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THE DISTRIBUTION OF LEWY BODIES IN THE CENTRAL AND AUTONOMIC NERVOUS SYSTEMS IN IDIOPATHIC PARALYSIS AGITANS

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The hyaline inclusions in the pigmented ganglion cells of the substantia nigra and the locus coeruleus in patients suffering from idiopathic paralysis agitans are known as Lewy bodies after their discoverer, Lewy (1913). A detailed description of these bodies was presented by Greenfield and Bosanquet in 1953. The intracytoplasmic bodies are always surrounded by a light halo, and often have a central core which stains differently from the remainder of the body. If these morphological and staining characteristics are taken into account, confusion with other cytoplasmic inclusions is impossible. Greenfield and Bosanquet found Lewy bodies in each of their 19 cases of idiopathic paralysis agitans, and in none of their 10 cases of post-encephalitic Parkinsonism or in their 22 control cases. These findings were confirmed by Bethlem and den Hartog Jager (1960) in 15 cases of idiopathic paralysis agitans, four cases of post-encephalitic Parkinsonism, and 20 control cases. We have since found the Lewy bodies in nine new cases of Parkinson's disease. We failed to find them in a case of Parkinson following CO intoxication and in the case of Friedreich's ataxia combined with hereditary Parkinsonism, previously described by Biemond and Sinnege (1955).

In contrast with the above are the findings of Redlich (1930) and Godlowski (1931), each of whom found Lewy bodies in two cases of post-encephalitic Parkinsonism. Alvord (1958) described Lewy bodies in four out of 14 post-encephalitic cases. Lipkin (1959) also found Lewy bodies in four out of nine verified cases of post-encephalitic Parkinsonism. Lewy bodies have so far been chiefly described in the pigmented ganglion cells of the substantia nigra and the locus coeruleus (Trétiakoff, 1919; Beheim-Schwarzbach, 1952; Greenfield and Bosanquet, 1953). Lewy himself (1913, 1923) described these bodies in the nucleus of the substantia innominata, the periventricular nucleus, and the dorsal vagal nucleus. Von Buttlar-Brentano (1955) found Lewy bodies in the nucleus of the substantia innominata (nucleus basalis) in each of 16 cases of paralysis agitans. In 13 cases of post-encephalitic Parkinsonism, no Lewy bodies were found in this nucleus. Bethlem and den Hartog Jager found Lewy bodies in the nucleus of the substantia innominata in nine out of 15 cases of Parkinson's disease.

Greenfield and Bosanquet described Lewy bodies as found in the oculomotor nucleus (Case 9) and in the nucleus of Roller (Case 10) in idiopathic paralysis agitans.

In idiopathic paralysis agitans, Lipkin found Lewy bodies in the ganglion cells of the dorsal vagal nucleus (three cases), the cerebral cortex (one case), and the inferior olive (one case). Herzog (1928), Wohlwill (1928), and Hechst and Nussbaum (1931) found Lewy bodies in the ganglion cells of the sympathetic vertebral chain in paralysis agitans, and were therefore the first investigators to encounter Lewy bodies outside the central nervous system. They do not indicate whether Lewy bodies were also present in the central nervous system in these cases. They did report having found Lewy bodies in the sympathetic ganglia in patients not suffering from paralysis agitans, although of considerably less marked intensity and spread.

The purpose of this paper is to present a description of the exact distribution of Lewy bodies in Parkinson's disease, both in the central and in the peripheral autonomic nervous systems.

Material and Methods

Eight sagittal sections were made through the left hemisphere of a 57-year-old male with the clinical diagnosis of idiopathic paralysis agitans (No. 585), and these sections were embedded in celloidin. All blocks were then submitted to serial section, every twenty-fifth section being stained with haematoxylin and eosin, and every fiftieth according to Weigert-Pal. A few orientating sections were obtained from the left half of the cerebellum. The entire brain-stem was studied in the same

