The Response to Stress after Corticosteroid Therapy

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Over the last few years, corticosteroids have been employed in the treatment of a wide variety of diseases. A major problem associated with their use, however, is the patient's inability to respond adequately to stress. This appears to be due to a depression as much of hypothalamic-pituitary function as of adrenal function. Collapse after surgery following corticotrophin therapy has been reported (*see* Ferriman & Page 1960) and a poor response to metyrapone or stress has been reported after corticotrophin (Ferriman & Page 1960, Solem & Brinck-Johnsen 1961, Plager & Cushman 1962, Savage *et al.* 1962, Brinck-Johnsen *et al.* 1963) or with a normal adrenal response to corticotrophin after corticosteroids (Holub *et al.* 1959, Engel *et al.* 1958).

Investigative procedures which will determine patients' responsiveness after steroids are clearly important, and these must test the integrity of the entire hypothalamic-pituitary-adrenal system. Although metyrapone has been extensively used for this purpose, it probably indicates ability to compensate for alteration in the level of plasma cortisol, rather than the potential to respond to stress. A preferable procedure would involve the use of a stressor agent. Various agents have been employed but the choice lies essentially between pyrogens and insulin-induced hypoglycæmia. Although both are effective, pyrogens produce effects which are somewhat disagreeable to the patient. It was thought at one time that insulin might carry some risk, but this appears to be slight if appropriate precautions are taken.

We wish to report on the response to insulin-induced hypoglycæmia in normal subjects and in patients at intervals after discontinuing corticosteroid therapy.

Material and Methods

Three groups of patients were studied. A control group consisted of 19 patients (3 men, 16 women) for whom steroid therapy was contemplated. Their ages ranged from 17 to 68. The second group comprised 31 patients (8 men, 23 women) on treatment with corticosteroids. Their ages ranged from 16 to 71. Corticosteroids were discontinued for forty-eight hours before testing. The third group contained 12 patients (2 men, 10 women) in whom corticosteroid therapy had been discontinued for one to sixty months before testing. Their ages ranged from 35 to 77.

Hypoglycæmia was induced by intravenous injection of insulin (0·1 unit/kg body weight) and the response assessed by measuring plasma cortisol at intervals thereafter.[1] Blood was withdrawn for assay of blood sugar and plasma cortisol and again thirty minutes later. This was necessary to permit the elevation of plasma cortisol, which may follow insertion of the needle, to return to basal levels. Insulin was then injected and blood withdrawn for blood sugar estimations 10, 20, 30, 50, 60 and 90 minutes, and for plasma cortisol assay 30, 60 and 90 minutes later. Ampoules containing 25 ml of 25% glucose, and 100 mg hydrocortisone were kept available. Undesirable reactions were rarely encountered; glucose was used on only 3 occasions out of 63 tests, and hydrocortisone was never required.

Considerable variations occurred in the degree of hypoglycæmia achieved. An attempt was considered desirable, therefore, to measure the degree of stress for each patient, taking into account the initial blood sugar level and duration of hypoglycæmia. An index of stress was obtained by dividing the initial blood sugar level by the sum of the blood sugars at 20, 30 and 50 minutes after injection of insulin.

A small group of patients was found in whom hypoglycæmia produced undesirable cardiac arrhythmias. These were elderly patients in whom ischæmic cardiac changes were likely to be present. We no longer employ the test in this type of patient.

Results

The results for the three groups of patients are set out in Figs 1–3, the index of stress being plotted along the abscissa, and the maximum rise of plasma cortisol, above the resting level, on the ordinate. Two small groups of patients have been excluded from analysis: the first consists of patients in whom the degree of hypoglycæmia was inadequate to produce stress (4 in Group 2); the second consists of nervous individuals in whom a high level of plasma cortisol is found not only immediately after insertion of the needle, but again thirty minutes later (2 in Group 1, and 3 in Group 2); this fails to produce an adequate basal level.

Fig 1 shows results in the control group. A relationship between stress and response is apparent, and this is statistically significant, r being 0·6 and $P < 0.01$. The parallelogram encloses the normal range and this has been superimposed on Figs 2 and 3.

