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Ultrastructure of Lewy Bodies in the Stellate Ganglion* **

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Summary. The Lewy body, a characteristic nerve cell inclusion in idiopathic parkinsonism, was examined by electron microscopy in the stellate ganglion, obtained from 9 patients at autopsy. Three main forms of Lewy bodies or Lewy body-related structures were demonstrated: A. Rare filamentous Lewy bodies, similar to Lewy bodies in the central nervous system. B. Granular Lewy bodies in nerve cell processes. C. Abnormal nerve cell processes, filled with heterogenous material. Large dense core vesicles were prominent in the last 2 forms. None of these abnormalities were found in 2 control groups consisting of 9 parkinsonism cases without central nervous system Lewy bodies, and 17 cases without parkinsonism.

The filamentous Lewy body (type A) was found in the perikaryon and was surrounded by neuromelanin, whereas the other forms (type B and C) were seen in nerve cell processes.

Mitochondrial inclusions, present mainly, but not exclusively, in neuromelanin-containing cells, were not related to Lewy body formation or to parkinsonism.

Key words: Lewy body — Electron microscopy — Parkinsonism — Dense core vesicles — Catecholamines — Mitochondrial inclusions.

Lewy bodies are hyalin, round or elongated, acidophilic inclusions in nerve cells or nerve cell processes. Lewy (1912) illustrated these structures in the innominate substance and the dorsal motor vagus nucleus in idiopathic parkinsonism. Lewy bodies in the pigmented nuclei of the brain stem have since become a halimark of idiopathic parkinsonism (Tretiakoff, 1919; Greenfield and Bosanquet, 1953). On the other hand, they are not pathognomonic, and their role in the nerve

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cell degeneration is still a subject for discussion (Lipkin, 1959; Forno, 1969; Escourolle et al., 1971; Forno and Alvord, 1971).

Lewy bodies in the sympathetic ganglia were first observed by Herzog (1928). He described them as elongated swellings resembling those demonstrated in the central nervous system by Lewy (1912). Wohlwill (1929) and Hechst and Nussbaum (1931) carried out similar studies of the sympathetic ganglia, but, as Herzog, they did not report on central nervous system findings in their cases. It remained for den Hartog Jager and Bethlem (1960) to establish the close relationship between Lewy bodies in the central nervous system and the sympathetic ganglia. They found a concurrence of Lewy bodies in the central and autonomic nervous system in 5 out of 6 patients with idiopathic parkinsonism. They also demonstrated that Lewy bodies in the sympathetic ganglia were common in nerve cell processes, but rare in perikarya.

Duffy and Tennyson (1965) first reported on the ultrastructure of Lewy bodies in the substantia nigra and locus caeruleus. They described a composition of filamentous material, radiating out from a denser central core and ending, without a membrane, among the neuromelanin granules. Circular profiles were also present. Further electron microscopic studies were published by Roy and Wolman (1969) and by Schochet (1972).

In this paper we report on the ultrastructure of Lewy bodies in nerve cells and nerve cell processes in the stellate ganglion in 9 cases. We found important differences from locus caeruleus and substantia nigra Lewy bodies. A preliminary presentation of three of these cases has been published in abstract form (Forno, 1973).

MATERIALS AND METHODS

The stellate ganglion was selected as representative of an autonomic ganglion, because of its size, easy accessibility and frequent involvement in parkinsonism (den Hartog Jager and Bethlem, 1960). The ganglion was removed at autopsy, 3 to 40 h post mortem, but usually within 24 h. Cases with parkinsonism and suspected parkinsonism were selected for study, along with cases without parkinsonism. The composition of the material, including the age at the time of death, is shown in the table. A total of 37 cases was examined. The average age of the 20 cases of parkinsonism was 67.6, ranging from 49 to 83 for the Lewy body group and 56 to 84 for the rest of the group with clinical parkinsonism. For the 17 cases without parkinsonism the corresponding figures were: average age 61.3 (range 36 to 102), with only one above age 84.

We used a combination of clinical and neuropathological data for diagnosis and classification of the cases. Ten cases examined in this manner (Table) had Lewy bodies in the pigmented nuclei in the brain stem. Eight of these 10 also had Lewy bodies in paraffin and epon sections of the stellate ganglion. One such case was classified as an "incidental Lewy body case" (Forno, 1969). An additional case, with mild and early parkinsonism, had Lewy bodies in paraffin and epon sections of the stellate ganglion, but not in the central nervous system.

The control cases fell into 2 groups: a) cases with a partial or complete parkinsonism syndrome, but without Lewy bodies in the central nervous system; and b) cases without parkinsonism. The latter included a large number with neurological disorders (see Table).

A portion of the stellate ganglion was cut into thin slices and immediately placed in 1.5% glutaraldehyde adjusted to pH 7.4 with cacodylate buffer. The slices were subsequently sectioned into approximately 1 mm^3 blocks. The blocks of tissue were post-fixed in cold osmium tetroxide buffered to pH 7.4 with Sorenson's phosphate buffer. After

dehydration in graded alcohols the tissue was embedded in either epon or an epon-araldite mixture (Mollenhauer, 1964). One μ thick sections were cut and stained with toluidine blue and examined by light microscopy for the presence of nerve cells, and for Lewy bodies and other pathological features. Selected blocks were thin sectioned and stained with uranyl acetate and lead citrate. One block was examined in serial sections with alternate "thick" and "thin" sections. The sections were viewed with an RCA EMU-3H electron microscope.

