Shy-Drager Syndrome. Neuropathological Correlation and Response to Levodopa Therapy

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SUMMARY: *The post-mortem examination of the nervous system of a patient with Shy-Drager syndrome successfully treated with levodopa (Sharpe et al, 1972) revealed features of striato-nigral degeneration and amyotrophic lateral sclerosis, a cerebellar system degeneration and a loss of approximately 75% of sympathetic preganglionic neurons. Lewy bodies were not present and no detectable changes were observed in the sympathetic prevertebral ganglia.*

While the limited and transient beneficial effect of levodopa on the bradykinesia in our case is possibly due to the progressive loss of striatal dopaminergic receptors seen in striato-nigral degeneration, we propose that in Shy-Drager syndrome, levodopa therapy benefits orthostatic hypotension because of a suppression of the central depressor action of this drug. This suppression is attributable to functional disconnection of sympathetic ganglia secondary to the loss of preganglionic neurons or to degeneration of central autonomic catecholaminergic systems.

RÉSUMÉ: *L'examen post-mortem du système nerveux d'un patient avec le syndrome de Shy-Drager traité avec succès à la Levodopa (Sharpe et al., 1972) révélait des signes de dégénérescence striatonigrale et de sclérose latérale amyotrophique, une dégénérescence systémique cérébelleuse et une perte approximative de 75% des neurones preganglionaires sympathiques. Les corps de Lewy n'étaient pas présents et aucun changement ne fut observé dans le ganglion prevertébral sympathique, alors que l'effet bénéfique limité et passager de la Levodopa sur la bradykinésie chez notre patient est possiblement dûe à une compensation de la perte progressive des récepteurs dopaminergiques striataux vus dans la dégénérescence striato-nigrale. Nous proposons cependant que dans le syndrome de Shy-Drager, la thérapie à la Levodopa est bénéfique pour l'hypotension orthostatique à cause d'une suppression de l'action dépressive centrale de cette drogue. Cette suppression est attribuable à la disconnection fonctionnelle des ganglions sympathiques secondaires à une perte de neurones preganglionaires ou à une dégénérescence des systèmes catécholaminergiques autonomiques centraux.*

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INTRODUCTION

In 1925, Bradbury and Eggleston described a clinical syndrome of primary orthostatic hypotension in three patients in whom there was no evidence of diseases such as diabetes mellitus, porphyria, adrenal insufficiency, syphilis or amyloidosis. This syndrome, which is characterized by a fixed pulse rate, impotence, bowel and bladder disturbances, decreased sweating or Horner's syndrome, has been attributed to progressive autonomic failure (Thomas and Schirger, 1970).

Subsequent reports have shown that patients with this syndrome of progressive autonomic failure develop permanent neurologic symptoms within a period of one month to ten years (Thomas and Schirger, 1970). Several cases initially thought to have orthostatic hypotension without neurological signs were found, with extended observation, to develop clinical evidence of motor system degeneration (Chokroverty et al, 1969).

Shy and Drager (1960) reported the neuro-anatomical description of a 46-year-old man with a six-year history of progressive autonomic failure associated with features of Parkinsonism, motor neuron disease and cerebellar system degeneration. These authors suggested that this syndrome might be a primary degenerative disorder. Gray matter degeneration in the intermediolateral horn of the spinal cord is a characteristic feature reported in all 20 neuropathological studies of Shy-Drager syndrome (table II), however, two distinct neuropathological and clinical sub-types have been recognized among these cases (Bannister and Oppenheimer, 1972). The first group is characterized by cytoplasmic inclusion bodies of the Lewy

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TABLE I

Mean neuron counts in the nucleus intermediolateralis thoracolumbalis pars principalis. Figures in brackets indicate the number of sections examined at each level.

	Present Case	Control (Johnson, 1966)	Levels
T1 - T3	5.1 ± 0.3 (48)	15.8 ± 1.0 (50)	3
T4 - T9	2.4 ± 0.2 (48)	9.2 ± 0.7 (80)	5
T10 - L1	1.4 ± 0.2 (48)	9.5 ± 0.7 (50)	3

type in the pigmented neurons of the substantia nigra, locus coeruleus and dorsal vagal nucleus, with or without cell loss in these nuclei. The average age at the onset of symptoms is 65 and the associated central nervous system disorder, if any, is restricted to Parkinsonism. The second group is associated with multiple system atrophy of olivo-ponto-cerebellar or striato-nigral type with cell loss in the striatum, pontine nuclei, pigmented nuclei, cerebellar cortex or inferior olives. The average age at the onset of symptoms is 50 in the second group. However, in the case of Thapedi et al, (1971), both Lewy bodies and features of multiple system atrophy were found suggesting a continuum.