Fig 2 shows results in the group of patients taken off corticosteroids for forty-eight hours. Response is commonly inadequate but has

[1]Landon *et al.* 1963

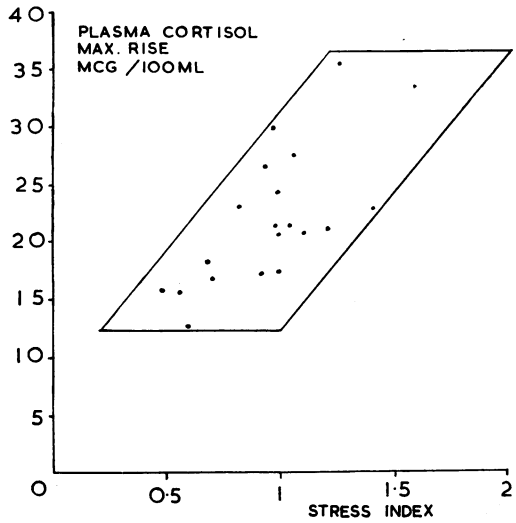

Fig 1 *Plasma cortisol response to hypoglycæmic stress. Control subjects*

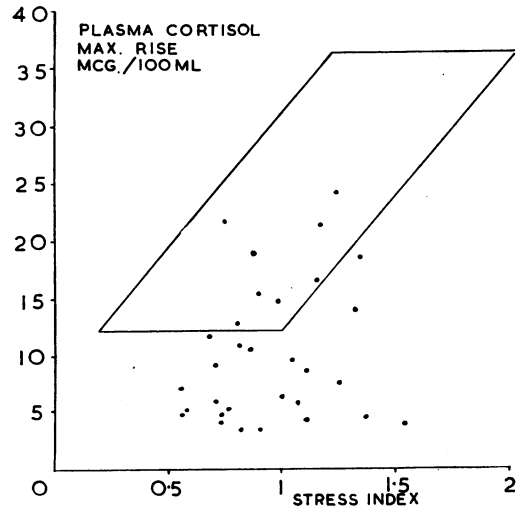

Fig 2 *Plasma cortisol response to hypoglycæmic stress. Patients off corticosteroids forty-eight hours*

returned to normal levels in a number of patients. No obvious relationship could be discerned between types of response and duration of therapy, daily dose level or total dosage.

Fig 3 shows responses in patients who had discontinued corticosteroids for longer periods. The numbers shown represent the time in months from discontinuance of therapy. Two numbers have been ringed; these concern a patient who was tested twice, at different intervals after discontinuing steroids. Responsiveness in most patients is within normal limits. Of the two with inadequate response one had discontinued therapy for one month only and normal responsiveness had returned a month later. The second was being treated with a phenothiazine derivative for psychiatric symptoms; this group of drugs is known to depress response to stress.

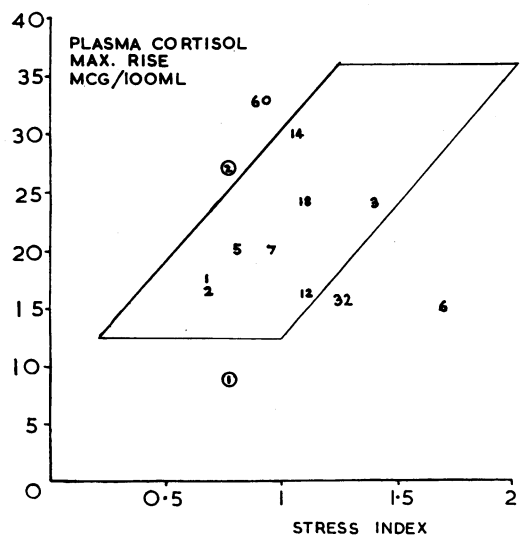

Fig 3 *Plasma cortisol response to hypoglycæmic stress. Patients off corticosteroids for one to sixty months*

Discussion

Factors likely to affect hypothalamic-pituitary-adrenal responsiveness after corticosteroid therapy are duration of treatment, daily dose levels, lapse of time after discontinuance and individual susceptibility to suppression.

