PAPERS AND ORIGINALS

Bromocriptine Treatment of Acromegaly

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Summary

The effects of oral bromocriptine in acromegaly have been studied. A dose of 5 mg six-hourly suppressed circulating growth hormone (GH) levels in nine out of 11 patients treated for seven to 11 weeks. This was associated with considerable clinical improvement in all patients, with abolition of excessive sweating, reduction in soft-tissue thickening, loosening of rings, decrease in shoe size, improvement in facial features, and loosening of dentures. Metabolic changes included improvement in glucose tolerance and reduction in hydroxyproline excretion. Unlike the actions of growth hormone release inhibiting hormone the suppression of GH was not accompanied by a reduction in insulin or glucagon secretion, though prolactin levels were suppressed. Side effects other than mild constipation were not seen when the full dose regimen was reached by slowly increasing the dose from 2·5 mg once daily. Bromocriptine holds promise as a safe and orally effective medical treatment to augment surgical or radiotherapeutic measures directed at the pituitary tumour. Its efficacy during long-term administration remains to be established.

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Introduction

Conventional treatment of acromegaly is directed at the pituitary gland—firstly, to prevent or reverse any local effects of the tumour (for example, compression of the optic nerves and chiasm leading to field defects), and, secondly, to lower growth hormone (GH) levels and correct the complications consequent on the metabolic effects of GH. Surgery and irradiation of the tumour do not always produce rapid or adequate clinical improvement or reduction in circulating GH levels. Thus an effective form of medical treatment has been sought to augment the effects of these procedures but to date no such treatment has been available.

GH secretion is under hypothalamic control. Neuropharmacological studies have suggested that GH secretion is modulated by catecholamines (Rees *et al.*, 1970; Frohman, 1972). In man α-adrenoreceptor stimulation leads to an increase in circulating GH levels, while stimulation of β-adrenoreceptors results in a fall (Blackard *et al.*, 1970). Levodopa, a precursor of dopamine, noradrenaline, and adrenaline, increases circulating GH levels in normal people (Eddy *et al.*, 1971; Kansal *et al.*, 1972) but in acromegalic patients there is a paradoxical response leading to suppression of GH (Liuzzi *et al.*, 1972; Mims *et al.*, 1973). Bromocriptine (2-brom-α-ergocryptine; CB 154) is an orally active ergot alkaloid which suppresses the secretion of prolactin by an action on the pituitary (Flückiger and Wagner, 1968; Pasteels *et al.*, 1971). Recently it has been shown to be a dopaminergic agonist, and for this reason Liuzzi *et al.* (1974) studied its effects in acromegaly. They showed that single doses of 2·5 mg apparently lowered circulating immunoreactive GH levels acutely but the cross-reactivity of prolactin in their GH assay was not reported, so that the specificity of this action relating to GH was uncertain.

We report the results of continuous bromocriptine therapy in 11 acromegalic patients during the initial 11 weeks of treatment. Our aims were, firstly, to confirm the observations of Liuzzi *et al.* using a GH assay known not to cross-react appreciably with prolactin; secondly, to establish whether the GH suppression could be sustained during long-term treatment; and,

thirdly, to attempt to establish a satisfactory regimen for the treatment of acromegaly.

Patients

The seven women and four men patients (aged 36-66 years) gave informed consent to the study. All had active acromegaly. Nine had had external pituitary irradiation, and one of these had also had a partial hypophysectomy. Two (cases 8 and 11) had not been previously treated. Case 11 was treated for seven weeks and then treatment was temporarily withdrawn to see whether any effects noted were indeed due to the drug and to determine whether these persisted after it was stopped. This patient is omitted from our figs. 1 to 8.