TABLE I

FREQUENCY OF LEWY BODIES IN LOCUS COERULEUS AND SUBSTANTIA NIGRA

No. of Cells Counted	One Lewy Body	Two Bodies in One Cell	Three Bodies	Four Bodies	Five Bodies	Six Bodies	Seven Bodies	Total of Cells Containing One or More Lewy Bodies	Extracellular Bodies
Locus coeruleus 3,180	256	64	18	9	2	1	1	351 (11·0%)	79
Substantia nigra 3,357	60	16	7	—	—	—	—	83 (2·4%)	11

way, every twentieth section being stained with haematoxylin and eosin, and every fortieth according to Weigert-Pal. A half-centimetre slice of pons was embedded in paraffin and submitted to complete serial section (7μ thickness), and stained with haematoxylin and eosin. In every eighth section the cells of the locus coeruleus were counted, and a count was also made of the number of Lewy bodies per section. In the same way, half a centimetre of the right substantia nigra at the level of a section through the centre of the nucleus ruber was processed and counted.

At necropsy on six patients with the clinical diagnosis of idiopathic paralysis agitans, the peripheral autonomic nervous system was removed in addition to the central nervous system and parts of the peripheral nervous system. The material was embedded in paraffin and stained with haematoxylin and eosin.

Results

Frequency of Lewy Bodies in Locus Coeruleus and Substantia Nigra.—In Case 585, 3,180 cells were counted in 37 locus coeruleus sections; of these, 351 cells (11%) were found to contain one or several Lewy bodies. In this same case, 3,357 cells were counted in nine substantia nigra sections, including 83 cells (2·4%) containing one or several Lewy bodies (Table I).

Distribution of Lewy Bodies in Central Nervous System.—In the case examined in serial section (No. 585), Lewy bodies were found not only in the substantia nigra, substantia innominata, and locus coeruleus, but also in other groups of nuclei of the brain-stem and the diencephalon. A survey of these is presented in Table II. In four cases, Lewy bodies were found in the ganglion cells of the lateral horns of the spinal cord (Figs. 1 and 2). In one case (No. 617) a Lewy body was present in a ganglion cell of the posterior horn (Fig. 3).

TABLE II

DISTRIBUTION OF LEWY BODIES IN NUCLEI OF DIENCEPHALON AND BRAIN-STEM IN CASE 585

Diencephalon
- Nucleus dorsomedialis hypothalami
- Nucleus basalis
- Nucleus periventricularis
- Nucleus mammilo-infundibularis
- Nucleus intercalatus hypothalami

*Brain-stem**
- Nucleus substantiae nigrae
- Griseum centrale mesencephali
- Nucleus oculomotorius principalis
- Nucleus supratrochlearis
- Nucleus tegmenti pedunculopontinus, subnucleus compactus
- Nucleus tegmenti pedunculopontinus, subnucleus dissipatus
- Nucleus locus coeruleus
- Nucleus subcoeruleus
- Nucleus pontis centralis oralis et caudalis
- Processus griseum pontis supralemniscalis
- Nucleus centralis superior, subnucleus medialis
- Nucleus gigantocellularis
- Nucleus paragigantocellularis lateralis et dorsalis
- Nucleus raphae pallidus
- Nucleus dorsalis motorius nervi vagi
- Nucleus medullae oblongatae lateralis, subnucleus ventralis

* Nomenclature according to Olszewski and Baxter (1954).

Distribution of Lewy Bodies in Peripheral Autonomic Nervous System.—In five of the six cases in which the peripheral autonomic ganglia were examined, Lewy bodies were found in the right and

TABLE III

OCCURRENCE OF LEWY BODIES IN CENTRAL AND AUTONOMIC NERVOUS SYSTEMS

Localization	Case 600	Case 601	Case 603	Case 617	Case 619	Case 623
Substantia nigra	+	+	+	+	+	+
Locus coeruleus	+	+	+	+	+	+
Spinal cord	−	+	0	+	+	+
Ganglion cervicale superius	−	+	+	+	+	+
Ganglion stellatum	−	+	+	+	+	+
Ganglia thoracalia	−	+	+	+	+	+
Ganglia lumbalia	−	+	+	+	+	+
Ganglia sacralia	−	+	+	+	+	+
Ganglion coeliacum	−	+	+	+	+	+
Ganglia around adrenals	0	−	−	−	+	+
Posterior root ganglia	−	−	0	−	−	−
Ganglion Gasseri	0	0	−	−	−	+
Ganglion ciliare	0	−	−	−	−	−
Intramural ganglion cells of trachea, oesophagus, stomach, duodenum, and colon	−	−	0	−	−	−

\+ = Lewy bodies present. − = No Lewy bodies present. 0 = Not examined.