The remainder of the stellate ganglion was processed for paraffin embedding and light microscopy studies.

RESULTS

Lewy bodies were demonstrated by light and electron microscopy in the stellate ganglion in 9 cases (Table).

Three main forms of Lewy bodies with transition between them were observed:

A. *Filamentous Lewy Body.* This Lewy body had a dense central core and radiating filaments; it was located in the nerve cell perikaryon and surrounded by pigment granules (Fig. 1 and 2). The appearance was identical with that of the Lewy body most commonly encountered in the locus caeruleus and substantia nigra. This form was rare and observed only twice.

B. *Granular Lewy Body.* The second form had a dense core with a periphery made up of coarse, ill-defined granules, or granules mixed with vesicles and filaments. This was the characteristic Lewy body in the stellate ganglion (Fig. 1 and 3). It was situated in nerve cell processes. Mitochondria, multivesicular bodies and other organelles could be seen among the granules. Dense core vesicles were sometimes present just outside the core; at other times they were seen near the peripheral, non-membrane-bound border of the Lewy body inclusion. Occasionally, alternating bands of granulo-vesicular and filamentous material were seen circling the central core (Fig. 4a and b).

C. *Lewy Body-Related Swelling.* The third form was less characteristic in appearance, but extremely common. We regard it as either a Lewy body or a structure closely associated with Lewy bodies, because it was found only in cases with Lewy bodies by light microscopy in epon and paraffin sections. It consisted of swollen cell processes with various mixtures of dense material, filaments, membranous structures, and dense core vesicles. A regular arrangement was the rule, often in the form of an inside-out Lewy body appearance with less electron dense material in the center and denser material with dense core vesicles in the periphery (Figs. 1, 5 and 6). At other times dense core vesicles, granular and filamentous material were seen throughout the swelling in the plane of sectioning. Some Lewy bodies in this category might actually be granular Lewy bodies in tangential cuts.

The appearance of the 3 forms of Lewy bodies in a 1 μ thick epon section is illustrated in Figure 1.

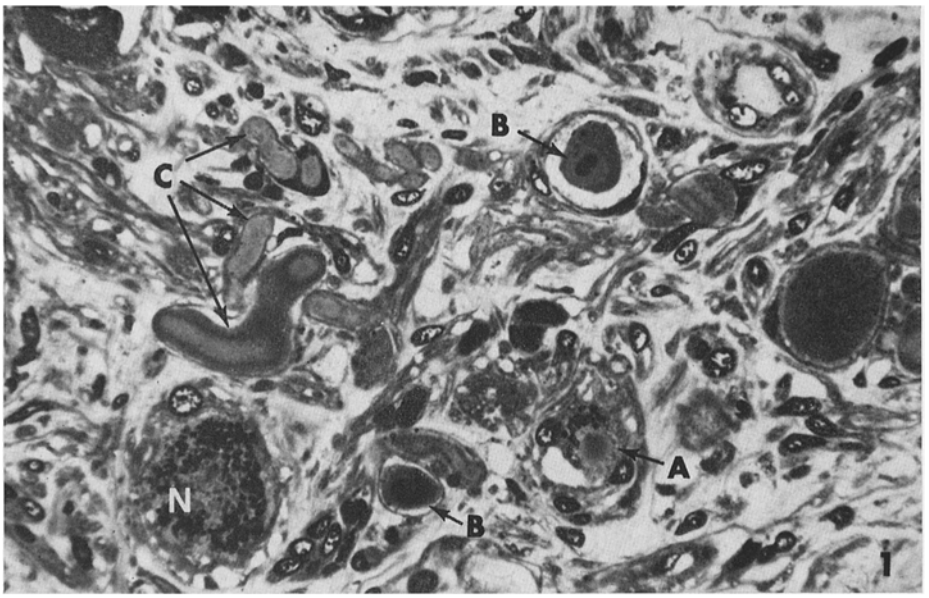
In the 2 cases with a filamentous Lewy body in the nerve cell perikaryon the other 2 forms predominated. The other 7 cases had both granular Lewy bodies (type B) and Lewy body-related swellings (type C). There was a tendency towards clustering of the Lewy bodies, possibly due to sectioning of the tortuous cell processes more than once. At least some of the cell processes could be identified as