We here report the post-mortem study of a case of Shy-Drager syndrome which was treated with L-dopa (Sharpe et al, 1972). The anatomical basis of the autonomic failure is discussed and tentatively correlated with the pharmacological effects of L-dopa.

TABLE II

Degenerative changes in the peripheral autonomic system in neuropathologically documented cases of Shy-Drager syndrome.

	Sympathetic Preganglionic Neurones	Sympathetic Ganglionic Neurones
Shy and Drager (1960)	++++	+
Fichefet (1965)	+++	+
Johnson (1966) I	++++	N
Johnson (1966) II	++++	N
Nick (1967)	++++	+
Schwarz (1967) I	++++	+
Schwarz (1967) II	++++	N
Martin (1968)	++++	N
Graham (1969)	++++	N
Hughes (1970)	?	+
Vanderhaeghen (1970)	?	+
Thapedi (1971)	++++	+
Roessman (1971)	++++	+
Bannister (1972) I	++++	N
Bannister (1972) II	++++	N
Bannister (1972) III	++++	?
Bannister (1972) IV	++++	?
Evans (1972)	N	+
Schober (1975) I	+++	+
Schober (1975) II	+++	+
Present case	++++	N

N: Normal +: Minimal changes ++ Mild changes
+++ Moderate changes ++++:Severe changes

Case Report

The extensive clinical and laboratory study of this case reported by Sharpe et al (1972) is summarized as follows:

A 58-year-old miner was admitted with a four-year history of progressive dizziness after standing suddenly, decreased sweating, bladder and bowel disturbances, impotence, and shaking and slowness of movements. On examination, his intellect was normal. He had an akinetic facies and a right Horner's syndrome. He showed generalized bradykinesia and slight postural flexion deformities of the trunk as seen in Parkinsonism. Passive mobilization of his limbs induced moderate rigidity and cogwheel phenomenon. He had also a 5 c.p.s. resting tremor and a minimal intention tremor. Sensory examination was entirely normal. Myerson's sign was present while the jaw jerk and facial reflexes were increased. The left ankle jerk was slightly depressed. Both plantar responses were flexor. His blood pressure was 120/80 mm Hg. Supine and systolic pressure fell to 50 mm Hg. when he stood up. In this condition, his heart rate remained unchanged at 72 per minute and he lost consciousness. His skin was warm and dry except for both axillae which were moist. Rebound hypertension and bradycardia did not develop during the Valsalva manoeuvre. Immersion in cold water was without effect on blood pressure and heart rate. There was no hypersensitivity following infusion of norepinephrine. The right pupil did not dilate after installation of 0.1% epinephrine and showed diminished reactivity to 3% cocaine. Glucose tolerance test showed a mild diabetic curve while VDRL was negative. EMG revealed minimal denervation of the right extensor digitorum brevis muscle on needle examination.

He was treated with fluorocortisone (0.2 mg daily), tranylcypromine (2.5 mg every five hours) and L-dopa (100 mg/50 mg alternate

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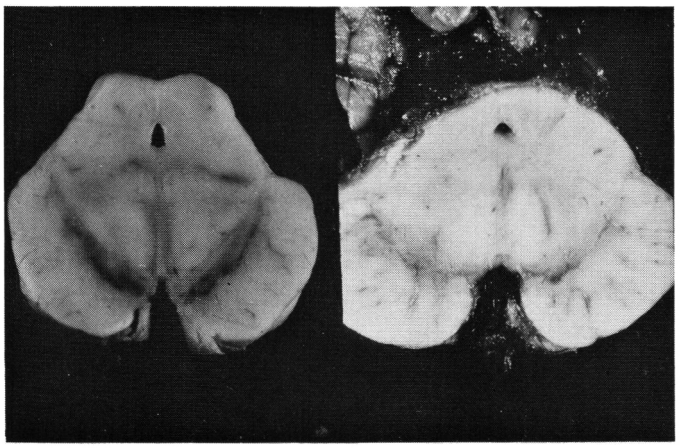

Figure 1—Marked loss of pigmentation in the substantia nigra (right) in comparison with a control (left). Upper midbrain level.

