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Brain Dopamine and the Syndromes of Parkinson and Huntington

Clinical, Morphological and Neurochemical Correlations*

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INTRODUCTION

Evidence for the physiological role of dopamine [DA;3-hydroxytyramine or beta-(3,4-dihydroxyphenyl)ethylamine] in the functioning of the extrapyramidal centres of the brain has been obtained from(a) the characteristic distribution of this biogenic amine and its metabolite homovanillic acid (HVA) in the caudate nucleus, the putamen (these nuclei constitute the corpus striatum or striatum), the pallidum (globus pallidus), and the substantia nigra (Bertler and Rosengren 1959; Sano, Gamo, Kakimoto, Taniguchi, Takesada and Nishinuma 1959; Ehringer and Hornykiewicz 1960; Bertler 1961; Sharman 1963; Bernheimer 1964; Gottfries, Rosengren and Rosengren 1965); (b) the reduction in the concentration of DA and HVA in these nuclei in brains from patients with Parkinson's disease (Ehringer and Hornykiewicz 1960; Bernheimer, Birkmayer and Hornykiewicz 1963; Bernheimer and Hornykiewicz 1965; Hornykiewicz 1963; Hornykiewicz, Lisch and Springer 1968); and(c) the remarkable clinical response of akinesia and rigidity in patients with Parkinsonism to levodopa (L-3,4-dihydroxyphenylalanine), the immediate precursor of dopamine (Birkmayer and Hornykiewicz 1961, 1962; Barbeau, Sourkes and Murphy 1962; Cotzias, Van Woert and Schiffer 1967; Yahr, Duvoisin, Hoehn, Schear and Barrett 1968; Cotzias, Papavasiliou and Gellene 1969; and many others). In laboratory animals, localized experimental lesions in the pallidum (Seitelberger, Petsche, Bernheimer and Hornykiewicz 1964), the ventromedial tegmentum of the mesencephalon (Andén, Carlsson, Dahlström, Fuxe, Hillarp and Larsson 1964; Poirier and Sourkes 1964, 1965; Sourkes and Poirier 1966; Goldstein, Anagnoste, Owen and Battista 1966; Goldstein, Anagnoste,

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Battista, Owen and Nakatani 1969), or the zona compacta of the substantia nigra (Moore, Bhatnagar and Heller 1971), also resulted in a lowered concentration of the striatal DA. The existence of a direct ascending nigro-striatal DA pathway received support from the good correlation which was found between the degree of cell loss in the substantia nigra and the nucleus parabrachialis pigmentosus and the decreased concentration of DA in the ipsilateral striatum following lesions in the ventromedial tegmental area of Tsai at the upper midbrain level in the monkey (Poirier and Sourkes 1964, 1965; Sourkes and Poirier 1966; Goldstein *et al.* 1966, 1969), the cat (Poirier, Singh, Boucher, Bouvier, Olivier and Larochelle 1967; Moore *et al.* 1971), and the rat (Faull and Laverty 1969), as well as following lateral hypothalamic lesions in the monkey (Parent and Poirier 1969; Parent, Saint-Jacques and Poirier 1969) and the cat (Bédard, Larochelle, Parent and Poirier 1969). Recent anatomical and chemical studies confirmed the existence of a direct, dopaminergic nigro-striatal projection in the cat (Moore *et al.* 1971), and provided an anatomical demonstration of direct nigro-striatal fibres in the Rhesus monkey (Carpenter and Peter 1972). The experimentally-induced interruption of the nigro-striatal DA fibres not only resulted in a lowered concentration of striatal DA and HVA, but also interfered with the synthesis of DA from L-tyrosine and levodopa (Poirier, Singh, Sourkes and Boucher 1967; Goldstein *et al.* 1969). The metabolic impairment is apparently a consequence of the associated disturbance of the enzymatic mechanisms responsible for the biosynthesis of DA from its precursors, since interruption of nigro-striatal connections resulted in decreased activities of L-tyrosine hydroxylase and levodopa decarboxylase (Goldstein *et al.* 1969; Poirier, McGeer, Larochelle, McGeer, Bédard and Boucher 1969), enzymes involved in the synthesis of DA from L-tyrosine and levodopa respectively. The loss of enzymes was proportional to the extent of destruction of the nigro-striatal projection (Moore *et al.* 1971; Hockman, Lloyd, Farley and Hornykiewicz 1971). Recently, a marked decrease in levodopa decarboxylase activity in the striatum of patients with Parkinson's disease has been demonstrated by Lloyd and Hornykiewicz (1970).

The purpose of this paper is(a) to report the clinical and morphological findings obtained in a series of necropsy cases of Parkinsonism with particular reference to the severity and topical distribution of the lesions in the zona compacta of the substantia nigra, the putamen and the pallidum;(b) to analyse the relationship between the DA metabolism in the caudate nucleus, putamen and pallidum and the degree and pattern of cell loss in the substantia nigra, the putamen and the pallidum; (c) to relate the severity of the Parkinsonian symptoms as well as the degree of the anti-akinesia effect of levodopa with the degree of disturbance of DA metabolism in the extrapyramidal nuclei of the basal ganglia; and (d) to compare the biochemical findings obtained in cases of Parkinsonism with those in Huntington's chorea.

MATERIAL AND METHODS

Clinical and neuropathological studies were performed in 69 cases of Parkinsonism. In 28 of these cases biochemical analyses of the brains were carried out. In addition, biochemical examinations were performed in the brains of 14 patients with the clinical picture of Huntington's chorea and of 28 controls free of neurological disease. In the former group, histological examinations were only performed on 4 brains; in the control group, macroscopic, but no microscopic, examination of the brains was carried out.

Clinical criteria

Except for a few cases, the clinical data have been derived from long-term observations of patients at the Neurological Department of the Hospital for Chronic Diseases, Vienna-Lainz. The classification of Parkinson's syndrome followed the common clinical criteria (*cf.* Hoehn and Yahr 1967; Selby 1968; Siegfried 1968). In a number of patients the acute anti-akinesia effect of levodopa following slow i.v. injection of 150 mg of the drug was examined. (For further details and quantitative evaluation, see Birkmayer and Hornykiewicz 1962).

Morphological methods

Material. From the brains in which biochemical assays were performed, formalin-fixed material from one or both sides of the brain stem and from one side of the basal ganglia was embedded in paraffin. From the rostral brain stem, either coronal (at right angles to the axis of Forel) or transverse (at right angles to the axis of Meynert) serial sections were taken from 2 to 4 levels, each consisting of 30–50 slices of 10 μm thickness. Every second section was stained either with cresyl violet or haematoxylin and eosin; in addition, 2–5 sections of each series were stained for myelin sheaths according to Heidenhain and Klüver-Barrera, for glial fibres according to Arendt-Kanzler (Arendt 1956), and for axis cylinders according to Bodian. From the basal ganglia, coronal serial sections of one side were taken at different planes and stained as described above; the other side of the forebrain was frozen immediately after removal of the brain and used for biochemical analyses (see below).

The (formalin-fixed) brains of 41 cases with Parkinsonian syndrome derived from the files of the Neurological Institute were also examined. Since in these cases no biochemical analyses were performed, the whole brain was available for the morphological examination. Semi-serial sections were taken from the different regions of the cerebral cortex, the basal ganglia and the brain stem, as well as some orienting sections from other brain regions, and stained as described above.

Evaluation of morphological changes. The morphological changes in the regions examined were evaluated in a semiquantitative manner. The *degree of nerve cell loss* was expressed according to the following scale: 0, no cell loss detectable; 1, mild parenchymal damage (up to approximately 15% of normal cells lost), no gliosis; 2, moderate cell loss (up to approximately 30% of normal), mild cell and fibre gliosis; 3, marked cell loss or partial devastation of neuronal population (up to approximately 50% of normal), moderate degree of gliosis; 4, severe to subtotal cell loss with only sporadic neurons preserved, dense gliosis; 5, total devastation of neuronal population, *i.e.* no nerve cells detectable, dense glial scar.

Within the zona compacta of the substantia nigra, both the rostral and caudal portions of each side were evaluated separately. For the purpose of topographical orientation, a simplified version of Hassler's classification (Hassler 1938) was chosen (Fig. 1). In addition, an overall evaluation of the degree of cell loss in the whole of the zona compacta was also performed; this evaluation was based on the above scale. The criteria of this scale were also used for the semiquantitative evaluation of neuronal loss in the putamen and the pallidum.

The *degree of the état criblé* and *vascular damage* respectively, in the putamen and the pallidum was assessed according to the following 4 criteria: 0, absent; 1, mild (*i.e.* only sporadic lacunes in the whole of the nucleus); 2, moderate (*i.e.* single lacunes per visual field, no focal necroses); 3, severe (*i.e.* numerous lacunae, *i.e.* small softening cysts, or focal necroses and/or scars).

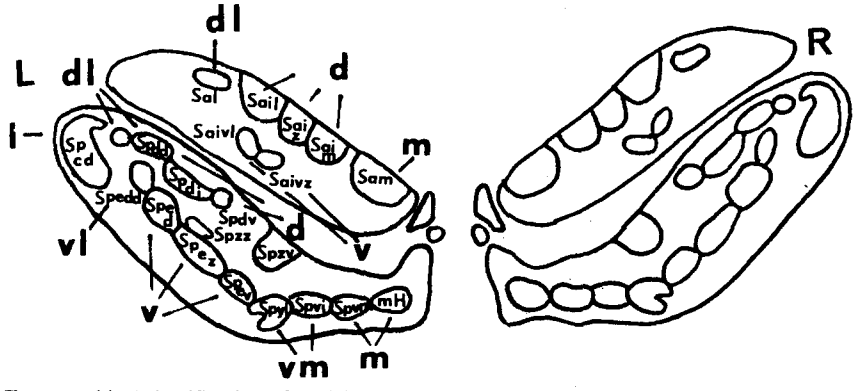

Fig. 1. Topographical classification of nuclei of the zona compacta of substantia nigra used in this study (modified from Hassler (1938); see small-print letters). For abbreviations see footnote to Table 1.

The *occurrence of Lewy bodies* and *Alzheimer's neurofibrillary changes (tangles)* within the neurons was assessed according to the following criteria; 0, none detectable; 1, 1 per low power field or the whole of the nucleus; 2, several per low power field; 3, several per medium or high power field.

The *degree of the neuroaxonal degeneration* of the (red) zona reticularis of the substantia nigra was evaluated according to the criteria of Jellinger (1968).

Nosology of the Parkinsonian syndromes

For the classification of the cases examined, morphological criteria were, in principle, decisive (Hassler 1938; Klaue 1940; Greenfield and Bosanquet 1953; Hallervorden 1957; Denny-Brown 1962; Forno 1966, 1969; Duvoisin, Stadler, Yahr and Wolf 1966; Alvord 1968; Earle 1968), but clinical data were also taken into consideration. Accordingly, the cases with Parkinsonism examined were divided into 4 groups:

Group I. Postencephalitic Parkinsonism: positive history of encephalitis; severe to total devastation of the cellular population of the zona compacta of the substantia nigra associated with frequent occurrence of Alzheimer's neurofibrillary changes.

Group II. Idiopathic (degenerative) Parkinsonism = Paralysis agitans: no history of encephalitis; severe but incomplete and focal cell loss in the zona compacta of the substantia nigra associated with frequent occurrence of Lewy bodies.

Group III. "Arteriosclerotic"-senile Parkinsonism: positive vascular lesions in the substantia nigra as part of a vascular encephalopathy.

Group IV. Unclassified and atypical forms of Parkinsonism which either (a) morphologically did not fit into any of the above 3 groups; (b) showed irreconcilable discrepancies between the clinical and morphological picture; or (c) had cell loss in the substantia nigra as part of other degenerative changes in the central nervous system; (d) 1 case of manganese encephalopathy is included in this group.

Group V. For comparison, we examined also brains of patients with Huntington's chorea. In 4 of the cases the diagnosis was verified histologically according to the well-known criteria(Hallervorden 1957); in the other cases, the diagnosis was established clinically and macroscopically upon the dissection of the brains.

Biochemical determinations

All biochemical analyses were performed in unfixed autopsy material. The brains were removed from the skull 4–18 hr after death. Discrete brain areas were immediately isolated from sections made at different planes (coronal, transverse) and stored until analyzed at −20°C. No division of the various parts of the striatal nuclei was performed.

DA was extracted from perchloric acid homogenates by adsorption on aluminium oxide, eluted with acetic acid and assayed fluorimetrically according to a combination of the methods described by Sourkes and Murphy (1961) and Weil-Malherbe (1961); for details see Bernheimer *et al.* (1963). HVA was extracted (ether extraction) and estimated as described by Andén, Roos and Werdinius (1963). In the case in which serotonin (5-hydroxytryptamine) was estimated (see "Manganese-Parkinsonism") this was done according to the method (butanol extraction) described by Udenfriend, Weissbach and Brodie (1958); in this case, noradrenaline was also estimated (see above, method for DA).

The results of the biochemical analyses were submitted to a simple analysis of variance. The significance for adjacent values was determined by means of Student's *t*-test; for values not adjacent, the Duncan *t*-test was applied (Mittenecker 1964). Regression lines were calculated according to the formula $y = a + bx$, where $b = \frac{\Sigma(x-\bar{x})y}{\Sigma(x-\bar{x})^2}$, and $a = \bar{y} - b\bar{x}$.

RESULTS

Clinical and Morphological Observations

Group I. Postencephalitic Parkinsonism

This group consisted of 12 cases (8 females, 4 males). Ten of the patients had a positive history of encephalitis (8 of them between the years 1920–1926, and 1 each in 1935 and 1942); in 2 patients the history of encephalitis was questionable. The age of the patients at the onset of clinical Parkinsonism ranged between 2 and 68 years (average 42.3 ± 5.5). The interval between encephalitis and manifestation of Parkinsonism was 2–30 years (mean 16.1 ± 2.9). The duration of the disease was 2–45 years (mean 20.6 ± 3.7). The age of the patients at death ranged between 43 and 78 years (mean 62.9 ± 3.2).

