Bromocriptine treatment in Parkinson's disease

J. D. PARKES, C. D. MARSDEN, I. DONALDSON, A. GALEA-DEBONO,
J. WALTERS, G. KENNEDY, AND P. ASSELMAN

*From the University Department of Neurology, The Institute of
Psychiatry, and King's College Hospital, London*

SYNOPSIS Thirty-one patients with Parkinson's disease were treated with the ergot alkaloid bromocriptine, a drug which stimulates dopamine receptors. Bromocriptine had a slight therapeutic effect in patients on no other treatment and an additional effect in patients on levodopa. The mean optimum dosage of bromocriptine, established over a 12 week period, was 26 mg daily. In 20 patients bromocriptine was compared with placebo in a double-blind controlled trial. Active treatment caused a significant ($P < 0.02$) reduction in total disability and akinesia scores. The least disabled patients showed the greatest response. Side-effects of bromocriptine—nausea, vomiting, hallucinations, and abnormal involuntary movements—were similar in nature to those of levodopa. In most normal subjects, bromocriptine causes an increase in plasma growth hormone concentration. This was determined in 20 patients with Parkinson's disease after 1–15 mg bromocriptine. Only a single patient showed an obvious increase up to 120 minutes after dosage. Bromocriptine was not an effective treatment in two patients who had not previously responded to levodopa and replacement of this drug by bromocriptine in patients with end-of-dose akinesia after chronic levodopa treatment did not totally abolish response swings.

Four dopamine agonists, drugs which stimulate dopamine receptors, apomorphine, piribedil, and the ergot alkaloids lergotril and bromocriptine, have been used to treat patients with Parkinson's disease. Apomorphine is of little clinical value as it must be given by injection, the effects are short lived, and it causes profound vomiting (Cotzias *et al.*, 1970). Piribedil, although effective in animal models of Parkinsonism, causes slight or no improvement in man, and adverse reactions, vomiting, and sedation are frequent (Vakil *et al.*, 1973). Lergotril has a definite anti-Parkinsonism effect, particularly upon tremor, but some patients rapidly become tolerant (Lieberman *et al.*, 1975). All these drugs inhibit prolactin secretion, and bromocriptine, 2- α -ergocryptine, was developed for this purpose (Pozo *et al.*, 1972). In an attempt to improve the treatment of the considerable number of patients with Parkinson's disease who respond poorly to levodopa, or in whom this drug causes severe side-effects, Calne *et al.* (1974), gave bromocriptine to patients with idiopathic

Parkinson's disease. This caused a 10–20% reduction in the disability of patients already receiving levodopa. The side-effects of bromocriptine treatment, emesis and involuntary movements, were similar to those caused by levodopa, although the duration of drug action, eight to 12 hours, was longer than that of levodopa. As well as inhibiting prolactin secretion, bromocriptine has other hormonal effects and causes a variable increase in the plasma concentration of growth hormone in normal subjects, and a reduction in acromegalics (Cammani *et al.*, 1975). These changes in plasma growth hormone concentration are likely to be due to the effects of bromocriptine on hypothalamic dopamine receptors.

We have studied the anti-Parkinsonism action of bromocriptine in untreated patients with Parkinson's disease and in others on levodopa therapy. The dosage of bromocriptine that causes clinical improvement or side-effects varies in individual patients, so optimum dosage was first determined separately in each patient, followed by a double-blind controlled trial of

placebo and bromocriptine. Plasma growth hormone concentration was also determined to see whether changes in this accompanied clinical improvement due to bromocriptine.

METHODS

PATIENTS Thirty-one patients with idiopathic Parkinson's disease attending King's College Hospital were treated with bromocriptine. Eleven patients had not been treated previously with levodopa, and eight of these had received no previous medication. The disability of most of these patients was slight. In the remaining 20 patients, bromocriptine was added to levodopa treatment. These patients were selected for bromocriptine treatment as they had only a slight or moderate response to levodopa and other anti-Parkinsonism drugs, or were unable to tolerate full therapeutic doses because of side-effects. These patients were mostly moderately or severely disabled.