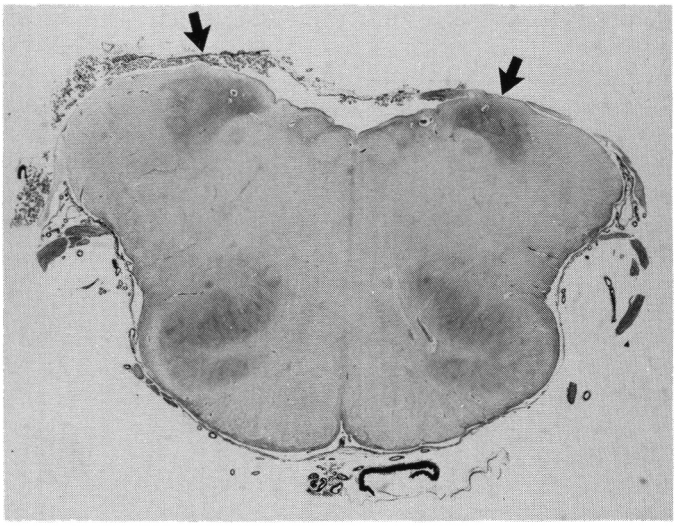

Figure 2—Gliosis in the nucleus cuneatus lateralis and in the nucleus vestibularis medialis (arrow). Holzer stain.

hours). On this original combination of L-dopa and MAOI (Sharp et al), the Parkinsonian syndrome slightly improved and the blood pressure varied between 200/90 and 150/60 while supine and between 160/80 and 100/60 on standing.

When L-dopa and tranylcypromine were stopped for a trial period, the pressure fell to 100 systolic in the afternoon and the patient complained of increasing feebleness of his legs and slowness of movement. When L-dopa was restarted without a MAOI his blood pressure rose to 220/115 lying and 140/100 one minute after standing and also his bradykinesia seemed to be reduced. No significant change in his blood pressure was obtained when disimipramine 50 mg, t.i.d., was added to L-dopa 50 mg six times a day. Over the following months, he became very stiff and depressed. The wheezing respirations, which were previously present only at night, increased and were present in the day. One morning, six years after the onset of his disease, he was found dead by his wife.

Material and Methods

The post-mortem examination was carried out by Dr. S. J. Strong, who very kindly submitted the brain, the spinal cord, portions of the sympathetic chains, and other tissues to the Department of Pathology at the Toronto Western Hospital for detailed examination.

After fixation in neutral formalin, transverse sections were made of the brain, spinal cord and prevertebral ganglia.

Representative samples were embedded in paraffin, and sections were stained with hematoxylin-eosin, Luxol Fast Blue, Holzer, Bielschowsky, Holmes and Woelcke methods. Serial 20 micron thick sections of the spinal cord were stained with the method of Nissl.

The brain of a 60-year-old man who died of a myocardial infarct was prepared in similar fashion and studied as a control.

The anatomical terminology is from Olszewski and Baxter (1954), Truex and Carpenter (1969) and also Petras and Cummings (1972). The atlas of Morrison (1959) was used to study the spinal cord.

Results

General autopsy revealed only congestion of the lungs, bronchopneumonia, and recent focal hemorrhages of both adrenal glands.

The brain weighed 1360 grams and was of normal macroscopic appearance except for a mild degree of diffuse cerebral atheroma, a small cystic infarct in the right thalamus, 8 mm in diameter, and marked depigmentation of the substantia nigra (Fig. 1) and locus coeruleus. The basal ganglia were grossly normal.

Microscopic examination

Sections of the cerebral iso-cortex and of the hippocampal gyrus were of normal appearance. The substantia innominata showed minimal neuronal loss but no Lewy bodies. The centrum semiovale showed multiple tiny areas of infarcted tissue attributable to repeated hypotensive episodes.

The basal ganglia were of normal size. The caudate nucleus was of normal microscopic appearance. The lateral and dorsal part of the putamen was of spongy appearance with marked loss of neurons and astrocytic proliferation. Large striatal neurons seemed better preserved than the small ones. There was loss of myelinated fibers in the globus pallidus, especially in the outer segments. Only a minimal neuronal loss and gliosis was present in this latter structure. The claustrum appeared intact, apart from occasional lipofuscinosis.