TABLE 1

CLINICAL DATA

(for abbreviations, see p. 421)

A. Postencephalitic Parkinsonism

Case No.	1	2	3	4	5	6	7	8	9	10	11	12
Age (years), sex	74 f	68 m	49 f	78↑	62 f	75 f	43 f	63 m	64 m	63 f	47 f	69 m
Duration of illness (years)	19	38	23	10	15	19	10	2	14	37	45	15
Symptoms-free interval (yrs)	10	2	19	?	30	22	16	7	21	7	?	27
Rigidity	2	3	3↑	2	2	2↑	2	2	2↑	2	2	2
Tremor	2	3	3	3	3↑	2↑	2	2	3↑	3↑	2	2
Akinesia	3↑	2↑	2↑	2↑	2	2	2	2	2↑	2↑	1	2
Amimia	2	2↑	2	1	2	1	1	1	2↑	2↑	2	2
Aphonia	1	2↑	2↑	1↑	2↑	2↑	1	1	2	2	1	2
Paralysis of eye muscles	1	1	1	1	1	1	1	1	1	2	±	2
Oculogyric crises (and equivalents)	0	3↓	2	0	1	0	2	1	1	2↓	1	0
Mask-like face	0	1	1	1	1	0	1	1	1	1	±	1
Seborrhea	0	1	1	1	1	0	1	1	1	1	1	.
Sudoresis	0	1	1	1	1	1	?	?	1	1	?	1
Sialorrhea	0	1	1	2	1	1	1	1	1	1	0	1
Hyperthermia	0	1	1	0	1	1	?	?	?	?	0	0
Asymmetry of symptoms	2	1	1	1	1	1	1	1	1	1	1	0
Other neurological symptoms	0	+	+	0	+	+	0	0	+	0	Hp	0
Depression	0	1	1	0	1	1	0	1	0	2	0	0
Dementia	0	0	0	1	0	1	0	0	1	0	1	0
Nocturnal confusion	0	0	0	0	0	0	0	0	0	0	0	0
Anti-akinetic effect of levodopa (i.v.)	ne	2	3	2	2	2	ne	ne	ne	ne	ne	2

B. Idiopathic Parkinsonism (paralysis agitans)

Case No.	13	14	15	16	17	18	19	20	21	22	23	24	25
Age (years), sex	69 m	67 f	82 f	74 f	78 f	67 f	75 f	65 m	65 m	65 m	64 f	73 f	71 f
Duration of illness (years)	13	21	4	4	9	19	21	3	14	3	6	12	1
Rigidity	2	2↑	2↑	2	1	2	2	2	3	2↑	2	3	2
Tremor	2	2	2↑	2	2	2	3↑	2	3	2↑	1	2	1
Akinesia	1	2↑	1	2↑	1	2	1	2	2	2	2	1	1
Amimia	1	0	1	2	1	2	1	1	2	2	2	1	0
Aphonia	0	0	1	1	0	0	1	1	1	1	1	0	0
Paralysis of eye muscles	0	0	0	1	0	0	0	0	0	0	0	0	1
Oculogyric crises	0	0	0	0	0	0	0	0	0	0	0	0	0
Mask-like face	0	0	0	0	0	0	0	0	0	0	1	0	0
Seborrhea	0	0	0	0	0	0	0	0	0	0	±	0	0
Sudoresis	0	0	0	0	0	0	0	0	0	0	0	0	0
Sialorrhea	0	0	0	0	0	0	1	0	0	0	0	0	0
Hyperthermia	0	0	0	0	0	0	0	0	0	0	0	0	0
Asymmetry of symptoms	0	0	1	1	0	0	0	0	0	0	0	1	0
Other neurological symptoms	0	Hp	Hp	+	+	+	0	Hp	0	0	0	0	0
Depression	0	0	1	0	1	0	0	0	0	0	0	0	0
Dementia	0	0	2	0	1	0	0	0	0	1	1	1	0
Nocturnal confusion	1	0	1	1	1	1	0	0	0	1	1	1	0
Anti-akinetic effect of levodopa (i.v.)	0	ne	±	1	1	1	1	ne	0		±	1	ne

TABLE 1 (continued)

Case No.	26	27	28	29	30	31	32	33	34	35	36	37	38
Age (years), sex	64 m	79 f	51 m	60 m	50 f	70 m	74 f	66 f	64 m	52 f	70 m	70 m	75 m
Duration of illness (years)	7	9	4	8	?	7	2	5	10	9	12	8	10
Rigidity	2	2	3	1	2	3↑	3	3	2	3	?	2	2↑
Tremor	2	2	2	2	1	2	3↑	2	2	3	±	1↓	3↓
Akinesia	1	1	1	1	2	2	2	4↑	3	2	4	3↑	2↑
Amimia	1	0	1	0	1	1	1	1	2	1	2	2	2
Aphonia	0	1	0	1	0	1	1	2↑	0	0	2	0	0
Paralysis of eye muscles	0	0	0	0	0	1	0	0	0	0	0	0	0
Oculogyric crises	0	0	0	0	0	0	0	0	0	0	0	0	0
Mask-like face	0	0	0	0	0	0	0	0	0	0	0	0	0
Seborrhea	0	0	0	0	0	0	0	0	0	0	0	0	0
Sudoresis	0	0	0	0	0	0	0	0	0	0	0	0	0
Sialorrhea	0	0	0	0	0	0	0	0	0	0	0	0	0
Hyperthermia	0	0	0	0	0	0	0	0	0	0	0	0	0
Asymmetry of symptoms	0	0	2	0	0	0	1	1	1	1	0	0	±
Other neurological symptoms	0	0	Hp	0	+	0	0	0	0	0	0	0	Hp
Depression	0	0	0	0	0	2	0	0	0	0	0	0	0
Dementia	1	1	0	0	0	1	0	0	0	0	0	0	±
Nocturnal confusion	0	0	0	1	0	1	0	0	0	0	0	0	0
Anti-akinetic effect of levodopa (i.v.)	ne	ne	ne	ne	ne	ne	ne	2	ne	ne	ne	ne	ne

Case No.	39	40	41	42	43	44	45	46	47	48	49	50	51
Age (years), sex	67 f	66 f	68 f	63 m	72 f	62 f	69 m	69 m	67 f	47 m	79 f	72 m	69 m
Duration of illness (years)	13	7	10	7	4	12	9	7	4	27	15	8	9
Rigidity	2↑	3↑	2	3↑	3↑	2	1	3	3↑	3↑	3↑	3	3
Tremor	3	2↓	1	3↓	3↓	2	3	3	1↓	2↓	1↓	2↓	2
Akinesia	3	3	2	3	3↑	2	1	3	3	3	2	2	2
Amimia	2	3	1	2	2	1	1	2	2	2	2	2	1
Aphonia	0	0	0	0	1	1	0	1	0	0	0	1	0
Paralysis of eye muscles	0	0	0	0	0	0	0	0	0	0	0	0	0
Oculogyric crises	0	0	0	0	0	0	0	0	0	0	0	0	0
Mask-like face	0	1	0	0	0	1	0	0	0	0	0	0	0
Seborrhea	0	0	0	0	0	0	0	0	0	0	0	0	0
Sudoresis	0	0	0	0	0	0	0	0	0	0	0	0	0
Sialorrhea	0	0	0	0	0	0	0	0	0	0	0	0	0
Hyperthermia	0	0	0	0	0	0	0	0	0	0	0	0	0
Asymmetry of symptoms	0	0	0	0	0	1	0	0	1	0	0	0	0
Other neurological symptoms	0	0	0	0	0	0	0	0	+	0	+	+	0
Depression	2	2	2	0	1	2	1	1	1	0	1	0	0
Dementia	0	0	0	1	1	0	3	2	0	0	1	0	0
Nocturnal confusion	0	0	1	0	0	0	2	2	0	0	1	0	0
Anti-akinetic effect of levodopa (i.v.)	ne	1	1	ne	ne	2	ne	ne	ne	ne	1	ne	ne

C. "Arteriosclerotic"-senile Parkinsonism

Case No.	52	53	54	55	56	57	58
Age(years), sex	66 f	81 f	66 f	83 f	84 f	77 f	85 f
Duration of illness (years)	4	3	2	2	1	2	4
Rigidity	2	1	1	1	1	2	1
Tremor	2	2	2	1	1	2	1
Akinesia	1	1	1	1	1	2	1
Amimia	1	±	±	±	±	1+	1

TABLE 1 (continued)

Aphonia	0	0	1	0	0	0	0
Paralysis of eye muscles	0	0	0	0	0	0	1
Oculogyric crises	0	0	0	0	0	0	0
Mask-like face	0	0	0	0	0	0	0
Seborrhea	0	0	0	0	0	0	0
Sudoresis	0	0	0	0	0	0	0
Sialorrhea	0	0	0	0	0	0	0
Hyperthermia	0	0	0	0	0	0	0
Asymmetry of symptoms	1	1	0	0	0	0	1
Other neurological symptoms	Hp	+	+	+	Hp	Hp	+
Depression	1	0	0	0	0	0	1
Dementia	0	1	1	1	1	1	1
Nocturnal confusion	0	1	0	1	0	1	1
Anti-akinetic effect of levodopa (i.v.)	ne	ne	ne	ne	ne	ne	ne

D. Unclassified and atypical cases with parkinsonian symptomatology

Case No.	59	60	61	62	63	64	65	66	67	68	69
Age (years), sex	72 f	56 f	71 m	66 f	50 f	56 f	72 f	73 f	50 m	69 m	67 f
Duration of illness (years)	4	3	1	2	2	12	20	4	3	10	23
Rigidity	3	3	2	2	1	3	1	3	4	3	3
Tremor	1	1	1	1	±	1	±	±	±	1	2
Akinesia	3	1	2	1	3	3	±	4	4	4	2
Amimia	1	1	1	?	1	3	±	2	2	2	2
Aphonia	0	0	0	0	1	3	0	3	1	1	1
Paralysis of eye muscles	1	0	0	0	0	±	0	0	0	0	±
Oculogyric crises	1	0	0	0	0	0	0	1	0	0	0
Mask-like face	1	0	0	0	0	0	0	0	1	0	0
Seborrhea	0	0	0	0	0	0	0	0	1	0	0
Sudoresis	1	0	0	0	0	0	0	0	0	0	0
Sialorrhea	1	0	0	0	0	0	0	0	0	0	0
Hyperthermia	0	0	0	0	0	0	0	0	0	0	0
Asymmetry of symptoms	1	0	0	0	0	1	0	0	0	0	0
Other neurological symptoms	0	0	0	0	Bp	0	Qp	Bp	+	0	0
Depression	0	0	0	0	1	0	0	0	0	0	1
Dementia	0	0	1	0	1	3	±	2	0	1	±
Nocturnal confusion	0	0	1	0	0	2	0	0	0	0	0
Anti-akinetic effect of levodopa (i.v.)	ne	ne	ne	ne	ne	±	ne	1	ne	ne	ne

↑: increasing, ↓: decreasing intensity of symptom during course of disease; +: other neurological symptoms present; 0: absent. The severity of the parkinsonian symptoms has been assessed on a 0–4 scale, the anti-akinesia effect of i.v. levodopa on a 0–3 scale; Birkmayer and Hornykiewicz (1962).

List of abbreviations:

Af: Alzheimer's fibrillary tangles; asP: "arteriosclerotic"-senile Parkinsonism; At: atrophy, numbers = degree of cell loss, see METHODS; BL: bilateral; Bp: bulbar paralysis; c: caudal (part of the zona compacta of the substantia nigra); Caud: caudate nucleus; ChH: Huntington's chorea; cl. diag.: clinical diagnosis; CO-I: carbon monoxide poisoning; Cy: cyst or cystic necrosis; DA: dopamine; dif: diffuse cell loss, accompanying number = degree of cell loss, see METHODS; Dur. illn.: duration of illness; d,v,m,l,vm,vl,ld(dl),md: dorsal, ventral, medial, lateral, ventromedial, ventrolateral, laterodorsal (dorsolateral), mediodorsal (part of the zona compacta of the substantia nigra), accompanying number = degree of cell loss, see METHODS; Ec: état criblé, numbers = degree of tissue damage, *see* METHODS; f: female; fN: focal scars (due to microinfarcts); Gls: gliosis, numbers = degree of glial scarring, *see* METHODS; Hp: hemiparesis; HVA: homovanillic acid; L: left; Lb: Lewy bodies; levodopa: L-3,4-dihydroxyphenylalanine; Les: lesion, numbers = overall degree of cell loss, *see* METHODS; m: male; MnE: manganese encephalopathy; Ms: multiple sclerosis; Nad: syndrome of neuroaxonal dystrophy, numbers = degree (Jellinger 1968); ne: not examined; No.: number; ns: not significant; o: oral (rostral, part of the zona compacta of the substantia nigra); Pa: paralysis agitans (idiopathic Parkinsonism); Pall: globus pallidus; pe: globus pallidus external (lateral) part; peP: postencephalitic Parkinsonism; pi: globus pallidus, internal (medial part); pm: globus pallidus, intermediate part; prot. No.: protocol number; Put: putamen; Qp: quadriplegia; R: right; Z. comp.: zona compacta of the substantia nigra; Z. ret.: zona reticularis of the substantia nigra.

Clinical picture. In this group the clinical picture was rather uniform (Table 1). All patients displayed marked rigidity, tremor and progressive akinesia as well as marked amimia, aphonia and paralysis of convergence. Oculogyric crises or their equivalents (*e.g.* crying attacks, etc.) were observed in 8 cases, a mask-like face in 10. Most of the cases showed some autonomic disturbances of vagomimetic (cholinergic) nature (increased salivation and seborrhea in 9; excessive sweating in 8; hyperthermia in 4; in 2 of the latter patients, hyperthermia was the immediate cause of death). In 11 cases the Parkinsonian symptoms showed some degree of asymmetry. In some cases additional neurological symptoms were present: in 4 cases uni- or bilateral pyramidal tract signs (1 of these cases had hemiparesis); in 2 cases increased tendon reflexes. In 6 patients affective crises of the endogenous-depressive type were noticed. Four patients had a mild degree of organic dementia.

The anti-akinesia effect of levodopa. The effect of an i.v. test dose of levodopa on akinesia was, in this group of patients, generally good to excellent (2 to 3) (Table 1).

