Parkinsonian abnormality of foot strike: a phenomenon of ageing and/or one responsive to levodopa therapy?

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1 Normally during walking, the heel strikes the ground before the forefoot. Abnormalities of foot strike in idiopathic Parkinson's disease may be amenable to therapy: objective measurements may reveal response which is not clinically apparent. Occult changes in foot strike leading to instability may parallel the normal, age-related loss of striatal dopamine.

2 The nature of foot strike was studied using pedobarography in 160 healthy volunteers, aged 15 to 91 years. Although 16% of strikes were made simultaneously by heel and forefoot, there were no instances of the forefoot preceding the heel. No significant effect of age on an index of normality of foot strikes was detected ($P > 0.3$).

3 The effect on foot strike of substituting placebo for a morning dose of a levodopa/carbidopa combination was studied in a double-blind, cross-over trial in 14 patients, aged 64 to 88 years, with no overt fluctuations in control of their idiopathic Parkinson's disease in relation to dosing. On placebo treatment there was a highly significant ($P = 0.004$) reduction in the number of more normal strikes, i.e. heel strikes plus simultaneous heel and forefoot strikes. The effect appeared unrelated to the corresponding difference between active and placebo treatments in plasma concentration of levodopa or a metabolite of long half-time, 3-*O*-methyldopa (3OMD). However, it correlated negatively ($P < 0.05$) with the mean of the 3OMD concentrations.

4 It appears that some abnormalities of foot strike due to Parkinson's disease are reversible. Employing test conditions, designed to provoke abnormalities of foot strike, might be useful in screening for pre-clinical Parkinson's disease.

Keywords Parkinsonism foot strike age levodopa

Introduction

Normally during walking, the heel strikes the ground first, followed by the forefoot. Other modes of contact, where the forefoot and heel strike simultaneously, the forefoot precedes the heel or (at worse) only forefoot and toes make any contact with the ground, may produce instability. Abnormal foot strike, especially if

associated with an irregular gait and/or other abnormalities of posture, may thus increase the risk of falling (Murray, 1967). Whilst short steps and hesitancy of gait are easily recognised Parkinsonian features, the characteristic abnormality of foot strike (Murray *et al.*, 1978) may be variable and difficult to assess clinically. The normal

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age-related deterioration of dopamine-containing cells in the substantia nigra (Calne & Langston, 1983) could, then, be associated with abnormal foot strike before the threshold for overt Parkinsonism is reached. Moreover, the increased prevalence of falling with age may, to some extent, be a consequence of increasing abnormality of foot strike. However, the reversibility of Parkinsonian abnormalities of foot strike by dopamine replacement therapy has not been documented.

We have carried out a preliminary investigation of the effect of age on the nature of foot strike, using 160 healthy volunteers aged 15 to 91 years. The nature of foot strike and its response to omission, or not, of a morning dose of levodopa/carbidopa maintenance therapy was then studied in 14 elderly patients with idiopathic Parkinson's disease.

Methods

Healthy volunteers

The nature of foot strike was assessed by pedobarography (see below) in 80 healthy volunteers of either sex, in whom there were no foot problems requiring treatment. The minimum age for recruitment was 15 years, the numbers recruited for each age grouping (Table 3) being balanced.

Patients with idiopathic Parkinson's disease

Fourteen elderly patients with idiopathic Parkinson's disease gave informed consent to participate in the study. Although a clinical response to levodopa therapy had been documented in each patient in the past, currently any overt fluctuations in their clinical state were not related to individual doses. Each had been established on an anti-Parkinsonian regimen of Sinemet Plus (Merck, Sharp and Dohme Ltd) alone. No patient was receiving any sedative, hypnotic, psychotropic or anticonvulsant drug.