The thalamic nuclei were of normal appearance except for a small infarct several weeks of age in the vicinity of the right dorsomedial nucleus. The subthalamic nucleus was of spongy appearance with neuronal loss and astrocytic proliferation. Only a minimal loss of fibers was observed in the comb system the ansa lenticularis, the thalamic and lenticular fascilculi. No lesion was

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detectable in the supra-optic and mammillary portions of the hypothalamus.

Marked loss of pigmented neurons with associated pigment deposition in macrophages and in tissue, and astrogliosis were present in the subnucleus compactus and reticularis of the substantia nigra and also in the nucleus paranigralis and parabrachialis pigmentosus. In the substantia nigra, pathological changes were severe in the middle to lateral cell groups at caudal levels. No Lewy bodies were seen. Examination of the nucleus of Edinger-Westphal revealed a few hyperchromic neurons and a minimal neuronal loss. There was a minimal neuronal loss in the nucleus of Darkschewitsh. The nucleus oculomotorius principalis and the nucleus nervi trochlearis were normal apart from occasional lipofuscinosis.

The locus coeruleus showed severe neuronal loss with associated pigment deposition in tissue and in macrophages but Lewy bodies could not be found. The basis pontis and the superior cerebellar penduncle were normal.

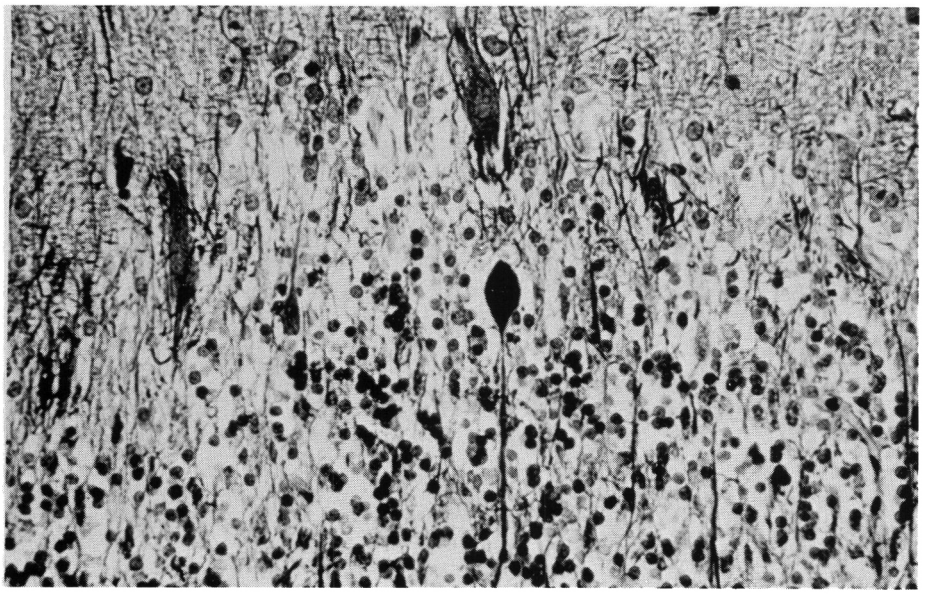

Figure 3—Photomicrograph of the cerebellum showing a "torpedo" in the granular layer. Bielschowsky stain X 40.