Methods

Ten patients were assessed clinically and biochemically as outpatients and one, a diabetic, was stabilized as an inpatient. All blood samples were obtained through forearm venous cannulae. The following methods of biochemical assessment were carried out. (1) A control study (the *control day curve*), in which six blood samples were taken between 11.00 and 19.00 hours. These data were obtained in five cases. (2) Construction of a *bromocriptine day curve*, in which 12 blood samples were taken at intervals between 08.30 and 19.00 hours after a test dose of bromocriptine (2·5 mg) at 08.30 hours with the patient recumbant through the day. This test was repeated when the patient had been stabilized on 2·5 mg 12-hourly for one to nine weeks and again when established on 5 mg six-hourly for one to four weeks. (3) An oral glucose tolerance test (G.T.T.); this was performed before treatment and at three, seven, and 11 weeks. Two basal blood samples were obtained followed by half-hourly samples for two and a half hours. (4) Collection of 24-hour urine specimens from seven patients before treatment and three and seven weeks afterwards.

Serum GH was measured in all blood samples and, in addition, blood sugar, serum insulin, and plasma glucagon were measured during the G.T.T. and serum prolactin was measured during the period of the *day curves*. GH and hydroxyproline were measured in the urine.

DOSE REGIMEN OF BROMOCRIPTINE

A dose of 2·5 mg was taken by mouth with food on retiring at the start of treatment and increased to 2·5 mg 12-hourly after three days. After a further three to nine weeks the patients increased their dose at three-day intervals as follows: 2·5 mg eight-hourly, 2 5 mg six-hourly, and 5 mg six-hourly. In one patient (case 6) the dose was increased to 40 mg/day. When side effects occurred the dose was reduced and gradually increased again (case 3).

ASSAYS

The following were measured by specific radioimmunoassays: serum GH (Forsyth *et al.*, 1971) and urinary GH (Hanssen, 1972), the first international reference preparation being used as standard (5 mg prolactin per l showed no cross-reactivity in the serum GH assay); serum insulin (Sönksen *et al.*, 1973) with M.R.C. standard 66/304; plasma pancreatic glucagon (C-terminal antiserum) (Bloom, 1971) with M.R.C. standard 69/104; and serum prolactin (McNeilly, 1973) with Friesen standard. Blood sugar was measured by a neocuproine method (Technicon). Urinary peptide hydroxyproline was measured by using a semiautomated modification of the methods of Stegemann and Stalder (1967) and Klein (1970). Urinary creatinine was measured by using the standard AutoAnalyzer method N-11. The urinary hydroxyproline:creatinine ratio was calculated from these values, the upper limit of the normal range for adults being 0·027 μmol:μmol (Le Roy, 1967).

Results

The basal GH levels in the 11 patients varied from 6 to 90μg/l and failed to suppress to less than 4μg/l during the G.T.T. There was a paradoxical rise in seven patients after the oral glucose load.

GH LEVELS THROUGHOUT THE DAY

The serum GH levels in one patient during a control day and after the first 2·5-mg dose of bromocriptine are shown in fig. 1 and for the group as a whole in the table and fig. 2. GH levels were suppressed in nine of the 11 patients after the first 2·5-mg dose, and these remained suppressed throughout the study day except in one (case 1), whose levels rose after 10½ hours. During the continuous bromocriptine therapy the GH levels were clearly suppressed in nine of the 11 patients (fig. 2, table).

In six of the nine responding patients the lowest mean levels of GH were seen with the highest dose of bromocriptine (20 mg/day), but in the remaining three a dose of 5 mg/day was as effective. In several patients (see, for example, fig. 3) GH levels did not remain suppressed throughout 12 hours on a twice-daily dose regimen, the levels rebounding after less than eight hours. In these patients the circulating GH levels remained lower and well suppressed on a six-hourly dosage regimen. The mean serum GH levels in the responding patients were reduced from 8 to 95 μg/l to 5 to 32 μg/l on 20 mg bromocriptine daily.

