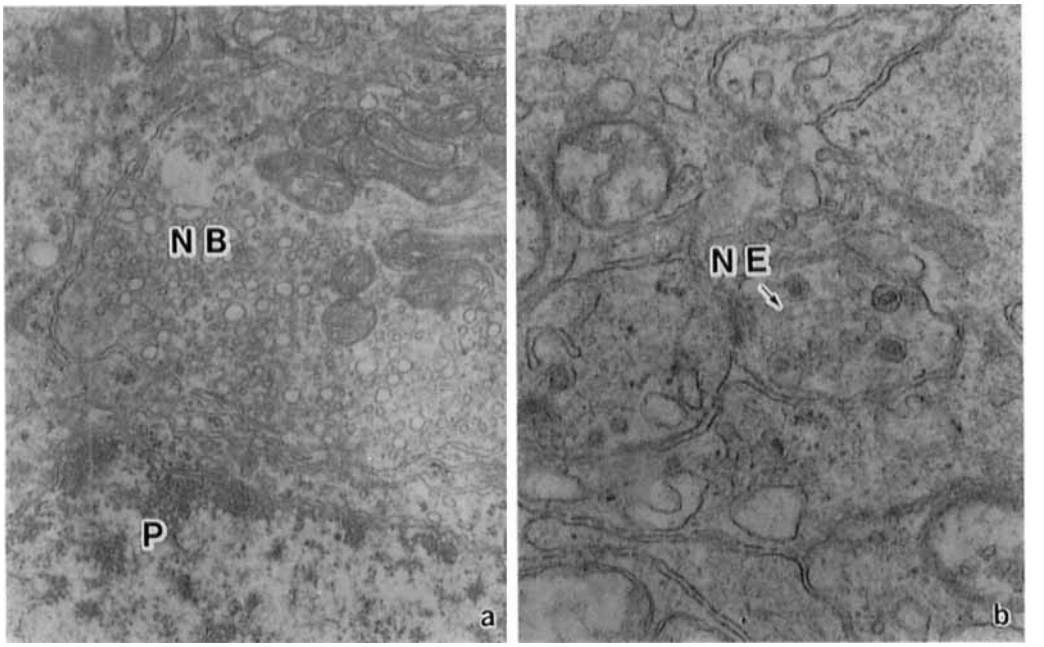


**Figure 13.** Electron microscopy of two types of nerve bouton. **a.** Nerve bouton (NB) filled with numerous clear presynaptic vesicles, making synapse-like contact with a pineal parenchymal cell (P) (×20,000). 73-year-old male. **b.** Nerve ending (NE) containing cored and clear vesicles (×35,000). 71-year-old female.

### Innervation

No myelinated nerve fibers were found in the perivascular space of the pineal. In the pineal parenchyma, electron microscopy showed two types of nerve bouton. The first type contained numerous clear presynaptic vesicles, each measuring about 50-100 nm in diameter, consistent with those of parasympathetic nerve endings containing acetylcholine, and made synapse-like contact with the plasma membrane of pinealocytes (Fig. 13a). The second type occurred in the nerve endings, containing cored (granular) and clear vesicles, the former measuring 120 nm in external diameter with a 60-nm dense core, and the latter, 60 nm in diameter, which were consistent with those of peripheral sympathetic nerves and the central nervous system (Fig. 13b). The former type of bouton was larger and contained more vesicles than the latter.

### Age-related changes

Except for an increase in the amount of lipofuscin granules, no remarkable age-related changes in the basic architecture and ultrastructure of the pineal were found. The thickness of the interstitial tissue varied from case to case and no age-related increase could not be confirmed in this rather small number of cases. The synaptic ribbons and fields did not appear to decrease in number with aging.

## DISCUSSION

Electron microscopic observations of the human pineal gland reported up to now have been confined to those on the embryo (3), the fetus (4, 5), and the infant (6) and to our knowledge this is the first investigation on the ultrastructure of pinealocytes in aged humans with a qualitative comparison with those of younger adults. The autopsy materials in this study, obtained within a short post-mortem interval, showed previously undescribed ultrastructural features, with many implications in the context of pineal phylogenesis and ontogenesis.

In lower vertebrates, the pineal has been demonstrated morphologically and functionally to be a photoreceptor. After evolutionary change, the pineal of higher mammals has developed a solid and parenchymal structure and is generally accepted to be a neuroendocrine transducer (1). There have been many reports on the ultrastructure of the pineal in rodent species, showing coexistence of photoreceptor and endocrine elements, but few studies have been done on primates including humans. The present study confirmed the presence in the pineal of aged human subjects of synaptic ribbons, modified centrioles and ciliary derivatives with a 9+0 configuration, and lamellar structures suggestive of the outer segments of photoreceptor cells, although the inci-

dental presence of 9+0-type cilia and lamellar structures may not indicate any functional significance. Microtubular sheaves, cilia with a 9+0 pattern, and lamellated structures seemed to represent an abortive effort of pinealocytes to differentiate to photoreceptor cells. These findings are consistent with the hypothesis that the human pinealocyte is phylogenetically derived from the photoreceptor cells of lower vertebrates. On the other hand, since typical secretory granules like those in the pineal of other mammals were not found in the cytoplasm of the pinealocytes in the present series including younger subjects, it could be hypothesized that their marked decrease in number is characteristic in humans. In comparison with our previous study demonstrating the presence of numerous secretory granules in the cytoplasm of mouse pinealocytes even in 24-month-old animals (7), these findings as a whole seem to indicate the predominance of the synaptic and photoreceptor elements over the secretory elements in human pinealocytes. Furthermore, the view that the presence of synaptic ribbons and 9+0-type cilia in the pinealocytes of the human embryo and fetus is only transient and represents evolutionary remnants from the pineal of lower vertebrates, which probably have no functional significance, might have to be reconsidered. From a teleological viewpoint, it seems rather implausible that highly differentiated organelles such as synaptic ribbons would remain completely 'functionless' after being retained in such large numbers in individuals aged up to 100 years. The functional significance and developmental change of the human pineal gland seem much more difficult to interpret and the possibility that some photoreceptor, neural or neuroendocrine functions are retained even in old age cannot be ruled out.