Pathology. The morphological picture in these cases was characterized by a severe, bilateral, occasionally asymmetrical, nerve cell loss in the zona compacta of the substantia nigra (Table 2, Fig. 2). Particularly affected were the rostral (oral) and caudal portions of the zona compacta. Within the rostral portion, the neuronal population in the medial and ventromedial cell groups was extensively devastated with a corresponding degree of glial scarring; in the caudal portion, the ventral, medial and frequently also the dorsal and dorsolateral cell groups showed a total or almost com-

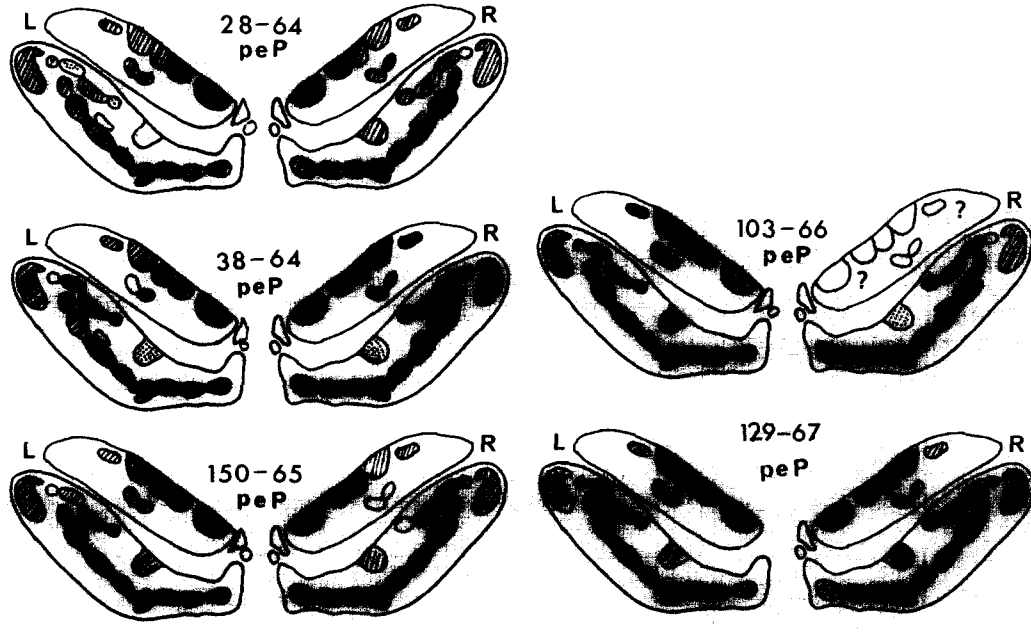

Fig. 2. Distribution and severity of anatomical lesions in the zona compacta of the substantia nigra in selected cases of postencephalitic Parkinsonism (for case numbers see Table 2). Intensity of lesions: □ = grade 0; ▨ = grade 1; ▨ = grades 2 and 3; ▩ = grade 4; ■ = grade 5.

TABLE 2

POSTENCEPHALITIC PARKINSONISM. MORPHOLOGICAL AND BIOCHEMICAL DATA

Case no. *Prot. no.* *Cl. diag.*	*Putamen* *Ec*	*At*	*Pallidum* *Ec*	*At*	*Substantia nigra* *les*	*zona compacta* *main localisations*	*Lb*	*Af*	*z. ret.* *Nad*	*Dopamine (μg/g)* *Caud*	*Put*	*Homovanillic acid (μg/g)* *Caud*	*Put*	*Pall*
1-28/64 peP	4	fN, L	2	2	4	o, L : m, mv5 ; dl3 (BL) c, R : v, vm, vl5 ; m, dl, d3 c, L : v, vm4 ; m, dl3 ; d2	0	+	3	0.09	< 0.01	1.10	1.20	0.34
2-38/64 peP	1	1(?)	0	2, pe 2, pi	(4–5)	o, R : dif5 ; o, L : dif4 c, R : dif5 ; c, L : v5 ; vm, m d4 ; dl3	+	+	2	< 0.01	< 0.01	< 0.01	0.09	0.24
3-81/64 peP	0	1(?)	0	1(?)	4	0 : ne ; c : dif4 (BL)	0	+	ne	< 0.01	< 0.01	< 0.25	0.34	0.33
4-153/64 peP	2	1(?)	1	2(?)	4–5	o : ne ; c : dif4–5 (BL)	0	0	2	0.07	0.03	0.31	0.51	0.31
5-102/65 peP	0	0	0	1, pi	4–5	o, L : m, v4–5 ; c, L : v, m5 dif4 (BL)	0	+	3	0.04	0.04	0.06	0.11	0.14
6-103/66 asP	3	1	2	1, pe 1, pi	(4–5)	o, BL : dif5 ; m4(L) ; c, L : dif. 5 ; dl, 14 ; c, R : v, vm m5 ; dl, 14	0	+	3	< 0.01	< 0.01	< 0.01	< 0.01	0.05
7-72/50 peP	0	0	0	1 BL	4–5	o, BL : dif4–5 ; dl4 c, BL : dif4–5, dl4	0	0	2					
8-106/51 peP	0	1 BL	0	1 BL	4	o, BL : dif4 ; vm3 c, BL : dif4 ; dl5	0	+	2					
9-37/57 peP	3	1 BL	2	2 BL	4	o : ne ; c, R : dif4–5 c, L : 4 ; dl3 (BL)	0	0	3					
10-150/65 peP	0	1 BL	0	1 BL	4–5	o, L : dif4 ; v, dl3 ; o, R : dif5 ; v, dl3 ; c, BL : v, d5 m, mv4 ; dl2	0	+	3	chemically not analysed				
11-129/67 peP	0	0	0	0	5	o, BL : dif5 ; v, dl4 c, BL : dif5 ; mv, dl4	0	+	0					
12-85/69 peP	0	0	0	0	4–5	o, BL : dif4–5 ; dl3–4 c, R : dif4–5 ; L3 c, L : dif4 : m, vm3	0	+	2					

For explanation of abbreviations, see Table 1.

plete nerve cell loss and dense gliosis; this was accompanied by a practically complete loss of melanin pigment (Fig. 2). In 9 of the 12 brains, neurofibrillary changes were observed in nigral neurons; in 1 case Lewy bodies were present. In addition, 4 cases showed a moderate cell loss in the pallidum; the degree of akinesia was severe in 2, mild in the other 2. In another 5 brains, a mild degree of pallidal cell loss was detected. In 4 cases the putamen showed a higher degree of état criblé; this was also true of the pallidum in 3 cases. In 1 case each there was a mild degree of état criblé present in the putamen and pallidum respectively. In the remaining cases the pallidum and putamen were morphologically inconspicuous.

Group II. Paralysis agitans

This group consisted of 39 cases (21 females, 18 males); none of them had any history of encephalitis. The age of the patients at the onset of the disease ranged between 20 and 78 years (mean 58.9 ± 1.6), and at death 47–82 years (mean 67.7 ± 1.3). The duration of the disease was 1–27 years (mean 9.3 ± 0.9).

Clinical picture. It was dominated by marked rigidity, tremor, increasing akinesia (Table 1) and a progressive course of the disease. Rigidity was mild in 3 cases; tremor was mild in 7 and nearly completely absent in 1 case. In 11 patients akinesia was severe and in a further 11 it was mild. Amimia was noticed in 35 cases, aphonia in 17. Autonomic disturbances were rare (3 cases with mask-like face, 1 with seborrhea, 1 with excessive salivation). Paralysis of convergence was present in 3 cases. None of the patients in this group had any oculogyric attacks. Asymmetry of the Parkinsonian symptoms was seen in 11 cases. Other neurological symptoms included: pyramidal signs in 6 cases; intermittent or preterminal hemiparesis in 5 cases. In 12 patients depressive mood changes were noticed; 14 patients had a mild to moderate degree of organic dementia, 9 of them with nocturnal episodes of mental confusion.

The anti-akinesia effect of levodopa. With the exception of 2 cases, the effect of an i.v. test dose of levodopa on akinesia was only slight (0–1; Table 1).

Pathology. The morphological examination in these cases showed consistently marked to severe focal degenerative changes (symmetrical or asymmetrical) in the zona compacta of the substantia nigra. However, within this group of patients, the degree of cell loss and glial scarring displayed considerable variability (Table 3). Within the rostral portion of the zona compacta, marked changes were seen in the medial and ventral cell groups; in 2 cases only (cases 43 and 44) these changes were severe (almost total devastation of neuronal population). Within the caudal portion of the substantia nigra, the most pronounced changes involved the ventral, the ventromedial and ventrolateral cell groups, where the cell loss was frequently subtotal and accompanied by the corresponding degree of glial scarring. Other parts of the substantia nigra were less affected. Thus, the cell loss in the medial, dorsal and lateral cell groups was rather variable in degree (Fig. 3). Occurrence of Lewy bodies in nigral neurons was detected in all but 3 cases. Lewy bodies were, as a rule, also seen in the locus caeruleus whose cellularity showed only mild to moderate decrease. Alzheimer's neurofibrillary changes were observed only in 1 case (no. 19). In 11 brains, the pallidum, especially its external portion, showed a moderate degree of cellular atrophy; in 19 cases the pallidal atrophy was only mild in degree. There was no clear-cut relationship between the

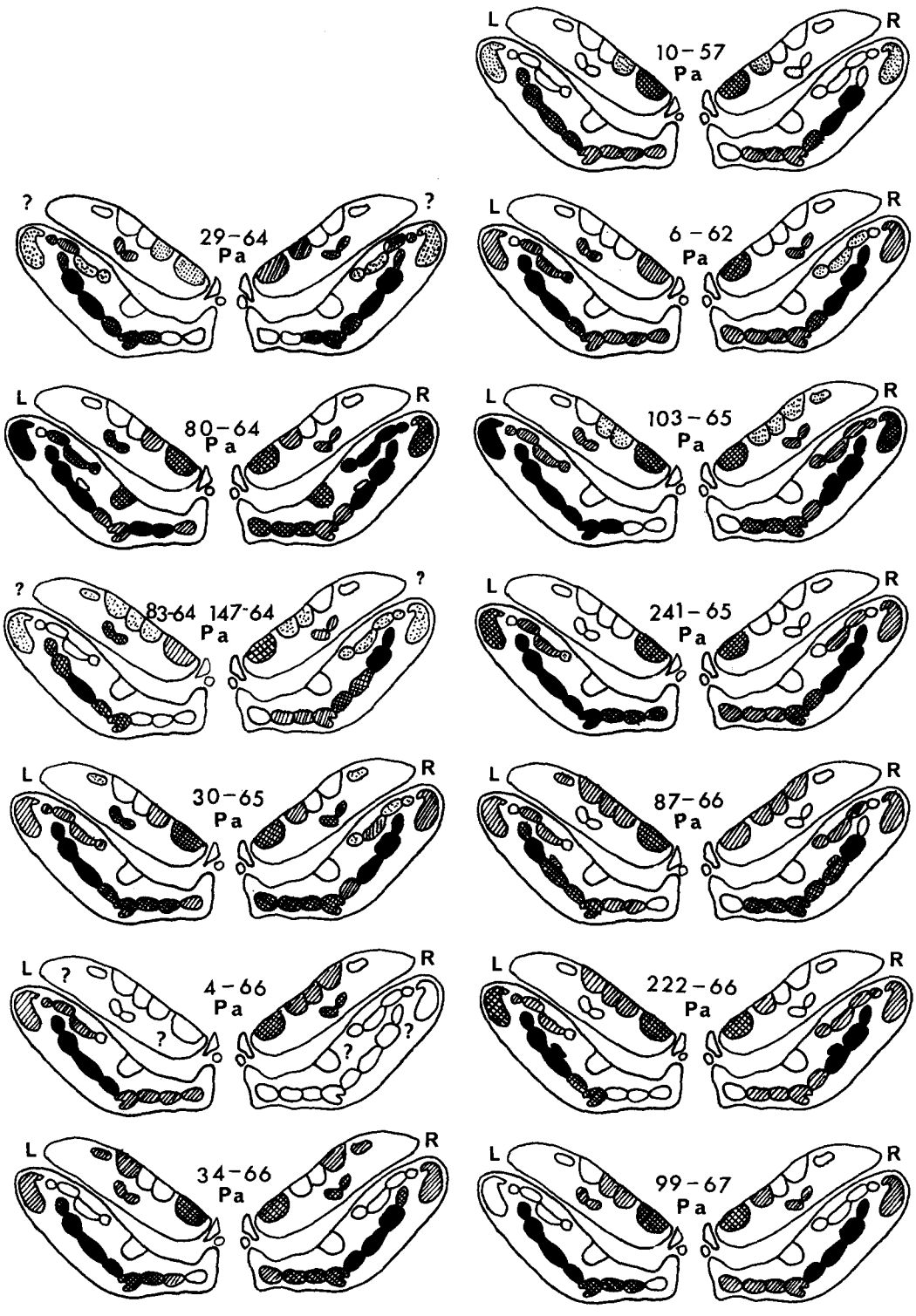

Fig. 3. Distribution and severity of anatomical lesions in the zona compacta of the substantia nigra in selected cases of idiopathic Parkinsonism (for case numbers see Table 3). For intensity of lesions see Fig. 2.