Eleven patients (eight on levodopa, three on no other treatment) did not persist with bromocriptine treatment because of adverse reaction or absence of obvious short-term clinical improvement. The remaining 20 patients completed a 12 week period taking increasing doses of bromocriptine to establish each individual's maximum tolerated dose up to a limit of 40 mg daily. These 20 patients then took part in a double-blind controlled trial of bromocriptine and placebo treatment. Eleven of these patients were male and nine female, aged 51–72 years (mean 62). Disease duration was from one to 33 years (mean 12.9), and disability was slight in six patients, moderate in nine, and severe in five. Before bromocriptine treatment, the total disability score was from 4–84 (mean 42). Three patients had a unilateral thalamolysis, and two had bilateral.

Bromocriptine was given as the only treatment to five patients and was added to existing medication in 15. Twelve of these patients were on levodopa, and eight were not. Four patients were on a stable dose of levodopa (1.5–7 g daily), and eight were on levodopa combined with a dopa decarboxylase inhibitor, L-alpha methyl dopa hydrazine (Sinemet), 1.5–6 tablets daily. Levodopa treatment had been taken for one to five years (mean 3.9). Two of these patients had not shown a useful response to levodopa. Eight patients were taking anticholinergic drugs, and eight amantadine 200–300 mg daily. All medication apart from bromocriptine was continued unchanged throughout the trial period.

TRIAL DESIGN AND DISABILITY ASSESSMENT The trial of bromocriptine lasted for 16 weeks. During the

first 12 weeks, the optimum bromocriptine dosage was established. Bromocriptine 2.5 mg tablets or capsules were given after meals initially as a single dose with subsequent increments of 5 mg twice weekly until a daily dosage of 40 mg (given in three divided doses) was achieved after four weeks, or side-effects limited dosage. Once established, the maximum tolerated bromocriptine dosage was continued unchanged for the remainder of the trial period. One patient took bromocriptine 2.5 mg daily, one 7.5 mg daily, seven 15–20 mg, six 25–30 mg, and five 35–40 mg daily. The mean bromocriptine dosage at 12 weeks was 25.6 mg daily. The dosage of bromocriptine was determined by a single observer according to the presence or absence of any adverse reaction, patients initially being seen weekly for this purpose. The therapeutic response was determined by different observers who were not aware of the bromocriptine dosage.

After this initial 12 week period of treatment, a random allocation to bromocriptine or placebo medication was made. Bromocriptine, in the optimum dosage determined previously, or a similar number of tablets of a matching placebo, was administered each for a two week period.

Patient disability was determined before the trial, at four, eight, and 12 weeks during the period of dose increase, and at two week intervals during the bromocriptine/placebo double-blind crossover period. Total disability scores, and sub-scores for tremor, akinesia, rigidity, postural deformity, functional disability, and mood were determined by the use of a standard proforma (Marsden *et al.*, 1973). Total and sub-scores were compared before and after bromocriptine treatment during the open trial phase, and then scores on bromocriptine were compared with scores on placebo treatment.

Patients were questioned as to the severity and occurrence of specified side-effects at each attendance, and asked to express any preference (whether better, worse or unchanged), for bromocriptine or placebo treatment.

HUMAN GROWTH HORMONE The plasma concentration of human growth hormone (HGH) was determined before and after the initial 2.5 mg bromocriptine dosage in 11 patients, before and after 5 mg in six patients, before and after 10 mg in two patients, and before and after 1, 5, 10, and 15 mg in one patient. Five of these patients had received no previous anti-Parkinsonism treatment, three were taking anticholinergic drugs and/or amantadine, and 12 had been taking levodopa for a period of one to five years. Bromocriptine was given by mouth. The 2.5 mg dosage was given at 14.00 h. Patients given other dosages remained

fasting until 09.00 h, and were given no previous treatment. A first blood sample was then taken, followed by bromocriptine with 500 ml milk; subsequent blood samples were taken at 30 minute intervals for 120–240 minutes. Patients remained ambulant throughout. The plasma concentration of HGH was determined by the double antibody technique of Schalch and Parker (1964).

BIOCHEMICAL DETERMINATIONS Haemoglobin, white blood cell count and differential, ESR (Westergren), Coombs test, plasma electrolytes, urea, sugar, liver function tests, and cholesterol were determined before and during bromocriptine treatment. The ECG, blood pressure, and pulse rate were recorded.