Table 1

Case No.	Sex	Age	Lewy bodies				Mito-chondrial inclusions	Diagnosis
			in CNS	in stellate ganglion				
				paraffin	epon	EM		
69A146	M	57	+	+	+	+	0	Idiopathic parkinsonism
69A177	M	61	0	+	+	+	+	Idiopathic parkinsonism
70A63	M	50	+	+	+	+	+	Idiopathic parkinsonism
70A146	M	82	+	+	+	+	0	Idiopathic parkinsonism
72A138	M	83	+	+	+	+	+	Idiopathic parkinsonism
73A33	M	70	+	+	+	+	+	Idiopathic parkinsonism
73A39[a]	M	73	+	+	+	+	+	Shy-Drager syndrome. Idiopathic parkinsonism
73A79	M	71	+	+	+	+	0	Dementia of mixed etiology
74A97	M	79	+	+	+	+	+	Idiopathic parkinsonism
72A156	M	49	+	0	0	0	+	Mesothelioma. Idiopathic parkinsonism
71A113	M	70	+	0	0	0	0	Postencephalitic parkinsonism
67A156	M	56	0	0	0	0	+	Postencephalitic parkinsonism
70A43	M	63	0	0	0	0	0	Alzheimer tangle parkinsonism
73A23	M	84	0	0	0	0	0	Alzheimer's disease with mild parkinsonism
72R10[b]	F	56	0	0	0	0	+	Shy-Drager syndrome with striato-nigral degeneration
70A127	M	77	0	0	0	0	0	Arteriosclerotic parkinsonism
73A35	M	57	0	0	0	0	0	Arteriosclerotic parkinsonism

74A122	M	82	0	0	0	0	+	Arteriosclerotic parkinsonism
75R98	M	59	0	0	0	0	+	Shy-Drager syndrome with mild parkinsonism
70A19	M	73	0	0	0	0	+	Schizophrenia. Old leucotomy. Mild parkinsonism
70A152	M	102	0	0	0	0	0	Senile and arteriosclerotic brain disease
71A162	M	78	0	0	0	0	+	No neurological disease
72A68	M	60	0	0	0	0	+	Atherosclerotic cerebrovascular disease
72A94	M	59	0	0	0	0	+	Hypertensive and arteriosclerotic brain disease
72A25	M	54	0	0	0	0	0	Presenile dementia, unclassified
72A151	M	77	0	0	0	0	+	Alzheimer's disease
71A111	M	40	0	0	0	0	+	Multiple sclerosis
72A8	M	51	0	0	0	0	0	Multiple sclerosis
72A37	M	48	0	0	0	0	+	Multiple sclerosis
74A31	M	36	0	0	0	0	0	Multiple sclerosis
72A159	M	60	0	0	0	0	0	Giant cell arteritis
73A88	F	84	0	0	0	0	0	Senile and arteriosclerotic brain disease
74A25	M	50	0	0	0	0	+	Jakob-Creutzfeldt disease
74A30	M	54	0	0	0	0	0	Huntington's chorea
74A83	M	59	0	0	0	0	+	Spino-cerebellar degeneration
74A171	M	83	0	0	0	0	+	Posttraumatic and arteriosclerotic brain disease
75A27	F	47	0	0	0	0	+	Anoxic encephalopathy, chronic stage

[a] Case 2, Schober et al., European Neurology **13**, 177—188 (1975).
[b] Case 1, ibidem.



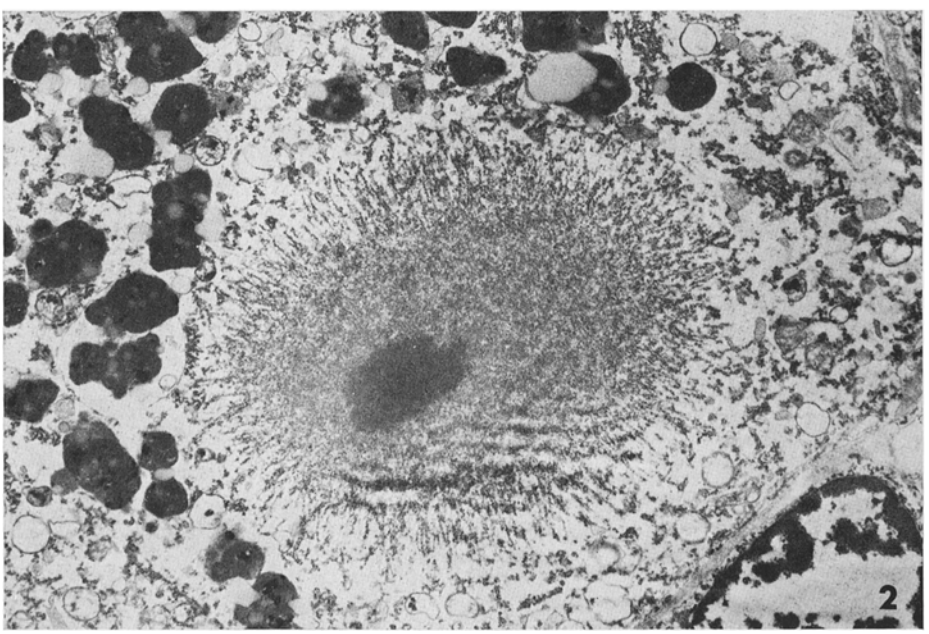


Fig. 1. One μ thick epon-embedded section from the stellate ganglion, stained with toluidine blue. The 3 forms of Lewy bodies are seen: Filamentous Lewy body (*A*). The same Lewy body can be seen again in Fig. 2. Granular Lewy body (*B*). Lewy body-related swelling (*C*). A normal nerve cell (*N*) with pigment granules is noted at the lower left. Case 72A138. $\times 480$

Fig. 2. Filamentous Lewy body (the same as in Fig. 1) in the perikaryon of a nerve cell. Note central core, radiating filaments and surrounding pigment granules. The nucleus of a satellite cell is seen in the lower right hand corner. Case 72A138. $\times 6000$