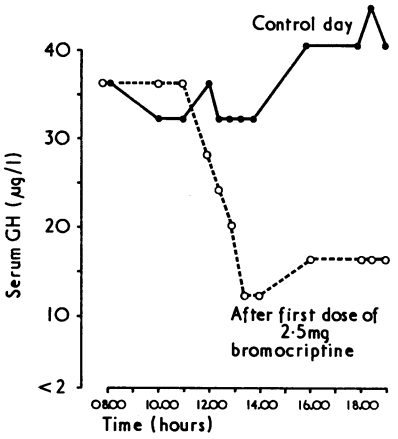

FIG. 1—Serum GH levels in woman with acromegaly during control day and after initial 2·5 mg bromocriptine dose given at 08.30 hours.

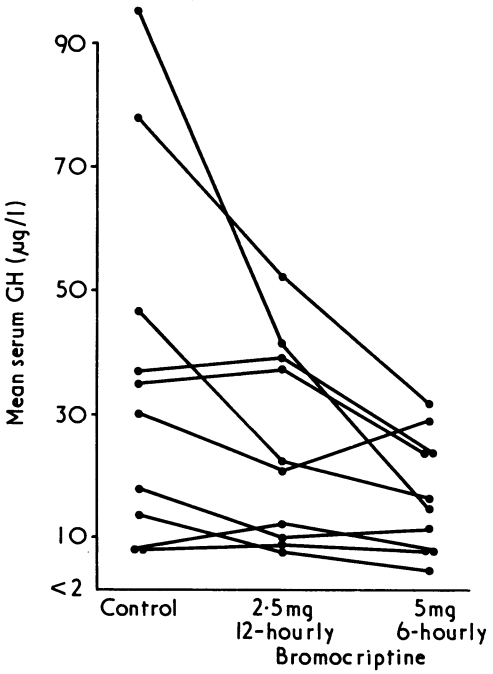

FIG. 2—Mean serum GH levels during control days and bromocriptine day curves on 2·5 mg 12-hourly and 5 mg six-hourly.

Serum GH (μg/l) during Day Before (Control) and when on Treatment with Bromocriptine