Abundance of fibrous astrocytes and their processes with glial filaments (8) appears to be one of the characteristic features of the human epiphysis in comparison with their rarity in mice (9). In the present study, however, the numerical ratio of astrocyte perikarya to pinealocyte perikarya seems very small, probably much less than 1 : 10, as the perikarya projecting these processes were identified only rarely based on electron microscopic criteria including high electron density of the cytoplasm, a smaller number of nuclear invaginations, presence of glial filaments and a larger amount of rough endoplasmic reticulum. Similarly, the processes with glial filaments forming a dense network between the pinealocytes seemed to outnumber glial cell perikarya on electron micrographs, raising the question whether all the processes with glial filaments in the pineal parenchyma originate from the occasionally identified 'dark' cells. Meanwhile, the cytoplasmic processes projecting from the perikaryon of pinealocytes containing synaptic ribbons were filled with only loose bundles of microtubules, and never with the above-mentioned type of glial filament bundles. Therefore it is true also in humans that there are at least two distinct populations of cells in the pineal parenchyma, that is, pinealocytes, which are only one type of parenchymal cell, and glial cells (fibrous astrocytes). In the previous study on age-related changes in the mouse pineal gland (9), the authors considered that so-called light and dark pinealocytes represent an immersion-fixation artefact and/or different stages of a single cell type, and that distinct glial cells are extremely rare in mice. Because of this large variation in the amount of processes associated with glial filaments between species, it seems essential to study the pineals of many kinds of non-human primate from the viewpoint of orthogenesis, to evaluate the phylogenetic status of the structure and function of the human pineal.

Peculiar nuclear structures in the pineal parenchymal cells, 'Kernkugeln', have been described and variously interpreted (10, 11). By electron microscopy, the nuclear membrane of the pinealocytes was shown to have many foldings, and to date the nuclear pellets of pinealocytes have been considered an artefact in light-microscopic sections due to obliquely sectioned cytoplasmic invaginations into the nuclei (11). In this study these invagination contained cytoplasmic organelles such as rough endoplasmic reticulum, Golgi apparatus and lysosomes. In the mouse pineal examined by electron microscopy, the number of these nuclear lobulations increased linearly in proportion to age (9). However, the invaginations were narrow and organelles were seldom present within them. The age-related changes in nuclear profiles of human pinealocytes, including changes in the number of 'Kernkugeln', remain to be investigated. Nuclear pores with diaphragms have rarely been described in human pinealocytes and there are few data on the size of these pores. In this study the nuclear envelope of pinealocytes did not show any unusual features, suggesting retention of metabolic and cytogenetic activity in the senile human pineal.

Synaptic ribbons have been observed in the photoreceptor cells and pinealocytes of vertebrates. Circadian changes in the number of synaptic ribbons have been well established in the pineals of many vertebrates (1, 12, 13) and such numerical changes have generally been accepted to reflect the functional state of pinealocytes in rodents. Therefore, our finding of an unexpectedly frequent occurrence of synaptic ribbons in human pinealocytes in aged individuals provides the first qualitative support for the hypothesis that the pineal maintains some function throughout life. This situation, however, appears to contradict the true physiological

picture, since the autopsies in this series were performed near noon after a short post-mortem interval, when the number of synaptic ribbons ought to have been minimal.

At least two types of synaptic contact between nerve endings and pinealocyte perikarya were observed in the aged human pineals. One type of nerve ending filled with clear presynaptic vesicles was consistent with a parasympathetic nerve ending and the other containing cored and clear vesicles was certainly sympathetic or aminergic. These synaptic contacts seem to be involved in the tranfer of signals from nerve fibers to pinealocytes. The mammalian pineal has been reported to be innervated principally by postganglionic sympathetic nerve fibers derived from the superior cervical ganglia, whereas parasympathetic innervation had been demonstrated somewhat exceptionally only in monkey (14), kitten (15) and rabbit (16) untill recently. The present results suggest that the human pineal is not only under sympathetic, but also parasympathetic control. The functional significance of such parasympathetic control in humans remains to be investigated further.

One interesting observation in this study was that the perivascular space contained occasional fibrous long-spacing collagen. FLSC has been reported not only in neural neoplasms, Schwannoma and meningioma, but also in a variety of other epithelial and mesenchymal tumors, reactive lymphadenopathies and lymph node neoplasms (17, 18). Although this is the first report of the existence of FLSC in the pineal of aged humans, which contains no myelinated nerve fibers, its significance and relationship to aging remains unsettled.

In a study based on 168 autopsied individuals older than 49 years, no significant decrease in the cellularity of the pineal parenchyma was found in proportion to age, despite the occasional occurrence of cysts and calcium deposition (2). The present electron microscopic observations including a qualitative comparison with the pineals of younger adults also did not necessarily confirm the general notion that the human pineal is merely a rudimentary organ without functions which degenerates progressively after adulthood, showing the inadequacy of our basic understanding of the human pineal. There are ample medical reasons why we should search for further insights into the enigmatic function of the human pineal gland, since it might hold the key for disclosing the nature of the new disease entities of hyperpinealism and hypopinealism.

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