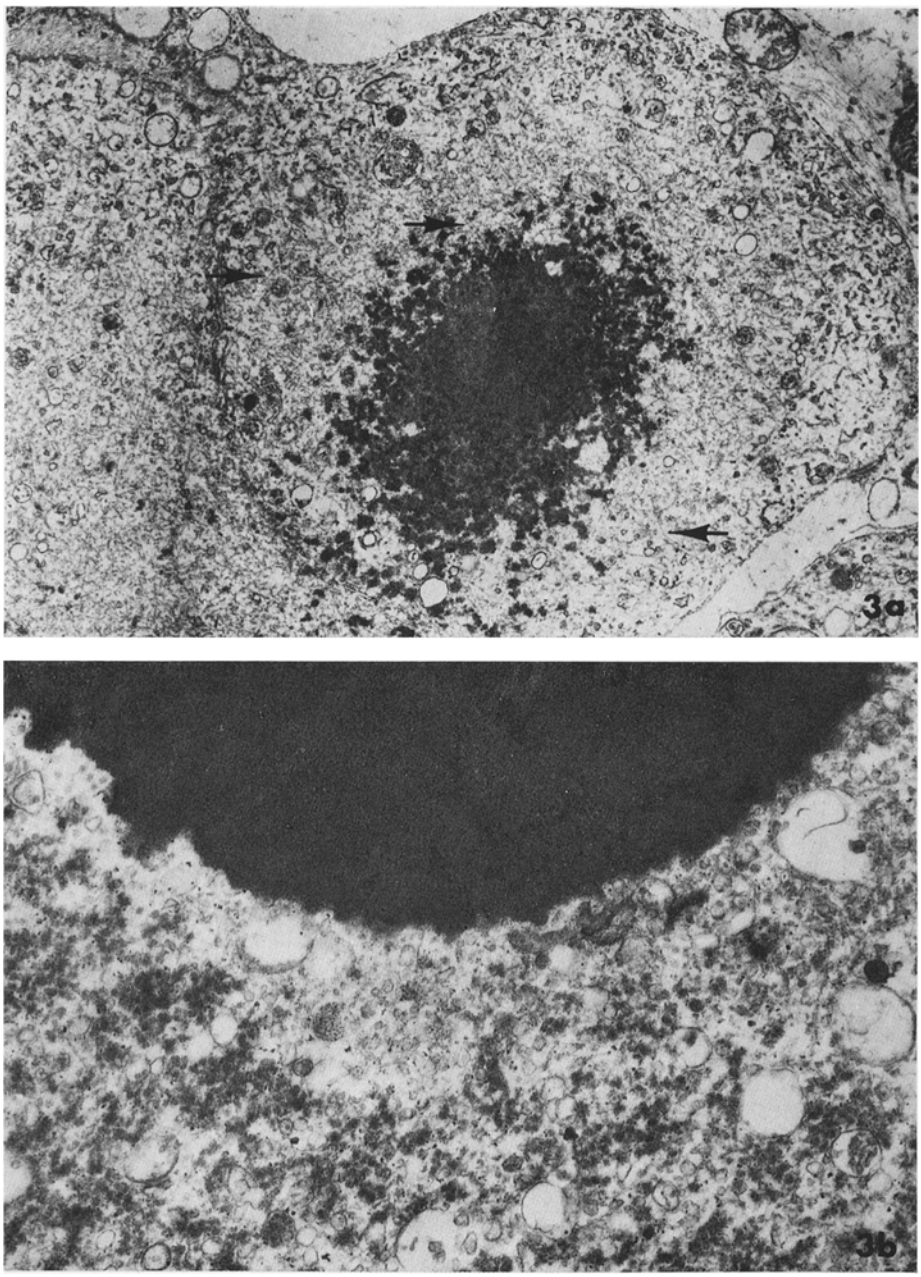


Fig. 3. (a) Granular Lewy body (*B*) with central core surrounded by dense granules. Filaments (arrows) can be seen among the granules and at the periphery. Case 73A33. ×11000. (b) A portion of a granular Lewy body with granules and vesicles just outside the electron dense core. Case 69A177. ×16000