RESULTS

PATIENT'S SUBJECTIVE RESPONSES Eleven of the 31 patients did not complete the initial 12 week period of bromocriptine dosage increase, two because there was no obvious response so both stopped treatment and nine because of side-effects. The remaining 20 patients did not develop adverse effects of any severity. Thirteen of these 20 patients thought that the severity of

their symptoms of Parkinsonism was reduced during bromocriptine treatment, but seven stated that their symptoms were unchanged. Three patients described the benefit as considerable, and 10 as moderate or slight. Individual patients described improvement in walking, reduction in limb and trunk stiffness, and, in one case, a slight improvement in tremor.

Sixteen of 20 patients completed the double-blind trial period. Two stopped active treatment, one because of nasal stuffiness and one because of increased tremor. Two stopped placebo treatment as their condition deteriorated on this, the code was broken, and they were replaced on bromocriptine. Of the 16 patients who completed the double-blind phase, five considered active treatment better than placebo, and one worse. The remaining 10 patients did not distinguish between active and placebo treatment.

OBSERVERS' SUBJECTIVE IMPRESSION The impression of the trial observers was that bromocriptine had a definite slight or moderate

FIG. 1 Mean change in scores in 20 patients on bromocriptine after 12 weeks of treatment compared with pre-bromocriptine scores. NS = not significant using Wilcoxon's signed-rank test.

TABLE 1

MEAN SCORES (± 1 SEM) IN 20 PATIENTS BEFORE AND DURING BROMOCRIPTINE TREATMENT (16 DURING DOUBLE-BLIND PHASE)

	Pre-bromocriptine	Bromocriptine			Double-blind	
		4 weeks	8 weeks	12 weeks	Placebo	Bromo- criptine
Mean bromocriptine dosage (mg)		25 $\pm$ 2.6	23.6 $\pm$ 2.6	25.6 $\pm$ 2.8		25.9 $\pm$ 2.7
Total disability score	42.3 $\pm$ 4.3	32.1 $\pm$ 4.4	29.5 $\pm$ 4.4	32.5 $\pm$ 5.2*	33.4 $\pm$ 5.0	29.3 $\pm$ 5.0
Tremor	1.6 $\pm$ 0.5	0.5 $\pm$ 0.1	0.7 $\pm$ 0.2	0.9 $\pm$ 0.3	0.9 $\pm$ 0.3	0.4 $\pm$ 0.2
Akinesia	10.2 $\pm$ 0.8	7.6 $\pm$ 0.8	6.9 $\pm$ 0.9	8.0 $\pm$ 1.0*	8.2 $\pm$ 1.0	6.8 $\pm$ 0.9†
Rigidity	5.8 $\pm$ 0.7	4.1 $\pm$ 0.7	3.0 $\pm$ 0.7	3.6 $\pm$ 0.7*	3.8 $\pm$ 0.7	3.5 $\pm$ 0.7
Posture	5.4 $\pm$ 0.9	3.8 $\pm$ 0.9	4.0 $\pm$ 1.1	3.9 $\pm$ 1.1*	3.9 $\pm$ 1.1	3.3 $\pm$ 0.9

* Significant difference; pre-bromocriptine: 12 week bromocriptine score $P < 0.01$.† Double-blind phase; placebo: bromocriptine $P < 0.01$, Wilcoxon's signed-rank test.

FIG. 2 Individual changes in total disability and sub-scores in 16 patients on bromocriptine and placebo treatment. Mean change in each score shown by horizontal line. ●: on levodopa. ▲: not on levodopa.

