BROMOCRIPTINE AND DOPAMINE RECEPTOR STIMULATION

A. GALEA DEBONO, C.D. MARSDEN, P. ASSELMAN & J.D. PARKES

The University Department of Neurology, King's College Hospital and the Institute of Psychiatry, London SE5 9RS

- 1 The response to different doses of bromocriptine (12.5, 25, 50 and 100 mg) has been established in six patients with Parkinson's disease.
- 2 Bromocriptine, like levodopa, causes improved mobility in patients with Parkinsonism, emesis, hallucinations, a fall in supine and erect blood pressure, increase of plasma growth hormone and suppression of prolactin concentration.
- 3 Bromocriptine (50 or 100 mg) has as great an anti-Parkinsonian effect as average therapeutic doses of levodopa, and a longer duration of action, 6-10 hours.
- 4 In the dose range studied, bromocriptine appears to be a complete dopamine agonist, although 100 mg was less effective than 50 mg in two patients.
- 5 The different actions of bromocriptine and other dopamine agonist drugs may result from stimulation of different types of dopamine receptor.

Introduction

Dopamine-neurones are present in the human brain in the nigrostriatum, medulla, hypothalamus and limbic system, and by analogy with animals may also occur in the cortex (Nobin & Björklund, 1973; Hökfelt, Ljungdahl, Fuxe & Johansson, 1974). In the periphery, dopamine is found in the gut wall, blood vessels, pancreatic islets and kidney (Thorner, 1975). Dopamine may act as a neurotransmitter at these various sites inside and outside the brain and the therapeutic and side effects of levodopa, when used in the treatment of Parkinsonism, are likely to be dependent on stimulation of different dopamine systems. The return of normal movement accompanied by fragments of abnormal movements probably results from an increased striatal dopamine content, whilst nausea and vomiting, changes in plasma growth hormone and prolactin concentration, and neuro-psychiatric disturbances may be due to stimulation of medullary, hypothalamic and cortical dopamine systems respectively. Levodopa also causes a reduction in both erect and supine blood pressure owing to a central action and peripheral effect on baroreceptors (Calne, Brennan, Spiers & Stern, 1970). In our patients with Parkinson's disease, 80% improve on average therapeutic doses of levodopa (2 g daily), which causes a mean 40-50% reduction in disability, dyskinesias occur in 80% of patients, emesis in 90%, symptomatic postural hypotension in 5% and rise in plasma growth hormone concentration in 95%.

Bromocriptine is an ergot alkaloid which in animal models of Parkinsonism appears to stimulate dopamine receptors. The effect of bromocriptine on animal motility is not dependent upon dopamine synthesis for it is not blocked by tyrosine hydroxylase inhibition (Fuxe, Corrodi, Hökfelt, Lidbrink & Ungerstedt, 1974). On account of its effect on hormones, bromocriptine has been used in man to inhibit lactation, and also in certain cases of infertility and acromegaly (Pozo, Brun Del Re, Varga & Friesen, 1972; Cammani, Massara, Belforte & Molinatti, 1975). In an attempt to improve the treatment of patients with Parkinson's disease, many of whom do not respond to levodopa or who develop marked response fluctuations on this drug, Calne and his co-workers showed that bromocriptine had definite anti-Parkinsonian activity (Calne, Teychenne, Claveria, Eastman & Greenacre, 1974). This drug may not be as potent as levodopa, although clinical experience is still limited and large doses have not yet been widely used (Debono, Donaldson, Marsden & Parkes, 1975).

The characteristic property of receptors, like enzymes, is their specificity, and if bromocriptine is a dopamine agonist drug in man, its actions should mimic those of levodopa and be prevented by drugs with the pharmacological property of dopamine receptor blockade. We have investigated the effects of different doses of bromocriptine on movement, dyskinesia, emesis, blood pressure, plasma prolactin and growth hormone concentra-

tion in patients with Parkinson's disease. In this condition, at least one dopamine system, the nigro-striatal, is partially destroyed, but dopamine receptors in the striatum may be preserved. The normal growth hormone and emetic response to levodopa suggests that the tubero-infundibular and medullary emetic dopamine systems are intact. At present, it is not certain if the mesolimbic and presumed cortical dopamine system are involved in Parkinsonism.

Methods

Six patients, four male and two female, aged 52-65 years (mean, 59), with idiopathic Parkinson's disease were treated with bromocriptine. The duration of illness was 2-11 years (mean, 7), and before treatment disability was moderate in four subjects and severe in two. A unilateral thalamotomy had been done in one patient and a bilateral operation in another.

