Neuropathology of Parkinson's Disease

LYSIA S. FORNO, MD

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INTRODUCTION

Parkinson (1) gave a nearly complete description of Parkinson's disease (PD), then called Paralysis agitans, but Charcot's lectures (2), which are still worth reading, give further details about the manifestations of the disease and its course as it presented itself over 100 years ago. The cardinal features were then as now rigidity, the resting tremor which Charcot described as imitating the spinning of wool, and bradykinesia. He found it instructive to compare the clinical picture of PD with that of multiple sclerosis using separate groups of patients. He pointed out that the movement disorder of PD was not a true paralysis, and although Parkinson had described the intellect as intact Charcot mentioned that in the late stage of the disease the mind would become clouded and the memory lost. The frequent presence of cognitive impairment and occasional association with Alzheimer's disease (AD) is now well appreciated.

PD was not recognized as a disease entity prior to 1817, but it probably existed long before this time. According to Stern (3) the manifestations of the disease were described by Leonardo da Vinci sometime between 1489 and 1506. Galen may also have observed the frightening gait, and a description of an Egyptian papyrus (1350–1200 BC) suggested the presence of parkinsonism in old age.

In this review the pathology of the disease will be discussed with emphasis on the inclusion bodies described by Lewy (4, 5) and on the substantia nigra (SN) (Fig. 1). Although the disease process is not limited to the SN and the nigrostriatal pathway, the SN plays a key role in the pathobiology of PD, a fact that for a long time was not appreciated. The existence of SN was known since Soemmerring first described it in 1778 (6), but PD was long regarded as having no known pathological substrate. This was the case not only in Charcot's time but practically up to the levodopa era. However, in the late part of the nineteenth century at least 2 cases (one described twice) of unilateral clinical parkinsonism associated with a tuberculoma in one peduncle were reported (7). Such cases made Brissaud (8, 9) suggest that "a lesion of the locus niger might well be the anatomical substrate for Parkinson's disease."

During the first decades of the twentieth century several movement disorders such as Wilson's disease and Huntington's chorea were found to have pathology involving the basal ganglia (here defined as the caudate nucleus, putamen, and globus pallidus). Vogts made detailed studies of these nuclei (10) without reporting on the state of the SN, but in 1919 Tretiakov (11) reported SN degeneration in 16 cases of different forms of parkinsonism and asserted that there was a relationship between rigidity and tremor and nerve cell loss in SN. This view was vigorously debated in the following years, although Foix and Nicole (12), as well as Walter Freeman (13) confirmed the finding of SN degeneration in PD. By that time the pandemic of encephalitis lethargica (1917–1925 and tapering off in the following years) had occurred and pathological studies had revealed that at least in this form of parkinsonism the SN was an important site of the disease process. Later Hassler (14) and Klauer (15) examined 2 large series of brains from PD and postencephalitic parkinsonism patients and established the SN degeneration beyond doubt. Hassler demonstrated the focal distribution of the lesions in PD with relative sparing of the medial portion of the SN and made a comparison with the diffuse and more severe nerve cell loss in postencephalitic parkinsonism. Klauer, who examined 100 brains, did not feel that the 2 forms of parkinsonism could be clearly separated. Greenfield and Bosanquet's (16) work on the same subject brought the SN degeneration in PD to the attention of the English-speaking world.

Nevertheless, giants in neurology and neuroanatomy such as Mottler (17) and Denny-Brown (18) continued to downplay the role of the SN in PD until the dopamine (DA) story began to unfold. Mottler felt that "the attribution of such a complex clinical syndrome to a rather small and relatively homogenous structure [meaning the SN] has not appeared logical." Denny-Brown thought that the main lesions in PD were in the globus pallidus. Some of the abnormalities in the basal ganglia, for example, status cribriformis, were later found to be common age-related changes, but it must be remembered that the case material examined may also have included examples of striatonigral degeneration (SND) or progressive supranuclear palsy (PSP). Because the connections between the SN and the striatum were not known, the SN had.