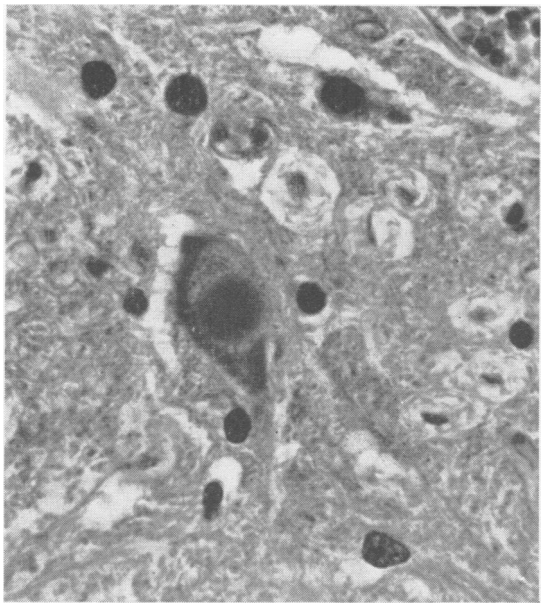


FIG. 1.—Ganglion cell of the lateral horn of the spinal cord with Lewy body, showing typical halo. Haematoxylin-eosin.

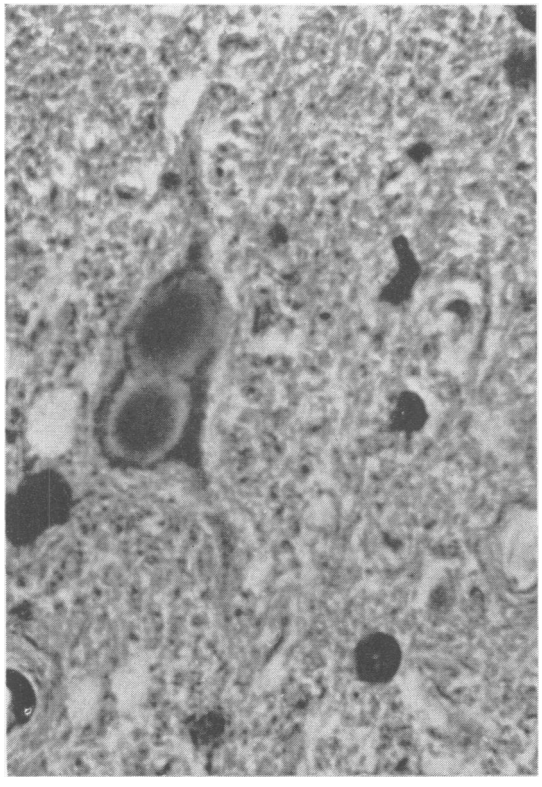


FIG. 2.—Two Lewy bodies in a ganglion cell of the lateral horn of the spinal cord. Haematoxylin-eosin.