Four patients were established on levodopa (600 mg-6 g daily, mean 3.2 g) which they had taken for 3-4 years, and were also taking anticholinergic drugs and amantadine. Two patients were not on any anti-Parkinsonian treatment before they were given bromocriptine. Patients were selected for this trial by their ability to tolerate high dosages (> 100 mg daily) of bromocriptine with improvement and without severe side effects.

Bromocriptine was given as a single treatment to two patients and added to existing medication in the four others. The dosage of bromocriptine was gradually increased by 5 mg increments twice weekly, until a total daily dosage of 100 mg or higher was achieved. After a 3-4 month period, four patients took 100 mg daily, one 150 mg, and one 300 mg. This resulted in a 10-45% reduction in total disability scores, as compared with previous treatment.

Once patients were established on bromocriptine, the response in each patient to four separate dosages (12.5, 25, 50 and 100 mg) was determined and is described below. On the day before testing, patients took their usual treatment. On the day of test, patients remained fasting until 09 h 30 min, when they received one of the above dosages of bromocriptine, but no other anti-Parkinsonian drug. The dosage order was randomized, different doses being given at 1-week intervals. Food was given at 10.00 hours.

The functional disability score was determined in each patient on each separate dosage, 30 min before, and then at 30 min intervals after bromocriptine was given, for a 4 h period. This score indicated the severity of tremor, postural

deformity, akinesia and rigidity, a high score indicating considerable disability (Marsden, Barry, Parkes & Zilkha, 1973). The erect and supine blood pressure was measured at 30 min intervals, the occurrence of nausea, vomiting, dyskinesia or other side effects recorded, and blood taken by an indwelling venous catheter in the forearm for plasma growth hormone and prolactin determination (Schlach & Parker, 1964; McNeilly, 1973).

Results

All patients improved on bromocriptine treatment, both during the initial period of dose increase and also when given single 12.5, 25, 50 and 100 mg dosages. The two patients taking bromocriptine as a single treatment found it easier to walk and move, felt less stiff and had less tremor. In the four patients treated for 3 months with bromocriptine combined with levodopa, and then given the above doses of bromocriptine without levodopa, the highest dosages of bromocriptine caused a similar but not greater degree of improvement to that previously produced by levodopa alone. In these patients, bromocriptine produced a more stable response through the day than that given by levodopa, when the effect of each separate dose declined after 1-3 hours. The higher doses of bromocriptine (50 and 100 mg) caused subjective improvement for a 6-10 h period.

On the lowest dosage of bromocriptine (12.5 mg), four patients improved, with a reduction in total disability score, and two did not. One of these two patients also did not respond to 25 mg, but did improve on higher dosages. All five other patients improved with each separate dose of bromocriptine, 25, 50 and 100 mg.

In four patients, the higher doses of bromocriptine caused a greater reduction in disability than the lower doses, although two patients showed 7% and 10% less peak improvement respectively on 100 mg than on 50 mg. Bromocriptine caused a mean peak reduction in total disability score in all six patients, of 17% with 12.5 mg, 25% with 25 mg, 42% with 50 mg and 48% with 100 mg. The time at which peak improvement occurred was different in each patient, and the mean improvement in all six patients at a given time, was less than these peak values (Figure 1). Over a 4 h period the mean scores were lower on 25 mg than on 12.5 mg. Improvement was first obvious 30-60 min after all dosages of bromocriptine, and peak improvement occurred at 2-4 hours.

The period of improvement lasted 3-5 h with 12.5 and 25 mg bromocriptine, and 6-10 h with 50

Figure 1 Mean change in total disability scores and plasma growth hormone concentration ($\bullet$, ng/ml $\pm$ 1 s.e. mean) over 4 h period of six patients with Parkinson's disease, following separate doses of bromocriptine (a 12.5 mg; b 25 mg; c 50 mg; d 100 mg). The % improvement in total disability score compared with pretreatment value is shown.

and 100 mg bromocriptine. Tremor, rigidity, akinesia and flexion of the limbs all improved after bromocriptine, and there was a slight improvement in the severe flexion postural deformity of the trunk in one patient. Reduction in tremor, akinesia and rigidity was simultaneous, and one symptom was not more obviously improved than the others.