TABLE 2

RESPONSE TO BROMOCRIPTINE COMPARED WITH PLACEBO IN SEVEN PATIENTS NOT ON LEVODOPA AND NINE PATIENTS ON LEVODOPA

	<i>Not on levodopa</i>	<i>On levodopa</i>
Bromocriptine dosage (mg)	24.3 ± 3.2	27.2 ± 4.4
Pre-bromocriptine total disability score	36.1 ± 8.7	46.4 ± 4.0
Score after 12 week's bromocriptine	22.7 ± 9.5	34.6 ± 6.2
Change in scores: bromocriptine; placebo		
Total disability	6.4 ± 2.6	2.3 ± 2.3
Tremor	0.7 ± 0.4	0.3 ± 0.4
Akinesia	2.0 ± 0.3	1.0 ± 1.2
Rigidity	0.5 ± 0.4	0.2 ± 0.8
Posture	1.0 ± 1.1	0.3 ± 0.2

Mean changes in total disability and sub-scores in two patient groups on bromocriptine compared with placebo. There is no significant difference ($P > 0.1$) between the mean change in scores in subjects not on levodopa, and on levodopa.

anti-Parkinsonism effect in some but not all patients. A dramatic response with complete abolition of all signs was not observed in any patient. Improvement first occurred within two to seven days of starting bromocriptine, and further improvement accompanied increasing dosages. Once optimum bromocriptine dosage was established, the degree of improvement was constant throughout the trial period. In the dosages used, bromocriptine was not as effective as levodopa, although possibly more active than either anticholinergic drugs or amantadine given as a single treatment. One patient taking bromo-

criptine 40 mg daily had no obvious therapeutic response or adverse reaction to this. The sudden withdrawal of established bromocriptine treatment and replacement by placebo caused a significant deterioration in only two patients. Adverse reactions to bromocriptine were mainly similar to those caused by levodopa, although nausea and vomiting were less common with bromocriptine. Involuntary movements occurred in one otherwise untreated patient, and the severity of levodopa dyskinesias was increased by bromocriptine. A single patient complained of faintness after the first, but not subsequent, bromocriptine dosage.

PATIENTS' OBJECTIVE RESPONSES Parkinsonian disability was reduced in all patients during the initial 12 week period of bromocriptine treatment. Mean total disability, tremor, akinesia, rigidity, and posture scores all showed a significant improvement compared with pre-bromocriptine scores (Fig. 1). In 12 patients on levodopa, the mean total disability score was reduced by a further 10.0 (21%) on the addition of bromocriptine, and in eight patients not on levodopa, by 9.4 (26%). In the five patients on no other treatment, the mean total disability score was reduced by 9.3 (44%). The response was similar in both sexes, the reduction in mean total disability score being 9.6 in men and 10.0 in women. The degree of disability before commencement of bromocriptine treatment was

TABLE 3

SIDE-EFFECTS OF BROMOCRIPTINE IN PATIENTS NOT ON LEVODOPA

	<i>Pre-bromocriptine</i>	<i>12-week bromocriptine</i>	<i>Double-blind phase</i>	
			<i>Bromocriptine</i>	<i>Placebo</i>
Nasal stuffiness	0	0	0	0
Constipation	4	2	2	1
Dry mouth	1	1	1	1
Difficulty in focusing	0	0	0	0
Hallucinations	0	1	1	0
Nausea	0	2	2	1
Vomiting	0	1	1	1
Orofacial dyskinesia	0	0	0	1
Dystonic posture	0	0	1	0
Limb chorea	0	0	0	0
Sleep disturbance	0	0	0	0
Postural faintness	1	1	1	0

Side-effects in seven patients not on levodopa who completed the double-blind trial of bromocriptine and placebo. The number of patients reporting each side-effect is shown.

FIG. 3 Plasma HGH concentration in response to separate doses of bromocriptine 1, 5, 10, and 15 mg in a 61 year old female with idiopathic Parkinson's disease, on no other treatment.

similar in both sexes. The effect of gradual increase in dosage over a four week period was a progressive reduction in disability scores, the response being stable from four to 12 weeks (Table 1). Mood scores did not change during bromocriptine treatment.