No routine doses of Sinemet Plus were given after the 22.00 h dose on the night before a study day, until after the assessments had been made. Patients were allocated to receive randomly a tablet of Sinemet Plus or an identical placebo at 10.00 h, with the alternative treatment at least 3 days later. A light, low protein breakfast was given 1.5 h before a 10.00 h treatment, no other food or drinks being allowed for a similar period of time after. At 12.00 h, lying and standing blood pressure was measured and

a blood sample taken for assay of levodopa and a metabolite, 3-*O*-methyldopa (3OMD). This was followed directly by pedobarography and simultaneous video recording of gait.

Assessment of gait

(a) *Video recording* A video camera, 2 m from the patient, and at foot level, recorded movement of the lower half of the body as the patient walked past. A global assessment of gait was made from the recordings by an independent observer, blind to the order of treatments.

(b) *Pedobarography* A computerised pedobarography system was used (Duckworth *et al.*, 1982). The method is based on a simple optical principle. A thick plate of glass is lit from two opposite edges: light travels through it by total internal reflection. Where pressure is applied to a plastic sheet on top of the glass, the conditions necessary for total internal reflection are destroyed locally and light escapes, the amount being proportional to the pressure applied.

The computer is programmed to plot pressure against time for defined areas of interest. These are delineated on a display of the distribution of the highest pressures recorded from the time a foot first makes contact with the ground to when it is lifted off. In this case the areas of interest were the heel and forefoot. Examples of printouts illustrating normal and abnormal patterns of contact are shown in Figure 1.

The simple index of foot strike shown in Figure 2 was calculated. An index of one is normal, whereas an index of zero implies that the initial strike is always with the forefoot.

Biochemical methods

Plasma was separated immediately from the blood samples and stored at -20°C . Levodopa was separated from 3OMD by passing deproteinised plasma through phenylboronic acid (PBA) cassettes (Benedict & Risk, 1984). Levodopa was eluted from the PBA using perchloric acid (0.2 M) containing ethylenediamine-tetraacetic acid (0.25%). The eluates containing levodopa and those containing the 3OMD were analysed separately, using ion-pair, reversed-phase, high performance liquid chromatography with electrochemical detection.

Quantitation was achieved by calculation of the ratio of peak height to that of internal standards added to the plasma prior to extraction. The resultant peak height ratios were compared with a standard curve derived from spiked

Figure 1 The figure shows from above downwards, a normal pattern of pressure distribution during walking, that is heel strike preceding contact with the ground by the forefoot, heel and forefoot striking the ground simultaneously, forefoot and toes making contact before the heel, and only the forefoot making contact. (Orientation to the initial pedobarograph frame is given by an outline of those parts of the foot from which pressure was recorded during that foot/ground contact).

$$\frac{(\text{Number of heel strikes}) + (\text{number of simultaneous heel and forefoot strikes}/2)}{\text{Total number of steps studied}}$$

Figure 2 Foot strike index.

plasma, carried through the extraction procedure with the patient samples. The inter-assay coefficient of variation for levodopa was 7.4% at a concentration of 500 ng ml⁻¹, and for 3OMD was 2.5% at 3.0 µg ml⁻¹.

Results

Determinants of foot strike index in healthy volunteers

In none of the 954 foot strikes, recorded in the 160 healthy subjects aged 15 to 91, mean (s.d.) 50 (22) years, did the forefoot precede the heel in making contact with the ground, but 16% of all foot strikes were made simultaneously by heel and forefoot. Table 1 gives the average foot strike index according to gender and age. Abnormal foot strikes tended to be more prevalent in females than males, but the difference in foot strike index did not reach significance at the 5% level (Mann-Whitney U-test, $P = 0.105$).