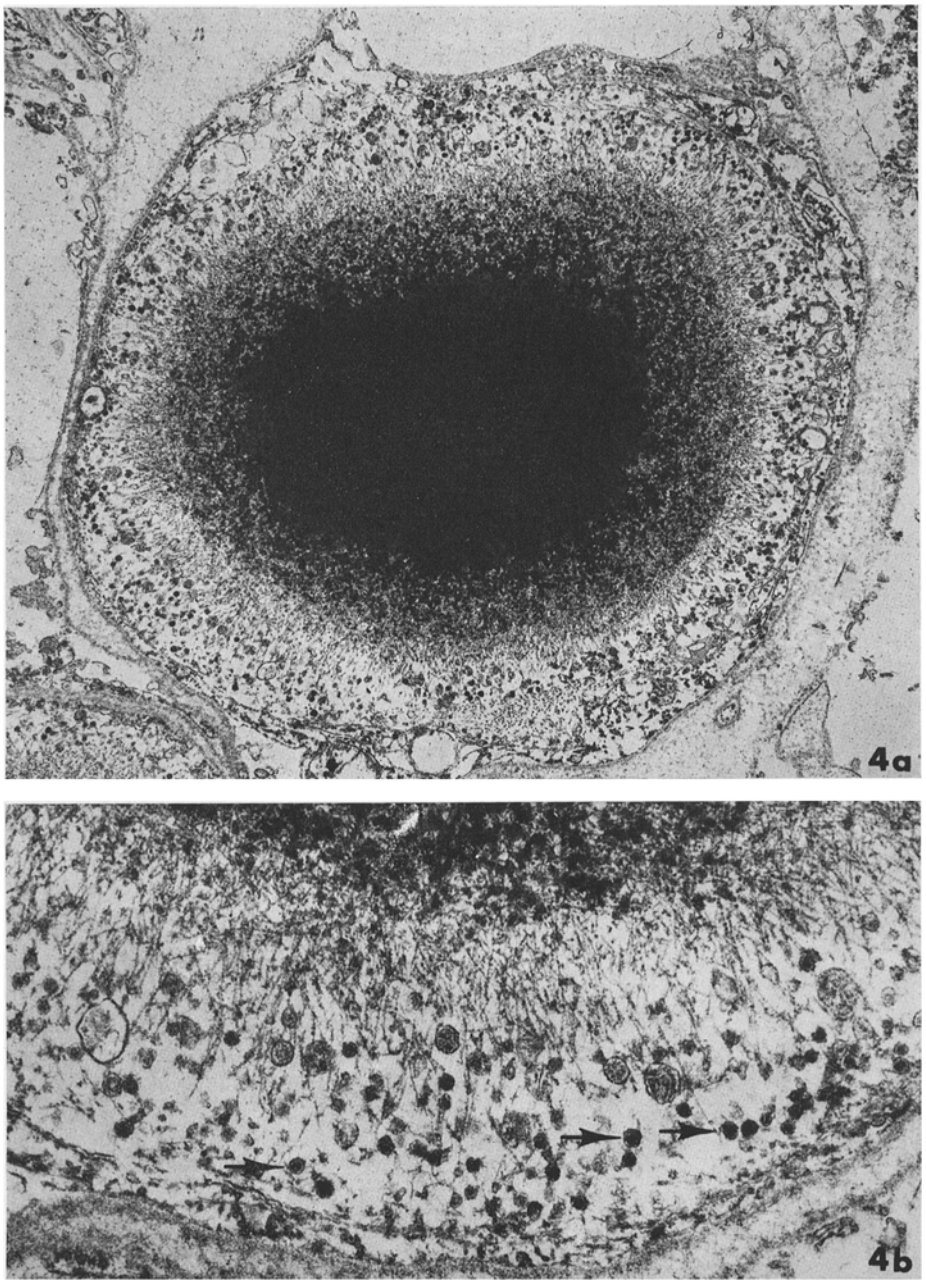
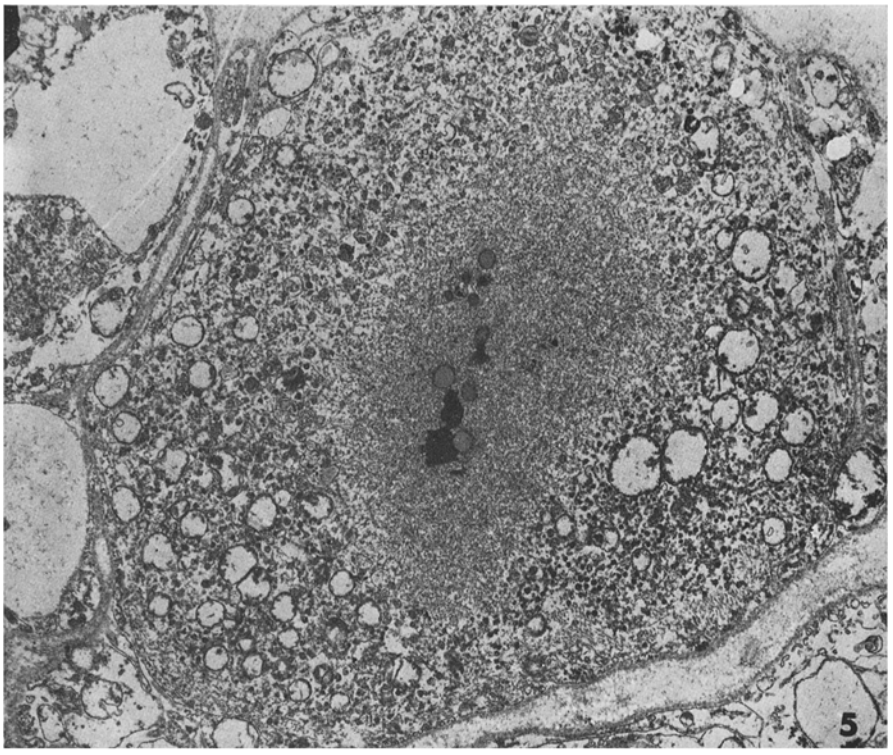