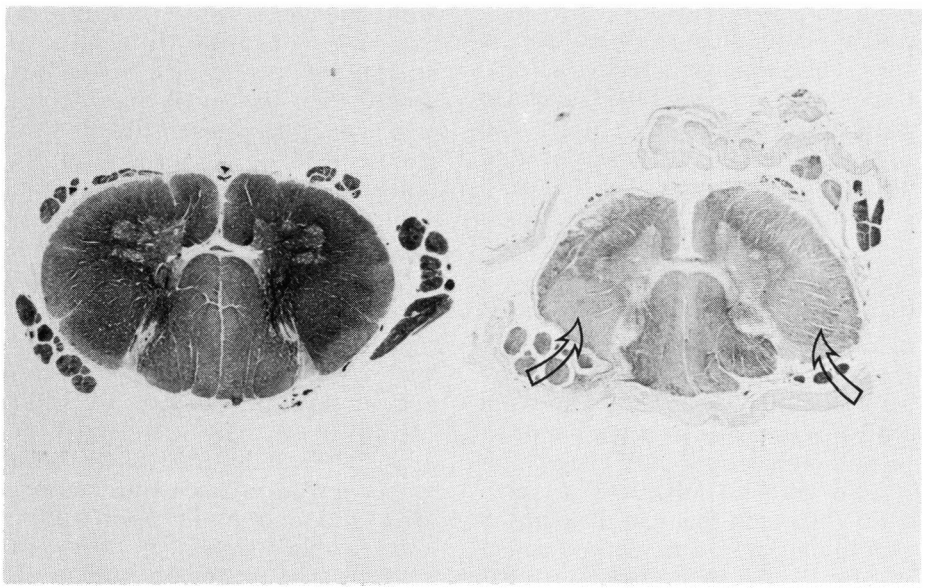

Figure 4—Demyelination of lateral column (arrows) in comparison with a control (left). C6 level and Woelcke's myelin method.

The pyramids were pale and no significant changes were present in the nuclei olivaris inferior.

The nucleus dorsalis motorius nervi vagi showed marked neuronal loss in the pigmented and non-pigmented neurons. Lewy bodies were not seen. There was minimal neuronal loss in the nucleus hypoglossi. There was marked astrogliosis and moderate neuronal loss in the nuclei vestibularis medialis and cuneatus lateralis (Fig. 2). Marked neuronal loss and astrocytic proliferation were present in the nucleus reticularis lateralis. The nucleus ambiguus, the nucleus solitarius and the perihypoglossal nuclei showed no abnormalities.

There was a moderate diffuse loss of Purkinje cells and occasional "torpedoes" in the cerebellar cortex (Fig. 3). The rest of the cerebellar cortex, the corpus medullare and the deep nuclei were normal.

The lateral and anterior funiculi of the spinal cord were markedly pale apart from the fasciculi proprii which were spared. The sites of the lateral corticospinal tract and of the spino-cerebellar tracts were markedly demyelinated (Fig. 4). The posterior white columns were normal except for mild pallor of the medial part of the fasciculus gracilis. Similar pallor in posterior columns was present in the control sections and is attributed to simple aging. Neuron counts revealed a loss of 50% of anterior horn cells. Lamina VI to X of Rexed were gliosed. In the nucleus intermediolateralis thoracolumbalis pars principalis, neuron counts showed a loss of more than 75% as illustrated in table I and in figure 5. There was also neuronal loss in the sacral parasympathetic nucleus. More than 50% of the neurons were absent in the nucleus of Clarke (Fig. 6). There was no demonstrable change in the posterior horn.

The thoracic prevertebral sympathetic ganglia showed a minimal

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loss of neurons. No Lewy bodies or hyaline eosinophilic bodies, as described by Fichefet et al (1965), were seen.

The carotid body and the sensory ganglia were not available for neuropathological examination.

DISCUSSION

The present case belongs to the second of the two groups of cases described above, that is, the group with neuronal loss and gliosis but without Lewy bodies. In the light of the neuropathological findings in this case and in similar cases in the literature, the effects of L-dopa on both Parkinsonism and hypotension will be discussed.

In our case, in addition to the autonomic nervous system, degenerative changes were seen in three divisions of the motor system.

In the nigro-striato-pallidal system, the neuropathological findings described above are compatible with what is referred to as striato-nigral degeneration (Adams and Van Bogaert, 1964) and are associated clinically with the bradykinesia.

The effect of L-dopa on the bradykinesia has been reported in 15 neuropathologically documented cases of striato-nigral degeneration without orthostatic hypotension (Table III). While a moderate improvement lasting a few months has been found in 6 cases, no detectable effects have been observed in 9 cases (Table III). Levodopa therapy also has been reported in another neuropathologically documented case of Shy-Drager syndrome (Schober et al, 1975). As in the present case, the neuropathological findings were of multiple system atrophy with features of striato-nigral degeneration and, following the administration of L-dopa, the decrease in the bradykinesia was moderate and transient. Conceivably, the limited benefit of Levodopa therapy in striato-nigral degeneration with or without autonomic degeneration is attributable to a progressive loss of functional dopaminergic receptors in the striatal neurons (Hornykiewicz, 1970).

In addition to the nigro-striato-pallidal system, degenerative changes were observed in our case in the corticospinal system where the findings were reminiscent of amyotrophic lateral sclerosis (Fig. 4) (Greenfield, 1963) and also in the cerebellar system. In this latter system, degenerative changes were present in some structures known to project upon the cerebellum, such as the nucleus of Clarke (Fig. 6), the nucleus vestibularis medialis (Fig. 2), the nucleus cuneatus lateralis (Fig. 2) and the nucleus reticularis lateralis. On the other hand, no detectable change was found in the griseum pontis and in the nucleus olivaris inferior and only a moderate loss of Purkinje cells was found (Fig. 3).