BROMOCRIPTINE COMPARED WITH PLACEBO In the 16 patients who completed the double-blind trial, the mean total disability score was reduced by 4.1 as compared with placebo. This reduction was not as great as that occurring during the initial 12 week period, when the score at 12 weeks was compared with that before bromocriptine treatment. However, in the double-blind trial, there was a statistically significant reduction in mean total disability and akinesia scores ($T = 17$, $P < 0.02$, and $T = 14$, $P < 0.01$, respectively; Wilcoxon paired rank test) on bromocriptine compared with placebo. Mean scores for tremor, rigidity, and postural changes were not altered. The mean reduction in total disability scores of patients not on levodopa was

greater than in patients on levodopa, although the difference was not statistically significant. ($t = 2.3$, Student's t test, $P > 0.1$, Table 2). Ten patients showed a reduction in total disability score during bromocriptine compared with placebo, three showed little change, and three showed an increase. In the majority of patients, sub-scores for tremor, akinesia, rigidity, and posture were less during bromocriptine than during placebo treatment, although akinesia scores were higher in three patients, and rigidity scores in four, on active treatment.

FACTORS DETERMINING BROMOCRIPTINE RESPONSE In the 16 patients who completed the double-blind trial, no definite clinical factor could be identified which determined response to bromocriptine, although the least disabled patients, and also those not on levodopa, had the greatest reduction in total disability score on bromocriptine compared with placebo. However, there was no significant correlation between age, sex, disease duration, or thalamolysis, and the reduc-

TABLE 4
SIDE-EFFECTS OF BROMOCRIPTINE AND PLACEBO

	Pre-bromocriptine	12-week bromocriptine	Double-blind phase	
			Bromocriptine	Placebo
Nasal stuffiness	0	1	1	0
Constipation	5	4	4	4
Dry mouth	7	4	4	4
Difficulty in focusing	1	0	0	0
Hallucinations	0	1	1	0
Nausea	2	2	2	1
Vomiting	1	2	2	1
Orofacial dyskinesia	1	3	2	2
Dystonic posture	1	1	3	0
Limb chorea	1	1	1	0
Sleep disturbance	1	2	2	2
Postural faintness	1	1	1	0

Side-effects in 20 patients, 12 on levodopa and eight not, before bromocriptine, after 12 weeks' bromocriptine treatment, and during a four week period, two weeks on bromocriptine and two weeks on placebo. The number of patients reporting each side-effect is shown.

tion in score on bromocriptine treatment compared with placebo.

Patients on high bromocriptine dosage did a little better than those on low dosage. Thus four of five patients who were able to tolerate bromocriptine 35–40 mg daily improved, while three of four patients who developed side-effects on a bromocriptine dosage higher than 15 mg did not. Patients on both high (6 g daily) and low (0.5 g) levodopa dosages responded to bromocriptine as compared with placebo. Patients not on levodopa had a greater reduction in mean total disability scores on bromocriptine compared with placebo, than patients on levodopa, although this difference was not statistically significant. Four of the five patients taking no other treatment had a reduction in total disability scores on bromocriptine compared with placebo, as also did the two patients not on levodopa but taking anticholinergic drugs and amantadine.

Patients who were slightly disabled responded better to bromocriptine than patients with more severe degrees of disability. Thus, the two patients who were initially least disabled (one on levodopa and the other not) both had a 50% or greater reduction in total disability score on bromocriptine, while the two patients who were most disabled before bromocriptine treatment (one on levodopa and the other not) had little or no reduction in scores in bromocriptine.

Ten patients had a reduction in total disability

scores on bromocriptine as compared with placebo, three showed no change, and three an increase. All three of the patients who responded best to bromocriptine were moderately disabled (pre-treatment scores 20, 34, and 40) and the disease duration was one, nine, and 32 years respectively. The three patients who deteriorated on bromocriptine were also moderately disabled (pre-treatment total disability scores 20, 40, and 51). Two of these patients had previously responded well to levodopa. The duration of disease in these three patients was three, seven, and 10 years respectively.

HUMAN GROWTH HORMONE CONCENTRATION The mean fasting plasma HGH concentration in 20 patients with idiopathic Parkinson's disease was 4.8 ± 2.3 $\mu\text{g/l}$. After bromocriptine 2.5 mg (11 patients), 5 mg (six patients), and 10 mg (two patients), the mean HGH concentration at 60 minutes was 1.36 ± 0.3 $\mu\text{g/l}$, 1.1 ± 0.4 , and 0.1 ± 0.1 respectively; and after 120 minutes was 1.3 ± 0.5 , 2.6 ± 1.3 , and 1.5 ± 1.5 (mean $\pm$ 1 SEM). During this period no patient had an HGH concentration greater than 7.8 $\mu\text{g/l}$. One patient given 1, 5, 10, and 15 mg oral bromocriptine on different days had a peak HGH concentration above 40 $\mu\text{g/l}$ at 120 minutes after the highest dosage, but no response up to 120 minutes with lower dosages.