Bromocriptine dyskinesias occurred in three patients, in two on 25, 50 and 100 mg but not on 12.5 mg, and in one on 12.5, 25 and 50 but not 100 mg. These involuntary movements were exactly similar to those caused separately by levodopa in these patients. One patient did not have either levodopa or bromocriptine dyskinesias. The two patients not previously treated with levodopa did not develop dyskinesias on bromocriptine. Bromocriptine dyskinesias first occurred 30-90 min after dosage, and were of greatest persistence on the highest dosages, and of greatest severity on the highest dosages, at the time of greatest therapeutic improvement. This was

accompanied by oro-facial grimaces, choreiform movements of the limbs, dystonic postures of the hands and feet, abnormal postures and movements of the trunk, and a disturbance in respiratory rhythm.

Nausea was produced by bromocriptine in only three patients. This occurred 120-150 min after the time of dosage, was of short duration (10-20 min), accompanied by vomiting in one patient but not the others, and occurred on the two highest but not lower dosages. Nausea occurred just before peak improvement. Levodopa had previously caused nausea and vomiting in these three patients, although this was of greater severity and persistence than that due to bromocriptine.

Bromocriptine caused a fall in both erect and supine blood pressure in all patients, although in one, only on the highest dosage. In most patients, the fall in blood pressure was slightly greater on higher than lower dosages. Despite hypotension, no patients had symptoms of postural syncope.

The reduction in erect and supine blood pressure was comparable in magnitude. The mean peak reduction in systolic blood pressure after bromocriptine (12.5, 25, 50 and 100 mg) was 22, 25, 34 and 35 mm Hg respectively in the erect posture and 12, 29, 25 and 43 mm Hg when supine. The diastolic pressure fell by 13, 16, 34 and 28 mm Hg when erect and 15, 20, 30 and 23 mm Hg when supine, with increasing doses of bromocriptine. The fall in blood pressure occurred at the same time as clinical improvement.

Bromocriptine caused an increase in plasma growth hormone concentration in four patients, but not in the two others, in which the concentration did not exceed 4 ng/ml during a 4 h period, after any dose. Both of these patients who did not respond to bromocriptine showed a normal increase following levodopa (1 g). In the four other patients, peak plasma growth hormone levels of 6-40 ng/ml occurred 30-180 min after bromocriptine was given, and in two patients the greatest increase followed the highest dosage. Peak growth hormone levels occurred at the time of greatest therapeutic improvement. The mean peak concentration of growth hormone in the plasma in the four patients who responded was 11 ng/ml after 12.5 mg, 18 ng/ml after 25 mg, 11 ng/ml after 50 mg and 16 ng/ml after 100 mg.

Plasma prolactin levels were determined in four patients on bromocriptine 12.5-100 mg. The fasting prolactin levels in these patients were all low (< 4 ng/ml) and remained suppressed throughout the 4 h trial period.

The six patients investigated were selected on account of their ability to tolerate bromocriptine, and in these patients this drug did not cause any neuro-psychiatric effects. However, in a larger group of thirty-three patients treated with bromocriptine 10-50 mg daily, seven developed an acute confusional state accompanied in four by visual hallucinations.

No patient on bromocriptine (100 mg) daily or higher dose had any evidence of haematological or biochemical toxicity over a 5-month treatment period. Haemoglobin, white cell count, E.S.R. (Westergren) and Coombs test were all normal before and during treatment, and there was no change in electrolyte determinations, blood urea, creatinine or liver function test. No patient developed a cardiac dysrhythmia, symptoms of peripheral vascular disease or skin rash.

Discussion

Bromocriptine is an active anti-Parkinsonian drug which in some patients is as potent as levodopa. Both bromocriptine and levodopa cause im-

provement in all features of the motor disability of Parkinsonism. The effect of bromocriptine 100 mg lasts for 6-10 h whilst that of an equivalent dose of levodopa lasts only 3-4 hours. Improvement follows a single dose of bromocriptine whilst the maximum response to levodopa given without a peripheral inhibitor of dopa decarboxylase can take several weeks to establish. The sensitivity of receptors in the nervous system can be altered by the chronic use of agonist or antagonist drugs (Tarsy & Baldessarini, 1974; Voigtlander, Losey & Triezenberg, 1975), but over a 4-month period, response failure to bromocriptine did not develop. In our opinion, a true response failure to levodopa also does not occur after chronic treatment, and the apparent loss of drug effectiveness sometimes observed is likely to be due to the progression of Parkinsonism.