Case No.	Bromocriptine Treatment: Dose in mg	Duration in (Weeks)	Time (Hours): 08.30	10.00	11.00	12.00	12.30	13.00	13.30	14.00	16.00	18.00	18.30	19.00	Mean*
1	Control		—	—	80	120	—	70	—	100	120	—	—	80	95
	2·5 Initial dose		85	85	35	19	15	14	14	15	22	9	—	50	
	2·5 12-hourly	3	80	72	48	28	24	20	20	20	32	68	68	12	41
	5·0 6-hourly	2	—	15	15	9	12	12	12	12	12	18	21	21	15
2	Control		—	—	25	45	—	50	—	50	45	—	—	65	47
	2·5 Initial dose		76	62	24	7	—	5	—	5	7	7	—	19	
	2·5 12-hourly	9	12	10	10	9	11	12	18	30	30	30	36	45	22
	5·0 6-hourly	1	11	11	19	18	16	17	22	14	12	22	12	—	16
3	Control		—	—	110	80	—	90	—	80	80	—	—	90	88
	2·5 Initial dose		72	60	56	36	24	20	20	20	20	36	44	36	
	2·5 12-hourly	5	64	48	40	—	—	32	44	44	48	72	64	65	52
	5·0 6-hourly	1	28	20	20	28	28	32	36	44	33	32	40	40	32
4	Control		—	—	—	—	—	—	—	—	—	—	—	—	37
	2·5 Initial dose		38	38	38	30	28	28	16	18	16	26	24	26	
	2·5 12-hourly	3	42	27	—	24	24	30	33	36	42	62	45	48	39
	5·0 6-hourly	2	20	24	28	24	24	22	22	24	22	24	26	26	24
5	Control		—	—	45	40	—	45	—	40	45	—	—	45	43
	2·5 Initial dose		31	55	40	31	30	30	30	30	30	38	36	33	
	2·5 12-hourly	7	38	43	32	32	35	48	42	41	39	34	33	42	38
	5·0 6-hourly	2	16	21	29	22	21	24	24	24	31	22	21	28	24
6	Control		—	—	57	30	—	30	—	33	33	—	—	45	38
	2·5 Initial dose		43	14	9	8	—	7	—	7	12	12	16	15	
	2·5 12-hourly	1	24	20	20	12	10	7	8	10	18	24	23	26	16
	10·0 6-hourly	2	22	13	18	20	14	18	22	27	17	24	19	27	20
7	Control		—	—	—	—	—	—	—	—	—	—	—	—	30
	2·5 Initial dose		40	32	20	16	—	16	—	—	24	36	—	28	
	2·5 12-hourly	5	12	13	12	19	18	26	26	23	18	36	24	22	21
	5·0 6-hourly	2	—	12	38	42	30	34	30	38	18	32	22	18	29
8	Control		—	—	—	—	—	—	—	—	—	—	—	—	18
	2·5 Initial dose		21	21	8	5	5	4	5	6	5	33	12	9	
	2·5 12-hourly	3	10	11	11	8	8	6	6	6	8	17	13	—	10
	5·0 6-hourly	2	—	5	13	12	14	14	17	16	9	8	—	—	12
9	Control		—	—	—	—	—	—	—	—	—	—	—	—	8
	2·5 Initial dose		9	4	6	8	6	7	9	10	11	10	10	9	
	2·5 12-hourly	8	10	9	7	10	9	9	10	7	9	11	11	8	9
	5·0 6-hourly	2	9	12	8	8	8	10	8	7	7	—	7	7	8
10	Control		—	—	—	—	—	—	—	—	—	—	—	—	8
	2·5 Initial dose		9	4	6	8	6	7	9	10	11	10	10	9	
	2·5 12-hourly	7	9	8	12	15	14	9	8	10	21	11	19	11	12
	5·0 6-hourly	2	7	7	5	8	9	6	5	7	7	13	13	11	8
11	Control		—	—	—	—	—	—	—	—	—	—	—	—	14
	2·5 Initial dose		14	12	7	3	<2	<2	<2	<2	<2	3	3	3	
	2·5 12-hourly	3	3	<2	2	4	6	4	3	3	3	24	24	18	8
	5·0 6-hourly	1½	4	3	2	4	5	3	3	3	15	9	7	5	5
	5·0 6-hourly	4	12	9	5	7	8	10	8	5	6	10	8	10	8
	Off bromocriptine for one week		12	8	8	15	14	17	14	16	14	18	10	11	13

*Mean values for control observations were calculated from control day curve when available or alternatively from mean of the two basal pretreatment G.T.T. values and valu obtained before bromocriptine dose—that is, from the three basal values.

The lowest values seen on this dose during the day curve studies were between 3 and 20 μg/l. The two non-responding patients (cases 9 and 10) had a basal GH level of only 8 μg/l before treatment.

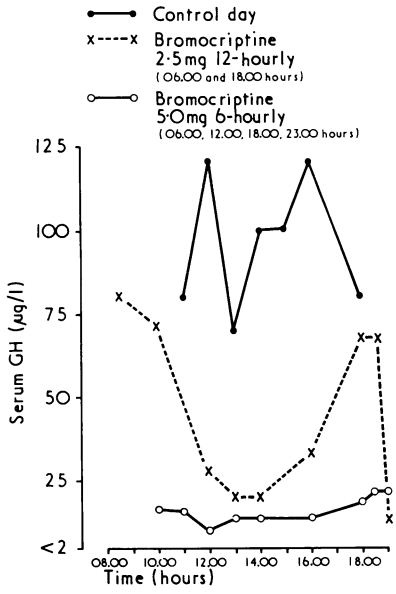

FIG. 3—Serum GH levels in woman with acromegaly (case 1) during control day (before treatment was started) and while on bromocriptine 2·5 mg 12-hourly and 5 mg six-hourly.

G.T.T.