The two patients with the greatest reduction in total disability scores on bromocriptine as com-

pared with placebo had no increase in plasma HGH concentration at 120 minutes after 2.5 mg bromocriptine. The three patients with no reduction in total disability scores on bromocriptine compared with placebo showed minor changes in plasma HGH concentration (from 0.5–2.7; 2.7–5.1, and 0.5–1.0 $\mu\text{g/l}$) before and 120 minutes after 2.5 mg bromocriptine. The single patient with a considerable increase in HGH concentration after bromocriptine 15 mg responded well to this dosage, with an 80% reduction in total disability score compared with placebo. The correlation between the plasma HGH concentration 120 minutes after 2.5 mg bromocriptine, and the change in disability on bromocriptine in optimum dosage compared with placebo was not statistically significant ($r=0.06$; $P>0.1$).

SIDE-EFFECTS OF BROMOCRIPTINE TREATMENT

Nine of 31 patients on bromocriptine developed side-effects of sufficient severity to prohibit prolonged treatment. Two patients taking 2.5 and 15 mg had persistent nausea and vomiting for four and 12 weeks, and four patients taking 2.5, 5, 17.5, and 20 mg became hallucinated during the initial eight weeks of treatment. One patient taking 2.5 mg developed stiffness of the neck and headache, and two patients taking 2.5 and 10 mg also on levodopa, had increasing severity of levodopa dyskinesias. None of these patients had a marked therapeutic response to bromocriptine during this period and so treatment was stopped. Two other patients developed no side-effects but did not continue bromocriptine.

In the remaining 20 patients, the side-effects attributed to bromocriptine were similar in nature to those caused separately by levodopa, with the exception of nasal stuffiness, headache, and aching of the neck muscles which occurred in one patient.

Nausea and vomiting was less common in patients on bromocriptine than previously experienced in other patients taking levodopa, 80% of whom were nauseated at some stage of treatment. A single patient complained of postural faintness after the initial 2.5 mg bromocriptine dosage but not after subsequent dosages; this may have been at least partly provoked by venepuncture. A dystonic foot

posture with clawing of the toes occurred in one patient on bromocriptine but no other treatment, and in four other patients the severity of levodopa dyskinesias was considerably increased on addition of bromocriptine. No other side-effects of bromocriptine were determined, and the frequency of constipation, dry mouth, and difficulty in focusing was the same during bromocriptine as placebo treatment. No patient developed a cardiac arrhythmia.

BIOCHEMICAL DETERMINATIONS There was no change in haemoglobin, white cell count, ESR, plasma electrolytes, liver function tests, and urea during bromocriptine treatment. Systolic and diastolic blood pressure and pulse rate were unchanged and no abnormality in the ECG was detected.

DISCUSSION

Bromocriptine was shown in this trial to possess therapeutic activity in Parkinson's disease, confirming the initial reports of Calne *et al.* (1974). In most patients the degree of improvement in motor disability was probably greater than that caused by anticholinergic drugs when given alone, but not as great as that produced by levodopa in conventional dosages. Improvement began within a few days of starting bromocriptine in patients taking no other treatment. Over the three month period of the study about two-thirds of patients showed some response but a third did not. Some of these patients who did not respond to bromocriptine had previously responded well to levodopa. There was some evidence to suggest that the therapeutic action of bromocriptine is dose-dependent, although dosage was often limited or treatment had to be stopped because of side-effects. However, greater benefit may be obtained by doses higher than the maximum administered in this trial (40 mg) provided that the patient can tolerate them.