From the VA Palo Alto Health Care System, Palo Alto, CA 94304.
Correspondence to: Lysia S. Forno, MD, VA Palo Alto Health Care System, Department of Pathology (113), 3801 Miranda Avenue, Palo Alto, CA 94304.
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Fig. 1. Two levels of midbrain and one of rostral pons to show pallor of the substantia nigra and locus ceruleus in a case of Parkinson's disease.

appeared to be an unlikely site for the pathology. The nigrostriatal fiber tract was suspected to be present after DA was found to be a neurotransmitter—one which was diminished in the striatum in PD and postencephalitic parkinsonism (19). Anden et al (20) first demonstrated the nigrostriatal pathway in the rat. Subsequently its existence also became accepted for the human brain. The full impact of the degeneration of the SN and the resulting DA deficiency became evident when administration of levodopa resulted in a dramatic reversal of the parkinsonian manifestations. For further information about the levodopa story, including chronological time tables, see references 21–23.

The importance of the SN and DA deficiency in PD was now well established, but disappointingly the levodopa treatment did nothing to halt the progressive and seemingly relentless loss of nerve cells in the SN. Over time this resulted in severe limitations of the effectiveness of the levodopa treatment, leaving the question of why the nerve cells in this particular anatomical region died prematurely and how this could be prevented or slowed down. We know now that nerve cells in the nor-
adrenergic locus ceruleus (LC) (Fig. 2) and in the cholinergic nucleus basalis of Meynert (NBM) also degenerate, but because the SN is responsible for supplying the striatum with DA, and DA is needed for normal motor function, the nerve cell loss in the SN has much more disastrous consequences.

Definition of Parkinson's Disease

In this review PD is defined clinically as a distinctive progressive disorder characterized by tremor, rigidity, and bradykinesia; and pathologically by nerve cell loss in the SN and the presence of Lewy's intraneuronal inclusion bodies. Clinically, a number of additional less constant findings such as masked face, postural instability, festinating gait, etc. are present, and pathologically Lewy bodies are nearly always present in other predilection sites than the SN, especially the dorsal motor nucleus of the vagus, the hypothalamus, and NBM (the 3 locations where Lewy described them), and in the LC, the Edinger-Westphal nucleus in the midbrain, the raphe nuclei, cerebral cortex, olfactory bulb (24), and autonomic ganglia (25). Obvious nerve cell loss in some of these locations is inconstant but is usually present in the LC and the NBM and frequently in the dorsal motor nucleus of the vagus. For the pathological diagnosis only the SN degeneration and the Lewy bodies are required in the setting of at least 2 of the main clinical traits. Using these criteria it becomes a simple matter for the neuropathologist to make or refute the diagnosis of PD, provided that tissue from the SN is available.

For the clinician the task of making the correct diagnosis is more difficult. When PD was first described, a number of conditions—PSP, SND, and others—that occasionally can imitate PD were unknown. Several investigators (26, 27) have documented the difficulties in predicting the diagnosis of PD during life. Hughes and associates (27) examined 100 brains from patients who had been examined by a neuropathologist during life and had been given the clinical diagnosis of PD. In only 76 cases could the diagnosis of PD be confirmed at autopsy. This uncertainty poses a significant problem when new treatments for PD are being evaluated.

How important are morphological characteristics such as Lewy bodies for the definition of a disease entity? If PD is regarded as a disease caused by many different influences with different pathologies (28) one might prefer to rely on the clinical diagnosis and require only SN degeneration for pathological confirmation. A separation
into Lewy body PD and neurofibrillary tangle (NFT) parkinsonism, which would include postencephalitic parkinsonism, has also been suggested (29, 30). On the other hand, some neuropathologists rely on the presence of Lewy bodies and SN degeneration for a diagnosis of PD, even in the absence of a history of clinical parkinsonism during life. There is therefore no complete agreement about the criteria to be used for the diagnosis of PD. Lewy bodies may not always accompany the nerve cell degeneration in SN in PD, and it is indeed unlikely that every dying nerve cell goes through a stage of Lewy body formation. Nevertheless, for now it seems practical to place into a separate group those cases that, except for the presence of Lewy bodies, have the identical pathology as Lewy body PD. It might then be possible to determine if the 2 types of PD are truly different. The recent realization that Lewy bodies can be found in a spectrum of Lewy body disorders (to be discussed later) has added to the uncertainty about the role of Lewy bodies in PD. However, a close relationship to the SN degeneration and to PD exists, since practically all Lewy body disorders display these inclusions in the SN or LC, with or without obvious nerve cell loss or clinical parkinsonism.