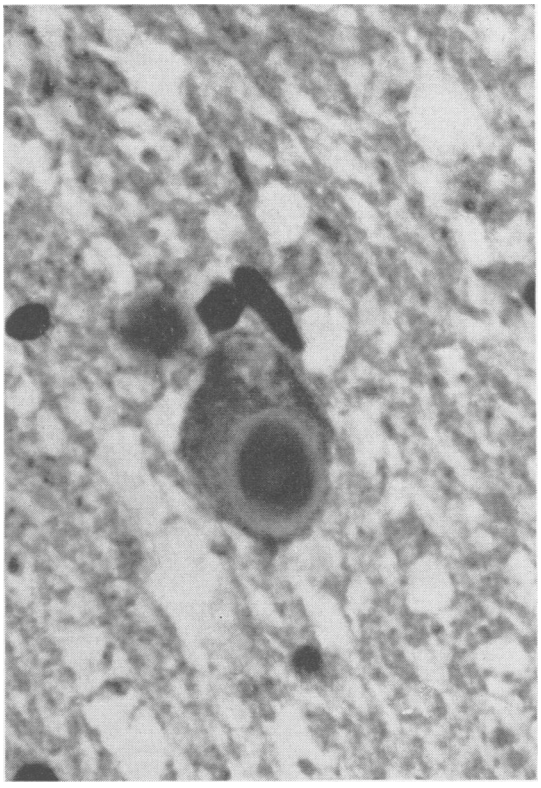


FIG. 3.—Lewy body in a ganglion cell of the posterior horn of the spinal cord. Note concentric structures with pale central core. Haematoxylin-eosin.

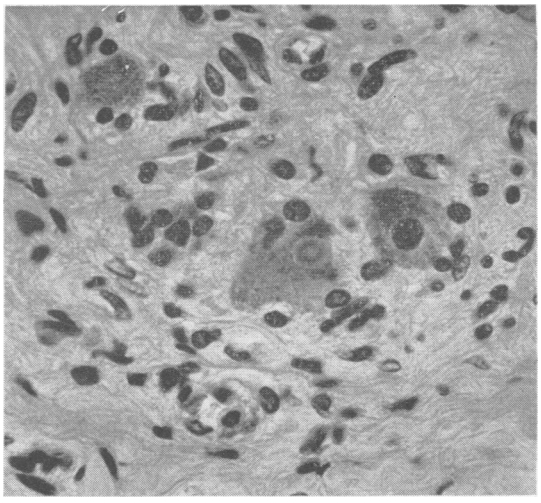


FIG. 4.—Lewy body in pigmented cell of the superior cervical sympathetic ganglion. Haematoxylin-eosin.

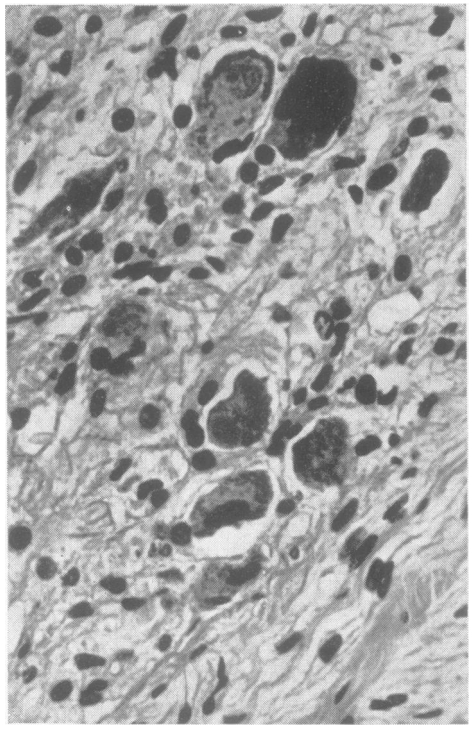


FIG. 5.—Lewy body in pigmented cell of the sympathetic ganglion around the adrenal. Haematoxylin-eosin.