The side effects of bromocriptine in the treatment of Parkinson's disease are similar to those of levodopa. Both drugs cause dyskinesias, nausea and vomiting, neuro-psychiatric disturbance, hormonal changes and hypotension, but the incidence and severity of the different effects with each drug are different. This may be due to a different penetration of both drugs into different brain areas, or the preferential stimulation by bromocriptine of certain dopamine receptors and not others. In equipotent doses, the incidence of dyskinesias is probably similar with levodopa and bromocriptine. In contrast, bromocriptine causes nausea less frequently than levodopa and this is of lesser severity. The emetic response to levodopa in dogs is determined by medullary stimulation, and is abolished if the area postrema is ablated (Peng, 1963). This area probably lies outside the blood brain barrier to dopamine (Klawans, Ilahi & Shenker, 1970), and bromocriptine would be expected to penetrate it as readily as other brain areas.

Also, in contrast to levodopa, neuro-psychiatric disturbances may be more common with bromocriptine. Hallucinations and disorders of awareness are caused separately by all effective anti-Parkinsonian drugs, including anticholinergics, and it is not established whether they result from dopamine receptor stimulation, possibly in the cortex. However, this may be the explanation since we have observed that hallucinations as a result of levodopa are sometimes prevented by the specific dopamine receptor blocking drug, pimozide, although at the expense of increasing Parkinsonism. The reason for their more ready provocation with bromocriptine than with levodopa is not apparent.

Levodopa causes an increase in the plasma growth hormone concentration in normal subjects and in most patients with Parkinson's disease

(Boyd, Lebovitz & Pfeiffer, 1970). Bromocriptine also causes an increase in growth hormone concentration in Parkinsonian subjects, although this is not invariable and some patients respond to levodopa and not to bromocriptine. The reason for this difference in response is uncertain. Hypothalamic neuronal systems involved in pituitary growth hormone control appear to lie within the blood brain barrier for dopamine, as the effect of levodopa on plasma growth hormone concentration is not abolished by peripheral decarboxylase inhibition (Mars & Genuth, 1973). In contrast, the effect of levodopa on prolactin may be partly dependent upon direct pituitary effects. Bromocriptine effectively suppresses abnormal lactation and causes a fall in prolactin concentration in normal subjects, although in the present patients with Parkinsonism, initial prolactin levels were low and further reduction due to bromocriptine could not be demonstrated. It is not at present certain whether bromocriptine has a different effect on the pituitary and hypothalamus, although this seems unlikely.

In average therapeutic dosages, levodopa causes a reduction in the erect blood pressure of around 10-20 mm Hg in normal and Parkinsonian subjects, and to a lesser extent lowers supine blood pressure (Calne *et al.*, 1970). The fall in supine blood pressure is likely to be due to a central action, and the fall in erect blood pressure is at least partly dependent upon the peripheral effects of levodopa on baroreceptor mechanisms. Bromocriptine causes a comparable fall in both standing and lying blood pressure to levodopa, although symptomatic postural hypotension is not often produced by either drug. Both levodopa and bromocriptine rarely cause cardiac ectopic beats (Calne *et al.*, 1974).

Bromocriptine appears to be a dopamine agonist drug in man, with similar therapeutic and side effects to levodopa. In animals, bromocriptine increases locomotor behaviour and in rodents with a unilateral 6-hydroxydopamine lesion causes contralateral circling, interpreted as being due to direct dopamine receptor stimulation (Corrodi, Fuxe, Hökfelt, Lidbrink & Ungerstedt, 1973). The specificity of dopamine receptor stimulation by bromocriptine has not, however, been established, and almost certainly this drug also affects serotonin and possibly noradrenaline receptors (Corrodi, Farnebo, Fuxe & Hamberger, 1975). In the doses studied in patients with Parkinson's disease, bromocriptine may act as a complete dopamine agonist and progressively greater improvement results from higher doses, although in two patients the 100 mg dosage was less effective than 50 mg. At times of peak plasma concentration, levodopa occasionally causes akinesia rather

than enhanced movement, possibly due to dopamine receptor depolarization rather than stimulation resulting from extremely high brain dopamine concentrations (Claveria, Calne & Allen, 1973). No patient has been described as yet who is akinetic as a result of extremely high bromocriptine dosages, but these cannot often be given due to the occurrence of dyskinesias. However, bromocriptine in such high dosages may cause receptor blockade as well as stimulation, and this is a possible explanation of the observation that two patients did not respond as well to 100 mg as to 50 mg doses.

