

appearance of the tumour but undetectable clinically. It may be argued that the improved outlook has only been shown in serial studies using historical controls and other factors such as staging and more intensive radiotherapy might be producing these results. But the improvement was so considerable that this is hardly likely. Furthermore, in a study by the Children's Cancer Study Group A<sup>3</sup> of 15 children treated by radiotherapy alone eight developed local recurrence or metastases compared with only three out of 17 children concurrently treated by radiotherapy and chemotherapy. This result was significant at the 5% level.

The chemotherapy used in this study has not produced any deaths and no undue short- or long-term toxicity. The best regimen, in terms of number of drugs, doses needed, and length of adjuvant therapy, is not yet known. Our regimen is less intense than some reported, yet it appears to give satisfactory results. Co-ordinated studies between centres will be important,

especially in view of the implications of these results for the treatment of the commoner adult solid tumours.

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## Short ACTH test in assessing hypothalamic-pituitary-adrenocortical function

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### Summary

The adrenocortical response to the simple 30-minute ACTH stimulation test was compared with the hypothalamic-pituitary-adrenocortical (HPA) response to insulin-induced hypoglycaemia in 25 patients with various degrees of hypothalamic-pituitary malfunction. The correlations between the increase in plasma cortisol during insulin hypoglycaemia and that during ACTH stimulation ( $r=0.66$ ) and between peak plasma cortisol levels during the two tests ( $r=0.90$ ) were highly significant. Peak plasma cortisol levels in individual patients were similar on both tests, no patient showing any major discrepancy between the two test results. Thus the simple 30-minute ACTH stimulation test seems to be reliable in detecting impaired HPA function.

### Introduction

Integrated hypothalamic-pituitary-adrenocortical (HPA) function is usually assessed by the insulin-induced hypoglycaemia test, whose clinical value has been clearly shown.<sup>1,2</sup> This test, however, is uncomfortable for the patient and requires strict supervision of him throughout the test. Theoretically the simple 30-minute ACTH stimulation test, easy to perform and without discomfort to the patient, tests only adrenocortical function and not the integrated HPA function. We have shown, however, that

the 30-minute ACTH stimulation test reliably predicts the integrated HPA response to surgical stress in patients treated with glucocorticoids.<sup>3</sup> We therefore compared the adrenocortical response to ACTH with the HPA response to insulin-induced hypoglycaemia in patients with various degrees of hypothalamic-pituitary malfunction.

### Patients and methods

Twenty-five patients were investigated (see table). Fourteen (cases 1-14) had undergone hypophysectomy because of pituitary adenoma or cyst, and eight of these patients (cases 1-8) were on glucocorticoid substitution treatment with 25 or 37.5 mg of cortisone acetate daily. Three patients (cases 15-17) had had a pituitary tumour diagnosed but had not yet been subjected to surgery. One patient (case 18) had galactorrhoea but no evidence of hypothalamic-pituitary tumour, and the remaining seven patients (cases 19-25) had various symptoms that made us suspect hypothalamic-pituitary disease. Clinical investigations, however, including neurological and ophthalmological examination, pneumoencephalography, EMI brain-scan, and electroencephalography, showed no evidence of hypothalamic-pituitary disease. Furthermore, secretion of growth hormone (peak plasma value during hypoglycaemia or arginine infusion, or both, 6.2-24  $\mu\text{g/l}$ ) and thyroid and gonadal function were normal in these eight patients (cases 18-25). None of the patients had hyperpigmentation or electrolyte disturbances. In the eight patients receiving glucocorticoid substitution treatment the last dose was given the evening before the study. All patients gave their informed consent.

On the day of the examination the patients were fasting, and an insulin hypoglycaemia test was begun between 10 and 11 am by giving crystalline insulin 0.15 IU/kg body weight intravenously. Blood for cortisol and glucose analysis was drawn from an intravenous cannula 10 minutes before and at the insulin injection and 30, 45, 60, 75, and 90 minutes after the injection. The test was considered adequate only if blood sugar fell to at least 2 mmol/l (36 mg/100 ml) and the patient sweated. In some patients a higher dose of insulin was used to achieve these conditions. On the same day between 3 and 4 pm an ACTH stimulation test was performed by injecting 250  $\mu\text{g}$  of  $\alpha^{1-24}$  ACTH (tetracosactrin) intravenously. Blood for cortisol determination was drawn immediately before and 30 minutes after ACTH injection.