TABLE 3

IDIOPATHIC PARKINSONISM (PARALYSIS AGITANS). MORPHOLOGICAL AND BIOCHEMICAL DATA

Case no. / Prot. no. / Cl. diag.	Putamen		Pallidum		Substantia nigra zona compacta				z. ret.	Dopamine (μg/g)		Homovanillic acid (μg/g)		
	Ec	At	Ec	At	les	main localisations	Lb	Af	Nad	Caud	Put	Caud	Put	Pall
13-29/64 Pa	0	±	0	1, pe 1, pi	3–4	o: v4, BL; mv, md3, R, 2L c, BL: v, vm4; dl3, 1, d2	2	0	3	0.15	< 0.01	1.80	1.70	0.51
14-80/64 asP	4	fN, R	3	2, R	3–4	o, BL: m, mv, vl3; c, L: v, vm, vl4; dl4–5; m, d2 c, R: v, vl, m, d3–4; vm, d2	1	0	3	0.36	0.06	1.44	0.93	0.98
15-82/64 asP	1	1(?)	1	1(?)	3	o: ne; c, ?: 1,1d4; m3 dl, d2	1	0	1	0.47	< 0.01	1.09	1.24	0.36
16-83/64 asP	1	1(?)	1	1(?)	3	o, ?: vl3; m, d, dl1; c, ?: v vl4; d, dl2	1	0	1	0.66	< 0.01	0.85	0.49	0.53
17-95/64 asP	2	1(?)	2	2, pe	3	o, ?: dif2; Cyl; c, ?: vm v4; vl1; fNL	2	0	2	1.11	< 0.01	0.40	0.45	0.38
18-147/64 peP	2	1(?)	0	2(?)	3–4	o, ?: m4; v3; d2; c, ?: vl5 v4; vm3; dl2	2	0	1	0.41	0.04	1.02	0.75	0.70
19-30/65 peP	2	1(?)	1	1(?)	3–4	c, BL: vm4; d2; dl1 c, BL: v4–5; m, vm4; d, dl2	2	+	3	0.31	0.06	0.78	1.18	ne
20-136/65 Pa	2	1(?)	2	2(?)	4	o, BL: m4; 1d4; d3 c, BL: v, dl4; m, d2–3	0	0	2	0.64	< 0.01	0.39	0.71	0.50
21-157/65 peP	1	0(?)	0	0(?)	3	o, L: v4; dl2; mcv1; c, L: v4; m, dl2; vm2, d1	1	0	1	0.06	0.03	1.18	1.61	0.73
22-4/66 Pa	0	± (?)	0	2, pe pi, R	3–4	o, R: m, v4; d3; c, L: v5 vm3; d, dl2	1	0	2	< 0.01	0.09	< 0.01	0.64	0.98
23-34/66 Pa	1	1(?)	1	2, pe pi	3–4	o, BL: m4; v3; d, dl2 c, BL: v, vm4; m3–4; d, dl2	2	0	2	0.09	< 0.01	1.02	0.67	0.53
24-35/66 asP	4	fN, R	2	2, R	2–3	o, BL: m, vl–2; c, BL: v vl4; vm, 1, d2	2	0	2	0.77	0.05	2.17	0.52	0.76
25-105/66 asP	0	± (?)	0	0–1 (?)	2–3	o, BL: v, m2; c, BL: v, vl 13; m, dl	1	0	3	0.57	0.13	1.54	0.66	1.92
26-80/53 Pa	2	1(?)	1	1, pi	3	o: ne; c, R; v, vl3; vm, dl d2; c, L: v, vl 4; vm, dl, d3; 12	2	0	3	ne	ne	ne	ne	ne

TABLE 3 (*continued*)

27-10/57 Pa	2	0(?)	2		2, pe, pi	3	o, BL:m4; dm, v2; c, L:v, vl4 m, vm3; dl, d2; c, R:v5; vm3; m2; dl2	2	0	2	
28-62/57 Pa	0 BL	0	0 BL		1	3, R 2, L	o, R:m3, d2; o, L:m, d2 c, R:v, vm, vl4; c, L:v, vm, vl2	2	0	1	
29-66/58 Pa	0 BL	0	0 BL		0	3	o:ne; c, L:v, 14; dl, d, m2; vm3 c, R:v4; vm2; d, dl1	1	0	2	
30-65/59 peP	0 BL	0	0 BL		0	3	o: ne; c, BL:v4; m, d, dl1	0	0	ne	
31-2/62 Pa	3 BL	1	1 BL		1	3–4	o, BL:m4; v3–4; c, BL:v4–5 vm3; m, 1, dl2	1	0	ne	
32-119/64 asP	0 BL	0	0 BL		1	2–3	o, BL:v, m2; c, BL:v, vl, dl3 m, vm2	2	0	1	
33-103/65 Pa	2 BL	1	1 BL		2	4	o, BL:m4; v3; d2; c, L:v, vl, 14–5; vm4, dl3; c, R:v4–5; vm3; 13	1	0	1	
34-241/65 Pa	0 BL	1	0 BL		2	3–4	o, BL:m3–4; c, L:v, vl4; m, vm 13; dl2; c, R: v4; vm3; m, 12	2	0	1	chemically not analysed
35-87/66 Pa	0 BL	0	0 BL		0	3	o, L:m3–4; d, dl2; o, R:m, d2 c, BL:v3; vm2–3; dl, 12	2	0	2	
36-222/66 Pa	1 BL	0	0 BL		2	3	o, L:m3; d, d12; o, R:m3; c, L: v, vl4; vm, 13; dl2; c, R:v4 vm, l, dl2	2	0	3	
37-99/67 Pa	3 BL	1	2 BL		1	3–4	o, BL:m2–3; v, d2; c, L:vl4; vm3; c, R:v, vl4; m, vm, 12	2	0	2	
38-308/67 Pa	2	1	1 BL	BL	1	3	o, BL:m2; c, L:v3; vm, d, 12 c, R:v4; vm3; m, 12	2	0	2	
39-81/68 Pa	1 BL	0	1 BL		0	3–4	o, BL:m4; v, 11; c, BL:v4–5 vl, dl2; m, d1	2	0	2	
40-87/68 peP	0 BL	0	0 BL		0	4	o, BL:m3; d, v1–2; c, R:v5 c, L:v4; c, BL:13; mv2	2	0	2	
41-144/68 Pa	0 BL	1	0 BL		1	3	o, BL:m, $\bar{v}$4; c, R:v4–5; c, L: v4; c, BL:vm, m, d, dl2	2	0	1	

TABLE 3 (*continued*)

Case no. / *Prot. no.* / *Cl. diag.*	*Putamen* Ec	*Putamen* At	*Pallidum* Ec	*Pallidum* At	*Substantia nigra* zona compacta les	*Substantia nigra* zona compacta main localisations	*Substantia nigra* zona compacta Lb	*Substantia nigra* zona compacta Af	*Substantia nigra* z. ret. Nad	*Dopamine* (μg/g) Caud	*Dopamine* (μg/g) Put	*Homovanillic acid* (μg/g) Caud	*Homovanillic acid* (μg/g) Put	*Homovanillic acid* (μg/g) Pall
42-151/68 CO-I	1 BL	0	1 BL	0	3	o, BL:m, v3; c, L:v, vm4; dl, l3 c, R:v, vm4; vl, l, dl2	2	0	2	chemically not analysed				
43-239/68 Pa	0 BL	1	0 BL	1	4	o, BL:m, v4–5; d2; c, BL:v l4–5; m, mv, dl3	1	0	1					
44-268/68 peP	1 BL	1	1 BL	1	4	o, BL:v, m4–5; v4; c, BL:v, vm 4–5; vl, d, dl2	0	0	1					
45-271/68 asP	1 BL	0	1 BL	0	3	o, BL:m3; v, d, dl1; c, L:v3; vl dl, l2; c, R:v4; vm, vl, l2	3	0	1					
46-273/68 Pa	0 BL	0	1 BL	1	3	o, BL:m3; c, BL:v4; vl, l, dl2	2	0	1					
47-294/68 Pa	0 BL	0	1 BL	1	3	o, BL:m4; c, BL:v4; vm3; m d, l2	2	0	2					
48-354/68 ?	0 BL	0	0 BL	1	3	o, BL:m, v4; c, L:v, vm, m4; l2 c, R:v, vm2, l, dl4	2	0	1					
49-45/69 Pa	1 BL	1	2 BL	1	3–4	o, BL:m, v4; d2; c, BL:v, vm vl4; d, dl2	1	0	1					
50-305/69 Pa	1 BL	1	1 BL	1	4	o, BL:m, v3, d2; c, L:v, vm4–5; m, l; dl4; c, R:v, vm4; m, l, dl4	2	0	2					
51-376/69 Pa	0	0	0	0	3	o, BL:m, v2; c, BL:m, vl1 v4–5; vm3; l, dl2	1	0	2					

For explanation of abbreviations, see Table 1.

degree of pallidal atrophy and the severity of akinesia. The putamen showed mild cellular atrophy in 21 cases; in 2 cases focal scars (due to micro-infarcts) were present. Higher degrees of état criblé were present in the pallidum of 1 patient, and in the putamen in 4 patients; the état criblé was mild in the pallidum in 15 cases, and in the putamen in 11 cases. The remaining cases were inconspicuous in this respect.

Group III. "Arteriosclerotic"-senile Parkinsonism

This group consisted of 7 cases (all females). The onset of clinical symptoms of Parkinsonism occurred between the ages of 62 and 83 years (mean 74.7 ± 3.6); the age of the patients at the time of death ranged between 66 and 85 years (mean 77.4 ± 3.1). The duration of the disease was between 1 and 4 years (mean 2.7 ± 0.16).

Clinical picture. It was dominated (Table 1) by mild to marked degrees of rigidity, tremor, hypokinesia and hypomimia; the intensity of the latter 2 symptoms was particularly mild. Aphonia and paresis of the ocular muscles were each present in only 1 case each. No vegetative disturbances were apparent. However, all patients had some other neurological symptoms, with hemiparesis occurring in 3 cases. Mild degrees of depressive illness were observed in 2 patients. Organic dementia was present in all patients but 1. Four patients had nocturnal episodes of mental confusion.

The anti-akinesia effect of levodopa. In this group of patients, the effect of levodopa on akinesia was not tested.

Pathology. The morphology was characterized by varying degrees of nigral damage on the basis of vascular changes which were manifested by the presence of cystic necroses and perivascular focal nerve cell loss and glial scarring (Table 4). In most cases these lesions were asymmetrical and occasionally only unilateral. They showed no preferential localisation within the substantia nigra. The amount of melanin pigment in the zona compacta was also somewhat reduced. In 3 cases, Lewy bodies were detected in nigral neurons; in 1 case neurofibrillary changes were present. The lacunar changes in the substantia nigra were accompanied by vascular lesions in the putamen and pallidum; these were marked to severe état criblé or multiple focal necroses (scars) and cysts. Additional infarcts or vascular damage were frequently noticed in other brain regions completing the overall picture of a vascular encephalopathy.

Group IV. Unclassified and atypical cases with Parkinsonian symptomatology

This group was comprised of 11 cases with diverse clinical and morphological syndromes which either could not be clearly classified in one of the above groups or presented a combination of nigral damage with other system atrophies or CNS diseases (Tables 1 and 5). In 2 cases (Cases 59 and 60) with a positive history of encephalitis—one of them with a clinical picture characteristic of postencephalitic Parkinsonism—the morphological findings (obtained in the limited brain material available) were irreconcilable with the clinical diagnosis. In 1 of these cases (Case 59) the biochemical findings (see concentrations of HVA) were also distinctly different from those usually observed in postencephalitic Parkinsonism. Another case (Case 61) displayed clinically a severe Parkinsonian syndrome and morphologically showed an unusually severe degree of senile "neuroaxonal dystrophy" in the zona reticularis of the substantia nigra; however, there was only a moderate degree of cell loss in the zona

TABLE 4

"ARTERIOSCLEROTIC"-SENILE PARKINSONISM. MORPHOLOGICAL AND BIOCHEMICAL DATA

Case no. / *Prot. no.* / *Cl. diag.*	*Putamen*		*Pallidum*		*Substantia nigra*					*Dopamine (μg/g)*		*Homovanillic acid (μg/g)*		
					zona compacta				*z. ret.*					
	Ec	*At*	*Ec*	*At*	*les*	*main localisations*	*Lb*	*Af*	*Nad*	*Caud*	*Put*	*Caud*	*Put*	*Pall*
52-75/64 Pa	3 BL	fN	2 BI	1	2	o:ne; c:Ec1; difdl dm2	1	0	2	1.65	0.97	1.63	1.67	1.67
53-122/64 asP	3	fN	3	fN	2–3	o:Ecm, d, l; dif2 c:Ecm, d; m3; l2	1	0	1	0.35	<0.01	2.33	2.79	ne
54-25/65 Pa	3	fN	3	fN	3–4	o, BL:fNdl; d4; difl–2 c, BL:Cyl; fNvl, dl; vm4	1	0	3	0.21	0.08	0.75	0.61	0.66
55-145/65 asP	4	fN, L	3	fN, L	1	o, L:Cym, v; dl c, BL:difl	0	0	1	1.08	1.39	3.65	2.69	2.63
56-72/66 asP	4	fN, L	2	2, L	2	o, L:dif2; o, R:difl c, L:Ecvm; c, BL:difl–2	0	0	3	0.95	0.09	1.32	1.85	0.95
57-19/67 asP	4 BL	fN	3 BL	fN	2–3	o:ne; c, R:vl, v, dl3 c, L:fN1; Ecv, vl, dl3	0	+	2	chemically not analysed				
58-266/68 asP	3 BL	fN	2 BL	2	1–2	o, L:fNd, dl c, BL:Ecm, vm; difl–2	0	0	3					

For explanation of abbreviations, see Table 1.

TABLE 5

UNCLASSIFIED AND ATYPICAL CASES WITH PARKINSONISM. MORPHOLOGICAL AND BIOCHEMICAL DATA

Case no. / Prot. no. / Cl. diag.	*Putamen*		*Pallidum*		*Substantia nigra*					*Dopamine (μg/g)*		*Homovanillic acid (μg/g)*		
					zona compacta				*z. ret.*					
	Ec	*At*	*Ec*	*At*	*les*	*main localisations*	*Lb*	*Af*	*Nad*	*Caud*	*Put*	*Caud*	*Put*	*Pall*
I. Postencephalitic Parkinsonism (?)														
59-S.E. peP	2	1	1	1	3–4	o: ne; c, ?: v, vm, vl4 dl2	0	1	2	0.14	0.14	1.38	1.38	1.41
60-2/62 peP	0	0	0	0	4	o, BL: m4–5 c, BL: v, m, vm4	0	0	0	ne	ne	ne	ne	ne
II. "Senile" Parkinsonism														
61-30/64 asP	2	1	2	2	2–3	o, BL: v, m2–3; Ecv c, BL: dif1–2	1	0	4	0.41	0.21	0.89	2.05	1.29
III. Parkinsonism of undetermined aetiology														
62-23/66 ?	1	1, R	1	1, R	1	o, BL: dif1; c, BL: dif1	0	0	1	0.46	2.58	1.94	4.89	3.26
IV. Paralysis agitans + olivo-ponto-cerebellar atrophy														
63-49/70 Pa	0	0	0	0	3–4	o, BL: m, v3; d1 c, BL: v, vm4; v, 1, vl, dl2	0	0	1	ne	ne	ne	ne	ne
V. Postencephalitic (?) Parkinsonism + Morbus Pick (temporal type)														
64-339/68 peP	0	0	0	0	4	o: ne; c, L: dif4–5; m3 c, R: dif4–5; mv, m3–4	0	0	1					
VI. Multiple sclerosis + paralysis agitans														
65-88/68 Ms	0	0	0	0	3–4	o, R: m, v1; o, L: v1–2; c, L: m, vm4–5; vl3, c, R: m, vm4 vl2; d, l1	2	0	1					
VII. Pallido-nigral degeneration + subcortical argyrophilic dystrophy										chemically				
66-132/67 ?	0	0	0	4, BL pe, pm	4	o, BL: v5; m, d, l4; c, L: v5 m, d, l, dl3; c, R: v4; m, dl3	0	2	2	analysed				
VIII. Striato-nigral degeneration														
67-248/65 Pa	0	4, BL	0	3, BL pe, pi	4	o, BL: m4; v4; d, dl2 c, L: v, vl4–5; vm, m, dl4, l2 c, R: v, vl4–5; m, vm, l, dl3, d1	2	0	1					
68-228/67 Pa	0	4, BL	0 BL, pe, pi	2–3	3–4	o, BL: m, v4–5; c, BL: v5 vm, l, dl4; m1	1	0	2					
IX. Manganese encephalopathy														
69-189/63 MnE	0 gliosis	1, BL	0 gliosis	1, BL	3	o: ne; c, BL: m4–5; vl, 13 v, dl1	1	0	1	0.35	0.04	ne	ne	ne

For explanation of abbreviations, see Table 1.

compacta. Therefore, the diagnosis of a "senile" Parkinsonism on the basis of excessive ageing (Seitelberger 1966) was made. In Case 62, a marked degree of Parkinsonian symptomatology was accompanied by a rather mild diffuse reduction of nigral cells without any other brain changes.

