RESPONSE OF ACROMEGALY TO LONG TERM BROMOCRIPTINE THERAPY: A BIOCHEMICAL AND CLINICAL ASSESSMENT

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ABSTRACT

The long term effects of bromocriptine in 12 acromegals treated for a mean duration of 10.2 months are reported. Seven showed a significant \((P < 0.05)\) and sustained fall in serum immunoreactive growth hormone (GH) levels throughout 24 h, 6 of whom had a 50 \% or greater reduction in mean circulating GH during glucose tolerance testing. Only one patient had mean serum GH levels throughout the day suppressed to normal \((< 5 \text{ mIU/l})\) but 3 had suppression of mean serum GH during GTT to normal or very near normal \((< 10 \text{ mIU/l})\). The effective dose was 20 mg daily. Only 4 patients reported any improvement in soft tissue swelling and acral features, which was unrelated to the GH response. Possible reasons for the discrepancy between clinical and biochemical responses are discussed. In 9 of the 12 patients bromocriptine was discontinued and pituitary ablative therapy offered. Three out of 4 patients who underwent trans-sphenoidal hypophysectomy had mean GH levels during GTT reduced to < 7 mIU/l. In the three who continued bromocriptine treatment GH suppression was maintained at less than 10 mIU/l for up to 3 years but with little change in acral features. Although bromocriptine is safe and well tolerated it is not as effective as existing forms of pituitary ablative therapy and should be reserved for those cases where ablation is contraindicated or unsuccessful.

Acromegaly is a disfiguring disease which, untreated, results in a reduction in life expectancy because of its complications \((\text{Wright et al. 1970b})\).
Until recently therapy has been aimed directly at ablation of the pituitary tumour either surgically or by various forms of radiotherapy. None of these methods consistently achieves a permanent and stable reduction in serum growth hormone (GH) levels or consistently cures the clinical manifestations of the disease. Furthermore approximately 25% of patients develop permanent hypopituitarism following such treatment (Williams et al. 1975; Linfoot et al. 1970; Wright et al. 1970a). Thus an effective oral therapeutic agent for suppressing GH secretion in acromegaly is highly desirable.

Following the discovery that the synthetic dopamine agonist, bromocriptine, acutely lowered serum GH levels in acromegals (Liuzzi et al. 1974) hopes were raised that chronic administration would specifically reduce serum GH levels to normal without effect on other pituitary hormone secretion. Initial short term studies showed that a stable reduction in GH secretion could be achieved (Chiodini et al. 1975; Thorner et al. 1975; Sachdev et al. 1975) but only rarely did levels fall to normal. Recent longer term studies confirmed these earlier reports (Wass et al. 1977; Belforte et al. 1977) and demonstrated that improvement in the clinical features of active disease occurred coincident with the suppression of GH secretion. In spite of reduction in GH levels of comparable degree to that reported above Cassar et al. (1977) were unable to demonstrate any clinical improvement after 6 months of treatment. The place of bromocriptine in the management of acromegaly therefore needs to be firmly established. We report here our results of growth hormone and clinical responses to bromocriptine in an unselected group of 12 acromegals treated for between 4 and 16 months with a range of bromocriptine dosages.

**PATIENTS AND METHODS**

**Patients and bromocriptine dosage schedule**

Details of the 12 patients, 7 men (27–58 years) and 5 women (25–53 years) are shown in Table 1. Duration of acromegaly was from 1–30 years. All patients had clinically and biochemically active disease as defined by failure to suppress persistently elevated GH levels to below 5 mIU/l during an oral 50 g glucose tolerance test (GTT). All patients had acral features of bone expansion and increase in soft tissue thickness of face, hands and feet. All patients had pituitary tumours as shown by enlargement of the pituitary fossa on tomography. Patients 9, 10, 11 had received previous pituitary ablative therapy which had terminated at least 15 months prior to entry into the study. Patients 10, 11 had concentric constriction of their visual fields whereas patient 9 and the untreated patients had no evidence of visual impairment on perimetry. Sweating was prominent in 4 patients and 5 had clinical evidence of carpal tunnel syndrome (CTS) confirmed by nerve conduction studies. Headache was troublesome in 5 patients and 2 patients were diabetic requiring insulin treatment. Two patients were hypertensive (diastolic BP > 95 mmHg) requiring treatment.