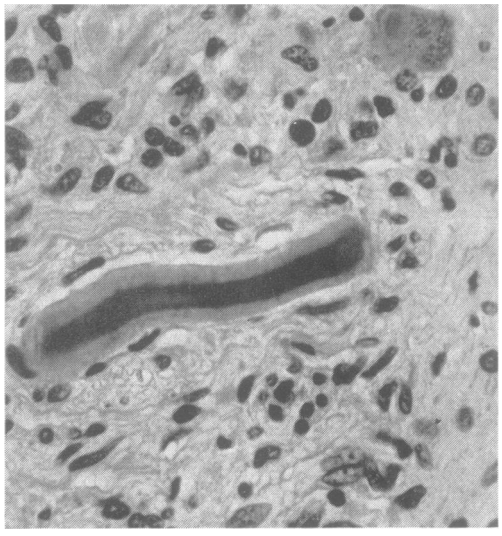
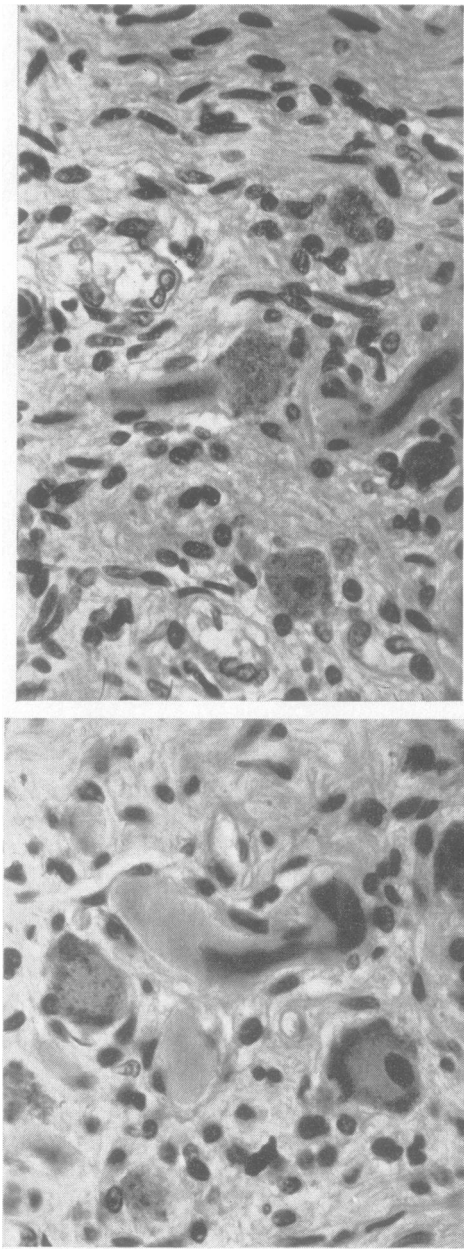


FIG. 6.—Stellate ganglion. Large elongated "extracellular" form of Lewy body, with acidophilic central core. In the left upper corner a cytoplasmatic Lewy body is seen in a pigmented ganglion cell. Haematoxylin-eosin.



FIGS. 7 and 8.—Degeneration of the Lewy type of the cell processes of ganglion cells in the stellate ganglion. Haematoxylin-eosin.

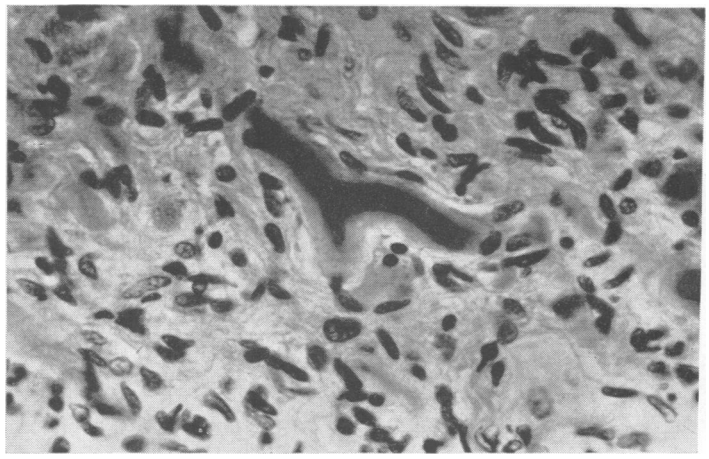


FIG. 9.—Stellate ganglion. Ramification of degenerated cell process. Haematoxylin-eosin.

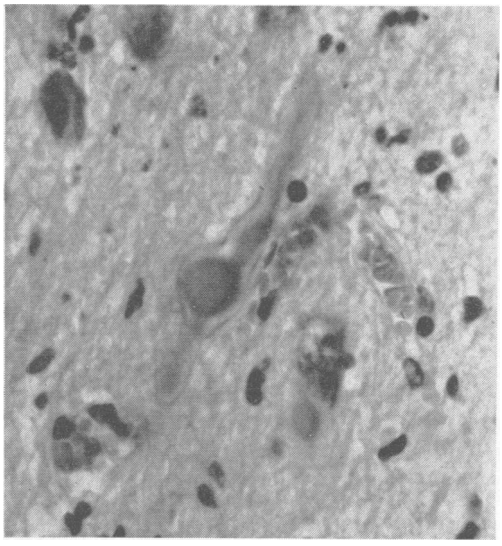


FIG. 10.—Longitudinal section of locus coeruleus. Globular thickening of degenerated axon. Haematoxylin-eosin.