Four cases (Cases 63, 66, 67 and 68) displayed the clinical picture of a predominantly *akinetic* Parkinsonism. One of these (Case 63) showed a spotty nigral degeneration typical of paralysis agitans combined with a clinically latent olivo-ponto-cerebellar atrophy (Jellinger and Tarnowska-Dziduszko 1971). Case 66 was morphologically a pallido-nigral degeneration with pronounced subcortical argyrophilic dystrophy (Seitelberger 1969), *i.e.* numerous neurofibrillary changes in the subthalamic nucleus, substantia nigra and the brain stem tegmentum, thus displaying analogies to a "heterogenic system degeneration" (Steele, Richardson and Olszewski 1964). The 2 other brains (Cases 67 and 68) showed the morphological picture of "striato-nigral degeneration" (Jellinger and Danielczyk 1968).

Case 65 represented a combination of multiple sclerosis and nigral damage, the latter being analogous to that seen in paralysis agitans; clinically only mild Parkinsonian symptomatology was apparent. Case 64 was that of a 56-year-old female who developed, 13 years following a severe episode of malaria, a rigid-akinetic form of Parkinsonism and severe organic dementia; the morphological examination disclosed a combination of Pick's atrophy (temporal type) with a severe diffuse nigral degeneration reminiscent of that of postencephalitic Parkinsonism (Neumayer 1971).

Chronic manganese encephalopathy was diagnosed in Case 69. This was a 67-year-old female who, in her mid-thirties, was exposed to manganese dioxyde when working for several years in a battery factory. Twenty-three years before death she developed progressive tremor and, later, rigidity and akinesia. About 10 years after giving up this work, the levels of manganese in her blood and urine were found to be 10 times higher than normal. The patient died with the clinical picture of a rigid-akinetic Parkinsonian syndrome. Morphological examination revealed generalized astroglial proliferation with a preference for certain cortical areas, and the putamen, pallidum and red nucleus; this was associated with a mild degree of pallidal atrophy and marked spotty degeneration in the zona compacta of the substantia nigra with occasional Lewy bodies in nigral neurons. Thus, this case was morphologically similar to the manganese encephalopathy described in man (Stadler 1936) and experimental animals (Pentschew, Ebner and Kovatch 1963).

Group V. Huntington's chorea

This group included 14 cases (12 females, 2 males). The age of the patients at death ranged from 54 to 75 years (mean: 65.6 ± 2.1). Clinically all cases showed a typical picture characterized by choreifom movements with or without progressive dementia. Histological examination of 4 cases (Table 6) revealed severe atrophy of the caudate nuclei and putamen with loss of small neurons and marked gliosis. The lateral pallidum showed conspicuous atrophy in 1, and slight shrinkage in the remaining 3 cases. The substantia nigra was examined in 3 cases (Cases 71, 72 and 73), 1 of which (Case 72) showed a very mild degree of diffuse nerve cell loss and gliosis; in the 2 other cases no changes could be detected.

TABLE 6

HUNTINGTON'S CHOREA. MORPHOLOGICAL AND BIOCHEMICAL DATA

Case no. Prot. no.	*Cl. Diag. Dur. illn.*	*Putamen*		*Caudate*		*Pallidum*		*Substantia nigra*			*Dopamine (μg/g)*			*Homovanillic acid (μg/g)*			
								z. comp.		*z. ret.*							
Age (years), Sex		*Ec*	*At*	*Ec*	*At*	*Ec*	*At*	*les*	*Gls*	*Nad*	*Caud*	*Put*	*Nigra*	*Caud*	*Put*	*Pall*	*Nigra*
70-52/64 ?f	ChH, ?	0	3, BL	0	3, BL	0	2–3 pe, pm	ne	ne	ne	0.64	2.65	ne	0.55	2.55	1.95	ne
71-36/65 59 f	ChH, 24	0	3, BL	0	4, BL	0	1, pe	0	0	ne	1.19	2.03	1.07	1.55	2.87	1.42	ne
72-73/66 54 f	ChH, 10	0	4, BL	0	4, BL	0	1, pe	1	+−	1	1.34	2.15	ne	1.61	1.85	1.42	ne
73-104/ 66, 66 f	ChH, 19	0	2–3 BL	0	2–3	0	±, pe	0	0	2	1.56	2.43	ne	2.11	3.75	1.75	2.58
74-29/64 71 f	ChH, ?	histologically not examined									1.11	1.90	ne	1.34	2.81	2.53	1.87
75-39/64 57 f	ChH, ?										2.95	4.98	ne	2.51	6.06	3.05	1.81
76-Ch1 67 f	ChH, ?										1.28	1.82	ne	ne	ne	ne	ne
77-Ch3 72 f	ChH, ?										1.94	4.34	0.38	ne	ne	ne	ne
78-CH_4 72 f	ChH, ?										1.73	2.95	ne	ne	ne	ne	ne
79-Ch5 57 f	ChH, ?										1.85	ne	0.36	ne	ne	ne	ne
80-9/65 67 f	ChH, ?										ne	ne	0.25	ne	ne	ne	ne
81-3/65 75 f	ChH, ?										ne	ne	0.51	ne	ne	ne	ne
82-30/63 ?m	ChH, ?										ne	1.83	ne	5.11	6.88	ne	ne
83-ChO 71 m	ChH, ?										1.56	2.71	ne	2.80	4.30	ne	ne

For explanation of abbreviations, see Table 1.

TABLE 7

SUMMARY OF BIOCHEMICAL DATA

Mean values for DA and HVA in controls and cases with Parkinsonism and Huntington's chorea

	Dopamine[a] *(mean in μg/g ± S.E.M.)*			*Homovanillic acid*[a] *(mean in μg/g ± S.E.M.)*			
	caudate nucleus	*putamen*	*substantia nigra*	*caudate nucleus*	*putamen*	*pallidum*	*substantia nigra*
Controls	2.64 ± 0.30(28)	3.44 ± 0.29(28)	0.49 ± 0.09(5)	3.23 ± 0.27(8)	4.29 ± 0.68(8)	2.12 ± 0.27(8)	1.79 ± 0.18(5)
Postencephalitic Parkinsonism (peP,-group I)	0.04 ± 0.02(6)	0.02 ± 0.01(6)	ne[b]	0.29 ± 0.17(6)	0.38 ± 0.18(6)	0.24 ± 0.05(6)	ne
Idiopathic Parkinsonism (paralysis agitans) (Pa,-group II)	0.43 ± 0.09(13)	0.04 ± 0.01(13)	ne	1.05 ± 0.16(13)	0.89 ± 0.12(13)	0.77 ± 0.12(12)	ne
"Arteriosclerotic"-senile Parkinsonism (asP,-group III)	0.85 ± 0.26(5)	0.51 ± 0.28(5)	ne	1.93 ± 0.49(5)	1.88 ± 0.40(5)	1.48 ± 0.42(4)	ne
Huntington's Chorea (ChH,-group V)	1.56 ± 0.20(10)	2.71 ± 0.35(10)	0.51 ± 0.15(5)	2.02 ± 0.48(8)	3.88 ± 0.63(8)	2.02 ± 0.27(6)	2.09 ± 0.25(3)

[a] Number of cases in parentheses.

[b] For explanation of abbreviations, see Table 1.

Biochemical Observations

The results of the biochemical analyses are shown in Tables 2–8. Table 9 shows the behaviour of DA, noradrenaline and serotonin in the nuclei of the basal ganglia, the hypothalamus and the reticular formation (floor of the IVth ventricle) in chronic manganese encephalopathy with Parkinsonian symptomatology (Case 69, see also Table 5).

Groups I, II and III. Postencephalitic Parkinsonism, paralysis agitans and "arteriosclerotic"-senile Parkinsonism

In these 3 clinically and morphologically well-defined groups of Parkinsonism a definite disturbance of DA metabolism in the caudate nucleus, putamen and pallidum was apparent. In general, the degree of the changes, that is reduction in DA levels, was related to the different forms of Parkinsonism: group I (postencephalitic) showed the most severe, and Group III ("arteriosclerotic"-senile) the mildest reduction in the concentrations of DA and HVA; the values for Group II (paralysis agitans) ranged between those for groups I and III (Tables 2–5; Table 7). In detail, the biochemical analyses gave the following results (Table 8).

TABLE 8

COMPARATIVE STATISTICAL EVALUATION OF THE BIOCHEMICAL DATA

Differences between groups "P levels"	*Caudate nucleus*		*Putamen*		*Pallidum*
	DA	*HVA*	*DA*	*HVA*	*HVA*
Controls–peP (I)	<1%	<1%	<1%	<1%	<1%
Controls–Pa (II)	<1%	<1%	<1%	<1%	<1%
Controls–asP (III)	<1%	<5%	<1%	<1%	ns
Controls–ChH (V)	<2%	<5%	ns	ns	ns
peP (I)–Pa (II)	ns	ns	ns	ns	ns
peP (I)–asP (III)	ns	<1%	ns	<5%	<1%
Pa (II)–asP (III)	ns	ns	ns	<5%	<5%
ChH (V)–peP (I)	<2%	<1%	<1%	<1%	<1%
ChH (V)–Pa (II)	<5%	<1%	<1%	<1%	<1%
ChH (V)–asP (III)	ns	ns	<1%	<1%	ns

For explanation of abbreviations, see Table 1.

Caudate nucleus. When compared with controls the degree of DA and HVA decrease in the caudate nucleus was statistically significant for all 3 groups of Parkinsonism. Although the chemical changes were mildest in Group III and most pronounced in Group I, with Group II having intermediate values, this apparent inter-group difference reached statistical significance only in the case of HVA when Group I and Group III were compared.

Putamen. The reduction in the concentration of DA and HVA in the putamen was statistically significant for all 3 groups of Parkinsonism. In the putamen, as was the

case in the caudate nucleus, the apparent inter-group differences did not reach statistical significance regarding DA; however, for HVA only the difference between Group I and Group II was not significant whereas the differences between Group I and Group III as well as between Group II and Group III were statistically significant at the 1 and 5% levels respectively.

Pallidum. Although the mean values for HVA in the pallidum were definitely subnormal in all 3 groups of Parkinsonism, on a statistical basis only the values for Groups I and II were significantly different from controls. The means for these 2 groups were also significantly different from each other.

Inter-regional comparison. Although in the control group, the levels of DA and HVA tended to be higher in the putamen than in the caudate nucleus, in the present material this difference was not statistically significant. In the pallidum, the concentration of HVA was significantly lower than in the putamen, but not significantly different from that in the caudate nucleus. Since in Group I the reduction of the DA concentration in both the caudate nucleus and putamen was of the same order of magnitude, the DA means in these 2 regions were again not statistically different from each other. In contrast, in Group II and Group III the reduction of DA was more pronounced in the putamen than in the caudate nucleus; for these groups, the difference between caudate and putamen reached statistical significance. In each of the 3 groups of Parkinsonism, the reduction in HVA levels in the caudate nucleus, putamen and pallidum was of about the same magnitude; therefore the HVA means for the 3 regions did not differ significantly from each other.

Group IV. Unclassified and atypical cases with Parkinsonism

Within this morphologically heterogeneous group, only 4 cases were analysed biochemically (Table 5). In all 4 cases a marked decrease in DA levels in the caudate nucleus was found; in the putamen DA levels were reduced in Cases 59, 61 and 69, but not in Case 62. In contrast to DA, the concentration of HVA showed, in those cases in which it was determined (Cases 59, 61 and 62), no significant differences from control values in any of the examined regions (caudate nucleus, putamen, pallidum).

Manganese encephalopathy. Case 69 represented a chronic manganese encephalopathy with the symptomatology of Parkinsonism.

As can be seen from Table 9, apart from a severe reduction in DA levels in the caudate nucleus, putamen and substantia nigra, there was also a distinct reduction in the concentration of noradrenaline in the hypothalamus. However, the serotonin concentrations in all areas examined remained within the range of control values; this is in contrast to the decrease in striatal serotonin (in addition to that of DA) observed in subacute poisoning produced by large doses of manganese oxide in the squirrel monkey (Neff, Barrett and Costa 1969).

Group V. Huntington's chorea

In the putamen, pallidum and substantia nigra of cases with Huntington's chorea the means for DA and HVA concentrations (Table 7) were not significantly different from the corresponding control values (Table 8). In contrast, the caudate nucleus displayed a moderate, but statistically significant reduction in the concentration of

TABLE 9

CHRONIC MANGANESE ENCEPHALOPATHY. "MANGANESE PARKINSONISM" (CASE 69). BIOCHEMICAL DATA

Brain region	*Dopamine*	*Noradrenaline (in µg/g fresh tissue)*[a]	*Serotonin*
Caudate nucleus	0.35 (2.64)	0.02 (0.07)	0.32 (0.33)
Putamen	0.04 (3.44)	0.04 (0.11)	0.44 (0.32)
Pallidum	ne[b]	ne	0.31 (0.23)
Thalamus	ne	ne	0.36 (0.26)
Hypothalamus	0.01 (0.22)	0.54 (1.29)	ne
Substantia nigra	< 0.01 (0.49)	0.10 (0.04)	ne
Floor of the 4th ventricle	ne	ne	0.38 (0.55)

[a] Control values in parentheses. (The means for controls are taken from the present study, and from: Bernheimer *et al.* 1963; Bernheimer, Birkmayer and Hornykiewicz 1961; Hornykiewicz 1963).
[b] For explanation of abbreviations, see Table 1.

both DA and HVA. Therefore, in Huntington's chorea the ratio "DA in the caudate nucleus to DA in the putamen" was shifted in favour of the putamen, where the concentration of DA was statistically higher than in the caudate nucleus; this is in clear contradistinction to the behaviour of DA in our controls and in cases with Parkinsonism (see above).