Bromocriptine, as 2.5 mg tablets or 10 mg capsules, was gradually introduced with
**Table 1.**
Clinical details of patients receiving bromocriptine.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Sex</th>
<th>Duration of disease (months)</th>
<th>Presenting symptoms/ signs</th>
<th>Previous therapy</th>
<th>Hypopituitarism</th>
<th>Duration of therapy (months)</th>
<th>Maximum bromocriptine dosage (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>52</td>
<td>M</td>
<td>12</td>
<td><strong>sweating headache CTS</strong></td>
<td>-</td>
<td>-</td>
<td>7</td>
<td>40</td>
</tr>
<tr>
<td>2°</td>
<td>36</td>
<td>F</td>
<td>120</td>
<td><strong>sweating headache CTS</strong></td>
<td>-</td>
<td>-</td>
<td>10</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>58</td>
<td>M</td>
<td>240</td>
<td>** - - + on replacement therapy**</td>
<td></td>
<td></td>
<td>9</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>53</td>
<td>M</td>
<td>180</td>
<td><strong>headache CTS, DM</strong></td>
<td>-</td>
<td>-</td>
<td>5</td>
<td>40</td>
</tr>
<tr>
<td>5°</td>
<td>54</td>
<td>M</td>
<td>360</td>
<td><strong>hypertension</strong></td>
<td>-</td>
<td>-</td>
<td>15</td>
<td>40</td>
</tr>
<tr>
<td>6°</td>
<td>57</td>
<td>M</td>
<td>96</td>
<td>** - - -**</td>
<td>-</td>
<td>-</td>
<td>16</td>
<td>40</td>
</tr>
<tr>
<td>7</td>
<td>25</td>
<td>F</td>
<td>36</td>
<td><strong>sweating</strong></td>
<td>-</td>
<td>-</td>
<td>14</td>
<td>80</td>
</tr>
<tr>
<td>8</td>
<td>53</td>
<td>F</td>
<td>72</td>
<td><strong>headache hypertension</strong></td>
<td>-</td>
<td>-</td>
<td>8</td>
<td>40</td>
</tr>
<tr>
<td>9°</td>
<td>26</td>
<td>F</td>
<td>36</td>
<td>** - external irradiation**</td>
<td>+</td>
<td></td>
<td>12</td>
<td>40</td>
</tr>
<tr>
<td>10°</td>
<td>29</td>
<td>F</td>
<td>38</td>
<td>** - hypox + external irradiation**</td>
<td>+</td>
<td></td>
<td>15</td>
<td>80</td>
</tr>
<tr>
<td>11</td>
<td>38</td>
<td>M</td>
<td>204</td>
<td><strong>sweating headache CTS, DM</strong></td>
<td>hypox + external irradiation</td>
<td>+</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>12°</td>
<td>27</td>
<td>M</td>
<td>36</td>
<td><strong>CTS</strong></td>
<td>-</td>
<td>-</td>
<td>7</td>
<td>80</td>
</tr>
</tbody>
</table>

* Hyperprolactinaemic (>640 mIU/l).
** Acral features.
CTS: carpal tunnel syndrome. DM: diabetic.
meals to a total daily dose of 10 mg over 7 days. Stepwise increments of 10 or 20 mg daily were made at six weekly intervals to a maximum of 80 mg daily. Doses were given at 06.00, 12.00, 18.00, 22.00 h. Duration of treatment ranged from 4 to 16 months initially (mean 10.2 months) but was continued for up to 3 years in 3 subjects.