The importance of duration of treatment has been demonstrated by Treadwell *et al.* (1963). Scrutiny of the data presented by these workers, and by Shuster & Williams (1961), indicates the importance of daily dose level. Our own observations indicate the likelihood of an eventual return of responsiveness in most patients, and this is supported by Robinson *et al.* (1962) and by the important studies of Graber *et al.* (1964) on return of blood corticotrophin and 17-hydroxy-corticosteroid levels after corticosteroid therapy.

An important possibility remains for discussion. Rats treated with high doses of corticosteroids have shown damage to hypothalamic nuclei (Castor *et al.* 1951). Kyle *et al.* (1957) report a patient whose plasma and urinary 17-hydroxy-corticosteroid levels had not returned to normal two years after removal of an adrenal adenoma. It is conceivable that a small group of patients exist who are susceptible to permanent damage from high dosage or long duration treatment with corticosteroids. If so, it will be important to detect such cases in clinical practice.

Summary
Pituitary adrenal responsiveness has been investigated in patients who have discontinued corticosteroid therapy for varying periods. The plasma cortisol increase following insulin-induced hypoglycæmia has been used as a measure of response. Implications of the findings and the factors underlying lack of responsiveness are discussed.

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Adrenal Response to Cardiac Surgery

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Cardiac surgery presents not only a challenge to the technical skill of the operator but also one of considerable magnitude to the homeostatic mechanisms of the body. Add to that the possible complications that may follow extracorporeal circulation (ECC or cardiopulmonary bypass), especially that of tissue anoxia, and we have a situation where one would expect that the endocrine system of the body is fully stressed. The response therefore should be greater than that after other forms of surgery. Such may seem to be an acceptable hypothesis, but is it a fact?

This was investigated in a larger study on the metabolic effects that may follow cardiac surgery, especially where ECC was used. In this paper are presented the results of attempts to measure the adrenocortical secretion along with some preliminary ones of the secretion from the adrenal medulla.

Materials and Methods
Twenty-four-hour urine collections were made for some days before and after operation as indicated in the various sections. The urine for catecholamines was kept acid by the addition of 10 ml N hydrochloric acid to the bottle before collection. The 17-hydroxycorticoids were measured by the method of Sobel *et al.* (1958) and the catecholamines by that of Grout (1961). Vanyl mandelic acid (VMA) was measured by the method of Connelian & Godfrey (1964).

Results
17-Hydroxycorticosteroids (17-OHCS): The urinary excretion of these was measured in two patients having closure of septal defects under ECC. They were studied two days before and four days after operation. After operation there was an increased excretion especially in the first two days, returning towards normal by the fourth day (Fig 1). (We wondered if this response was modified by equilibration of the steroids in the blood of the patients with that in the heart-lung machine.) The blood in the patient is interchanged with that in the Melrose heart-lung machine, which contains 3 litres of perfusing fluid – 2 litres of stored blood and 1 litre of 5% dextrose solution or low molecular weight dextran (Rheomacrodex). The 17-OHCS were measured in the blood of a patient during perfusion and in the machine before and after perfusion (Fig 2). There was a rise in blood cortisol in the patient during perfusion from 9 to 25 μg/100 ml. The perfusing fluid had a level of 8 μg/100 ml to begin with and 17 μg/100 ml at the end of perfusion. There was thus an accretion to the machine of 9 μg/100 ml or 270 μg in the

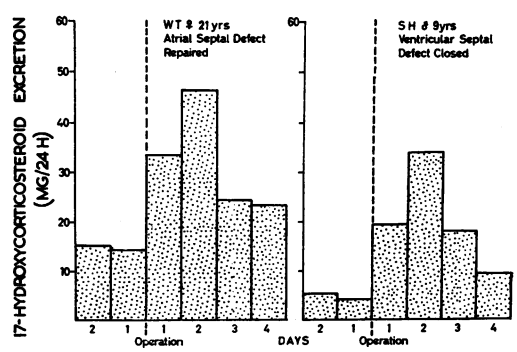

Fig 1 *Urinary 17-hydroxycorticosteroid excretion in two patients who had closure of septal defects under extracorporeal circulation*