The Lewy Body

Although the pathology and biology of the Lewy body have been the subject of a recent review in this journal (31), this inclusion still merits further discussion in a review of PD. The Lewy body now appears to play an important role not only in PD but also in several other neurodegenerative diseases.

Because of its eosinophilia and its distinctive core and peripheral halo, the Lewy body is usually easy to recognize in hematoxylin-eosin (HE) stain. Yet its morphology is more variable than that of other types of inclusion bodies (32, 33). What we now regard as a classical appearance (one or several spherical bodies with a dense core and a peripheral halo in the perikaryon of a pigmented nerve cell) (Figs. 3, 4) is quite different from what was shown in Lewy’s illustrations (4, 5) of inclusion bodies in the NBM, hypothalamus, and dorsal motor nucleus of the vagus. Elongated and sometimes serpiginous structures in nerve cell processes or aligned around the edge of the perikaryon or a dystrophic axon are shown, and indeed such often bizarre inclusions (Fig. 5) are frequently found in these locations (34), as well as in the sympathetic ganglia (25, 35). As a rule, Lewy bodies are located in the neuronal cytoplasm in the SN, LC (Fig. 6), raphe nuclei, and cerebral cortex, and as elongated forms in nerve cell processes in NBM, hypothalamus (Fig. 5), dorsal motor nucleus of the vagus, and autonomic ganglia, but both forms can be found in any of these anatomical areas. Contributing to the peculiar appearance of some of these inclusions is the admixture, best appreciated by electron microscopy (EM), of neuromelanin, lipofuscin, mitochondria, dense core vesicles, and other organelles as well as electron dense granular or amorphous material. In spite of this polymorphic appearance a peripheral halo or a concentric lamination set the inclusions apart from most axonal swellings and from other inclusions. The most important element which all Lewy bodies have in common is, however, the filamentous cytoskeletal component, now considered to consist of neurofilaments which have undergone a number of alterations, including phosphorylation, ubiquitination, proteolysis, and cross-linking (36).

The staining reactions of Lewy bodies and their immunocytochemistry have been the subject of several reviews and will not be described in detail here (see 31, 37–39). Briefly, Lewy bodies are periodic acid Schiff (PAS) negative, since they do not contain carbohydrate; they are light brown with most silver stains, and by immunocytochemistry they react or can be made to react with antibodies to all components of neurofilaments (40). Lennox and colleagues (41) demonstrated that Lewy bodies were ubiquitinated and that ubiquitin immunocytochemistry was useful for demonstrating Lewy bodies, especially in the cerebral cortex, where Lewy bodies usually lack the central core of brainstem Lewy bodies and therefore are less distinctive (Fig. 7). Because NFTs also react with antibodies to ubiquitin, the immunostaining is best used as a supplement to the HE stain. Lewy bodies can usually be distinguished from globose tangles and from Pick bodies by their lack of reaction to the microtubule-associated protein tau. While this is generally helpful, there is evidence (42) that some cortical Lewy bodies may react to tau, but this needs clarification and confirmation. In our own laboratory we have found this to be a problem in the amygdala-para-hippocampal region in cases with AD and Lewy bodies. The Gallyas silver method is quite specific for NFT, neuropil threads,
Fig. 4. A. Transmission electron micrograph of Lewy body in the substantia nigra. Note the dense core and the radiating filaments. 6,000×. B. Higher magnification of filaments in Lewy body to show thicker (arrow) and thinner (arrowhead) filaments. 65,000×.

and argyrophilic grains. It does not usually impregnate Lewy bodies or Pick bodies, but here too a positive reaction can sometimes be seen in a Gallyas plus eosin preparation. The presence by EM of small bundles of paired helical filaments (PHF) in cortical Lewy bodies (43) may have contributed to the positive reaction with tau antibodies, along with the coexistence of tau-positive material in the tissue.