When the mean values found for the Huntington's chorea group were compared, on a statistical basis, with the values for the 3 main groups of Parkinsonism, the following result was obtained (Table 8). In the putamen, the mean values for DA and HVA in all 3 main groups of Parkinsonism were significantly lower than in the Huntington's chorea group. In the caudate nucleus, a significant difference was seen between the Huntington's chorea group and Groups I and II, but not Group III, of Parkinsonism. In the pallidum, as in the caudate nucleus, the values for HVA of groups I and II, but not of Group III of Parkinsonism, were significantly lower than the corresponding value for the Huntington's chorea group.

Morphologico-Biochemical Correlation

The results of the correlation between the morphological observations and the biochemical data have been presented diagrammatically in Figs. 4 and 5. This comparison includes DA and HVA values of all morphologically-examined cases of Groups I-V. The only parameter for this comparison was the degree of nerve cell loss in the examined nuclei (substantia nigra, pallidum, putamen); *i.e.* the clinical and/or morphological classification of the corresponding cases (Parkinsonism and its subgroups, Huntington's chorea, etc.) was not considered. Since none of the control brains was

analysed morphologically, the chemical data obtained in these cases are not included in the comparison. In this connection it is important to note that the DA and HVA values shown in Figs. 4 and 5 for zero (0) degree of nigral cell loss (see upper panels) are entirely composed of cases with Huntington's chorea. As is evident from the foregoing section (see Group V, Huntington's chorea) for the caudate nucleus,this introduces a significant error if compared with the corresponding values for our controls which can be assumed to have had an intact substantia nigra. Therefore, for the caudate nucleus these values (set in parentheses in Figs. 4 and 5) were not considered when determining the corresponding regression lines.

Dopamine

As is evident from Fig. 4, the decrease in the concentration of DA in the caudate

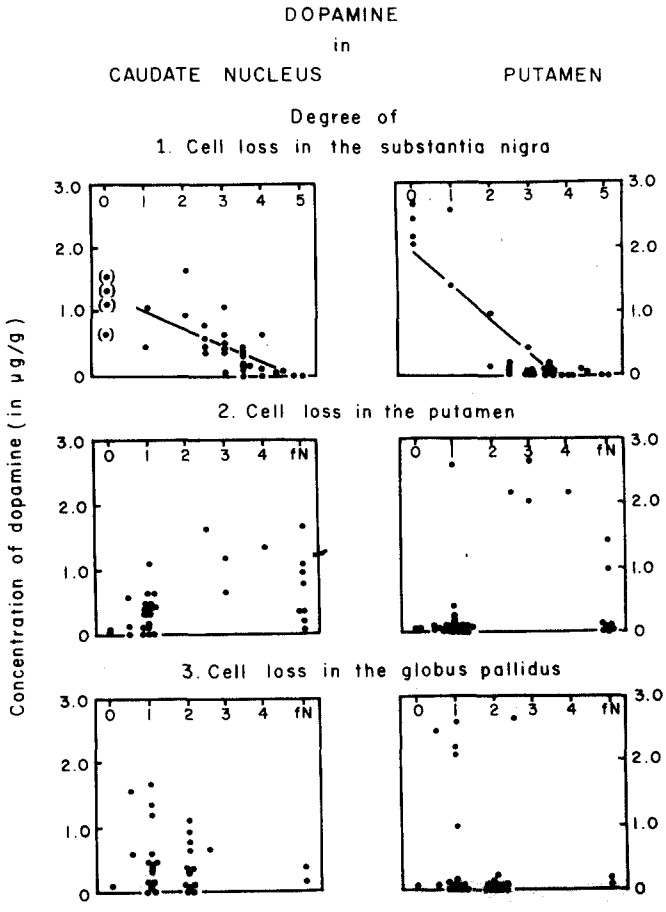

Fig. 4. Correlation between DA concentration (µg/g) in the caudate nucleus and putamen and the degree of cell loss in: (1) substantia nigra (upper panels); (2) putamen (middle panels); and (3) globus pallidus (lower panels). The correlation coefficient r, for degree of cell loss in substantia nigra and concentration of DA was for caudate nucleus: -0.671 ($n=29$, $P<0.001$); and for putamen: -0.865 ($n=33$, $P<0.001$). (The values in parentheses in the upper left hand panel have not been included in the calculation of the regression line; for explanation, see RESULTS).

nucleus and putamen showed a definite correlation with the degree of neuronal loss in the zona compacta of the substantia nigra (correlation coefficient r: caudate nucleus –0.671; putamen –0.865); this was not the case when the degree of chemical change was plotted against the degree of nerve cell loss in any of the other nuclei examined (pallidum, putamen). The figures also bear out the important fact that, when plotted against the degree of nigral cell loss, the reduction in DA levels was, with the exception of the most severe cases, more pronounced in the putamen than in the caudate nucleus (see slopes of the corresponding regression lines).

Homovanillic acid

The significant positive correlation between the decrease in HVA levels in the cau-

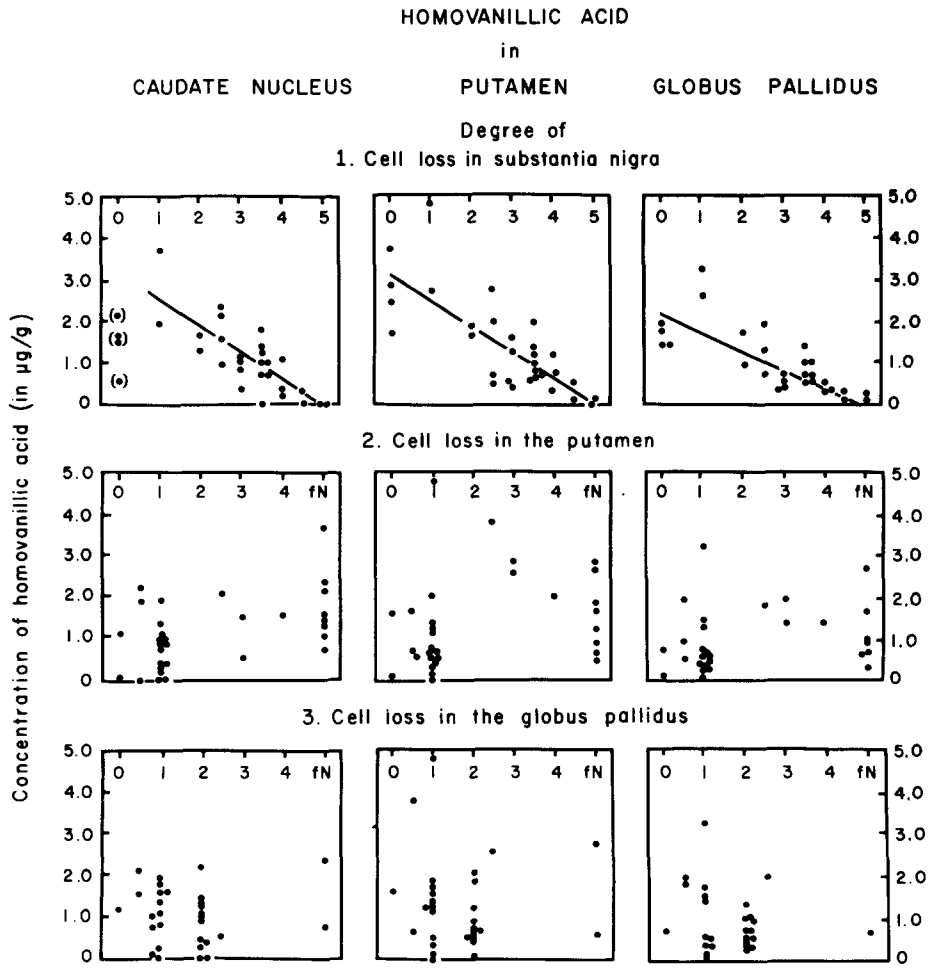

Fig. 5. Correlation between HVA concentration (µg/g) in the caudate nucleus, putamen and globus pallidus and the degree of cell loss in: (1) substantia nigra (upper panels); (2) putamen (middle panels); and (3) globus pallidus (lower panels). The correlation coefficient r, for the degree of cell loss in the substantia nigra and the concentration of HVA was for caudate nucleus: -0.790 ($n=27$, $P<0.001$); for putamen: -0.787 ($n=31$, $P<0.001$), and for globus pallidus: -0.762 ($n=29$, $P<0.001$). (The values in parentheses in the upper left hand panel have not been included in the calculation of the regression line; for explanation, see RESULTS.)

date nucleus, putamen and pallidum and the degree of neuronal loss in the substantia nigra is apparent from Fig. 5 (correlation coefficient r: caudate nucleus –0.790; putamen–0.787; pallidum–0.762). As in the case of DA, cell loss in the other nuclei of the basal ganglia did not seem to have any clear-cut effect on the concentrations of HVA in the striatum. This is illustrated by Fig. 5 for all cases examined morphologically and biochemically as well as by the results obtained specifically in cases with Huntington's chorea in which severe cell loss in the striatal nuclei was accompanied by no change (putamen, pallidum) or comparatively little (caudate nucleus) in their HVA (and DA) concentrations (Tables 6 and 7).

Clinico-Biochemical Correlations

Any attempt to correlate the degree of the chemical changes in the strio-pallidum with the clinical data has to be treated, in principle, with the same reservation. This is because the clinical methods permitted detection of only comparatively large differences in the severity of symptoms with sufficient reliability and consequently were not strictly comparable with quantitative chemical data. Keeping these obvious limitations in mind, the following interrelations between the clinical and chemical observations may be inferred.

Tremor, rigidity and akinesia versus DA and HVA levels in the strio-pallidum

In order to correlate the degree of the 3 main Parkinsonian symptoms, *i.e.* tremor, rigidity and akinesia, with the degree of DA and HVA decrease in the caudate nucleus, putamen and pallidum, we divided the Parkinsonian cases (Groups I–IV) according to the severity of their respective symptoms into 2 groups: Group A included the cases with mild symptoms (1 in Table 1), and Group B cases with marked symptoms (2 in Table 1); cases with symptoms more severe than 2 (Table 1) were not included in this comparison because (a) only a few cases were available in these categories, and (b) the disturbance of DA metabolism was, on the whole, already maximal in the patients in group B. The results are summarized in Table 10. Two aspects are noteworthy.

Degrees of DA deficiency and manifestations of Parkinsonism. From the mean values for Group A (with mild symptoms) it is quite obvious that akinesia, rigidity and tremor became clinically manifest only after the DA deficiency in the striatal nuclei reached comparatively high degrees (*e.g.* average DA decrease in the caudate nucleus: 70–80%).

Severity of symptoms and degree of regional chemical changes. Comparison between Groups A and B shows that the degree of *akinesia* was well correlated with the degree of DA and HVA decrease in the *caudate nucleus*; thus, for akinesia there was a statistically significant difference of caudate DA and HVA between Groups A and B, *i.e.* mild *versus* severe cases. There was a similar trend regarding the putamen and the pallidum; however, for these nuclei the differences in the chemical changes between mild and severe cases were not significant. Contrary to akinesia, the degree of *tremor* was best paralleled by the degree of HVA decrease in the *pallidum*. This is borne out by the fact that the difference between Group A and Group B was significant at the

TABLE 10

CORRELATION BETWEEN THE SEVERITY OF AKINESIA, TREMOR AND RIGIDITY AND THE DECREASE IN DA AND HVA IN THE STRIO-PALLIDUM

Figures represent means in μg/g ± S.E.M. Number of cases in parentheses.

	Severity of					
	akinesia		*tremor*		*rigidity*	
	1 (mild)	*2 (marked)*	*1 (mild)*	*2 (marked)*	*1 (mild)*	*2 (marked)*
Patient group:	*A*	*B*	*A*	*B*	*A*	*B*
Caudate nucleus						
DA	0.58 ± 0.12(13)	0.22 ± 0.08(9)[b]	0.53 ± 0.14(7)	0.55 ± 0.11(14)	0.74 ± 0.19(5)	0.43 ± 0.11(14)
HVA	1.68 ± 0.25(12)	0.59 ± 0.18(7)[c]	1.68 ± 0.35(7)	1.26 ± 0.20(11)	1.69 ± 0.59(5)	1.03 ± 0.16(13)
Putamen						
DA	0.44 ± 0.21(13)	0.05 ± 0.02(9)	0.65 ± 0.37(7)	0.12 ± 0.07(14)	0.31 ± 0.27(5)	0.32 ± 0.19(14)
HVA	1.60 ± 0.39(12	0.83 ± 0.28(7)	2.03 ± 0.55(7)	1.07 ± 0.22(11)[d]	1.68 ± 0.50(5)	1.28 ± 0.34(13)
Pallidum						
HVA	1.30 ± 0.32(10)	0.60 ± 0.17(7)	1.71 ± 0.36(7)	0.70 ± 0.12(10)[a]	1.16 ± 0.51(4)	0.94 ± 0.27(13)

[a] Significantly different from group A ($P < 0.01$).
[b] Significantly different from group A ($P < 0.05$).
[c] Significantly different from group A ($P < 0.02$).
[d] $0.05 < P < 0.10$.

1% level for the pallidum HVA, just outside the 5% level for putamen, and clearly not significant for the caudate nucleus. There was no statistically supported correlation between the degree of *rigidity* and reduction in DA and/or HVA in the strio-pallidum, although in the caudate nucleus a trend toward such a correlation was apparent (Table 10).

Sensitivity of akinesia to levodopa versus degree of DA and HVA deficiency in the strio-pallidum

In the attempt to compare the sensitivity to levodopa (injected in a single i.v. dose) of cases with different degrees of akinesia with the degree of DA and HVA decrease in the strio-pallidum, we divided the Parkinsonian cases, for which this clinical information was available, into 2 groups: Group 1 included cases whose akinesia showed "no" or only "moderate" reaction to an acute i.v. injection of levodopa (0–1 in Table 1); group 2 consisted of cases whose akinesia showed "good" to "excellent" response (2 to 3 in Table 1) to i.v. levodopa. As can be seen in Table 11, levodopa's acute beneficial effect on akinesia was more pronounced in cases with the more severe decrease in the levels of DA and HVA in the caudate nucleus, the putamen and the pallidum. With the exception of putaminal DA, all the chemical differences between group 1 and group 2 were statistically significant.