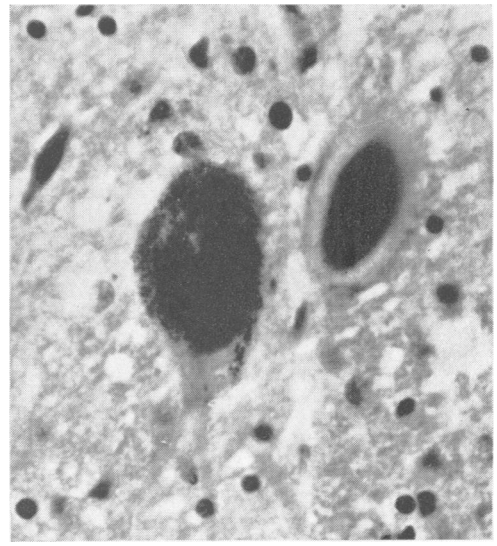
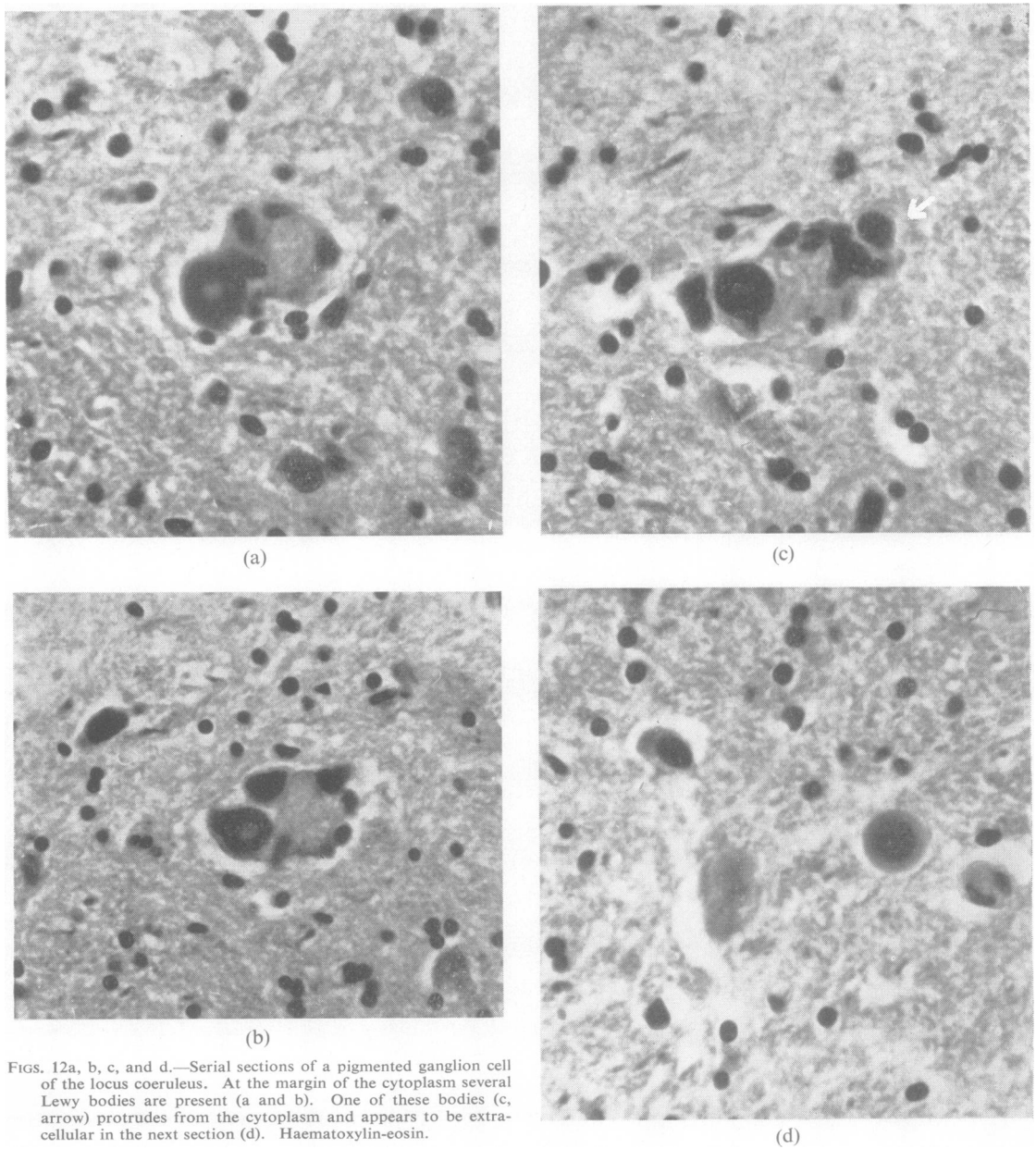