The anti-emetic drug, metoclopramide, has the pharmacological property of causing dopamine receptor blockade in the nervous system, although it does not alter the activity of the dopamine sensitive enzyme adenylate cyclase (Peringer, Jenner, Donaldson, Marsden & Miller, 1976). When given with levodopa to prevent emesis, metoclopramide does not prevent either the therapeutic effect of this drug or diminish the severity of levodopa dyskinesias (Tarsy, Parkes & Marsden, 1975). This may be partly dependent on the fact that metoclopramide given with levodopa causes an increased plasma dopa concentration. We have observed a single patient in whom the anti-Parkinsonian effect of bromocriptine, but not levodopa, was prevented by metoclopramide, in keeping with the concept that metoclopramide blocks dopamine receptors and bromocriptine stimulates them. It remains to be determined whether dose-effect curves to bromocriptine are shifted by metoclopramide.

The ideal of a specific nigro-striatal dopamine receptor stimulant drug to treat patients with Parkinson's disease has not yet been realized, although this may be a practical possibility. Of the dopamine agonist drugs used, apomorphine is of limited value since it must be given by injection and causes vomiting, although it has a very considerable clinical effect (Cotzias, Papavasiliou, Fehling, Kaufman & Mena, 1970). Piribedil has considerable activity in animal models of Parkinsonism, but has little or no anti-Parkinsonian effect in man, although it frequently causes neuro-psychiatric disturbances and emesis (Vakil, Calne, Reid & Seymour, 1973). Lergotrile has not yet been fully evaluated but may possess a greater effect upon tremor than other Parkinsonian symptoms (Lieberman, Miyamoto, Battista & Goldstein, 1975). Bromocriptine appears to possess the greatest therapeutic index between potency and side effects of this group of drugs, and may to some extent selectively stimulate nigro-striatal rather than hypothalamic or medullary dopamine receptors. It is not yet certain whether there are different types of dopamine

receptors in the central nervous system, corresponding to α and β adrenoceptors in the adrenergic system, although this is a possible explanation of the different anti-Parkinsonian, emetic, hormonal and neuro-psychiatric effects of different dopamine agonist drugs.

We gratefully acknowledge the help of Dr M.O. Thorner,

of the Department of Endocrinology, St Bartholomew's Hospital, who did the prolactin assays, the support of Dr G. Kennedy and Sandoz for the running of the King's College Hospital Parkinson's Disease Clinic, together with the gift of bromocriptine, and the secretarial assistance of Miss M. O'Rourke. A.G.D. was supported by a joint research grant from the Institute of Psychiatry, King's College Hospital and Medical School.