DISCUSSION

Unlike Huntington's chorea, in Parkinson's syndrome the autochthonous nervous cell parenchyma of the caudate nucleus and putamen remains morphologically intact.

TABLE II

CORRELATION BETWEEN THE ANTI-AKINESIA EFFECT OF LEVODOPA (I.V.) AND THE DEGREE OF DA AND HVA DECREASE IN THE STRIO-PALLIDUM

Figures represent mean values in μg/g ± S.E.M. Number of cases in parentheses.

	Anti-akinesia effect of levodopa (i.v.)	
	0–1 (weak) (Group 1)	2–3 (strong) (Group 2)
Dopamine		
caudate nucleus	0.46 ± 0.11 (10)	0.02 ± 0.01 (5)[a]
putamen	0.02 ± 0.001 (10)	0.01 ± 0.01 (5)
Homovanillic acid		
caudate nucleus	0.95 ± 0.21 (10)	0.12 ± 0.07 (5)[a]
putamen	0.81 ± 0.12 (10)	0.21 ± 0.09 (5)[b]
pallidum	0.65 ± 0.07 (9)	0.21 ± 0.05 (5)[c]

[a] Significantly different from Group 1 ($P < 0.02$).
[b] Significantly different from Group 1 ($P < 0.001$).
[c] Significantly different from Group 1 ($P < 0.002$).

In contrast, the disturbance of the striatal DA metabolism must be regarded as representing an important basis for the clinical picture of the Parkinsonian syndrome. Recent studies based on morphological, chemical and electrophysiological criteria have established the existence of direct nigro-striatal connections in the mammalian brain (Dahlström and Fuxe 1964; Fuxe, Hökfelt and Nilsson 1964; Andén *et al.* 1964; Poirier and Sourkes 1965; Fuxe and Andén 1966; Hökfelt and Ungerstedt 1969; Bédard *et al.* 1969; Moore *et al.* 1971; Carpenter and Peter 1972). Experimental lesions in the ventromedial tegmental area (Poirier and Sourkes 1964, 1965), at the level of the median forebrain bundle (Patent and Poirier 1969), or at the base of the internal capsule (Bédard *et al.* 1969) are associated with a marked cell loss in the ipsilateral substantia nigra and a decreased DA concentration in the corresponding striatum. These findings support the hypothesis that the DA-containing cells in the substantia nigra mainly project to the striatum (Andén *et al.* 1964; Andén, Dahlström, Fuxe, Larsson, Olson and Ungerstedt 1966; Poirier and Sourkes 1965). Hornykiewicz (1966) has reviewed evidence which indicates that in the striatum the physiological role of DA may be that of an inhibitory substance; correspondingly he proposed that the influence normally exerted by the nigro-striatal pathway could consist in inhibiting certain striatal functions. According to this hypothesis, in Parkinsonism the striatum can be assumed as being deprived of an inhibitory dopaminergic projection (Hornykiewicz 1966; Duvoisin 1967). Several findings suggest that DA satisfies many of the criteria (McLennan 1963; Werman 1966) of a synaptic transmitter released at the terminals of the nigro-striatal fibres: (a) DA in the striatum is highly concentrated in the nerve terminals of axons arising from the substantia nigra; (b) the ultrastructural demonstration of DA sites in the basal ganglia (Wood and Runyan 1969); (c) the presence, in the striatum, of enzymes necessary for DA's synthesis and catabolism (Hornykiewicz 1972a; Lloyd and Hornykiewicz 1972); (d) the demonstration that DA and HVA respectively are released in the striatum (McLennan 1965; Portig and Vogt 1969; Riddell and Szerb, 1971; Von Voigtlander and Moore 1971 a, b) upon electrical sti-

mulation of the substantia nigra; (e) the identical actions on single striatal units of both locally applied DA and electrical stimulation of the substantia nigra (Connor 1970; York 1970); and (f) the slowly-conducting nature of fibres of the nigro-putaminal pathway, which are in all probability identical with the poorly-myelinated dopamine-containing fibres of fine caliber (Albe-Fessard, Raieva and Santiago 1967; Connor 1968, 1970; Frigyesi and Purpura 1967). In the monkey and the cat, the nigro-striatal fibres course successively in the ventromedial tegmental area (Poirier and Sourkes 1965; Poirier *et al.* 1967), the lateral hypothalamus (Parent *et al.* 1969), traverse the posterior limb of the internal capsule and the pallidum before terminating in the striatum (Bédard *et al.* 1969; Moore *et al.* 1971; Carpenter and Peter 1972). In the human brain, the characteristic distribution pattern of HVA within the internal capsule shows the lowest concentrations in the caudal parts of the posterior limb and the highest levels in the anterior limb (Hornykiewicz *et al.* 1968). Among all nuclei situated at the caudal end of the internal capsule, in Parkinsonism only the substantia nigra shows a decreased HVA content comparable with that in the striatum and pallidum (Bernheimer and Hornykiewicz 1965; Hornykiewicz and Lisch 1967; Hornykiewicz *et al.* 1968). Therefore it has been concluded that also in the human brain DA-containing fibres are present in the internal capsule running in the caudo-rostral direction to reach the striatum. Since the concentration of DA and, especially, of HVA (Tables 2–5, and 7) was found to be lowered in the pallidum in Parkinsonism, degeneration of nigro-pallidal fibres which may contain DA has also been proposed (Hornykiewicz 1966).

From our present comparative clinical, morphological and neurochemical study, in patients with diverse Parkinsonian syndromes and Huntington's chorea, the following conclusions can be drawn.

Morphologic condition of the substantia nigra and Parkinson's syndrome

The histological examination of 69 cases with clinical Parkinson's syndrome confirmed the findings of previous authors that damage to the zona compacta of the substantia nigra with loss of nerve cells and melanin as well as gliosis is characteristic of Parkinsonism (Hassler 1938; Hallervorden 1957; Earle 1968; Alvord 1968; Forno 1966, 1969). It is likely that qualitative, quantitative, and topical differences in the lesion pattern of the substantia nigra found in the various forms of Parkinsonism are due to the different aetiological factors involved. According to morphological criteria, it was possible to define 3 main groups of Parkinsonism, *viz.* the postencephalitic (Group I), idiopathic or "degenerative" (paralysis agitans; Group II), and "arteriosclerotic"-senile (Group III); to these main groups a number of unclassified and atypical Parkinsonian cases (Group IV) was added. In postencephalitic and idiopathic Parkinsonism the substantia nigra showed the picture of a simple parenchymal atrophy with glial scarring in the manner of an "atrophizing process" (Spatz 1938). However, these 2 forms of Parkinsonism could be differentiated on a quantitative basis due to different degrees and extent of nigral damage, *i.e.* severe to subtotal diffuse atrophy and gliosis in postencephalitic Parkinsonism as contrasted by less severe and focal neuronal loss in the idiopathic variety. Additional qualitative differences, such as the occurrence of Lewy bodies in idiopathic Parkinsonism or of neurofibrillary

changes in the postencephalitic condition appear to be of minor importance, since they are considered as non-specific sequelae of disorders of cytoplasmic protein synthesis. Focal vascular lesions could be found occasionally in either form. In a small number of patients with Parkinson's syndrome of advanced age, and within the scope of a severe vascular encephalopathy, lesions of clearly vascular origin were observed in the substantia nigra and frequently in other nuclei of the basal ganglia. Since in these cases no other severe nigral damage could usually be detected, the changes related to vascular lesions must be regarded as the basis of the Parkinsonian symptomatology.

In a large number of patients with Parkinsonism, the above subdivision appears to be supported also by clinical criteria, uch as differences in the onset and duration of the disease (Hoehn and Yahr 1967; Siegfried 1968) as well as the presence or absence of specific symptoms (Table 1). However, in general, a strict correlation between the duration of the disease, clinical picture, and severity of nerve cell loss in the substantia nigra could not be clearly established. Table 12 represents an attempt at summarising differences between the 3 main groups of Parkinsonism.

A number of patients with Parkinsonian symptoms (Group IV) could not be placed in any of the 3 main groups. It is known that nigral cell loss may occur with or without Parkinsonian symptomatology within the scope of many degenerative processes and system atrophies (Pick's disease; olivo-ponto-cerebellar atrophy; striato-nigral degene-

TABLE 12

CLINICAL, MORPHOLOGICAL AND BIOCHEMICAL DIFFERENTIATION OF THE PARKINSONIAN SYNDROMES. A SYNOPSIS

	Post-encephalitic	*Idiopathic*	*"Arteriosclerotic"-senile*
Clinical criteria			
onset of illness (age in years)	42.3±5.5	58.9±1.6	74.7±3.6
duration of illness (years)	20.6±3.7	9.3±0.9	2.7±0.16
history of encephalitis	+[a]	−	−
akinesia, rigidity, tremor	+	+	+
oculogyric crises, sebo-sialorrhea	+	−	−
other neurological symptoms	rarely +	rarely +	+
mental depression	+	occasionally +	rare
dementia, mental confusion	−	+	+
anti-akinetic effect of levodopa	+	±	?
Morphological criteria			
cell loss in substantia nigra	diffuse loss	focal loss	focal necroses
Lewy bodies	usually −	usually +	rarely +
Alzheimer tangles	usually +	usually −	usually −
cell loss in pallidum	variable	variable	vascular lesions frequent
other lesions	frequent	rare	vascular lesions possible
Biochemical changes			
DA caudate	−>98%	−84%	−68%
putamen	−>99%	−98%	−85%
HVA caudate	−91%	−68%	−40%
putamen	−91%	−79%	−56%
pallidum	−89%	−63%	−30%

[a] +: present; −: absent.

ration, *etc.*), and in many other diseases of the CNS. Frequently these atypical forms manifest themselves as "akinetic" Parkinsonism (Duvoisin *et al.* 1966; Jellinger and Danielczyk 1968; Andrews, Terry and Spataro 1970) but do not necessarily show clinical deviations from "typical" forms. For the time being, their nosological classification must remain open (Sharpe, Rewcastle, Lloyd, Hornykiewicz, Hill and Tasker 1973).

Correlation between substantia nigra damage and DA decrease in the corpus striatum

Earlier studies on the human brain and in experimental animals furnished some suggestive evidence for the existence of a correlation between the degree of damage to the zona compacta of the substantia nigra and the disturbance of DA metabolism in the corpus striatum (Hornykiewicz 1963). Such a correlation has also been postulated on the basis of experimental findings (Andén *et al.* 1964; Poirier and Sourkes 1965; Poirier *et al.* 1967; Sharman, Poirier, Murphy and Sourkes 1967; Goldstein *et al.* 1969; Faull and Laverty 1969; Moore *et al.* 1971). The results of the present study demonstrate that there does exist a *definite correlation between the degree of nigral nerve cell loss and the degree of chemical changes in the striatum* (Figs. 4 and 5). This correlation was significant for both striatal DA and HVA. It is noteworthy, however, that in general the decrease in HVA in the strio-pallidum was distinctly less pronounced than that of DA, a difference which was the more apparent the milder the cases were. The fact that in Parkinsonism DA decreases, in general, to a larger extent than HVA, is reflected in the shifting of the ratio "DA : HVA" in favour of HVA; in controls this ratio is close to unity (Bernheimer and Hornykiewicz 1965). In order to explain this differential behaviour of DA and HVA in the Parkinsonian striatum it has been proposed that (a) in Parkinson's syndrome there might exist, apart from the degeneration of the nigro-striatal DA neurons, an additional decrease in the ability of striatal structures to store DA (Bernheimer and Hornykiewicz 1965) and (b) significant loss of the nigro-striatal DA neurons may lead to a compensatory overactivity of the neurons that are still intact, thus increasing the turnover of the amine in these neurons with the result of a shift of the ratio "DA : HVA" in favour of the latter (Hornykiewicz 1966). This possibility has also been considered by Sharman *et al.* (1967) in order to explain the analogous behaviour of DA and HVA in the caudate nucleus of monkeys with experimental nigral lesions.

Relation between the different forms of Parkinsonism and the disturbance of DA metabolism in the strio-pallidum

Our observation that the 3 main forms of Parkinsonism (postencephalitic, idiopathic and "arteriosclerotic"-senile) differed, generally speaking, from each other biochemically is not surprising. This is so because, on the whole, the 3 forms of Parkinsonism showed morphologically fairly characteristic and consistent differences in respect to the pattern and/or degree of nigral damage, and the latter has been found to be directly related to the degree of DA deficiency in the striatum (Figs. 4 and 5). However, due to the considerable scatter between individual values within each of the groups, the apparent differences between the 3 groups of Parkinsonism in regard to their mean values were not in all cases statistically significant. Therefore, a statistically supported biochemical distinction between postencephalitic and idiopathic Parkin-

sonism cannot be made on the basis of our case material. In contrast, the existence of the rare "arteriosclerotic"-senile Parkinsonism can be postulated as a form which is clinico-morphologically as well as biochemically distinct from the other 2 main forms of Parkinsonism. The "arteriosclerotic"-senile group (Group III) differed from controls in that it had significantly lower mean values for DA and HVA in the caudate nucleus and putamen, but not in the pallidum (HVA); and it was set apart from the other 2 main forms of Parkinsonism (Groups I and II) by having significantly higher mean values for HVA, but not for DA, in all the above nuclei (Tables 7 and 8).

From the above-demonstrated interrelationships the conclusions appear justified that: (a) the only factor directly determining the degree of DA and HVA decrease in the striatum in Parkinson's syndrome is the degree of parenchymal loss in the zona compacta of the substantia nigra; and (b) the aetiology of Parkinson's syndrome is reflected by the degree of striatal DA disturbance only insofar as the latter is determined by the degree and pattern of nigral damage which, from the morphological point of view, represents a characteristic feature for each of the 3 main forms of Parkinsonism.

These conclusions are well illustrated by the results obtained in a case (Case 69) of chronic manganese poisoning with Parkinsonian symptomatology. Although this case differed aetiologically and morphologically from the cases in each of the 3 main groups, in regard to the clinical picture, severity of nigral damage, and DA decrease in the striatum and substantia nigra it was, on the whole, comparable with other Parkinsonian cases that showed a similar degree of nigral damage (Tables 5 and 9). In striato-nigral degeneration the chemical results disclosed both similarities and differences to classical Parkinson's disease (Sharpe *et al.* 1973).