FIG. 11.—Large intracytoplasmic Lewy body filling the entire ganglion cell of the locus coeruleus. Haematoxylin-eosin.

left ganglia throughout the sympathetic vertebral chain (Fig. 4) and in the prevertebral ganglion coeliacum. In two cases, moreover, Lewy bodies were present in the ganglions around the adrenals (Fig. 5). In one case (No. 623) two extracellular Lewy bodies were present in one ganglion Gasseri. In all cases the most striking histological alterations were found in the ganglion stellatum.

In each of the six cases Lewy bodies were present in the locus coeruleus and the substantia nigra. Table III gives a survey of these findings.

Distinctive Morphology of Lewy Bodies in Sympathetic Ganglia.—In the sympathetic ganglia, the intracytoplasmic Lewy bodies proved to be relatively few. So-called extracellular forms, such as can also be found in the central nervous system (Table I), were far more numerous. They gave the same staining reactions as the intracytoplasmic bodies. Apart from round or more oval-shaped extracellular bodies, the sympathetic ganglia also contained numerous elongated forms (Fig. 6). In some instances these elongated forms were seen to



FIGS. 12a, b, c, and d.—Serial sections of a pigmented ganglion cell of the locus coeruleus. At the margin of the cytoplasm several Lewy bodies are present (a and b). One of these bodies (c, arrow) protrudes from the cytoplasm and appears to be extracellular in the next section (d). Haematoxylin-eosin.

arise directly from the cell body (Figs. 7 and 8). It is therefore highly probable that these forms are degenerated processes of cells (dendrites or neurites). Sometimes, moreover, they show ramification (Fig. 9). Whenever these degenerated cell processes are cut in transverse section, they have the round shape of the extracellular bodies also often found in transverse sections in the locus coeruleus or the substantia nigra. In longitudinal sections of the locus coeruleus, the elongated forms are also observed. Sometimes these degenerated cell processes show globular thickening (Fig. 10).

So-called extracellular Lewy bodies, therefore, can arise in three different ways: (1) An intracytoplasmic Lewy body becomes so large that it fills the entire cell, which finally degenerates; a so-called

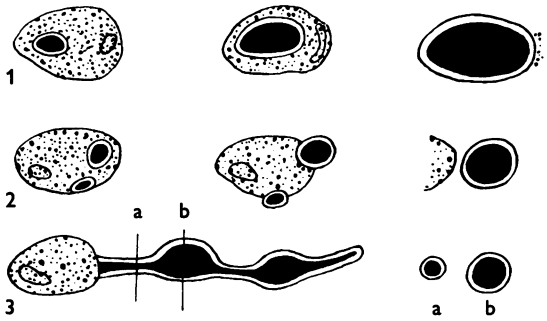


FIG. 13.—So-called extracellular Lewy bodies arise in three different ways: (1) an intracytoplasmic Lewy body becomes large and finally fills the entire ganglion cell, surrounded by a few melanin granules; (2) an intracytoplasmic Lewy body protrudes from the cytoplasm and when cut in another plane, it may sometimes appear to lie outside the cell; (3) when degenerated cell processes, with globular thickening, are transversely cut, small (a) or large (b) so-called extracellular Lewy bodies are seen.