Formation of Lewy Bodies

If Lewy bodies are truly a significant link in nerve cell degeneration, their composition and the molecular events that lead to their formation deserve a high priority for investigation. Recently several researchers have made attempts to learn how Lewy bodies are formed. Pollanen and associates (31, 36), using isolated Lewy body fibrils from cortical Lewy bodies, have studied this problem. Briefly, the authors proposed that Lewy bodies are formed in 3 overlapping steps involving self-assembly and aggregation of protein, followed by posttranslational phosphorylation and, last, proteolysis. Ubiquitination was felt to be a late step.
Lowe and colleagues (44), in discussing cortical Lewy bodies and other ubiquitin-immunoreactive inclusion bodies, put forward 2 hypothetical schemes for the development of ubiquitinated inclusion bodies. In one the disease process gives rise to abnormal proteins that become ubiquitinated and undergo proteolysis. A portion of the ubiquitinated proteins are non-degradable protein fragments and aggregate into inclusion bodies. In the second scheme the abnormal ubiquitinated proteins form the inclusion bodies.

In a recent study (45) Iwatsubo and associates purified cortical Lewy bodies from diffuse Lewy body disease (DLBD) and produced a monoclonal antibody, which specifically reacted with polyubiquitin chains. They concluded that Lewy bodies contain abundant polyubiquitin chains which might trigger ubiquitin-proteasome pathways with resulting partial degradation of proteins in the Lewy bodies.

A quite different approach to understanding Lewy body formation was recently presented by Montine, Farris, and Graham (46). In an in vitro study they demonstrated that products of non-enzymatically oxidized levodopa, DA, and dopac can lead to crosslinking of neurofilaments. They hypothesized that since the filaments in Lewy bodies in the SN are of neurofilamentous origin, Lewy bodies might be formed as a result of oxidative stress and increased oxidation of catechols with subsequent crosslinking in patients with PD. Since this scheme cannot be applied to non-catecholaminergic neurons, they favored the possibility that different types of

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**Fig. 6.** Nerve cell loss and Lewy bodies in nerve cell perikaryon (arrows) and in nerve cell processes (arrowheads) in the locus ceruleus in familial Parkinson's disease. Hematoxylin-eosin stain. 230X.

**Fig. 7.** Lewy bodies in the amygdala, stained with polyclonal antibody to ubiquitin. Hematoxylin counterstain. 235X.
Lewy bodies, for example, those in the cerebral cortex, might each arise by different pathogenetic mechanisms.

This is a rapidly advancing area of investigation. A number of recent publications have dealt with new information about the composition and immunoreaction of Lewy bodies. Some of these will be discussed in the following section.

The Spectrum of Lewy Body Disorders

The close relationship between Lewy bodies and SN in PD was not appreciated by Lewy (4, 5), and Tretiakoff (11) became the first to observe this constellation. Greenfield (16), Bethlem and den Hartog Jager (25), and Bernheimer and Bosanquet et al (47) later confirmed this association, but it was not known that Lewy bodies could be found in brains from individuals without known parkinsonism until 1952 when Behein-Schwarzbach (48) reported seeing Lewy bodies in the LC in 10 of 30 brains from elderly persons. Lipkin (49) reported that Lewy bodies were present in 4.9% of his control material, and Forno (50) observed the inclusions in 50 cases, representing 4.7% (excluding PD cases) of routine autopsies. The speculation was then that such cases might present preclinical or subclinical cases of PD, an idea also put forward by Gibb et al (33). Lewy bodies were therefore viewed as closely associated with PD. However, it is now well known that Lewy bodies are frequently seen as part of other diseases (32, 33, 39), especially AD (51) and diffuse Lewy body disease (DLBD) (52), conditions where Lewy bodies in the cerebral cortex are important features. Okazaki and associates (53) gave us the first glimpse of DLBD in their 1961 report of widespread Lewy bodies, including presence in the cerebral cortex, in 2 demented elderly individuals. The connection to AD and other mental disorders was made the following year by Woodard (54), but these two papers were not accorded the importance they deserved until large series of AD brains were studied; this in response to the renewed interest in AD and other forms of dementia in our increasingly aging population. Kosaka and associates (52) first called attention to cortical Lewy bodies and suggested that DLBD might represent a separate disease entity. Only relatively few cases of DLBD are free of Alzheimer changes in the form of NFT and neuritic plaques (NP), and the relationship between DLDB, AD, and PD is still being debated. Many DLBD cases have mild parkinson symptomatology and all have Lewy bodies in SN or LC, often together with some nerve cell loss. This is also true for AD cases with Lewy bodies. Most investigators now find Lewy bodies in AD in more than 25% (51, 55, 57) and up to 67% of the cases (56). The term *Lewy body variant of AD* is now frequently used (58).