Table 1 Foot strike index according to age and gender in 160 healthy volunteers. Ten subjects of each gender were studied in each of the age groupings specified below. Six foot strikes were analysed by pedobarography per person, an equal number being with the right and with the left foot. In each group there were some subjects with an index of 1, but the number varied from two (females, 30–39 years) to eight (males, 60–69, and females, 15–19 years)

Age) (years)	Average foot strike index (lowest)	
	Male	Female
15–19	0.935* (0.600)	0.958 (0.750)
20–29	0.942* (0.667)	0.904** (0.500)
30–39	0.958 (0.750)	0.802* (0.500)
40–49	0.942* (0.750)	0.925 (0.750)
50–59	0.917* (0.750)	0.908 (0.667)
60–69	0.950 (0.667)	0.950 (0.667)
70–79	0.933 (0.667)	0.917 (0.583)
> 80	0.900 (0.583)	0.867 (0.583)

* missing data on one or two (**) of six strikes in one subject

No significant effect of age on the index was detected (Spearman's rank correlation, $r_s = 0.07$, $t = 0.88$, D.F. = 158, $P > 0.3$).

Effect of Sinemet Plus on gait in Parkinsonian patients

On global assessment of the video recordings, gait was judged to be better in 10 patients, and worse in four, after active treatment as compared with after placebo: the magnitude of the differences was noted to be marginal. The apparent preference for active treatment did not reach statistical significance at the 5% level (Binomial test).

On comparison of the foot strike index, as measured by pedobarography, on active (mean 0.58) and placebo (0.44) treatments (Table 2), a significant difference was detected (Wilcoxon signed rank test, $P < 0.05$). Although the overall result favoured active treatment, this may have been due to a more favourable distribution of the number of foot strikes assessed. We, therefore, proceeded to apply Cochran's weighted test (Armitage & Berry, 1987). Using this, the proportion of normal (heel) strikes was not found to differ significantly between treatments ($P = 0.07$), but that of the sum of heel strikes alone plus simultaneous heel and forefoot strikes was found to do so ($P = 0.004$).

The treatment effect, as measured by the difference in foot strike index between active and placebo treatments, was not found to be related to age (range 64 to 88 years), Hoehn & Yahr staging of Parkinson's disease (2 to 5) or duration of levodopa therapy (6 to 178 months) (Spearman's rank correlation, $P > 0.05$ in each case). It was also not found to be related to the difference, 2 h post treatment, between active and placebo days in blood pressure, or in plasma levodopa or 3OMD concentration (Table 3). However, in contrast to levodopa, 3OMD has a sufficiently long $t_{1/2}$ (approximately 15 h, Kuruma *et al.*, 1971) for substitution of a single placebo dose during levodopa maintenance therapy to have little effect on the concentration 2 h later: a negative correlation, reaching significance only at the 5% level, was detected between the treatment effect and the mean of the 3OMD concentration on active and placebo days ($r_s = 0.59$, $t = 2.295$, d.f. = 10, $P < 0.05$).

Discussion

The 'senile disorders of gait', described by Critchley (1931) encompassed the postural abnormality and hypo/bradykinesia of the Park-

Table 2 Nature of foot strike 2 h after active and placebo treatments in 14 patients with Parkinson's disease

Patient	Order of treatments	foot strikes assessed*		Number of								Foot strike index***	
				heel strikes		simultaneous heel and toe strikes				toe strikes			
		A**	P**	A	P	A	P	A	P	A	P		
1	P/A	7	2	0	0	2	1	5	1	0.143	0.250		
2	P/A	9	10	1	0	6	3	2	7	0.444	0.150		
3	P/A	5	10	4	9	1	1	0	0	0.900	0.950		
4	A/P	3	5	0	0	2	3	1	2	0.333	0.300		
5	P/A	6	5	2	1	4	4	0	0	0.667	0.600		
6	P/A	6	6	6	5	0	0	0	1	1.000	0.833		
7	P/A	6	8	0	1	6	7	0	0	0.500	0.563		
8	A/P	6	4	1	0	4	3	1	1	0.500	0.375		
9	A/P	6	8	2	0	4	6	0	2	0.667	0.375		
10	A/P	8	6	0	0	7	4	1	2	0.438	0.333		
11	P/A	7	7	1	1	5	2	1	4	0.500	0.286		
12	A/P	1	5	1	0	0	1	0	4	1.000	0.100		
13	A/P	8	8	8	8	0	0	0	0	1.000	1.000		
14	A/P	6	6	0	0	1	1	5	5	0.083	0.083		

* Analysis of a minimum of six foot strikes (three with right foot and three with left) was the target. Patients were not always able to cross the walkway of the pedobarograph a sufficient number of times to achieve this.