Fig. 4. (a) Granular Lewy body with concentric bands of granular and filamentous material around a central core. Note the dense core vesicles in the periphery. Case 72A138. ×9500. (b) Higher magnification of periphery of Fig. 4a. Filaments, 8 to 12 nm in diameter, radiate from the granular zone into the periphery where dense core vesicles (arrows), 80 to 120 nm in diameter, are abundant. Case 72A138. ×25000



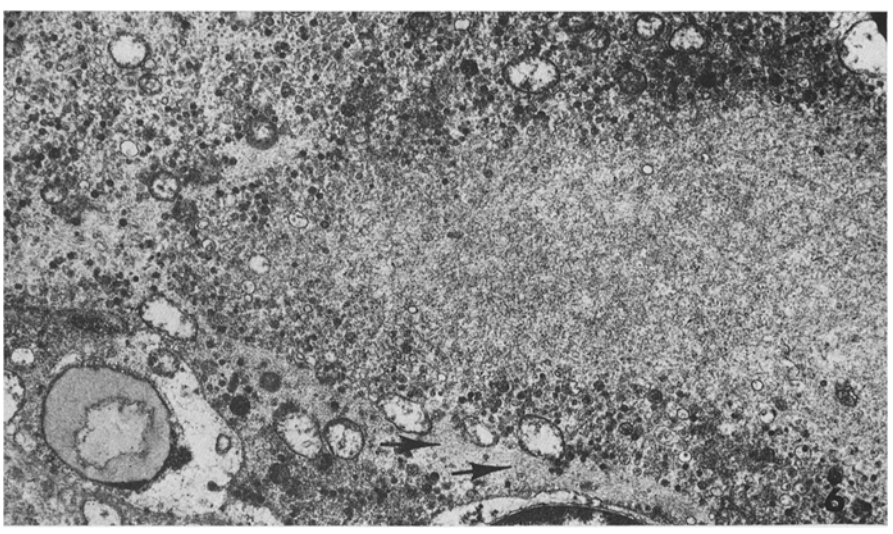


Fig. 5. Lewy body-related swelling with greater electron density in the periphery. Note the large dense core vesicle component here. Lipofuscin or neuromelanin pigment is seen within the ill-defined moderately dense material in the center. Case 72A138. ×7000

Fig. 6. Lewy body-related swelling. Oblique cut through a cell process. Similar peripheral dense core vesicle accumulation as in Fig. 5. The filamentous material (arrows) at the edge of the process may represent displaced neurofilaments. Case 74A97. ×8000

dendrites, since they contained ribosomes. All cell processes were enwrapped by satellite or Schwann cell cytoplasm, which contained many fine filaments and a basement membrane. None of the cell processes with Lewy bodies were myelinated. Synapses were not identified on these abnormal cell processes.

The material making up the Lewy body could not be completely characterized. Dense core vesicles, when present, were of the large variety, measuring 80 to 120 nanometer in diameter (Fig. 4a and b). They were conspicuous in most granular Lewy bodies and Lewy body-related swellings. The filaments observed measured from 8 to 15 nm in diameter, thus showing a greater variation than normal neurofilaments.

The Lewy bodies and Lewy body-related swellings contained few or none of the abnormal mitochondria and dense and lamellated bodies characteristic of "'axonal swellings" (Lampert, 1967; Jellinger, 1973). Such "axonal swellings" or "neuro-axonal dystrophic changes" were slightly more numerous in the Lewy body material than in the controls.

Except for the presence of Lewy bodies, ultrastructural differences between the above 9 cases and the control material were slight. Most features observed were normal characteristics of sympathetic ganglia (see Elfvin, 1963, and Pick, 1970). We want to mention only 3 nerve cell components, namely *dense core vesicles*, *neuromelanin* and *mitochondrial inclusions*. Dense core vesicles in non-Lewy body cases were extremely rare in our glutaraldehyde-fixed material and, when present, were seen in the vicinity of the Golgi apparatus or in the periphery of the nerve cell. In nerve cell processes large dense core vesicles, 80–120 nm in diameter, were seen in preganglionic terminals and sometimes in unidentified non-myelinated nerve cell processes, but rarely in dendrites. The small granule-containing cells (Grillo, 1974) were not identified. Practically all nerve cells showed pigment granules with a triphasic structure, consisting of a relatively electron lucent lipid globule or vacuole, a moderately dense component, and a coarse, patchy, extremely electron dense component. The latter is the distinguishing characteristic of neuromelanin and is lacking in lipofuscin pigment (Moses et al., 1966). Compared to the neuromelanin in the substantia nigra and locus caeruleus the dense, particulate material was often sparse, with marked variation from one nerve cell to another and even within the same nerve cell. Amorphous or finely granular, moderately electron dense inclusions were seen in the matrix of mitochondria in more than half of our cases (22 out of 37). No definite predilection for age, within the range of our material, or for parkinsonism could be established (see Table 1). A few nerve cells had clusters of mitochondria with inclusions. Multiple densities within one mitochondrion were sometimes present (Fig. 7a and c). The inclusion had no limiting membrane and its borders were fuzzy. Most mitochondrial inclusions were located among neuromelanin granules. The majority of nerve cells with lipofuscin and neuromelanin did not display the mitochondrial densities, however. Dense bodies and multivesicular bodies as well as dense material without a definite membrane were also present. No convincing transition forms between the mitochondrial inclusions and the pigment granules were identified. The mitochondrial densities were confined to nerve cell perikarya and occasional dendrites. They were not seen in satellite cells or Schwann cells.