Blood Sugar (fig. 4).—Glucose tolerance was considered diabetic when the two-hour blood sugar was greater than 6·1 mmol/l (110 mg/100 ml) and the peak greater than 8·9 mmol/l (160 mg/100 ml) (Keen, 1968). Six patients (cases 1, 2, 3, 5, 6, and 10) were diabetic before treatment; two (cases 5 and 10) were on chlorpropamide and one (case 6) was on insulin. With bromocriptine treatment glucose tolerance improved in all the patients, and the fasting blood sugar levels fell in those who had had levels above 4·4 mmol/l (80 mg/100 ml). Peak levels fell in all except case 9 and in cases 5 and 10, in which the oral hypoglycaemic agents had been stopped. Having been diabetic, glucose tolerance became normal in cases 2, 3, and 5. It was possible to stop the oral hypoglycaemic agents in cases 5 and 10 and the glucose tolerance remained normal. One patient (case 6) was able to reduce his daily insulin dose from 140 units soluble plus isophane insulin to 40 units insulin lente. The area under the blood sugar curves showed improvement in the diabetic patients (fig. 4).

Serum GH (fig. 5).—By three weeks of treatment the basal GH levels had fallen in seven patients. The individual means of the GH levels obtained during the G.T.T. were reduced in 10 patients and any paradoxical increase in GH seen before treatment was abolished (seven patients). GH levels remained suppressed in all responding patients at seven and 11 weeks except in case 6, in which the GH levels during G.T.T. rose between seven and 11 weeks though the clinical improvement persisted.

Serum Insulin and Plasma Glucagon.—There was no change in the basal or post-glucose serum insulin or plasma glucagon values during the G.T.T. after three to seven weeks of treatment (figs. 6 and 7).

URINARY GH

Urinary GH levels fell in five of the seven patients, becoming undetectable in three. In two the levels appeared to rise but the clinical response was maintained.

URINARY HYDROXYPROLINE

Urinary hydroxyproline (fig. 8) was raised in all seven patients. In five the levels fell by three weeks and in four this was to the normal range.

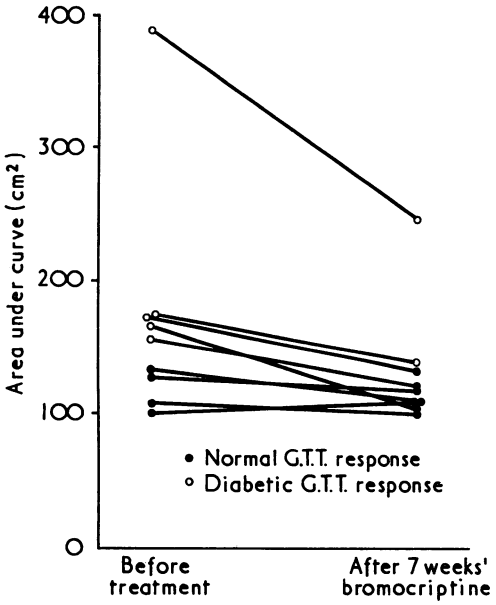

FIG. 4—Area under blood sugar curve during G.T.T. in nine acromegalic patients before and after seven weeks of bromocriptine therapy.

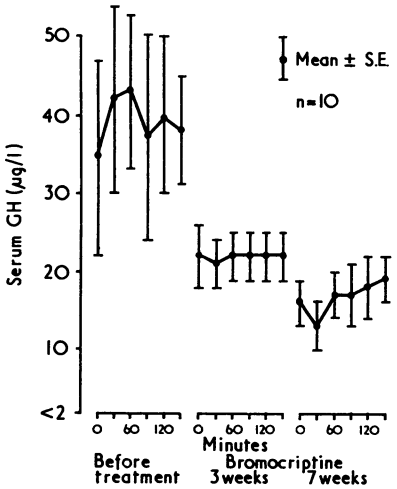

FIG. 5—Mean serum GH levels in 10 acromegalic patients before and while on bromocriptine therapy at three and seven weeks.