** A, one tablet; Sinemet-Plus; P, one placebo

*** by pedobarography

Table 3 Characteristics of the 14 patients and their therapy

Patient	Age (years)	Hoehn & Yahr staging	Duration of levodopa therapy (months)	Difference** between active and placebo treatments in		serum concentration levodopa (ng ml ⁻¹)	3OMD (µg ml ⁻¹)	Mean 3OMD concentration (µg ml ⁻¹)
				mean arterial BP***	postural fall			
				standing (mm Hg)	(mm Hg)			
1	81	5	78	-5.7	10.3	56	-0.8	7.4
2*	81	3	10	-4.0	-9.4	112	2.9	4.0
3	79	3	20	12.7	20.4	564	1.3	6.5
4	88	4	12	-21.3	-7.9	325	-0.3	3.9
5*	80	4	107	0.5	-13.1	123	1.1	6.3
6	76	2	95	-26.3	-7.6	244	1.6	5.4
7	77	4	100	-3.3	17.3	217	-0.8	6.0
8*	83	5	178	-32.0	-7.0	345	—	—
9	80	3	26	2.3	-7.7	592	0.2	2.7
10	75	3	6	-2.7	-19.4	756	0.0	5.1
11*	75	3	11	0.6	9.3	432	-0.1	3.0
12	74	4	22	-25.3	-34.7	342	0.1	4.9
13*	66	2	8	-6.7	-12.1	—	—	—
14*	64	2	36	-0.6	-13.3	288	0.3	3.2

* male

** 2 h after administration of treatment

*** Blood pressure

insonian syndrome and a broad-based gait. It is not clear whether what he described is a conglomerate of several distinct neurological gait disturbances, a manifestation of multiple pathologies, each insignificant in its own right, or a final common pathway, perhaps not only of discrete neurological, but also of musculoskeletal and psychiatric (e.g. dementia and depression) disorders of gait (Koller *et al.*, 1985;

Nutt, 1988). Assuming that idiopathic Parkinson's disease is an important component of senile disorders of gait, then its prophylaxis and treatment could be of benefit in reducing falls and fractures in old age.

Work on 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced Parkinsonism suggests that inhibitors of the B monoamine oxidase may help in halting the damaging effects

of a trigger event or preventing the effects of further, or continuing, insults. The success of such treatment may lie, however, in early detection of those with reversible damage, or with irreversible damage for which compensation can still be made (Jenner & Marsden, 1988). We suggest that increasing abnormality of foot strike may be a marker of pre-clinical Parkinsonism in the elderly. In our normal volunteers, simultaneous heel and forefoot strike was found to be common in all age groups, and is probably of multiple aetiology in the general population. Although strikes with the forefoot alone were not uncommon in Parkinsonian patients, none was seen in the volunteers, even in those of more than 80 years of age. A more provocative test, such as walking through a doorway or along a narrow corridor, may be as useful in inducing forefoot strike in those with pre-clinical Parkinsonism as it is in inducing hypokinesia where the syndrome is overt (Klenerman *et al.*, 1988).

In a previous study in healthy volunteers, Newman *et al.* (1985) measured the effect of levodopa on reaction time, tremor, visually evoked potentials and blink rate in 10 subjects aged 59 to 72 years. Despite the use of a placebo-controlled, cross-over design and total daily maintenance doses of 400 to 800 mg of levodopa, in combination with carbidopa, for 6 weeks, they were unable to demonstrate any treatment effect. It would have been more appropriate to test 'reversibility' had healthy volunteers been selected for test results outside a reference range, and towards or within the range associated with Parkinson's disease. We do recognise, however, that older subjects who participate in laboratory tests are always likely to be the more outgoing and physically and mentally fit.