There is no firm agreement about the correct definition of DLBD. The overlap between this entity and PD on one hand and AD with Lewy bodies on the other causes much uncertainty. Widespread Lewy bodies, including cortical Lewy bodies in both allocortex and neocortex, are usually required, and some authors accept any case with numerous cortical Lewy bodies as DLBD regardless of the presence of AD or PD. The problem with this approach is that if the cerebral cortex also has many NP and NFT, it is not possible to correctly assess the contribution of the Lewy bodies to the dementia. Although Lewy (4, 5) did not observe cortical inclusion bodies, his PD cases were not brainstem Lewy body cases, since hypothalamus and innominate substance (NBM) were involved. At the Palo Alto VA Neuropathology Laboratory we have reserved the term DLBD for cases without sufficient numbers of NP and NFT to warrant a diagnosis of AD. Cases with definite clinical parkinsonism during life are also excluded (57, 59). This definition is still not entirely satisfactory, because few DLBD brains are completely without NP or NFT, leaving open the question of how much the Lewy bodies or the disease process that leads to their formation contribute to the symptomatology.

In the face of this uncertainty in classification it would be helpful if all studies of DLBD would include information about how DLBD was defined. It is often difficult to make a sharp distinction between DLBD and PD, since in DLBD Lewy bodies are also present in the SN and/or LC, and some nerve cell loss is frequently present. Some of the familial PD cases recently reported, such as the family first reported by Spellman (60) and later by Muenzer et al (61), have abundant cortical Lewy bodies and might well be called PD-DLBD cases. Such cases again recall the close relationship between PD and DLBD.

It has been suggested, however, that characteristics of the Lewy bodies in DLBD differ from Lewy bodies in PD, for instance in their reaction to the tau antibody (42) and to tropomyosin (62). These authors found a positive reaction to tau and to tropomyosin in DLBD, but not in PD. Smith and Perry (63) regarded DLBD and PD as "two clinically and pathologically different diseases" and listed additional differences between the Lewy bodies in the 2 conditions. This separation into 2 different disorders will need to be confirmed in additional studies. If AD cases with Lewy bodies are included as part of the DLBD cases, some of these differences from PD might be due, as previously mentioned, to the abundance of tau in NFT and neuropil threads in the immediate environment.

An intriguing finding in DLBD and Lewy body AD of ubiquitin-positive abnormal neurites in the CA2/3 area of the hippocampus points toward a definite difference from AD without Lewy bodies (64, 65), but these authors also found the abnormal neurites in some cases of PD. In the family reported by Muenzer et al (61) similar ubiquitin-positive neurites have been found (Fig. 8). The association to Lewy bodies of the ubiquitin-positive neurites in CA2/3 have recently been confirmed in a large material
of neurodegenerative diseases with and without Lewy bodies (66).

A recent review (67) of DLBD contains a discussion of the clinical features most likely to favor an antemortem diagnosis of DLBD. Neuropsychiatric symptoms tended to be more pronounced than cognitive impairment early in the disease. Rapid progression was common but there was considerable fluctuation of the clinical picture, even sudden loss of consciousness, followed by lucid intervals. Marked sensitivity to neuroleptics was often present. In spite of such details, this remains a difficult diagnosis to make during life.