The side-effects of bromocriptine were qualitatively similar to those of levodopa. Hallucinations and mental confusion were common in patients in whom bromocriptine was added to levodopa but may be less common side-effects when bromocriptine is given as a single treatment. Other psychotic episodes were not produced by bromocriptine and this had little or no

effect on mood. In contrast with levodopa and apomorphine, nausea and vomiting were seldom caused by bromocriptine. Abnormal involuntary movements similar to those produced by levodopa were also caused by bromocriptine and the severity of levodopa dyskinesias was increased by this treatment. Bromocriptine did not cause symptomatic postural hypotension and no haematological or biochemical alterations were found during the period of this study.

Response variations of minor or major degree are a considerable problem of levodopa treatment. In some patients the clinical effects of a single oral dose of levodopa are obvious up to two to four hours, followed by deterioration until subsequent doses are taken. In others, 8% of our patients, the chronic use of levodopa leads to violent fluctuations in response (yo-yoing), not clearly related in time to separate dosages. In patients on bromocriptine alone the response throughout the day remained stable. However, attempts to treat two patients with response variations by the substitution of bromocriptine for levodopa, have not totally abolished these swings.

Some patients with Parkinson's disease do not respond to levodopa. Levodopa requires conversion to dopamine by dopa decarboxylase in the brain to exert its therapeutic action, and it is possible that in some patients with severe pathology insufficient quantities of this enzyme are present. A theoretical advantage of dopamine agonists such as bromocriptine is that their action is independent of that of dopa decarboxylase. In patients with severe degrees of nigrostriatal damage the receptor response to dopamine agonists may be increased if supersensitivity of denervated receptors occurs. These considerations might suggest that severely disabled patients would show the best response to bromocriptine and that some levodopa failures would benefit (Calne *et al.*, 1974). However, neither proved to be the case in this trial. The less disabled patients showed the best response to bromocriptine, and patients who had previously not responded to levodopa did not show any useful benefit.

Bromocriptine 2.5 mg given as a single oral dose causes a rise in plasma HGH concentration in most but not all normal subjects aged 28–40 years. The peak increase of 4.0–31 $\mu\text{g/l}$ (mean 12.5) occurs between 90 and 150 minutes after

dosage (Cammani *et al.*, 1975). In the present study no patient with Parkinson's disease showed an obvious increase in HGH concentration up to 120 minutes after this dosage of bromocriptine and only a single patient had an increase after higher dosage. The increase in plasma HGH concentration after the dopamine agonist apomorphine is less in older than younger subjects, and patients with Parkinson's disease on chronic levodopa treatment may not show the expected rise in HGH concentration after levodopa (Maany *et al.*, 1975; Malarkey *et al.*, 1974). However, untreated patients with Parkinson's disease show a normal rise in plasma HGH concentration after levodopa 0.5–1.0 g, and the failure of such patients to respond to bromocriptine 2.5 mg may be because this dosage is too small to cause significant stimulation of hypothalamic dopamine receptors. The single patient in whom bromocriptine 15 mg caused an increase in HGH concentration also had a good therapeutic response, although it is not known whether dopamine receptors at different sites in the nervous system respond in a similar or different manner to dopamine agonist drugs.

The anti-Parkinsonism activity and side-effects of bromocriptine, piribedil, apomorphine, and lergotril are similar in nature, although quantitatively different. None of these dopamine agonist drugs appears to have as potent a therapeutic effect as levodopa although all have considerable activity in animal models of Parkinsonism (Andén *et al.*, 1967; Corrodi *et al.*, 1971; Corrodi *et al.*, 1973; Calne *et al.*, 1974). Many of these animal models of Parkinsonism—and, in particular, the rotating animal with complete unilateral destruction of one nigrostriatal dopamine system but no other pathology—appear to be of limited value in predicting the value of different drugs in the treatment of human Parkinsonism. In dosages used in man, piribedil may be the least effective and apomorphine the most. Apomorphine almost always causes vomiting; this is uncommon with bromocriptine. Piribedil often results in psychotic episodes; these are less frequent with bromocriptine. Apomorphine sometimes reduces the severity of levodopa dyskinesias (Düby *et al.*, 1973), while these are increased by bromocriptine. All these drugs cause a reduction in plasma prolactin concentration, and those studied cause

an increase in growth hormone concentration. These different effects may result from the different dosages of each drug used and different degrees of penetration into the brain. Alternatively, there may be different dopamine receptor types within the central nervous system; however, the ideal of a specific nigrostriatal dopamine receptor agonist drug to treat Parkinson's disease has not been achieved. The action of these drugs may be partly dependent on presynaptic effects as well as due to direct receptor stimulation, and their therapeutic effects in Parkinsonism are possibly limited in the presence of presynaptic neuronal degeneration.