In the early stages of idiopathic Parkinson's disease, the only abnormality of posture is said to be the protruding head but, as the disease progresses, kyphosis of the thoracic spine, adduction in flexion of the hips and shoulders, flexion of the knees and elbows and shortening of the calf muscles may become apparent (Franklyn, 1986). With these changes in posture, the progressive changes illustrated in Figure 3, from the normal 'heel-toe' gait through a 'flat-footed' and a 'toe-heel' gait or a gait with forefoot strike only, might be expected. However, it is interesting to note that there was no relationship between severity of Parkinson's disease, according to the Hoehn and Yahr staging, and the foot strike index, either on active or placebo treatments, in the small sample of patients studied (Spearman's rank correlation, $P > 0.05$ in each case). Indeed, patient 14, whose posture

appeared normal, had the most abnormal foot strike, there being five forefoot strikes to one simultaneously with heel and forefoot.

No account was taken of potential determinants of the nature of foot strike, such as free walking speed and swing length. A group of 14 patients was selected in whom there were no overt fluctuations in control of their Parkinson's disease in relation to dosing with the levodopa/carbidopa combination. Nevertheless, in this pilot study, we were able to detect a highly significant ($P = 0.004$) effect on foot strike of substituting placebo for the morning dose of levodopa. Moreover, the more important component of this response to the placebo seemed to be an increase in the proportion of forefoot strikes, rather than in the less serious abnormality of simultaneous heel and forefoot strikes. On the surface this is surprising, since of the four cardinal signs of Parkinsonism, bradycardia, tremor, rigidity and postural abnormality, it is the first, and certainly not the last, which is said to be particularly responsive to levodopa therapy (Cotzias *et al.*, 1969). However, for Parkinsonism to be diagnosed at least two of the four signs

Figure 3 Normal posture (top) as compared with changes seen in Parkinson's disease (below).

must be present: the interrelationship of these signs in producing what are generally regarded as postural abnormalities of foot strike is ill defined. Our results need to be confirmed in a larger group of patients with a more comprehensive protocol, addressing such interrelationships. Repetition of the treatments on separate occasions in the same individuals may not have given confirmatory evidence. Having to step onto the demarkated pressure sensitive area may have provoked the abnormality initially: over familiarity might lead to extinction of any treatment effect.

Fluctuations in control, as described above, may be important functionally: poor balance and falls might occur as an end of dose effect. This could be an argument for frequent dosing with levodopa or use of a controlled release formulation even in those without clinically overt fluctuations in relation to dosing. Plasma levodopa concentrations have, of course, been related to performance within individuals with 'on-off' fluctuations (Fahn, 1974; Sweet & McDowell, 1974; Shoulson *et al.*, 1975; Tolosa *et al.*, 1975; Eriksson *et al.*, 1984), who, presumably, have loss of storage capacity for dopamine in the striatum (Leenders *et al.*, 1986). Moreover, Rossor *et al.* (1980) in a placebo controlled, cross-over study, using levodopa without a decarboxylase inhibitor, were able to find a correlation between plasma dopamine concentrations and response in patients defined as not suffering from rapid swings in performance. In our patient group, no correlation was detected between the magnitude of the 2 h treatment effect and the corresponding difference in levodopa concentrations between active and placebo days, despite a more

than thirteen fold variation between patients in the latter. Rinne *et al.* (1973), Hare *et al.* (1973) and Pilling *et al.* (1975) were also unable to find any between patient relationship of plasma levodopa concentrations to response, and no therapeutic range has been established.