Lewy Bodies Outside the Main Spectrum of Lewy Body Disorders

As already mentioned Lewy bodies are occasionally found in conditions which do not fulfill the criteria for a diagnosis of PD (32, 39, 68). When Lewy bodies are observed in older individuals they may belong to the percentage of routinely occurring incidental cases (50, 57, 68). In a recent study (57) of nearly 1,200 routine autopsies Lewy bodies were present in 8% of persons above the age of 50, increasing to 12.8% in those above age 70 and to 15.9% above 80. Although these figures decreased to 4, 9, and 11.6% respectively after removal of all AD brains, the chance finding of the inclusions may explain some of the cases where Lewy bodies coexist with another neurodegenerative disease. Lewy bodies in an individual under age 50 or 60 are less easily explained. SN degeneration, when present, forms a link with PD, but the presence of the inclusions cannot be explained on the basis of SN degeneration alone. For most neurodegenerative diseases the coincidence of Lewy body inclusions has been the exception, but Lewy bodies have been reported to occur in a number of cases of PSP (69, 70). In a recent publication (70) the authors found coexistent PSP and PD pathology in 2 out of 13 pathologically verified PSP cases. The frequent heterogeneity of neurodegenerative diseases was discussed and was thought perhaps to have led to the occasional coexistence of 2 diseases, such as PSP and PD, with distinctive and different neuropathological features.

Of more concern is a very different disease, amyotrophic lateral sclerosis (ALS), including ALS with dementia and frontal lobe dementia of ALS type. Hyaline inclusions, resembling Lewy bodies and sometimes called Lewy-like bodies have been reported in the spinal cord, first in familial ALS (71, 72), and subsequently also in

Fig. 8. Ubiquitin-immunoreactive neurites in CA 2/3 of the hippocampus in a case of familial Parkinson's disease. Hematoxylin counterstain. 230X.
sporadic ALS (73–75). Probably only some of the hyaline inclusions described in the literature are Lewy bodies, making it difficult to obtain accurate information about how common the finding is. However, Sasaki and Maruyama (75) had 6 out of 20 sporadic ALS cases with Lewy-like bodies, sufficient for speculations about the significance of the Lewy bodies in this disease and in this location.

Only some of the reports described Lewy bodies also in the SN, but in rare cases like the one by Oda et al (73) Lewy bodies were unusually widespread, including SN. This was also the case in a familial motor neuron disease (76).

In ALS there are in addition to the neurofilamentous accumulations in dystrophic axons, characteristic ubiquitin-positive inclusions in anterior horn cells, which are regarded as characteristic for ALS and ALS+ syndromes. As is evident from a recent review of pathological findings in ALS (77) the distinction between the ubiquitin-positive skein-like inclusions, the Bunina bodies, and the Lewy-like bodies is not entirely clear. Lowe has speculated that a development from skein-like inclusions over Bunina bodies to Lewy-like bodies may take place and that the hyaline Lewy-like bodies may be a late development. It has also been suggested that these Lewy-like bodies differ in composition and formation from brainstem Lewy bodies in PD. Against that are two recent papers (78, 79) describing Cu/Zn superoxide dismutase-like immunoreactivity to Lewy body-like inclusions in sporadic ALS as well as to Lewy bodies from PD. The authors did not find this immunoreaction in the skein-like inclusions or in Bunina bodies. Perhaps a Lewy body is always a Lewy body (63).

Extranigral Pathology in PD

It would be interesting to speculate about how the symptomatology in PD is influenced by the neuropathology in locations outside the nigrostriatal pathway, but there are few hard facts to discuss. The involvement of the hypothalamus (34) and the autonomic system (25, 80) probably has a role to play. The pathology in the NBM that is involved independently of coexistence of AD may be associated with cognitive changes. The neuron loss in LC is generally less severe than in AD, especially presenile AD, but in combinations of PD and AD and in the Lewy body variant of AD, the nerve cell loss is often so severe that only a few nerve cells remain at each level. This cell loss has been thought to account for depression in some studies or for impairment of attention and alertness according to others. The cortical involvement may, at least in part, bear responsibility for dementia when present. What does seem certain is that nobody develops parkinsonian manifestations from lesions of these anatomical areas without additional disease in the SN or striatum.