BASAL PROLACTIN LEVELS

These were raised (>20 μg/l) in two patients and were at the upper limit of normal in two others (range 4-40 μg/l). Levels suppressed, often becoming undetectable, in all patients when on bromocriptine therapy.

CLINICAL RESPONSE

Abolition of excessive sweating occurred during the first few days of bromocriptine treatment. All patients noticed a change in their soft tissues, particularly of their hands and feet. The most dramatic changes occurred in the patients with the highest pretreatment GH levels; by seven weeks four patients were wearing shoes a size smaller, and a fifth who wore surgical shoes because of the size and shape of his feet found that they were too loose. Rings became loose in six patients. Of these, two had been unable to wear their rings for over five years; they could put them on after only three to four weeks of therapy, and another could remove her ring for the first time in eight years. Palmar soft-tissue thickening was reduced rapidly, and one patient regained the ability to make a fist. Two other patients could intertwine their fingers again. Facial features also changed; particularly striking was the recession of swollen lips. Three patients noticed that their dentures became loose.

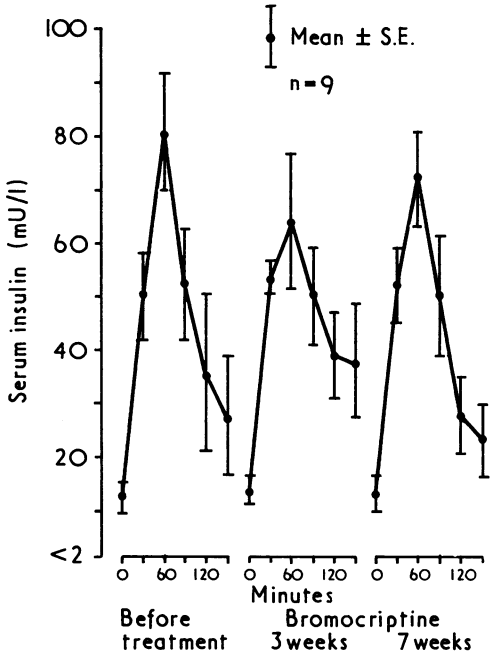

FIG. 6—Mean serum insulin levels in nine acromegalic patients before treatment and while on bromocriptine therapy at three and seven weeks.

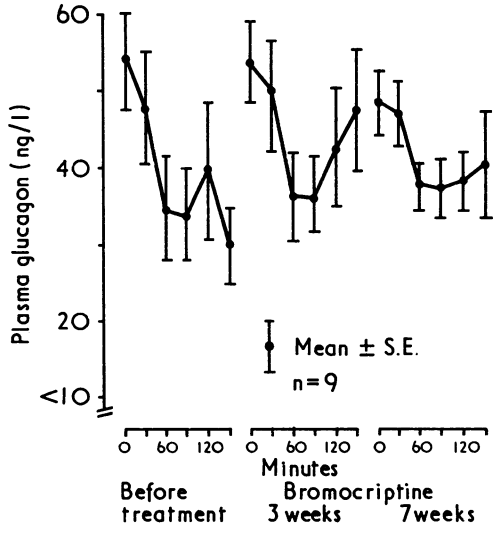

FIG. 7—Mean plasma glucagon levels in nine acromegalic patients before treatment and while on bromocriptine therapy at three and seven weeks.

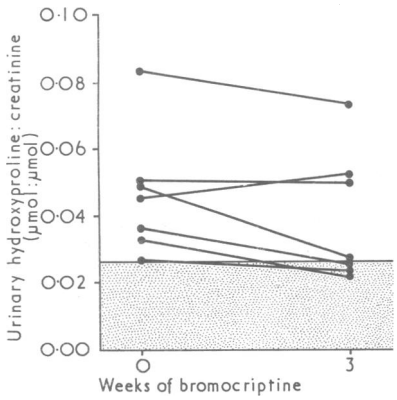

FIG. 8—Urinary hydroxyproline excretion in seven acromegalic patients before and while on bromocriptine therapy at three weeks.