Is, then, the state of destruction of relevant neuronal systems the major determinant of response to levodopa therapy, or are there potentially reversible factors? In our patients, the treatment effect appeared to be unrelated to the age of the sufferer, the severity of the disease, or the duration of levodopa therapy. However, there appeared to be a negative correlation between the treatment effect and the plasma concentration of 3OMD, a metabolite with a relatively long half-time. This finding is in agreement with those of Meunter (1972) and Rivera-Calimlim (1977), and consistent with the temporary increase in responsiveness produced by a drug holiday (Direnfeld *et al.*, 1978; Lee *et al.*, 1978; Weiner, 1979). As regards a potential mechanism for the deleterious effect of high concentrations of 3OMD, Wade & Katzman (1975) have demonstrated competition between levodopa and 3OMD for transport into the brain by the large, neutral amino acid carrier system. Substitution of a dopamine agonist, which is not subject to the same metabolic and uptake processes, would seem to be a solution, but the role of these agents in the management of Parkinson's disease 'has not yet been fully defined' (Jankovic & Marsden, 1988).

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References

- Armitage, P. & Berry, G. (1987). In *Statistical methods in medical research*, pp. 380–383. Oxford, London, Edinburgh: Blackwell Scientific Publications.
- Benedict, C. R. & Risk, M. (1984). Determination of urinary and plasma dihydroxyphenylalanine by coupled-column high-performance liquid chromatography with C8 and C18 stationary phases. *J. Chromatogr.*, **317**, 27–34.
- Calne, D. B. & Langston, J. W. (1983). Aetiology of Parkinson's disease. *Lancet*, **ii**, 1457–1459.
- Cotzias, C. G., Papavasiliou, P. S. & Gellere, R. (1969). Modification of Parkinsonism—Chronic treatment with L-dopa. *New Engl. J. Med.*, **28**, 337–345.
- Critchley, M. (1931). The neurology of old age. *Lancet*, **i**, 1221–1230.
- Direnfeld, L., Spero, L., Marotha, J. & Seeman, P. (1978). The L-dopa 'on-off' effect in Parkinson's disease: treatment by transient drug withdrawal and dopamine receptor resensitization. *Ann. Neurol.*, **4**, 573–575.
- Duckworth, T., Betts, R. P., Franks, C. I. & Burke, J. (1982). The measurement of pressures under the foot. *Foot and Ankle*, **3**, 130–141.
- Eriksson, T., Magnusson, T., Carlsson, A., Linde, A. & Granerus, A. K. (1984). 'On-off' phenomenon in Parkinson's disease: correlation to the concentration of dopa in the plasma. *J. Neurol. Transm.*, **59**, 229–240.
- Fahn, S. (1974). 'On-off' phenomenon with levodopa therapy in Parkinsonism. *Neurology*, **24**, 431–441.
- Franklyn, S. (1986). Parkinsonism—Management. In *Cash's Textbook of Neurology for Physiotherapists*, ed. Downie, P. A., pp. 426–434. London, Boston: Faber & Faber.
- Hare, T. A., Beasley, B. L., Chambers, R. A.,