DISCUSSION

The main findings in this study are the difference in morphology between most Lewy bodies in the central nervous system and those in the stellate ganglion, and the heterogenous composition of the Lewy bodies. The filamentous Lewy body (type A), so well described by Duffy and Tennyson (1965) in the substantia nigra

and locus caeruleus, is rare in the stellate ganglion (Fig. 2); instead we see granular Lewy bodies (type B) and Lewy body-related swellings (type C) in nerve cell processes (Fig. 3—6). An orderly arrangement of the material making up all types of Lewy bodies is the rule; type A and B have a central core, whereas some of the Lewy body-related swellings (type C) have a denser periphery. Both type B and C contain varying amounts of granular, vesicular and filamentous material. Dense core vesicles (80—120 nm in diameter) are prominent in the periphery of many Lewy bodies (Fig. 5 and 6) or just outside the central core. This sometimes gives the impression that the granules are a product of degenerating dense core vesicles. None of the Lewy body types have a membrane, and normal organelles are seen among other components of the Lewy body. The filamentous Lewy body (type A), whether seen in the central nervous system or in the stellate ganglion, is commonly surrounded by neuromelanin granules (Fig. 2). Such pigment is not seen at the periphery of type B and C Lewy bodies and has only rarely been found within their central portion (Fig. 5).

The difference in morphology between central and peripheral Lewy bodies has led some authors to regard "eosinophilic bodies" in nerve cell processes in the sympathetic ganglia as separate from Lewy bodies. The only paper we are aware of, dealing with the ultrastructure of these bodies, interprets them as axonal swellings in preganglionic terminals (Roessmann et al., 1971). Since ribosomes are present in some Lewy body containing nerve cell processes, at least some inclusions must be located in postganglionic dendrites. In fact, elongated Lewy bodies emerging from the cytoplasm of sympathetic ganglion cells can sometimes be seen in paraffin sections. The close association between Lewy bodies in the central and the autonomic nervous system (see Table) also leads us, with den Hartog Jager and Bethlem (1960) to accept all such sympathetic ganglion inclusions as forms of Lewy bodies.

We not only regard our type B and C inclusions as forms of Lewy bodies, but we also suspect that the same Lewy body variations will eventually be found in the central nervous system. The filamentous Lewy body (type A) is primarily found in the perikarya of nerve cells and may in some way be related to the presence of neuromelanin, which commonly surrounds the periphery of the inclusion (Fig. 2). In the central nervous system we have seen 2 examples of type B and C Lewy bodies in nerve cell processes in the locus caeruleus (Forno and Norville, 1975). That authentic Lewy bodies in nerve cell processes exist in the central nervous system is well documented in Lewy's original illustrations of Lewy bodies in the dorsal motor vagus nucleus and the innominate substance (Lewy, 1912). In our material such elongated Lewy bodies in nerve cell processes are common in the above areas as well as in the hypothalamus (Langston and Forno, to be published), but their ultrastructure has yet to be demonstrated. The reason for the difference in morphology of Lewy bodies in nerve cell perikarya and nerve cell processes has not been established, but Lewy bodies in nerve cell processes are mainly seen in areas where neuromelanin is sparse (sympathetic ganglia, dorsal motor vagus nucleus) or absent (innominate substance, hypothalamus). Circular profiles (Duffy and Tennyson, 1965; Schochet, 1972) in central nervous system filamentous Lewy bodies (type A) may represent a transition to the vesicular structures in the type B and C Lewy bodies.