**Laboratory assessment**

All samples were obtained through indwelling forearm venous cannulae. Assessments were made before treatment and immediately prior to each increment in bromocriptine dosage. Tests, except for the GH profile, began 2 h after the last dose of bromocriptine.

a) *Serum growth hormone profile*. As an index of daily GH secretion a profile was obtained from samples taken at 04.00, 10.00, 16.00 and 22.00 h on 2 separate days. During these days patients were allowed normal meals, were ambulant during the day and a sleep at 04.00, receiving no night sedation.

b) *Carbohydrate tolerance and GH secretion*. – A 50 g oral glucose tolerance test (GTT) was performed on one, often two, occasions at each assessment beginning at 09.00 h with sampling at 0, 30, 60, 90, 120 min for blood glucose and GH estimation. Patients were classified as diabetic according to the criteria of Keen (1968).

c) *Assessment of other pituitary hormones*. – A ‘combined pituitary stimulation test’ (Harsoulis et al. 1973) was performed before and whilst on maximal or near maximal dose of bromocriptine, to assess the effect of the drug on other anterior pituitary function. This consisted of the simultaneous intravenous administration of insulin (0.2–0.3 U/kg), gonadotrophin releasing hormone (100 µg) and thyrotrophin releasing hormone (200 µg) after an overnight fast.

**Clinical assessment**

At each biochemical assessment patients were asked to classify their major symptoms as unchanged, slight or moderate improvement, or complete disappearance. Particular attention was paid to soft tissue swelling and acral features, where changes in ring and shoe size and facial appearance were recorded. Heel pad thickness was measured radiologically. Any unwanted side effects of the drug volunteered by patients were recorded.

**Assay**

Pituitary hormones were measured by double antibody radioimmunoassay using the following reference preparations as standards:

LH: MRC 69/104; FSH: 69/104; TSH: MRC 68/38; prolactin: MRC 71/222; GH: MRC 66/217 (1 mIU MRC 66/217 = 1.0 ng/ml MRC std A). The intra- and inter-assay coefficients of variation for the GH assay were 4 and 7 %, respectively. Cortisol was measured by a competitive protein binding assay (Morris & Holder 1975). Blood glucose was measured by the glucose oxidase method. Statistical analysis of GH levels pre-treatment versus each dose of bromocriptine was by unpaired Student’s t-test. Before treatment and on each dose of bromocriptine four or more samples were available to allow assessment of spontaneous variation in GH levels. Differences due to the time of sampling were assessed by analysis of variance.

472
RESULTS

Growth hormone secretion

a) 09.00–10.00 h GH values. – The means of all growth hormone determinations available between 09.00–10.00 h in each patient on each dose of bromocriptine were compared with the means of pre-treatment values (Table 2). Two groups of patients are distinguished: group A 7/12 (cases 5–11) in whom a significant reduction in GH occurred at two or more dosages of bromocriptine are classed as ‘responders’ and group B 4/12 (cases 1–4) in whom no significant fall was observed with up to 40 mg bromocriptine daily, ‘non-responders’. There was an increase in mean serum GH in 3 patients on treatment (cases 2, 3, 12) though this only reached significance in one (case 12). The mean ± SEM of the GH levels at each treatment dose for the two groups are shown in Fig. 1. In the responders (group A) a significant effect was apparent on 10 mg bromocriptine daily with a further fall occurring on 20 mg/day, thereafter increasing the dosage was without further effect in the group as a whole. However, in the only patient (case 9) whose serum GH was suppressed to normal (< 5 mIU/l) this was only apparent after increasing the dosage from 20 to 40 mg daily. In 2 out of the 7 responders (cases 5, 7) increasing the dose above 30 mg/day resulted in ‘escape’ of control such that mean GH values were no longer significantly suppressed.