Blood glucose was measured by a glucose oxidase method and plasma cortisol fluorimetrically as 11-hydroxycorticosteroids.<sup>4</sup>

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Clinical and experimental data in 25 patients with various degrees of hypothalamic-pituitary malfunction studied with insulin hypoglycaemia test and 30-minute ACTH stimulation test

Case No	Age and sex	Clinical diagnosis*	Histology	Plasma cortisol (nmol/l)			
				ACTH test		Insulin-induced hypoglycaemia	
				0	30 minutes	0	Maximum
1	60 M	Pituitary adenoma	Mixed adenoma	304	442	442	386
2	52 M	Pituitary apoplexy	Cromophobe adenoma	248	331	248	248
3	63 M	Pituitary tumour	" "	110	248	138	221
4	43 M	" "	" "	110	221	138	193
5	52 M	" "	" "	55	166	83	166
6	60 F	" "	" "	55	83	193	221
7	58 M	" "	" "	248	331	166	331
8	32 F	Acromegaly	Cromophobe adenoma	55	193	55	83
9	13 M	Pituitary tumour	Pituitary cyst	193	469	276	607
10	49 F	Acromegaly	Cromophobe adenoma	276	635	359	635
11	64 F	Pituitary tumour	" "	276	662	304	662
12	24 F	" "	Pituitary cyst	304	773	331	800
13	25 F	" "	Pituitary cyst, empty sella	55	276	83	221
14	46 F	" "	Cromophobe adenoma	221	552	359	607
15	57 M	" "	" "	304	745	386	856
16	33 F	Acromegaly	" "	552	718	193	883
17	34 M	" "	" "	276	469	221	607
18	30 F	Galactorrhoea	" "	331	745	276	580
19	23 F	Suspected pituitary tumour	" "	304	635	359	607
20	61 M	" "	" "	552	994	552	1132
21	17 F	" "	" "	193	635	276	800
22	39 F	" "	" "	304	690	414	1021
23	26 M	" "	" "	166	580	359	718
24	48 F	" "	" "	331	745	221	469
25	55 M	" "	" "	166	828	359	773

\*All tumours, diagnosed or suspected, were non-secreting tumours.

Conversion: SI to traditional units—Cortisol: 1 nmol/l  $\approx$  0.036  $\mu$ g/100 ml.

## Results

The correlations between the increase in plasma cortisol during insulin-induced hypoglycaemia and that during ACTH stimulation (fig 1) and between the peak plasma cortisol during the insulin hypoglycaemia test and the peak during ACTH stimulation (fig 2) were highly significant. In individual patients the relation between the outcome of the tests as expressed by the increase in plasma cortisol was poor (fig 1) since basal plasma cortisol levels varied and thereby

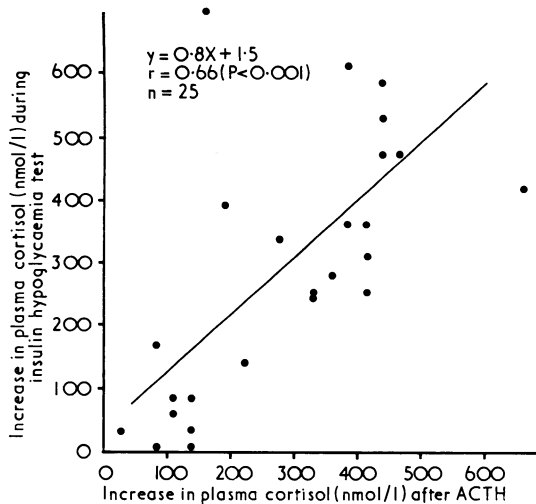


FIG 1—Comparison between adrenocortical response to 250  $\mu$ g of  $\alpha^{1-24}$  ACTH and HPA response to insulin-induced hypoglycaemia (increase in plasma cortisol during two tests) in 25 patients with various degrees of hypothalamic-pituitary malfunction.

Conversion: SI to traditional units—Cortisol: 1 nmol/l  $\approx$  0.036  $\mu$ g/100 ml.

influenced the test result. On the other hand, the relation between peak plasma cortisol during the two tests was very close in individual patients (fig 2), none showing any major discrepancy between the results. The regression line calculated by correlating the peak plasma cortisol levels during the two tests was not significantly different from the identity line  $y = x$  ( $P > 0.1$ ). Thus, the two tests apparently gave a uniform expression of the functional capacity of the HPA axis.

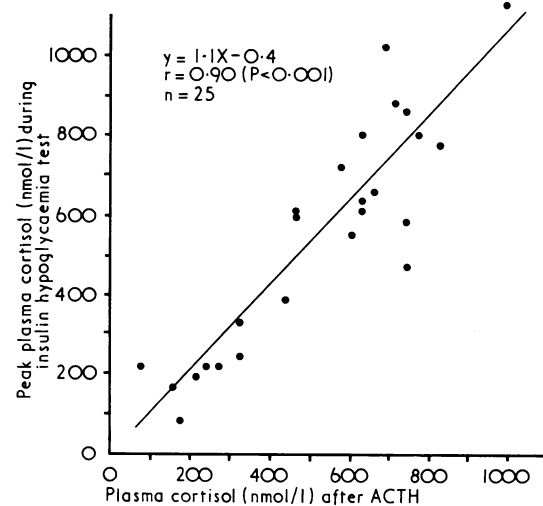


FIG 2—Comparison between adrenocortical response to 250  $\mu$ g of  $\alpha^{1-24}$  ACTH and the HPA response to insulin-induced hypoglycaemia (peak plasma cortisol level during the two tests) in 25 patients with various degrees of hypothalamic-pituitary malfunction.