We are indebted to Dr William P. Maclay and Sandoz Limited for supplies of bromocriptine and financial assistance. Mrs M. Spencer gave invaluable secretarial assistance. Dr Galea-Debono was supported by a grant from the Joint Research Committees of King's College Hospital and the Maudsley Hospital.

REFERENCES

- Andén, N.-E., Rubenson, K., Fuxe, K., and Hökfelt, T. (1967). Evidence for dopamine receptor stimulation by apomorphine. *Journal of Pharmacy and Pharmacology*, **19**, 627-629.
- Calne, D. B., Teychenne, P. F., Claveria, L. E., Eastman, R., and Greenacre, J. K. (1974). Bromocriptine in Parkinsonism. *British Medical Journal*, **4**, 442-444.
- Cammani, F., Massara, F., Belforte, L., and Molinatti, G. M. (1975). Changes in plasma growth hormone levels in normal and acromegalic subjects, following administration of 2-Bromo-alpha-ergocryptine. *Journal of Clinical Endocrinology and Metabolism*, **40**, 363-366.
- Corrodi, H., Fuxe, K., Hökfelt, T., Lidbrink, P., and Ungerstedt, U. (1973). Effect of ergot drugs on central catecholamine neurones: evidence for a stimulation of central dopamine neurones. *Journal of Pharmacy and Pharmacology*, **25**, 409-412.
- Corrodi, H., Fuxe, K., and Ungerstedt, U. (1971). Evidence for a new type of dopamine receptor stimulating agent. *Journal of Pharmacy and Pharmacology*, **23**, 989-991.
- Cotzias, G. C., Papavasiliou, P. S., Fehling, C., Kaufman, B., and Mena, I. (1970). Similarities between neurologic effects of L-dopa and of apomorphine. *New England Journal of Medicine*, **282**, 31-33.
- Düby, S. E., Cotzias, G. C., Papavasiliou, P. S., and Lawrence, W. H. (1973). Injected apomorphine and orally administered levodopa in Parkinsonism. *Archives of Neurology (Chic.)*, **27**, 474-480.
- Lieberman, A., Miyamoto, T., Battista, A. F., and Goldstein, M. (1975). Studies on the antiparkinsonian efficacy of lergotril. *Neurology (Minneapolis)*, **25**, 459-462.
- Maany, A., Frazer, A., and Mendels, J. (1975). Apomorphine: effect on growth hormone. *Journal of Clinical Endocrinology and Metabolism*, **40**, 162-163.
- Malarkey, W. B., Cyrus, J., and Paulson, G. W. (1974). Dissociation of growth and prolactin hormone secretion in Parkinson's disease following chronic L-dopa therapy. *Journal of Clinical Endocrinology and Metabolism*, **39**, 229-235.
- Marsden, C. D., Barry, P. E., Parkes, J. D., and Zilkha, J. K. (1973). Treatment of Parkinson's disease with levodopa combined with L-alpha-methyldopa hydrazine, an extracerebral inhibitor of DOPA decarboxylase. *Journal of Neurology, Neurosurgery, and Psychiatry*, **36**, 10-14.
- Pozo, E., Brun del Re, R., Varga, L., and Friesen, H. (1972). The inhibition of prolactin secretion in man by CB.154 (2-Br-alpha-ergocryptine). *Journal of Clinical Endocrinology and Metabolism*, **35**, 768-771.
- Schalch, D. S., and Parker, M. L. (1964). A sensitive double antibody immunoassay for human growth hormone in plasma. *Nature (London)*, **203**, 1141-1142.
- Vakil, S. D., Calne, D. B., Reid, J. L., and Seymour, D. A. (1973). Pyrimidyl-piperonyl-piperazine (ET 495) in parkinsonism. In *Progress in the Treatment of Parkinsonism*, pp. 121-125. Edited by D. B. Calne. Raven Press: New York.