b) GH levels throughout 24 h. – The plasma GH rise that follows the onset of sleep in normal subjects (Takahashi et al. 1968) is abolished in acromegalics (Cryer & Daughaday 1969; Carlson et al. 1972). Recently Chihara et al. (1977) reported that the administration of 5–10 mg of bromocriptine daily for 14 days resulted in significant reduction in GH levels throughout the 24 h period. We compared the GH levels at 04.00 h with those at the other sampling times in both groups of patients. Analysis of variance conducted on four pre-treatment GH values taken on 2 separate days at 04.00, 10.00, 16.00, 22.00 h showed no significant variation in GH levels due to the time of sampling. On treatment GH levels remained suppressed throughout the 24 h in all patients who showed a significant reduction in morning GH levels (Fig. 2).

c) GH levels during GTT. – Five patients, 3 responders (cases 5, 6, 7) and 2 non-responders (cases 1, 4) showed a paradoxical GH rise during the GTT prior to treatment. In only one of these, a responder (case 6) was this rise abolished by bromocriptine 20 mg/day. The remaining 7 patients either showed a fall or no change in GH levels throughout the GTT, this pattern being unchanged by bromocriptine treatment irrespective of the GH response.

Mean serum GH levels during GTT are shown in Table 3. The percentage reduction in mean serum GH in the non-responders was < 45 % whilst in all the responders except one (case 8) it was > 50 % on at least one dose of
Table 2.
Serum GH levels (mIU/l) at 09.00–10.00 h with increasing bromocriptine dosage.
Mean ± sem of 4–9 samples.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Pre-treatment</th>
<th>10 mg</th>
<th>20 mg</th>
<th>30 mg</th>
<th>40 mg</th>
<th>60 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>63 ± 10</td>
<td>–</td>
<td>–</td>
<td>35 ± 9 (40)</td>
<td>54 ± 2 (14)</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>88 ± 20</td>
<td>94 ± 37 (↑7)</td>
<td>103 ± 15 (↑17)</td>
<td>–</td>
<td>117 ± 7 (↑33)</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>89 ± 15</td>
<td>108 ± 19 (↑21)</td>
<td>108 ± 11 (↑21)</td>
<td>–</td>
<td>94 ± 10 (↑6)</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>68 ± 6</td>
<td>81 ± 15 (↑19)</td>
<td>80 ± 16 (↑18)</td>
<td>–</td>
<td>61 ± 12 (10)</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>76 ± 11</td>
<td>43 ± 3 (43)</td>
<td>31 ± 3 (59)</td>
<td>–</td>
<td>65 ± 25 (14)</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>110 ± 20</td>
<td>13 ± 6 (88)</td>
<td>12 ± 1 (89)</td>
<td>11 ± 1 (90)</td>
<td>13 ± 3 (88)</td>
<td>–</td>
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<tr>
<td>7</td>
<td>135 ± 32</td>
<td>101 ± 7 (25)</td>
<td>73 ± 8 (46)</td>
<td>65 ± 4 (52)</td>
<td>89 ± 6 (34)</td>
<td>92 ± 7 (32)</td>
</tr>
<tr>
<td>8</td>
<td>11 ± 0.6</td>
<td>6 ± 1 (45)</td>
<td>10 ± 0.8 (9)</td>
<td>11 ± 1 (0)</td>
<td>7 ± 0.3 (36)</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>41 ± 4</td>
<td>-</td>
<td>15 ± 1 (63)</td>
<td>9 ± 0 (78)</td>
<td>3 ± 1 (93)</td>
<td>6 (85)</td>
</tr>
<tr>
<td>10</td>
<td>28 ± 7</td>
<td>15 ± 2 (46)</td>
<td>16 ± 2 (43)</td>
<td>10 ± 4 (64)</td>
<td>11 ± 0.3 (61)</td>
<td>14 ± 0.6 (50)</td>
</tr>
<tr>
<td>11</td>
<td>134 ± 13</td>
<td>64 ± 8 (52)</td>
<td>45 ± 8 (66)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>27 ± 3</td>
<td>-</td>
<td>45 ± 3 (↑67)</td>
<td>-</td>
<td>51 ± 4 (↑89)</td>
<td>50 ± 3 (↑85)</td>
</tr>
</tbody>
</table>

Figures in brackets are mean % fall from pre-treatment values.