## Discussion

The number of methods for clinically evaluating the integrated function of the various endocrine systems have recently increased considerably owing to the availability of radio-immunological hormone assays and synthetic hypothalamic-pituitary releasing hormones. Although a more extensive endocrinological evaluation may be needed to localise the specific lesion in a patient with a proved dysfunction, simple inexpensive screening tests are still desirable. It has recently been reported that the pituitary secretion of five anterior pituitary hormones can be comprehensively classified within a few hours in well-equipped endocrinological centres.<sup>5</sup> The integrated function of the HPA axis may be evaluated by the metyrapone test; the pyrogen test; the lysine-vasopressin test; or the insulin hypoglycaemia test—of which the last is probably the most valuable.<sup>6</sup> The short ACTH stimulation test, which theoretically tests only the adrenocortical function, has been accepted as a test for

primary adrenocortical insufficiency<sup>7, 8</sup> but not for secondary adrenocortical insufficiency because of the possibility of a preserved normal adrenocortical function in secondary insufficiency. Nevertheless, we have recently shown in glucocorticoid-treated patients the value of the simple ACTH stimulation test in assessing the integrated HPA function in secondary insufficiency.<sup>3</sup>

We compared the result of the simple ACTH stimulation test with the HPA response to insulin hypoglycaemia in patients with or without hypothalamic-pituitary disease and varying degrees of adrenocortical insufficiency. A very close correlation was found between the peak plasma cortisol after ACTH and after insulin hypoglycaemia in each patient. It should be emphasised that a patient with borderline results on one test will also have borderline results on the other test, indicating that a borderline ACTH test result should be followed by further evaluation of the HPA function. Our results suggest that a definitely normal response to ACTH is most unlikely to coexist with an impaired response to insulin hypoglycaemia. Examples of such a discrepancy have been reported,<sup>2, 9</sup> but information

on whether both sweating and low blood glucose values were obtained during insulin hypoglycaemia was not given.

In conclusion, our results suggest that the simple 30-minute ACTH stimulation test is a reliable screening test for impaired HPA function.

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# Renin concentrations and effects of propranolol and spironolactone in patients with hypertension

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## Summary

In a crossover study 32 patients with hypertension were randomly allocated to treatment with spironolactone 200 mg/day for two months, propranolol 320 mg/day for two months, and a combination of both drugs at half the dose. Between the treatments placebo was given for two months. Both spironolactone and propranolol lowered the blood pressure significantly in both positions.

The initial plasma renin activity (PRA) levels ranged from 0.4 to 5.0  $\mu\text{g}$  angiotensin I  $\text{l}^{-1} \text{h}^{-1}$ , and there was a close correlation between these levels and the effects of the drugs: with increasing PRA the response to propranolol was better while the opposite was true for spironolactone. Spironolactone reduced the blood pressure more at eight than at four weeks, while no such difference could be shown for propranolol. Spironolactone and propranolol together decreased the blood pressure still further irrespective of the initial PRA. All patients achieved a normal supine blood pressure.

These results support the concept that the renin-angiotensin-aldosterone system may be involved in primary hypertension.

## Introduction

Recently much interest has been focused on the renin-angiotensin-aldosterone system and its role in primary (essential) hypertension.<sup>1</sup> It has been proposed that plasma renin activity (PRA) might have both prognostic<sup>2</sup> and therapeutic implications.<sup>3</sup> Bühler *et al*<sup>3</sup> showed that hypertensive patients with normal or high PRA responded more favourably to treatment with beta-adrenergic-blocking drugs, but others—for example, Morgan *et al*<sup>4</sup>—could not confirm this. Many studies have verified that low renin hypertension responds best to volume-depleting drugs, such as diuretics or aldosterone antagonists.<sup>5-7</sup>

Our aim was to see whether the response to propranolol or spironolactone was related to the initial PRA. We also wanted to compare the efficacy of propranolol, spironolactone, and the combination of the two drugs in the treatment of primary hypertension.

## Patients and methods

Thirty-two consecutive outpatients with hypertension, 14 men and 18 women ranging in age from 27 to 62 years (mean 46), entered the 10-month trial. The average known duration of hypertension was 3.4 years (range 0-20); 23 patients had grade I hypertension (World Health Organisation classification) and nine had grade II hypertension. None had eye-ground changes worse than grade II. Nineteen patients had never received antihypertensive treatment, and in the remaining 13 all medication had been withdrawn for at least four weeks. No patients with obstructive lung disease, diabetes mellitus, or hepatic or renal disorder were admitted. None had malignant or secondary

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