Hypothalami-pituitary-adrenal function in intrinsic non-atopic asthma

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The relationship of adrenocortical function and bronchial asthma has long been the subject of controversy (Editorial, 1965). Enhancement of bronchial hypersensitivity in guinea-pigs following adrenalectomy was reported by Képinov (1922), and Rackemann (1945) found low urinary 17-keto steroid excretion in one patient with asthma. Bronchial asthma may rarely be a presenting feature in Addison's disease (Green and Lim, 1971). Earlier reports from different authors of studies of adrenocortical function in asthma showed discrepancies which may have resulted from variations in the methods and accuracy of the hormonal assay employed. An association between intrinsic asthma and sub-normal adrenocortical function has been suggested (Robson and Kilborn, 1965). The present study examines hypothalami-pituitary-adrenal (HPA) function in patients with intrinsic non-atopic asthma.

Patients and Methods

Twenty patients with bronchial asthma were studied after admission to hospital for a trial of corticosteroids because of poor control of symptoms. Each patient had suffered persistent and, in some cases, continuous wheezing since the onset of asthma but had never been treated with adrenal stimulation or corticosteroids. At the time of the studies each patient had clinical and spirometric evidence of airways obstruction, but none had significantly abnormal blood gas tensions. All patients gave informed consent to the studies.

In all patients the blood eosinophil count was in excess of 500/mm³ and the sputum eosinophil count was 40% or more. Sixteen patients were classed as intrinsic non-atopic asthmatics because they had no history of hypersensitivity and showed no immediate or delayed reactions to skin prick tests with a range of 23 common allergens (see Appendix). The four remaining patients who were classed as extrinsic atopic subjects showed significant positive immediate reactions to two or more common allergens and reported symptoms related to exposure to house dust, pollens or domestic pets.

All studies were begun between 8.00 and 10.00 am with the patient semirecumbent after an overnight fast. Blood samples for estimation of plasma cortisol levels were obtained through an indwelling venous cannula inserted into a forearm vein one hour before the start of the study. Blood samples were centrifuged immediately, and plasma was stored at 4°C until cortisol levels were estimated, using a modification of the method of Mattingley (1962). Each sample was analysed in duplicate.

In six of the intrinsic non-atopic patients a standard insulin stress test was performed on the first day using a single intravenous injection of
soluble insulin, 0·15 unit per kg body weight. On the second day in these patients and in all the remaining patients a prolonged Synacthen (Tetracosactrin) stimulation test was performed with an intramuscular injection of 1 mg Synacthen Depot.

RESULTS
Statistical analyses of clinical and laboratory details for the two groups of patients are shown in Table I and for the responses to Synacthen stimulation tests and insulin stress tests are shown in Tables II and III.

Using $t$-statistics for unequal variances the results of the Synacthen stimulation tests in the 16 patients with intrinsic asthma were compared with values obtained in 107 normal subjects (Ciba), and the results of the insulin stress tests were compared with values for 12 normal subjects reported by Landon, Wynn, and James (1963). In every patient there was a brisk and sustained rise in plasma cortisol level in response to Synacthen with an increment above the resting level of at least 200 nmol/l at 30 minutes after injection. The mean and SD of the increment for the patients with intrinsic asthma (460±174 nmol/l) were not significantly different from those for normal subjects (457±223 nmol/l). The plasma cortisol levels for the intrinsic asthmatics were significantly higher ($p<0.05$) than for normal subjects at each interval to five hours after injection of Synacthen. Moreover in seven of these patients in whom levels were measured at 8 and 24 hours after injection there was evidence of a sustained response to stimulation (see Table II). Similar

### Table I

**Clinical Details of Patients with Asthma**

<table>
<thead>
<tr>
<th></th>
<th>Age (yr)</th>
<th>Duration of Asthma (yr)</th>
<th>Sputum Eosinophilia %</th>
<th>Blood Eosinophilia $\times 10^9$/l</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>16 intrinsic patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>51.3</td>
<td>9.6</td>
<td>63.1</td>
<td>0.790</td>
</tr>
<tr>
<td>SD</td>
<td>11.5</td>
<td>7.6</td>
<td>11.8</td>
<td>0.256</td>
</tr>
<tr>
<td>SEM</td>
<td>2.9</td>
<td>1.9</td>
<td>3.0</td>
<td>0.065</td>
</tr>
<tr>
<td><strong>4 extrinsic patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>28.8</td>
<td>18.5</td>
<td>56.3</td>
<td>0.770</td>
</tr>
<tr>
<td>SD</td>
<td>14.5</td>
<td>18.7</td>
<td>8.5</td>
<td>0.146</td>
</tr>
<tr>
<td>SEM</td>
<td>7.3</td>
<td>9.4</td>
<td>4.3</td>
<td>0.074</td>
</tr>
</tbody>
</table>

**Table II**

**Plasma 11-Hydroxycorticosteroid (11-OHCS) Levels after Injection of 1 mg SYNACTHEN DEPOT**

<table>
<thead>
<tr>
<th>Hours</th>
<th>Plasma 11-OHCS (nmol/l) after Synacthen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>16 intrinsic patients</td>
<td>377</td>
</tr>
<tr>
<td>Mean</td>
<td>121</td>
</tr>
<tr>
<td>SD</td>
<td>30</td>
</tr>
<tr>
<td>SEM</td>
<td>408</td>
</tr>
<tr>
<td>Mean</td>
<td>138</td>
</tr>
<tr>
<td>SD</td>
<td>69</td>
</tr>
<tr>
<td>SEM</td>
<td>1.9</td>
</tr>
</tbody>
</table>

*Number of intrinsic subjects = 7.