P vs. pre-treatment.

* = 0.05.

** = 0.01.

*** = 0.001.
bromocriptine. The only responder not to show reduction of this degree was the patient with the lowest mean pre-treatment GH levels (case 8). Indeed the fall in her mean 09.00 GH levels only just reached statistical significance ($P < 0.05$) (Table 2). Thus, this case apart, all those having significant GH suppression throughout 24 h also had reduction in mean serum GH during GTT of 50% or greater. Furthermore case 7 showed a rise in mean GH levels during GTT when treatment was increased above 30 mg/day, a pattern similar to that observed for her 09.00 h values. Similarly case 12 showed a progressive increase during the GTT.

d) Carbohydrate tolerance. – Two patients (cases 4, 11) had insulin dependent diabetes mellitus, in one of whom (case 4) there was a fall in blood sugar levels independent of GH suppression. No change in insulin requirements was observed in either case. A further two (cases 2, 8) had chemical diabetes before treatment which was corrected by bromocriptine (20 mg/day) in spite of no significant GH suppression in one (case 2). Eight patients (66%) had normal carbohydrate tolerance which showed only minor change with treatment even though in some (cases 5, 6, 7, 9, 10) GH secretion had been suppressed by 50% or more.

e) Effect of bromocriptine on other anterior pituitary hormones. – Basal serum prolactin levels were raised ($> 640$ mIU/l) in 6 cases (Nos. 2, 5, 6, 9,
10, 12) (50 %) in one of whom it was attributable to methyl dopa (case 5). In all cases normoprolactinaemia was restored with bromocriptine, irrespective of its effect on GH secretion. There was no change in the basal or incremental release of LH, FSH, TSH or cortisol with doses of bromocriptine from 10 to 80 mg daily.

**Clinical changes**

Only one of the 12 patients (case 7) had a worthwhile improvement in soft tissue swelling and acral features. In this patient GH levels fell significantly throughout the day and during the GTT. Of the remaining 11 there was no change or at best slight improvement (cases 1, 2, 3) despite a significant fall

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**Fig. 2.**

Serum GH levels throughout 24 h with bromocriptine dosage (mean \( \pm \) SEM) for A responders (n = 7) and B non-responders (n = 4).
Table 3.
Mean serum GH levels (mIU/l) during GTT.

<table>
<thead>
<tr>
<th>Case</th>
<th>Pre-treatment</th>
<th>Bromocriptine/day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>10 mg</td>
</tr>
<tr>
<td>1</td>
<td>120</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>96</td>
<td>103 (17)</td>
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<td>3</td>
<td>119</td>
<td>112 (6)</td>
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<tr>
<td>4</td>
<td>85</td>
<td>93 (↑9)</td>
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<tr>
<td>5*</td>
<td>92</td>
<td>54 (43)</td>
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<tr>
<td>6*</td>
<td>92</td>
<td>33 (64)</td>
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<td>7*</td>
<td>132</td>
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<tr>
<td>8*</td>
<td>7</td>
<td>6 (14)</td>
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<tr>
<td>9*</td>
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<td>27</td>
<td>11 (59)</td>
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<tr>
<td>11*</td>
<td>125</td>
<td>103 (18)</td>
</tr>
<tr>
<td>12</td>
<td>30</td>
<td>–</td>
</tr>
</tbody>
</table>

Figures in brackets = % reduction from pre-treatment values.
* Responders throughout 24 h.

in GH levels in 6. The 3 patients to report slight improvement were GH non-responders. In no case was there any significant (> 5 mm) reduction in heel pad thickness, even in the patient with a good clinical response.