Substantia Nigra and Striatum in Parkinson's Disease

**Substantia Nigra:** Much work on PD has centered on the SN and why this group of nerve cells are especially vulnerable to nerve cell degeneration (81). Some of the peculiarities of this nucleus are: (a) its production of DA and its being the site of origin of the nigrostriatal pathway; (b) the neuromelanin content in the nigral nerve cells; (c) its high content of iron, presumably unrelated to hemosiderin accumulation; and (d) its susceptibility to oxidative stress and formation of free radicals. These characteristics interact and influence each other, but there is much conflicting evidence in regard to the nature of these interactions. Neuromelanin, for example, has been thought to be neurotoxic or to have generated toxic products during its formation, but a possible protective role has also been discussed. The production of DA may give rise to free radicals, but it has also been proposed that DA itself may be acting as a scavenger of free radicals. Iron in the nervous system has recently been discussed in this journal (82). In the SN, the role played by iron and the exact location of the iron is still a controversial matter (83, 84). Mitochondrial abnormalities, especially a defect in complex I (85, 86) in PD, have been found and apparently are not present in some other neurodegenerative diseases with SN nerve cell loss, such as multiple system atrophy, but this still needs to be confirmed. Some of these issues have been discussed in a recent review (39), where further references can be found.

The morphological changes of the nerve cells in SN in PD have been the subject of several studies and were discussed in several posters and presentations at the 1995 meeting of the Society for Neuroscience. The TUNEL reaction (87) and EM (88) have been used and it has been proposed that nerve cell death in the SN in PD may occur by apoptosis, a programmed cell death generally associated with development and with certain toxins. During apoptosis the changes in the nucleus with chromatin condensation and fragmentation into nucleosomes precede changes in the organelles in the cytoplasm. In contrast, in excitotoxic cell death there is early swelling of dendrites and cytoplasm. Macrophage and other inflammatory activity are more pronounced than in apoptosis. In the human SN the nerve cells contain insoluble neuromelanin which is liberated and taken up into macrophages when the nerve cell dies, and a distinct glial scar is often formed where nerve cell loss has been most severe, usually in the ventral and lateral cell groups. It is difficult to recognize dying nerve cells in the SN (personal observation); only after the cell death has occurred is it replaced by a cluster of neuromelanin-containing macrophages (Fig. 9A). The nerve cells containing Lewy bodies may be misshapen and contain pale bodies (33), but TH reaction is present and by EM the nucleus and the organelles in the cytoplasm are usually intact. Only
rarely can one find Lewy bodies surrounded by macrophages (Fig. 8B) after the death of the nerve cell. Much still needs to be learned about the mechanism of nerve cell death in PD as well as in other neurodegenerative disorders.

Because of the vulnerability of the neuromelanin-containing human substantia nigra, it has usually been assumed that nerve cells with much neuromelanin pigment were more susceptible to the disease process of PD than non-pigmented or poorly pigmented nerve cells (89, 90), but Fearnley and Lees (91) found that nerve cells in the ventral lateral cell groups, which are most vulnerable to the disease process in PD, contained less neuromelanin pigment than the dorsal cell groups, and that PD pathology differed from normal aging in this respect. This finding will need further investigation.

The Striatum

In trying to understand the interactions between the SN and the basal ganglia one needs some knowledge about the chemical and structural anatomy and physiology of these nuclei which are so important for normal movements and for movement disorders, but this will not be reviewed in any detail here (see 92–95). Briefly, the caudate nucleus and the putamen have a similar architecture. Ninety to 95% of the nerve cells are GABAergic medium spiny nerve cells that project out of the nucleus to the globus pallidus and the SN reticulata (SNr). Those nerve cells which also contain the neuropeptide enkephalin (enk) project to the external globus pallidus (GPe), and those with substance P (SP) to the internal globus pallidus (GPi) and the Snr. The consequence of degeneration of the dopaminergic nerve cells and the nigrostriatal pathway is DA deficiency, and DA deficiency equals parkinsonism. This therefore seems very simple, but how the DA loss interferes with the normal function of the motor system and leads to bradykinesia, rigidity, and resting tremor is still incompletely understood. The earlier concept of a nigro-striato-nigral loop and an imbalance between cholinergic output from the large cholinergic nerve cells in the striatum and the DA input from the SN has had to be revised. It is now believed that the output from the striatum to the thalamus and the cortico-thalamic-cortical loop proceeds along two pathways (96). The direct (GABA/SP) pathway goes from the striatum to the Gpi and the Snr and from there to the thalamus, whereas the indirect pathway (GABA/enk) goes over the Gpe and the subthalamic nucleus (STN). Loss of DA, which has an excitatory effect on certain parts of the spiny neurons and an inhibitory effect on others, acts differently on the direct and the indirect pathway, leading to an imbalance with increased activity in the STN-Gpi axis and with resulting parkinsonism. The STN, although it looks entirely normal in tissue sections, is now regarded as a key player in the production of parkinsonism. In animal experiments it has been shown that destruction of certain portions of
this nucleus can ameliorate experimental parkinsonism in nonhuman primates (96). In humans this new insight has led to a resumption of pallidotomies as a treatment for PD. Since surgery on the STN would be too dangerous, the circuit is interrupted instead in the Gpi. Although results have been promising, the long-term outcome is not yet known.