References

- BOYD, A.E., LEOVITZ, H.E. & PFEIFFER, J.B. (1970). Stimulation of human growth hormone secretion by l-dopa. *New Engl. J. Med.*, **283**, 1425-1429.
- CALNE, D.B., BRENNAN, J., SPIERS, A.S.D. & STERN, G.M. (1970). Hypotension caused by l-dopa. *Br. med. J.*, **1**, 474-475.
- CALNE, D.B., TEYCHENNE, P.F., CLAVERIA, L.E., EASTMAN, R. & GREENACRE, J.K. (1974). Bromocriptine in Parkinsonism. *Br. med. J.*, **4**, 442-444.
- CAMMANI, F., MASSARA, F., BELFORTE, L. & MOLINATTI, G.M. (1975). Changes in plasma growth hormone levels in normal and acromegalic subjects following administration of 2-bromo-alpha-ergocryptine. *J. clin. Endocr.*, **40**, 363-366.
- CLAVERIA, L.E., CALNE, D.B. & ALLEN, J.G. (1973). 'On-Off' phenomena related to high plasma levodopa. *Br. med. J.*, **2**, 641-643.
- CORRODI, H., FARNEBO, L.O., FUXE, K. & HAMBERGER, B. (1975). Effect of ergot drugs on central 5-hydroxytryptamine neurones. Evidence for 5-hydroxytryptamine release or receptor stimulation. *Eur. J. Pharmac.*, **30**, 172-181.
- CORRODI, H., FUXE, K., HÖKFELT, T., LIDBRINK, P. & UNGERSTEDT, U. (1973). Effect of ergot drugs on central catecholamine neurones: evidence for a stimulation of central dopamine neurones. *J. Pharm. Pharmac.*, **25**, 409-412.
- COTZIAS, G.C., PAPAVALIOU, P.S., FEHLING, C., KAUFMAN, B. & MENA, I. (1970). Similarities between neurologic effects of l-dopa and of apomorphine. *New Engl. J. Med.*, **282**, 31-33.
- DEBONO, A., DONALDSON, I., MARSDEN, C.D. & PARKES, J.D. (1975). Bromocriptine in Parkinsonism. *Lancet*, **ii**, 987-988.
- FUXE, K., CORRODI, H., HÖKFELT, T., LIDBRINK, P. & UNGERSTEDT, U. (1974). Ergocornine and 2-Br- α -Ergocryptine. Evidence for prolonged dopamine receptor stimulation. *Med. Biol.*, **52**, 121-132.
- HÖKFELT, T., LJUNGDAHL, A., FUXE, K. & JOHANSSON, O. (1974). Dopamine nerve terminals in the rat limbic cortex: aspects of the dopamine hypothesis of schizophrenia. *Science*, **184**, 177-179.
- KLAWANS, H.L., ILAHI, M.M. & SHENKER, D.M. (1970). Theoretical implications of the use of l-dopa in Parkinsonism. *Acta neurol. scand.*, **46**, 409-441.
- LIEBERMAN, A., MIYAMOTO, T., BATTISTA, A.F. & GOLDSTEIN, M. (1975). Studies of the anti-parkinsonian efficacy of lergotril. *Neurology (Minneapolis)*, **25**, 459-462.
- MARS, H. & GENUTH, S.M. (1973). Potentiation of levodopa-stimulation of human growth hormone by systemic decarboxylase inhibition. *Clin. Pharmac. Ther.*, **14**, 390-395.
- MARSDEN, C.D., BARRY, P.E., PARKES, J.D. & ZILKHA, K.J. (1973). Treatment of Parkinson's disease with levodopa combined with l-alpha-methyl-dopa hydrazine, an inhibitor of extracerebral DOPA decarboxylase. *J. Neurol. Neurosurg. Psychiat.*, **36**, 10-14.
- MCNEILLY, A.S. (1973). Radioimmunoassay of human prolactin. *Proc. roy. soc. Med.*, **66**, 863-864.
- NOBIN, A. & BJÖRKLUND, A. (1973). Topography of the monoamine neuron systems in the human brain as revealed in fetuses. *Acta physiol. scand. suppl.*, **388**, 1-40.
- PENG, M.T. (1963). Locus of emetic action of epinephrine and DOPA in dogs. *J. Pharmac. exp. Ther.*, **139**, 345-349.
- PERINGER, E., JENNER, P., DONALDSON, I., MARSDEN, C.D. & MILLER, R. (1976). Metoclopramide and dopamine receptor blockade. *Neuropharmac.* (in press).
- POZO, E., BRUN DEIRE, R., VARGA, L. & FRIESEN, H. (1972). The inhibition of prolactin secretion in man by CB154 (2-Br-alpha-ergocryptine). *J. clin. Endocr.*, **35**, 768-771.
- SCHLACH, D.S. & PARKER, M.L. (1964). A sensitive double antibody immunoassay for human growth hormone in plasma. *Nature (Lond.)*, **203**, 1141-1142.
- TARSY, D. & BALDESSARINI, R.J. (1974). Behavioural supersensitivity to apomorphine following chronic treatment with drugs which interfere with the synaptic function of catecholamines. *Neuropharmac.*, **13**, 927-940.
- TARSY, D., PARKES, J.D. & MARSDEN, C.D. (1975). Metoclopramide and pimozide in Parkinson's disease and levodopa-induced dyskinesias. *J. Neurol. Neurosurg. Psychiat.*, **38**, 331-335.
- THORNER, M.O. (1975). Dopamine is an important neurotransmitter in the autonomic nervous system. *Lancet*, **i**, 662-665.
- VAKIL, S.D., CALNE, D.B., REID, J.L. & SEYMOUR, D.A. (1973). Pyrimidyl-Piperonyl-Piperazine (ET495) in Parkinsonism. In *Progress in the treatment of Parkinsonism*, ed Calne, D.B. pp. 121-130. New York: Raven Press.
- VOIGTLANDER, P.F., LOSEY, E.G. & TRIEZLENBERG, H.J. (1975). Increased sensitivity to dopaminergic agents after chronic neuroleptic treatment. *J. Pharmac. exp. Ther.*, **193**, 88-94.

(Received January 8, 1976)