Sweating improved dramatically in one (case 2) and slightly in 2 (case 1, 7) of 4 patients in whom this was a prominent symptom. Case 7 was a GH responder whilst cases 1, 2 were non-responders.

Headache was considerably improved in 3 of 5 (1 responder, 2 non-responders) whilst symptoms of carpal tunnel syndrome remained unaltered by treatment.

There was no change in visual field perimetry or radiological size of the pituitary fossa with up to 16 months of bromocriptine therapy. The improvement in acral features in the 33 % of (4/12) of patient who showed any benefit from treatment was maximal at a daily dose of 30–40 mg and was achieved within 13 weeks of starting therapy in 3 and by 19 weeks in the fourth.
Side effects

The drug was well tolerated in all patients provided they took their tablets with food. Constipation occurred for the first time in 3 patients at a daily dosage of 20–40 mg. This was not troublesome, being adequately treated with bulk laxatives alone. Digital vasospasm precipitated by cold, a side effect occurring for the first time in 33% of the cases reported by Wass et al. (1977), was not encountered. Severe side effects, requiring cessation of therapy occurred in only 2 patients: case 1 suffered severe nausea and epigastric pain on 30 mg daily, case 12 a delusional psychotic episode on 80 mg daily. Both improved dramatically on withdrawal of treatment. The remaining patients tolerated doses of 40–80 mg daily without side effects.

Subsequent management

Since the biochemical and clinical response to bromocriptine treatment was disappointing it was felt unethical to withhold alternative therapy. Four patients (case 1, 2, 4, 12) have undergone attempted complete hypophysectomy by the trans-sphenoidal approach. In three of these (cases 1, 4, 12) who were bromocriptine non-responders, mean GH levels during GTT were less than 7 mIU/l after hypophysectomy. Amelioration of the acral features has occurred in all three. In the fourth patient (case 2) a remnant of the adenoma could not be removed and mean GH during GTT remains elevated at 53 mIU/l.

Two patients who had received previous pituitary ablative therapy (cases 9, 10) and one previously untreated patient (case 6) continue to have GH levels suppressed to normal or near normal by bromocriptine after 3 years of treatment. Slight clinical improvement has been noted in only one of these three (case 9). Thus of the original 12 patients 3 (25%) have had a permanent and stable normalisation of GH levels by bromocriptine for a prolonged period, whilst in 9 (75%) bromocriptine was discontinued.

DISCUSSION

It has been claimed that bromocriptine is a safe and effective therapy for acromegaly (Thorner & Besser 1976). Wass et al. (1977) reported that 79% of 73 patients treated for a mean period of 12.8 months had a fall in serum GH levels of 7 μg/l (14 mIU/l) or greater. Sachdev et al. (1975), in a shorter term study, reported 90% of 21 patients had suppression of GH levels to less than 50% of pre-treatment values whilst Belforte et al. (1977) have shown a similar response in 70% of 30 patients treated for up to 2 years. We have found that 58% of patients (7/12) showed a significant fall in serum GH levels, a proportion somewhat lower than that previously reported. We are unable to account for this on the basis of patient selection since our cases
spanned the same age range, had had the disease for a similar time and contained a similar proportion of previously treated patients to those in the previous reports. We have no reason to suspect that the non-responders had defaulted from treatment, indeed in all patients prolactin levels fell on treatment (irrespective of initial values) strongly suggesting that medication continued as prescribed.

Suppression of mean daily GH values to normal (< 5 mIU/l) was uncommon occurring in only one patient (case 8) although mean GH levels during GTT were suppressed to normal or near normal in 3 patients (25 %) (cases 6, 9, 10). This proportion is very similar to the 20 % reported by Wass et al. (1977) and Sachdev et al. (1975). Two responders (cases 5, 7) appeared to "escape" control on doses of bromocriptine greater than 30 mg/day whether assessed on 24 h GH levels or GH values during GTT. A similar phenomenon has been previously reported (Sachdev et al. 1975) though the explanation is unknown.