Noteworthy is the fact that in idiopathic Parkinsonism the DA deficiency was usually distinctly more severe in the putamen than in the caudate nucleus. (A similar observation has recently been reported by Fahn, Libsch and Cutler (1971) in 2 cases with Parkinson's disease.) This difference between the putamen and the caudate nucleus was even apparent in cases with comparatively low degrees of nigral degeneration. It is conceivable that this behaviour indicates: (a) a characteristic somatotopic organization of the substantia nigra and the nigro-striatal fibre system respectively; and (b) that in Parkinsonism or some of its subforms (see below) the nigral parts projecting to the putamen are affected particularly strongly and early in the course of the disease. Recent studies provided both anatomical and chemical evidence that the nigro-striatal DA fibres establish a topographic relationship between the corresponding regions of the substantia nigra and the striatum, similar to that found for the striato-nigral pathway (Nauta and Mehler 1966; Szabo 1962, 1967; Voneida 1960). Thus, rostral (oral) portions of the substantia nigra are related to the head of the caudate nucleus and the caudal two-thirds of the substantia nigra are related to the putamen and suprathalamic parts of the caudate nucleus; lateral parts of the caudal two-thirds of the substantia nigra project fibres primarily to dorsal parts of the putamen, while medial portions project to ventral regions of the putamen (Bédard *et al.* 1969; Moore *et al.* 1971; Carpenter and Peter 1972). Since the material from our present cases which was available for histological examination was limited, it was frequently impossible to make an exact evaluation of the extent of degeneration in

all portions of the substantia nigra by performing a truly quantitative determination of the nerve cell loss in this nucleus based on cell counts (either by the method of Pakkenberg and Brody (1965) or by utilizing the recently introduced "microvideomate" (Orthner, Sabuncu, Tolppanen and Friedrich 1972). However the present comparative anatomico-neurochemical findings give some support for such a topographic organization of the substantia nigra. Thus, in postencephalitic Parkinsonism the extensive diffuse atrophy of both the rostral and caudal portions of the substantia nigra and its medial and lateral parts was accompanied by a severe striatal DA deficiency which was quite similar in degree both in the caudate nucleus and the putamen (Tables 2 and 7). This is in clear contradistinction to the idiopathic and "arteriosclerotic"-senile Parkinsonism both of which show conspicuous differences in DA decrease between the caudate nucleus and the putamen (Tables 3, 4 and 7). In agreement with the literature, in our cases of idiopathic Parkinsonism the medial cell groups of the rostral portion of the substantia nigra were only slightly involved as compared to the constant and severe damage to the caudal parts of this nucleus. Since clinical signs of speech disorders occur late, if at all, in the idiopathic form, the intact medial cell groups have been assumed to subserve, in a somatotopic manner, the region of the head; based on this, the existence of a medio-lateral somatotopic organization of the substantia nigra has been postulated (Hassler 1955). Analogously, the almost constant aphonia in postencephalitic Parkinsonism can be related to the severe damage to the rostromedial cell groups of the substantia nigra which is a regular feature in this form of Parkinsonism. The above observations may, therefore, account for the lesser decrease in DA concentration in the medial or rostromedial striatum, *i.e.* the caudate nucleus in idiopathic Parkinsonism as contrasted with the postencephalitic condition. Similar considerations apply to the "arteriosclerotic"-senile form of Parkinsonism, inasmuch as the often irregularly-scattered vascular (necrotic) lesions of the substantia nigra are likely to cause degeneration of varying portions of the nigro-striatal pathway, and hence topographically variable biochemical disturbances in the striatum.

It is obvious that the quantitative differences between the caudate nucleus and putamen in regard to the degree of DA disturbance may be quite significant and may play an important role in the pathophysiology and symptomatology of Parkinson's syndrome. In a large proportion of cases with Parkinson's syndrome (especially idiopathic Parkinsonism) the DA concentration in the caudate nucleus was significantly higher than in the putamen. This "dopaminergic predominance" of the caudate nucleus may be important in view of the possible functional differentiation between the caudate nucleus and putamen as suggested by the recent electrophysiological observations made in the cat. Thus, unit activity in the caudate nucleus has been shown to be predominantly inhibited both by electrical stimulation of the substantia nigra, and DA applied directly onto the same caudate neurons (Connor 1970), whereas the activity of putaminal units was mainly facilitated by both procedures (York 1970).

Severity of clinical symptomatology, degree of DA depletion in the striatum, and sensitivity to levodopa

Our results have indicated that: (a) the 3 leading symptoms of Parkinson's syndrome (akinesia, tremor, rigidity) became clinically manifest only with a rather mar-

ked DA decrease in the striatum; (b) the severity of these symptoms (especially akinesia) was directly related to the degree of striatal DA deficiency; and (c) there was a positive correlation between the sensitivity of the patients to an acutely (i.v.) administered test dose of levodopa and the severity of their extrapyramidal symptomatology (especially akinesia) (Tables 10 and 11).

From the observation that mild, clinically just detectable cases with Parkinson's syndrome showed a marked decrease of striatal DA (Group A in Table 10), it can be assumed that lesser degrees of DA deficiency can be compensated for functionally by the striatum over longer periods of time. The possibility of such a compensatory mechanism is further supported by our biochemical observation that in the Parkinsonian striatum the ratio "DA: HVA" is markedly shifted in favour of HVA, indicating an increase in DA turnover in the still preserved nigro-striatal DA neurons. In the case of postencephalitic Parkinsonism this compensatory mechanism may play a part in the phenomenon of the frequently longer latency between the acute infection and manifestation of the clinical symptomatology (Table 1). From this the idea suggests itself that clinically manifest Parkinsonism represents the second, decompensated stage of a biochemical disturbance characterized by a progressive DA deficiency in the striatum. It is certainly striking in this context that drugs, such as reserpine, which may produce a Parkinsonian syndrome in man, cause symptoms of akinesia and rigidity in experimental animals only in doses which produce rather high degrees of depletion of striatal DA (Hornykiewicz 1972b).

Of special significance are the observations that in patients with clinically manifest Parkinsonism ("decompensated stage" of the striatal DA deficiency) the degree of akinesia and the sensitivity of the patients to the anti-akinetic effect of an acute test dose of levodopa were directly related to the degree of DA deficiency (especially in the caudate nucleus; Tables 10 and 11). It is probable that these 2 phenomena are related to each other, since degeneration of the nigro-striatal DA pathway may produce a supersensitivity of the striatal DA receptors, and the degree of this "denervation" supersensitivity might be reflected directly by the degree of the striatal DA deficiency. Thus, cases with higher DA deficiency in the striatum (and correspondingly more severe akinesia) will be expected to be more sensitive to the levodopa anti-akinesia effect than milder cases. This explanation is not necessarily incompatible with clinical observations(Barbeau, 1969; Birkmayer 1970) showing that chronic treatment of patients with Parkinson's disease with maximally tolerated daily doses of levodopa produces an optimal therapeutic response basically irrespective of the severity of the Parkinsonian condition; although denervation of a tissue may produce supersensitivity of the receptor sites it does not change, as a rule, the maximal response to the corresponding agonists.

Finally, the possibility, derived from our study, that the degree of the Parkinsonian symptoms, especially akinesia and tremor, might be correlated with the degree of disturbance of DA metabolism in the nuclei of the basal ganglia (particularly the caudate nucleus and the pallidum) deserves particular mention. Obviously the possibility of a causal relationship between these symptoms (and their severity) and regional neurochemistry is of considerable theoretical and practical importance. Our observations are in keeping with the notion that each of the main Parkinsonian (extra-

pyramidal) symptoms has its own anatomical basis within the basal ganglia. To support this possibility observations can be quoted showing that (a) therapeutic lesions of the pallidum or its thalamic projections exert a favourable effect on tremor but have, if anything, a negative effect on akinesia, and (b) of all Parkinsonian symptoms, akinesia responds most favourably and tremor least easily to levodopa. It has been shown recently that in patients with Parkinson's syndrome treated chronically with high oral doses of levodopa, the highest concentrations of DA and HVA accumulated in the striatum (Davidson, Lloyd, Dankova and Hornykiewicz 1971; Rinne, Sonninen and Hyypa 1971) depending on the time and size of the last dose of levodopa administered. (The latter facts explain why some authors reported no differences in chronically treated cases; Greer, Collins and Anton 1971.) The whole body of evidence obtained in this study supports directly the assumption that levodopa therapy represents a specific, though probably predominantly symptomatic, treatment of the main symptoms of Parkinson's syndrome.

Huntington's chorea

The observations on brain DA metabolism obtained in patients with Huntington's chorea are of particular interest for 2 reasons. First of all, they form an important basis for our conclusion, drawn primarily from the study of the Parkinsonian brains, that the DA metabolism in the striatum is dependent directly and solely on the morphological condition of the substantia nigra. Thus, the DA and HVA values in the putamen, pallidum and substantia nigra of the examined cases of Huntington's chorea were within the normal range; and the morphological assessment of 4 of the 14 chemically analyzed brains showed that in spite of severe nerve cell loss in the caudate nucleus and putamen, little change was observed in the zona compacta of the substantia nigra. This is in agreement with the literature (Hallervorden 1957; Bruyn 1968) and in contrast to Parkinson's syndrome. In addition, these observations make the possibility rather unlikely (Hornykiewicz 1964) that the striato-nigral pathway, which degenerates in Huntington's chorea as a result of the striatal damage (Vogt and Vogt 1937), is dopaminergic in nature. On the other hand, the striatal efferents to the pallidum and substantia nigra are rich in acetylcholine esterase activity; they may represent a cholinergic feed-back mechanism in a suggested striato-nigro-striatal loop by which the striatum would regulate its own content and need in dopamine (Bédard *et al.* 1969; Olivier, Parent, Simard and Poirier 1970).

The cause of the small but statistically significant reduction of DA and HVA in the caudate nucleus in Huntington's chorea needs further elucidation. It should be noted, however, that in some instances of Huntington's chorea the substantia nigra may show mild degrees of nerve cell loss and gliosis, which, if localized in the appropriate parts of the substantia nigra, could result in mild biochemical changes confined to the caudate nucleus. Thus, our Case 72 did in fact show some slight reduction of nigral cells (and gliosis).

The near normal DA values in the putamen of patients with Huntington's chorea, with caudate DA slightly but significantly subnormal, also deserve attention. Clinically Huntington's chorea represents in many ways the mirror image of Parkinsonism. In particular, the extrapyramidal symptoms of Huntington's chorea can be controlled

to a certain extent with drugs (reserpine, phenothiazines) that may cause a Parkinson-like syndrome (Hornykiewicz 1966); this suggests the existence of a functional predominance, in Huntington's chorea, of monoaminergic mechanisms within the extrapyramidal centres. In our study the striatal DA concentrations were calculated per unit weight of tissue. Since in Huntington's chorea the majority of the small striatal neurons are destroyed, there would be a decrease of receptor sites for the available amines, assuming that the small and medium spiny cells are receptors for afferent fibres (Kemp and Powell 1971). On the other hand, DA-containing nigral terminals remain by and large intact (Sluga 1966); therefore, the relation of DA concentration to the number of striatal receptor cells may be shifted in favour of DA, and this might result in a functional dopaminergic predominance, aggravating the condition due primarily to striatal cell loss. In agreement with this possibility is the clinical observation that administration of levodopa exacerbates acutely the chorea (Gerstenbrand, Pateisky and Prosenz 1963; Klawans 1970). Alternatively, the fact should be kept in mind that in Huntington's chorea the dopaminergic balance between the caudate nucleus and putamen is shifted in favour of the latter, suggesting a predominance of the putaminal dopaminergic mechanisms in this disorder. The possibility we have mentioned of a difference between the caudate nucleus and putamen with regard to the functions they may subserve assumes special significance. In fact, the putaminal dopaminergic predominance in Huntington's chorea may represent an important biochemical feature of this disorder, setting it clearly apart from both the controls and cases with Parkinson's syndrome (Bernheimer and Hornykiewicz 1973).

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SUMMARY

A clinical, morphological and neurochemical correlative study in patients with Parkinson's syndrome and Huntington's chorea is reported. In the former group of patients, 69 brains were examined morphologically and 28 biochemically; in the latter group, 4 brains were examined morphologically and 14 biochemically. The results were as follows: (1) The main morphological alteration common to all forms of Parkinsonism was damage to the substantia nigra with a loss of the melanin-containing nerve cells in the zona compacta; the degree and pattern of this cell loss varied in a manner characteristic of the different forms of Parkinsonism. (2) Neurochemically, Parkinson's syndrome was characterized by a decrease in the concentrations of dopamine (DA) and its metabolite homovanillic acid (HVA) in the striatum (caudate nucleus and putamen) and pallidum. (3) A satisfactory positive correlation could be established between the degree of cell loss in the zona compacta of the substantia nigra and the disturbance of DA metabolism in the nuclei of the basal ganglia. (4) The nosological classification of Parkinson's syndrome (based on clinical and morphological criteria) into 3 main groups, *viz.* postencephalitic, idiopathic and "arteriosclerotic"-senile, was supported by distinct, though not in all cases statistically significant, differences in the degree of disturbance of striatal DA metabolism. (5) In general, mild Parkinsonism, just manifest clinically, was associated with a disproportionately high degree of striatal DA deficiency. From this it was concluded that: (a) clinically manifest Parkinsonism represents the late, "decompensated", stage of a disease characterized by a progressive striatal DA deficiency; and (b) the striatum can compensate functionally for lower degrees of DA deficiency. (6) Positive correlations could be established, within a certain range, between the severity of individual Parkinsonian symptoms (especially akinesia and tremor) and (a) the degree, and also the site, of the disturbance of DA metabolism within the nuclei of the basal ganglia; and (b) the sensitivity of the patients to levodopa's acute anti-akinesia effect. The latter observation was interpreted as suggesting that in Parkinsonism there exists a supersensitivity (probably of the "denervation type") of striatal receptors to DA. (7) Based on the correlations, levodopa therapy can be regarded as a specific, though probably predominantly symptomatic, treatment of the main extrapyramidal symptoms of Parkinson's syndrome. (8) In Huntington's chorea the concentrations of DA and HVA in the putamen, pallidum and substantia nigra showed no significant deviation from control values; however in the caudate nucleus there was a small but statistically significant reduction in the levels of these compounds (9). The possible functional significance of the observed correlations for the pathophysiology of disorders of the basal ganglia such as the diseases of Parkinson and Huntington is discussed.

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