extracellular Lewy body occurs, often surrounded by cell débris or melanin granules (Fig. 11); (2) an intracytoplasmic Lewy body slightly protrudes from the cytoplasm and may sometimes appear to be extracellular in a succeeding section (Figs. 12a, b, c, and d); (3) degenerated cell processes are transversely cut, and the resulting "extracellular" Lewy bodies are entirely similar to intracytoplasmic bodies, in shape, size, and staining reactions (Fig. 13).

Comment

In idiopathic paralysis agitans, Lewy bodies have so far been described in the ganglion cells of the substantia nigra, locus coeruleus, dorsal vagal nucleus, nucleus basalis, oculomotor nucleus, nucleus of Roller, cerebral cortex, inferior olive, and sympathetic ganglia.

In one case of idiopathic paralysis agitans, which was studied in serial sections, we found Lewy bodies in 14 other nuclei, all localized in the brain-stem and the diencephalon. In five of six cases of Parkinson's disease, with Lewy bodies in the substantia nigra and the locus coeruleus, these bodies were encountered in the ganglia of the sympathetic system and in the ganglion coeliacum. In four of these cases, moreover, Lewy bodies were observed in the lateral horns of the spinal cord. The Lewy bodies, therefore, occur in a considerably larger number of nuclear regions than has hitherto been understood. A striking feature is the occurrence of Lewy bodies in the central and the peripheral autonomic nervous system, and we believe that every investigation into the pathogenesis of idiopathic paralysis agitans will have to make allowance for this widespread neuronal degeneration.

In view of the fact that the Lewy bodies are present in a great many nuclei of the central nervous system, the question may be raised as to whether the substantia nigra does in fact occupy such a central position in the pathology of idiopathic paralysis agitans. In our Case 585, the number of ganglion cells containing Lewy bodies in the substantia nigra was much smaller, percentually, than that in the locus coeruleus. On the other hand, the presence of Lewy bodies does not constitute the sole pathological change in these nuclear regions. In particular a loss of cells in the substantia nigra has been reported by many authors (Hassler, 1938; Klaue, 1940; Greenfield and Bosanquet, 1953).

This investigation, too, confirmed the predilection of Lewy bodies for pigmented (melanin-containing) ganglion cells not only in the brain-stem but also in the sympathetic ganglia. They were absent, however, from the melanin-containing pigmented cells of the posterior root ganglia, whereas they did occur in non-melanin-containing ganglion cells of the brain-stem and diencephalon.

An unexplained feature in this investigation was the occurrence of Lewy bodies in the sympathetic ganglia of five patients with paralysis agitans, whereas they were entirely lacking in the sympathetic ganglia in a sixth case. This patient was clinically observed by both authors and followed up for several years; he showed the classical features of an advanced stage of Parkinson's disease, and Lewy bodies were found in the substantia nigra and the locus coeruleus.

Histological examination of the sympathetic ganglia revealed that cellular degeneration in the form of Lewy bodies spreads into the cell processes in idiopathic paralysis agitans. The same can be observed, albeit less frequently, in the involved nuclei of the central nervous system.

Summary

A systematic study of the brain in a case of idiopathic paralysis agitans showed that cellular degeneration in the form of Lewy bodies occurred in 14 nuclei of the diencephalon and the brain-stem, in which these bodies have not previously been described. Lewy bodies were likewise found in the lateral horns of the spinal cord. It was also established that Lewy bodies occurred in ganglion cells not containing melanin pigment.

In five of six cases of idiopathic paralysis agitans, Lewy bodies were found in the ganglia of the sympathetic vertebral chain and the prevertebral ganglion coeliacum. The study of these ganglia revealed that cellular degeneration of the Lewy type also occurs in the cell processes.

The pathology of Parkinson's disease is not confined to the well-known involvement of the substantia nigra, because Lewy bodies were found elsewhere, particularly in the central and peripheral autonomic nervous systems.

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