With one exception (case 8) a significant suppression of GH secretion throughout 24 h by bromocriptine was also reflected by a 50 % or greater reduction in mean serum GH during the GTT. Therefore for assessment of response to therapy a single GTT for serum GH may be all that is required. When GH levels were suppressed this was continued during sleep. Indeed there was no significant difference between 04:00 h GH levels and those obtained at other times.

The dosage of bromocriptine required to produce maximum biochemical effect was between 20–40 mg daily which is in agreement with the findings of others (Sachdev et al. 1975; Wass et al. 1977; Cassar et al. 1977). Further increases in dosage conferred no additional benefit.

Glucose tolerance bore no relationship to GH responsiveness since it improved considerably in one diabetic non-responder (case 4) whilst showing a slight deterioration in a diabetic responder (case 11). Chemical diabetes was corrected in a non-responder (case 2) and a doubtful responder (case 8). Thus it would appear that carbohydrate tolerance can be improved despite no change in circulating immunoreactive GH levels. It might be argued that bromocriptine exerts a direct effect on the pancreatic islets though this seems unlikely since serum levels of both insulin and glucagon are unchanged by bromocriptine therapy (Thorner et al. 1975).

Clinical response to treatment was disappointing with only 33 % (4/12) reporting any change in their acral features. In 3 of these improvement was only slight and unrelated to changes in GH secretion (cases 1, 2, 3 'non-responders'). Only one out of 7 responders (case 7) reported significant subjective change, the other 6 remaining unchanged in spite of dramatic reduction in circulating GH in some (cases 6, 9). This may relate to the long duration of tissue exposure to high GH levels with irreversible changes or an inadequate
time on treatment for an effect to be observed even though the responders had been on therapy for a mean period of 12 months. More likely the absence of a clinical response is due to the persistence of abnormally high levels of GH. Our data here agrees closely with that of Cassar et al. (1977) who in spite of falls in mean GH during GTT of between 56–93%, did not note any important clinical changes in 12 patients treated for 6 months. The finding of a clinical response in the absence of a change in circulating GH reported here and by others (Wass et al. 1977; Sachdev et al. 1975) requires explanation. One possibility proposed is that bromocriptine therapy preferentially suppresses monomeric biologically active GH secretion while total immunoreactive GH levels remain unaffected (Besser et al. 1976). This awaits confirmation.

This and previous reports have relied heavily on subjective changes as reported by the patient. The only data on objective measurement of soft tissue change comes from the report of Wass et al. (1977) in which 30/34 (88%) of patients showed a reduction in ring size after 1 year of therapy. However, the reduction was small (<4 mm) in the majority, with only 7/34 (20%) showing a reduction which was significant (>4 mm) (Boardman & Hart 1967). This proportion is very similar to that in which bromocriptine reduces mean GH levels to normal (<5 μg/l); 20% of patient reported by Wass et al. (1977), Sachdev et al. (1975) and Belforte et al. (1977); 25% Cassar et al. (1977). Therefore it seems likely that only about 20% of acromegalics treated with bromocriptine will achieve a worthwhile amelioration of acral features. Furthermore this is only likely to occur if GH levels are suppressed to normal. In 3 (25%) of our original 12 patients who remain on bromocriptine all have maintained suppression of GH levels below 10 mIU/l but even after 3 years' treatment there has been no dramatic improvement in acral features in any.

We have found treatment with up to 80 mg daily to be safe and without serious side effects and to confer the advantage over pituitary ablation of not causing hypopituitarism. However, because of its limited clinical and biochemical efficacy it is not, in our experience, “an effective medical treatment for acromegaly” (Brit. med. J. 1977). Our management of this disease remains, where possible, attempted complete ablation of the tumour by hypophysectomy. This is followed by external irradiation if GH levels are not normalised, with bromocriptine being used as an adjunct whilst awaiting the full effects of radiotherapy.

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482