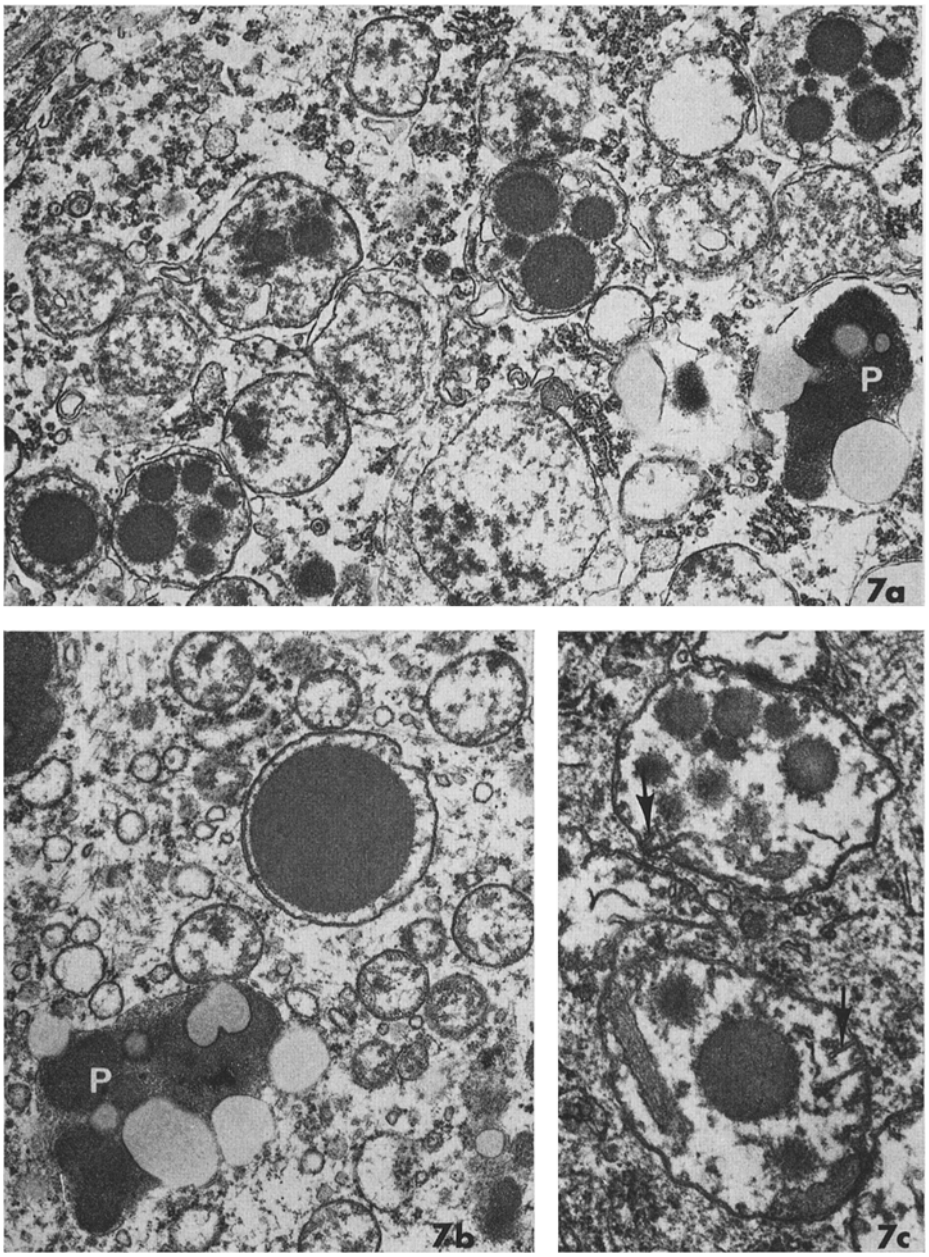


Fig. 7 a–c. Mitochondria with single or multiple inclusions in stellate ganglion nerve cells. Pigment granules (*P*) can be seen nearby in Fig. 7a and b; mitochondrial cristae (arrows) are preserved in Fig. 7c. (a) Case 72A138. ×15000; (b) Case 72A156. ×17000; (c) Case 72A151. ×28000

Apart from the Lewy bodies very few differences have been found between the idiopathic parkinsonism cases and the 2 groups of control cases. The usual difficulty in distinguishing between "normal" age changes and disease-related abnormalities applies to many subtle alterations seen. This is also the case for the mitochondrial inclusions (Fig. 7) which were found in more than half of our material (see Table), without definite predilection for the Lewy body cases or for parkinsonism. Similar inclusions were seen in half of our cases in the locus caeruleus (Forno and Norville, 1975). They were first noted by Pick (1964, 1967 and 1970) in the human sympathetic ganglia of persons over age 50. We suspected originally, with Hirosawa (1968) that a relationship to neuromelanin formation existed, because of the presence of the inclusions in neuromelanin containing nerve cells in humans and monkeys (Pick, 1970; Beaver et al., 1965; Hirosawa, 1968). Similar inclusions have now been demonstrated in the human frontal cortex (Herrlinger et al., 1975) and in the lateral geniculate body in the monkey (Hasan and Glees, 1972), both areas which do not contain neuromelanin on light microscopic examination. We have recently observed a small number of similar mitochondrial densities in the human hypothalamus, and the relationship of such inclusions to neuromelanin is therefore obscure.

Assuming that all 3 forms of Lewy bodies are interrelated and expressions of the same or a closely related "degenerative" process, no one organelle appears to be the main component of the Lewy body. Indeed, we cannot even be certain that the filaments in the Lewy body represent neurofilaments, or that the dense core vesicles are catecholamine storage vesicles. The latter possibility suggests that Lewy bodies may contain degenerated catecholamine storage granules; the Lewy body might then represent the morphological expression of the abnormal catecholamine metabolism present in parkinsonism. The absence of dense core vesicles in the filamentous type of Lewy body (type A) makes this hypothesis less likely. Moreover, an accumulation of catecholamine storage vesicles, normally present in small numbers, could be secondary to a disturbance of axonal or dendritic flow, related to or aggravated by the Lewy body formation. It is also possible that the dense core vesicles are a product of lysosomal activity, unrelated to catecholamine storage.

Other explanations of the origin of the Lewy body include a general cytoplasmic degeneration, or a formation of Lewy bodies as a result of excess production or deficient breakdown of normal or abnormal protein. The Lewy body contains mainly protein (Lipkin, 1959; Bethlem and den Hartog Jager, 1960) along with a sphingomyelin component (den Hartog Jager, 1969). Further chemical characterization of the Lewy body and its components should be the next step on the way to understanding this unique form of nerve cell degeneration.

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