Pathological changes in the autonomic nervous system in our material were present in the nucleus intermediolateralis pars principalis (Table II and Fig. 5) which is the major nucleus containing sympathetic preganglionic neurons (Petras

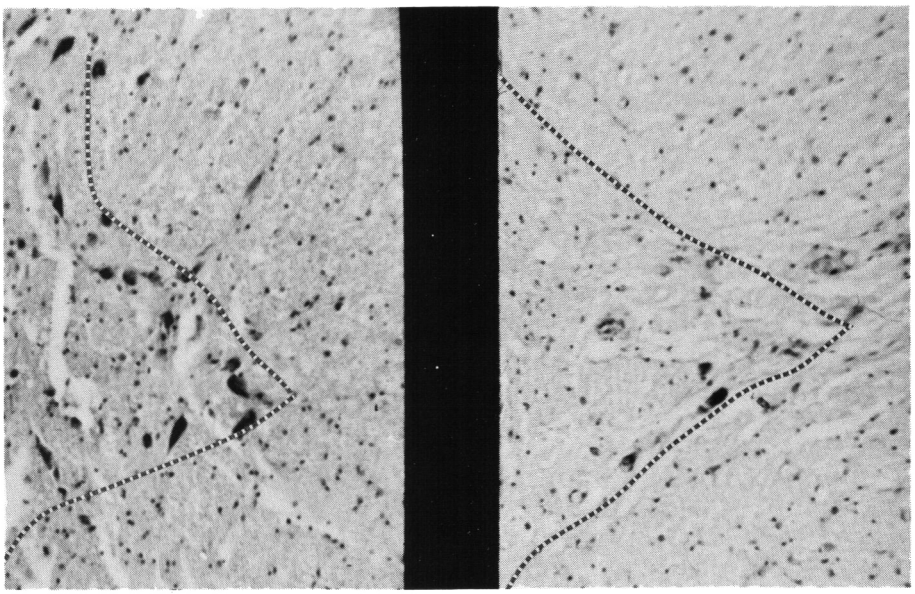

Figure 5—Neuronal loss in the nucleus intermediolateralis pars principalis (right). A control also is shown (left). T6 level, Nissl stain X 4. The demarcation between grey and white matter is indicated by dotted line.

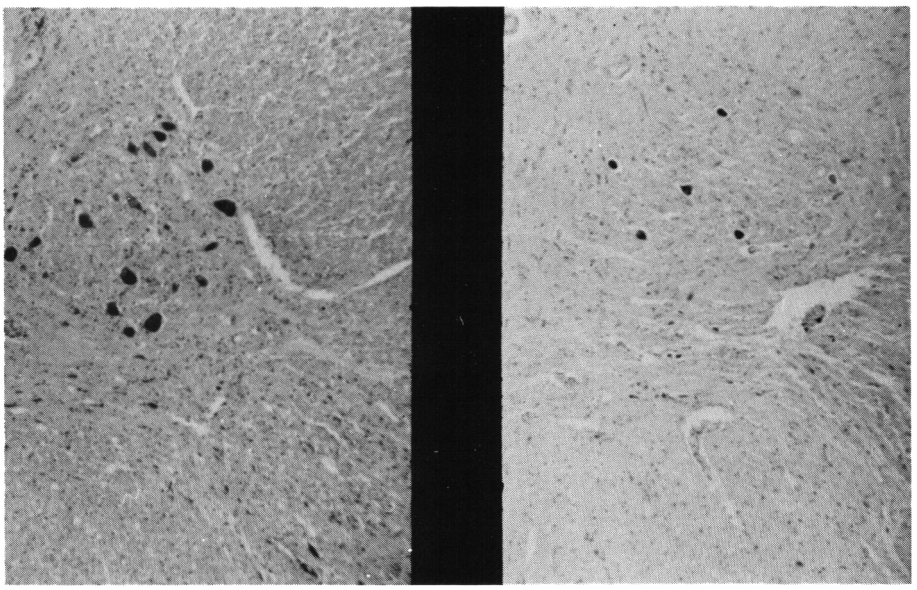

Figure 6—Neuronal loss in the nucleus of Clarke (right) in comparison with a control (left) T12 level, Nissl stain X 4.