This oversimplified explanation will no doubt have to be further modified. Many other aspects of basal ganglia anatomy and physiology should be considered, such as the dopamine receptors, the striatal mosaic with patch (also called striosomes), and matrix components (93). Much of what has been learned about the basal ganglia is of equal importance for the understanding of other basal ganglia disorders. In PD it must be emphasized that in routinely stained material no pathology is visible in the striatum, in contrast to SND and Huntington’s disease. Even the decrease in TH-positive nigrostrial nerve fibers in PD is difficult to demonstrate in routine paraffin sections.

It has generally been assumed that the disease process in PD attacks mainly the nerve cell bodies, but it cannot be ruled out that the disease process might begin in the striatum, perhaps as a feedback signal transmitted from the terminals to the cell body, or as a retrograde or dying-back degeneration beginning in the terminals.

Animal Models for Parkinson’s Disease

Much has been learned about basal ganglia function from animal models, first the reserpine-treated akinetic rabbits, which Carlsson treated in 1959 with dopa injections (21, 22). Later came the 6-hydroxydopamine model, still used especially in the rat, for production of unilateral parkinsonism. The MPTP model (97) has been the most successful model so far and has contributed tremendously to understanding of basal ganglia function because of its great similarity to PD, and because it inadvertently was first developed in humans. In spite of the similarities, however, no human PD develops in quite the same way. Inclusion bodies in aged MPTP-treated squirrel monkeys have both similarities and differences from human Lewy bodies (98). PD has not, as far as is known, been found in nonhuman primates, but recently an interesting genetically determined rat model has been described (99). This rat, which has not been studied neuropathologically in detail, develops akinesia after a period of hyperactivity, and loss of neurotransmitters has been found in the SN, the LC, and perhaps in the raphe nuclei.

The Cause of Parkinson’s Disease, Environmental or Genetic

For several years it was thought that genetic factors were rather unimportant in PD. The discovery of the MPTP model reinforced this belief, and the possibility that PD was caused by either an environmental or an endogenous toxin is being seriously considered. In the meantime several families with autosomal dominantly inherited parkinsonism have been found (60, 61, 100, 101). The pathology in the 2 largest families has been that of PD with Lewy bodies, confirmed in 4 autopsies in the Spellman family. An earlier negative twin study has been reevaluated and the consensus appears to be that there is an interplay between genetic and environmental factors especially in the more common sporadic cases.

A marker for PD is being sought, but is not as yet available. There are also important questions to be answered, such as how long does the disease process go on before the patient becomes symptomatic. We still do not know if persons with incidental Lewy bodies have subclinical PD.

Treatment of Parkinson’s Disease

Levodopa treatment of PD is still important and often continues to be effective for many years. Monoamine oxidase inhibitors are being used and may retard the disease process. Pallidotomy has already been mentioned, and transplants of fetal and other tissues have received much attention but are still in the experimental stage (96).

Outlook for the Future

In spite of the many uncertainties and unanswered questions, the outlook for protective treatment of the SN nerve cells appears much better than for most other neurodegenerative diseases, such as AD, where the pathology is far more complex and involves the cerebral cortex to a severe degree. In PD the problem is much simpler: if the nerve cell death in the SN can be prevented or at least slowed down, the PD patient will be able to live a useful and reasonably happy existence for many years. Those of us interested in the peculiar inclusions of Lewy have reason to hope that unraveling how these bodies are formed may hold a clue to the nerve cell death and to its prevention.

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