WITHDRAWAL OF THERAPY

One patient (case 11) was treated for seven weeks, during which his GH levels fell appreciably both during his day curve studies and during the G.T.T. Two weeks after stopping bromocriptine, however, the circulating GH and blood sugar levels during the G.T.T. and the urinary hydroxyproline excretion had risen. Excessive sweating had also returned.

SIDE EFFECTS

With the regimen described no side effects other than mild constipation were seen except in one patient when he reached 20 mg/day. After reducing the dose his nausea disappeared and he was later able to increase the dose again to 20 mg/day. Mild constipation occurred in six patients, and this was reduced by the daily administration of Isogel. Salivary duct obstruction occurred in two patients but this was temporary. It was relieved after sialography in each case. There was no evidence of calculus formation.

Discussion

Bromocriptine was effective in lowering the circulating GH levels in nine of the 11 patients studied. In two (cases 9 and 10) there appeared to be no suppression of circulating GH levels. In one (case 9), however, urinary GH excretion became undetectable, reflecting a reduction in 24-hour secretion. In the other there was a good clinical response, associated with a reduction in 24-hour urinary hydroxyproline excretion, despite the lack of a clear change in the serum GH level. Glucose tolerance was improved in six diabetic patients and in three it became normal. All the patients responded clinically with the abolition of sweating and a considerable reduction in soft-tissue thickening leading to a reduction in shoe size, improved dexterity, loosening of rings and dentures, and improvement in facial features. We have thus confirmed the observation of Liuzzi *et al.* (1974) that bromocriptine lowers GH levels in acromegaly after single doses and, in addition, shown that this effect is maintained during continuous therapy for at least 11 weeks. The circulating immunoreactive GH levels were not reduced to normal; nonetheless, there were marked clinical and metabolic responses, including an improvement in glucose tolerance and a reduction in hydroxyproline excretion. Presumably the reduction in GH achieved was sufficient to reduce greatly the damaging metabolic effects of exposure of the tissues to excessive GH. We do not yet know whether more-prolonged therapy or an increase in dosage will lower GH levels further without inducing unacceptable side effects.

Bromocriptine is effective in lowering prolactin levels in a dose of 2·5 mg eight-hourly (Besser *et al.*, 1972; Leutenegger *et al.*, 1972; Del Pozo *et al.*, 1973; Varga *et al.*, 1973; Thorner *et al.*, 1974). Evidently, however, a greater dose is required to lower GH than prolactin in acromegaly and a six-hourly regimen is necessary.

Side effects were not a problem when the slowly increasing dose regimen described here was adopted. Our experience using this compound in patients with galactorrhoea has shown that when treatment is begun with a large dose in a fasting state nausea, vomiting, and postural hypotension may be expected. This does not occur when the slowly increasing dose regimen is adopted. Side effects were not a problem though six patients developed mild constipation. This may have been due to stimulation of peripheral dopaminergic receptors, leading to decreased gastrointestinal mobility, and this may also account for the flattened oral glucose tolerance curve noted in two cases.

Bromocriptine holds promise as a safe, effective, non-invasive method of controlling GH levels in acromegaly. The only other medical treatment which will reliably lower GH levels in acromegaly is growth hormone release inhibiting hormone, but this also inhibits secretion of thyroid-stimulating hormone, glucagon, insulin, and gastrin and in the form currently available its action is only short lived, so that it has to be administered by infusion (Hall *et al.*, 1973; Besser *et al.*, 1974 a, 1974 b; Bloom, 1974; Mortimer *et al.*, 1974). By contrast, bromocriptine does not appear to alter glucagon or insulin secretion and thyroid function remains normal. Prolactin secretion is, however, suppressed. In addition to the patients described in detail here we have treated a further 10 patients (one is shown in fig. 1), all of whom showed similar improvement.

We suggest that bromocriptine may provide an important medical treatment of acromegaly to augment local measures directed at the pituitary tumour.

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