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and Cummings, 1972). No detectable change was present in the sympathetic ganglionic neurons or in the hypothalamus. The nucleus solitarius, which receives fibers from the carotid sinus (Crill and Reis, 1968) also was normal in our material. Such a loss of sympathetic preganglionic neurons with intact sympathetic ganglionic neurons has been reported consistently in Shy-Drager syndrome (Table II), except for one case (Evans et al, 1972). Hughes et al (1970) reported the nucleus intermediolateralis as normal in their case, but did not count the neurons. Apart from a single case (Shy and Drager, 1960), the hypothalamus has been reported as normal.

The findings in our case and in similar cases in the literature suggest that the most consistent detectable neuropathological abnormalities in the autonomic nervous system in the Shy-Drager syndrome are a degeneration of sympathetic preganglionic neurons. In the present case, the neuropharmacological investigation (Sharp et al, 1972) seems to support such a view. An abnormal Valsalva manoeuvre and an abnormal cold pressor test indicated that there was at least a lesion in the efferent part of the autonomic nervous system. Normal pupillary reactivity to instillation of cocaine and norepinephrine is strongly suggestive of intact sympathetic ganglionic neurons. On the other hand, the absence of detectable lesions in the central autonomic nervous system above the level of the preganglionic neurons in our case and in similar cases does not allow us to conclude that such lesions are non-existent in the Shy-Drager syndrome. Conceivably, this could explain why there was no detectable loss of preganglionic neurons in the unique case of Evans et al (1972).

Levodopa therapy has been reported to have beneficial effects on the orthostatic hypotension in two pathologically documented cases (present case and Schober et al, 1975) and in 2 of 5 clinically studied patients with the Shy-Drager syndrome (Aminoff et al., 1973). In our case, administration of levodopa was as beneficial when given along as when associated with a MAO-inhibitor, and also the therapeutic benefit of levodopa seemed to be sustained. Similar beneficial effects on the orthostatic hypotension have been reported following administration of a MAO-inhibitor combined with pyramine (Diamond et al, 1970) or with amphetamine (Seller, 1969) and also following L-5-HTP therapy (Schober et al, 1975). Such a beneficial effect of levodopa is paradoxical, considering that levodopa therapy is frequently associated with orthostatic hypotension in patients with Parkinsonism (Calne et al, 1969).

There is evidence in laboratory animals for a central depressor and a peripheral pressor action of levodopa (Henning and Rubenson, 1970; Torchiana et al, 1972). In addition, this central depressor action of levodopa seems to be attributable to increased central noradrenergic rather than dopaminergic activity (Torchiana et al, 1972) and seems to be exerted at medullary and spinal level (Schiuitt et al, 1973). On the other hand, anatomical studies have mapped noradrenergic neurons located in the medulla, as well as descending noradrenergic pathways in the spinal cord (Dahlstrom et al, 1964). In the light of these data, levodopa-induced hyotension in laboratory animals seems to be due to a central action of this drug upon a descending noradrenergic bulbospinal system which exerts an inhibitory influence upon the peripheral sympathetic activity.

It is difficult to apply the latter experimental date in human physiology. However, in the light of the neuropathological findings in the autonomic nervous system in Shy-Drager syndrome the beneficial effects of levodopa may be attributable to a reduction or a suppression of the central hypotensive action of this drug. This would be consistent with degeneration of the sympathetic preganglionic neurons causing a functional disconnection (Aminoff et al, 1971) of the sympathetic ganglia from the central autonomic nervous system. Another possibility is a failure of the degenerated central noradrenergic system which, as discussed above, is probably the site of the depressor action of levodopa.

TABLE III

Effects of L-dopa in the bradykinesia in neuropathologically documented cases of striato-nigral degeneration.

	Decrease in the brady-kinesia	No change in the brady-kinesia
Izumi (1971)I		+
Izumi (1971) II		+
Greer (1971)	+	
Rajput (1972) I		+
Rajput (1972) II		+
Fhan (1972) I		+
Fhan (1972) II		+
Fhan (1972) III	+	
Trotter (1973)	+	
Takei (1973)	+	
Sharpe (1973)	+	
Michel (1976) I		+
Michel (1976) II		+
Boudin (1976) I		+
Boudin (1976) II	+	

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