**Table III**

**Six Patients with Intrinsic Asthma: Plasma 11-OHCS Levels Following IV Injection of Soluble Insulin 0.15 μg/kg Body Weight**

<table>
<thead>
<tr>
<th>Lowest Blood Sugar (mmol/l)</th>
<th>Plasma 11-OHCS Levels (nmol/l) after iv insulin</th>
<th>Maximum Increment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td>Mean</td>
<td>1.43</td>
<td>388</td>
</tr>
<tr>
<td>SD</td>
<td>0.31</td>
<td>157</td>
</tr>
<tr>
<td>SEM</td>
<td>0.12</td>
<td>63</td>
</tr>
</tbody>
</table>
results were obtained for the four patients with extrinsic asthma but the small numbers made statistical comparisons less valid. The insulin stress test in six patients with intrinsic asthma showed normal responses. In every patient the blood sugar level fell below 2.22 mmol/l, the maximum plasma cortisol exceeded 550 nmol/l, and the increment above the basal level was at least 275 nmol/l. The mean and SD for the maximum increment was 587±196 nmol/l in patients with asthma compared with 353±102 nmol/l in normal subjects.

**DISCUSSION**

In the present study adrenocortical function was normal in patients with extrinsic asthma, and this agrees with previous reports (Blumenthal et al., 1966; Weller et al., 1968). Weller et al. (1968) found that cortisol production rates were normal in patients with extrinsic asthma in the ambulant state but were diminished at rest. The adrenal response to ACTH infusions was normal in their patients but the response to pyrogen stimulation tests was slightly but significantly impaired. Robson and Kilborn (1965) studied patients with continuous asthma and inferred from the experience of Ogilvie (1962) that their asthma was intrinsic in type. In these patients, cortisol production rates were normal at rest but the response to ACTH stimulation was impaired in 68%. There was an inverse relationship between the duration of symptoms and the response to ACTH. Both Weller et al. (1968) and Robson and Kilborn (1965) discussed the possibility that adrenocortical insufficiency may precede or result from the effects of asthma. The association of asthma with Addison's disease appears to be uncommon in the absence of previous steroid treatment (Carryer, Sherrick, and Gastineau, 1960; Green and Lim, 1971). Similarly, in patients admitted to hospital with status asthmaticus signs of hypoadrenalism are uncommon even in patients who have received previous treatment with corticosteroids (Cayton and Howard, 1973). Adrenal atrophy has rarely been recorded in patients dying of asthma in the absence of previous steroid treatment (Speizer et al., 1968; Green and Lim, 1971; Fraser et al., 1971). Airways obstruction of itself does not seem to be associated with impaired adrenocortical function, for in patients with chronic bronchitis and severe fixed airways obstruction Weston and Kind (1969) found normal adrenocortical responses to ACTH.

The present study has failed to show any relationship between intrinsic non-atopic asthma and impairment of HPA responses. There was no evidence that increasing age or duration of asthma affected the adrenocortical response to stimulation by stress or Synacthen. The plasma cortisol levels recorded in our patients were higher than those previously reported for normal subjects using the same assay methods (Ciba; Landon et al., 1963). This suggests that in patients subjected to the stimulus of persistent asthma adrenal mass may be increased, as has been reported in patients dying with cardiovascular diseases and malignant neoplasms (Studzinski, Hay, and Symington, 1963). Examination of reports of necropsy findings in patients dying of asthma has failed to reveal details of adrenal size in most patients (Houston, Nevasquez, and Trounce, 1953; Speizer et al., 1968).

It seems unlikely that impaired responsiveness of the HPA axis is an important or common factor in precipitating or maintaining airway obstruction in patients with asthma except where previous corticosteroid treatment has resulted in suppression. Clinical experience of the efficacy of supraphysiological plasma levels of cortisol or synthetic substitutes in the treatment of asthma may have resulted in an over-emphasis of the role which impaired HPA responses play in asthma.

**APPENDIX**

All patients were tested for hypersensitivity by standard prick test with the following solutions produced by Bencard Ltd:


**REFERENCES**


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Ciba. Synacthen, Table 2, p. 10. Ciba, Horsham, Surrey.


Requests for reprints to: Dr. J. V. Collins, The Lung Function Laboratory, St. Bartholomew's Hospital, London EC1.
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