- Boehme, D. H. & Vogel, W. H. (1973). Dopa and amino acid levels in plasma and cerebrospinal fluid of patients with Parkinson's disease before and during treatment with L-dopa. *Clin. Chim. Acta*, **45**, 273–280.
- Jankovic, J. & Marsden, C. D. (1988). Therapeutic strategies in Parkinson's disease. In *Parkinson's disease and movement disorders*, eds Jankovic, J. & Tolosa, E., pp. 95–120. Baltimore-Munich: Urban & Schwarzenberg.
- Jenner, P. & Marsden, D. (1988). MPTP induced Parkinsonism as an experimental model of Parkinson's disease. In *Parkinson's disease and movement disorders*, eds Jankovic, J. & Tolosa, E., pp. 37–48. Baltimore-Munich: Urban & Schwarzenberg.
- Klennerman, L., Dobbs, R. J., Weller, C., Leeman, A. L. & Nicholson, P. W. (1988). Bringing gait analysis out of the laboratory and into the clinic. *Age and Ageing*, **17**, 397–400.
- Koller, W. C. (1985). Senile gait. A distinct neurologic entity. *Clinics in Geriatric Medicine*, **1**, 661–669.
- Kuruma, I., Bartholini, G., Tissot, R. & Pletscher, A. (1971). The metabolism of L-3-O-methyldopa, a precursor of dopa in man. *Clin. Pharmac. Ther.*, **12**, 678–682.
- Lee, T., Seeman, P., Rajput, A., Farley, I. J. & Hornykiewicz, O. (1978). Receptor basis of dopaminergic supersensitivity in Parkinson's disease. *Nature*, **273**, 59–61.
- Leenders, K. L., Palmer, A. J., Quinn, N., Clark, J. C., Firnau, G., Garnett, E. S., Nahmias, C., Jones, T. & Marsden, C. D. (1986). Brain dopamine metabolism in patients with Parkinson's disease measured with positron emission tomography. *J. Neurol. Neurosurg. Psychiatr.*, **49**, 853–860.
- Meunter, M. D., Sharpless, N. S. & Tyce, G. M. (1972). Plasma 3-O-methyldopa in L-dopa therapy of Parkinson's disease. *Mayo Clinic Proc.*, **47**, 389–395.
- Murray, M. P. (1967). Gait as a total pattern of movement. *Am. J. physical Med.*, **46**, 290–333.
- Murray, M. P., Sepic, S. B., Gardner, G. M., Downs, W. J. (1978). Walking patterns of men with Parkinsonism. *Am. J. physical Med.*, **57**, 278–294.
- Newman, R. P., LeWitt, P. A., Jaffe, M., Calne, D. M. & Larson, T. A. (1985). Motor function in the normal ageing population: treatment with levodopa. *Neurology*, **35**, 571–573.
- Nutt, J. G. (1988). Gait disorders. In *Parkinson's disease and movement disorders*, eds Jankovic, J. & Tolosa, E., pp. 377–384. Baltimore-Munich: Urban & Schwarzenberg.
- Pilling, J. B., Baker, J., Iversen, L. L., Iversen, S. D. & Robbins, T. (1975). Plasma concentrations of L-dopa and 3-methoxydopa and improvement in clinical ratings and motor performance in patients with Parkinsonism treated with L-dopa alone or in combination with amantadine. *J. Neurol. Neurosurg. Psychiatr.*, **38**, 129–135.
- Rinne, U. K., Sonninen, V. & Sirtola, T. (1973). Plasma concentrations of levodopa in patients with Parkinson's disease—Response to administration of levodopa alone or combined with a decarboxylase inhibitor and clinical correlations. *Eur. Neurol.*, **10**, 301–310.
- Rivera-Calimlim, L., Tandon, D., Anderson, F. & Joynt, R. (1977). The clinical picture and plasma levodopa metabolite profile of Parkinsonian non-responders. Treatment with levodopa and decarboxylase inhibitor. *Arch. Neurol.*, **34**, 228–232.
- Rossor, M. N., Watkins, J., Brown, M. J., Reid, J. L. & Dollery, C. T. (1980). Plasma levodopa, dopamine and therapeutic response following levodopa therapy of Parkinsonian patients. *J. neurol. Sci.*, **46**, 385–392.
- Shoulson, I., Glaubiger, G. A. & Chase, T. N. (1975). On-off response clinical and biochemical correlations during oral and intravenous levodopa administration in Parkinsonian patients. *Neurology*, **25**, 1144–1148.
- Sweet, R. D. & McDowell, F. H. (1974). Plasma dopa concentrations and the 'on-off' effect after chronic treatment of Parkinson's disease. *Neurology*, **24**, 953–956.
- Tolosa, E. S., Martin, W. E., Cohen, H. P. & Jacobson, R. L. (1975). Patterns of clinical response and plasma dopa levels in Parkinson's disease. *Neurology*, **25**, 177–183.
- Wade, L. A. & Katzman, R. (1975). 3-O-methyldopa uptake and inhibition of L-dopa at the blood brain-barrier. *Life Sci.*, **17**, 131–136.
- Weiner, W. J., Koller, W. C., Perlik, S., Nausieda, P. A. & Klawans, H. L. (1980). Drug holiday and management of Parkinson's disease. *Neurology*, **30**, 1257–1261.

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