Conclusion

We would agree with Grant (1961) that every attempt should be made to avoid giving steroid therapy continuously, but that in many cases it is the only effective treatment available: some patients can be kept well by occasional short courses, but these are the exceptions in cases of true chronic asthma. The benefits of well-managed corticosteroid therapy far outweigh the risks involved.

Summary

Results and side-effects of prolonged treatment of 317 patients with steroids and corticotrophin are described: in 205 of them for over two years, in 118 for over three years, and in 46 for over four years. All were patients *in whom all other measures of treatment had been tried but had failed.* Patients were given the smallest dose of steroid to keep them reasonably but not totally free from asthma; 58% had one and a half to two tablets of prednisone or its equivalent daily and 42% half to one tablet daily.

It would appear that the long-term use of steroids has reduced the frequency of status asthmaticus and the numbers of deaths from asthma.

Striking clinical improvement occurred in 56%. There was a complete failure of 5%.

There were no deaths attributable to steroids or corticotrophin. Four patients had compression fractures of the spine and two bled from peptic ulceration.

Our experiences suggest that long-term therapy is beneficial in cases of chronically intractable asthma in which all other measures have failed. The serious side-effects are difficult to assess, since we have no control group of asthmatics for comparison, but the benefits obtained seem to outweigh any possible risks.

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ADRENAL FUNCTION AFTER PROLONGED CORTICOSTEROID THERAPY

BY

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Corticosteroid therapy is now being used with increasing frequency for the treatment of a wide variety of disorders. Some of these are diseases which are likely to necessitate the steroid therapy being continued indefinitely, but some of the disorders treated will have a self-limiting course so that the corticosteroid therapy may be eventually stopped.

The adrenal inhibition which results from such steroid therapy becomes important only when the therapy is stopped. That the patient's own adrenal activity should be inhibited during corticosteroid therapy is inevitable unless corticotrophin is given as well. But after the period of steroid therapy has ceased there may persist for a greater or less period of time a sluggishness of reaction of the whole or some part of the pituitary–adrenal axis. The resultant impairment of adrenal function is not easy to assess objectively, but clinical experience suggests that there is a wide individual variation in the rate of recovery (Bayliss, 1958). Indeed, the suggestion was early made (Salassa *et al.*, 1953; Lewis *et al.*, 1953; Hayes and Kushlan, 1956) that impaired adrenal function may persist in some patients for months or even years after treatment has been stopped.

A variety of methods for testing pituitary and adrenal function in such circumstances have been proposed at various times (Forsham *et al.*, 1950; Engleman *et al.*, 1953; Christy *et al.*, 1956; Holub *et al.*, 1959; Amatruda *et al.*, 1960), but these are generally either too difficult to apply to many routine clinical situations or do not sufficiently test out the whole pituitary–adrenal axis. It would be of great clinical value to have some simple way in which to pick out those patients in whom the recovery of adrenal function was delayed, but to be useful it must be one which tests out the whole pituitary–adrenal axis.

A strong natural stimulus to corticotrophin release is provided by an abnormally low plasma cortisol level. This indeed is the basis of the tests using the 11-beta-hydroxylase inhibitor, metopiron (SU 4885). But the same stimulus is automatically provided when the steroid therapy is suddenly stopped, for then the adrenal is atrophic and inert and the plasma cortisol level falls to near zero. Recovery of adrenocortical function and rise of plasma cortisol to normal levels can then occur only if the corticotrophin-releasing centres are sensitive to the stimulus of low plasma cortisol and can act on the adrenal cortex. A spontaneous rise of plasma cortisol to normal levels will thus indicate recovery of pituitary–adrenal function. The only important

difference between this spontaneous reaction and the stimulus provided by metopiron is that the stimulus to spontaneous recovery will cease when normal adrenal activity has been achieved, whereas with metopiron the stimulus of low plasma cortisol will persist until a high degree of adrenal activity has been provoked. The latter thus throws a greater strain on the pituitary–adrenal axis. But the spontaneous rise in plasma cortisol is nevertheless of considerable clinical value, and with modern methods of estimating plasma cortisol (Mattingly, 1962) can provide information quickly.

Numerous reports exist in the literature of sudden collapse and of other untoward incidents following upon steroid therapy, but in most of these there is no objective evidence of adrenal inadequacy. By the very nature of such incidents, their relative rarity, and the acute emergency which they create, objective evidence is difficult to obtain. A great deal more information about the behaviour of the pituitary–adrenal axis after steroid therapy is badly needed.

In an effort to determine the extent to which long-continued corticosteroid therapy damages the pituitary–adrenal axis we have tested the integrity of this axis by following the spontaneous rise in plasma 17-hydroxy-corticoid concentration after the sudden cessation of steroid therapy.

We have compared the response found in those patients who had been on prolonged corticosteroid therapy with control subjects whose adrenals were acutely suppressed for 24 hours with dexamethasone, and also with patients whose pituitary function had been damaged with implantation of seeds of ^{90}Yt. In some subjects cortisol-secretion rates have also been determined as a check on the validity of the conclusions drawn from the plasma estimations.

All these long courses of steroid therapy were being terminated at the time of study for purely clinical reasons. The hypopituitary subjects underwent the brief steroid withdrawal as a routine test of the efficacy of their pituitary implants and were aware of this. The one patient (Case 13) who experienced withdrawal symptoms had collaborated actively with the steroid withdrawal study, as he was anxious to learn whether steroid therapy could be stopped.

Methods

Free plasma 17-hydroxycorticosteroids (17-O.H.C.S.) were determined by the method of Peterson *et al.* (1957). About 90% of the Porter–Silber chromogens measured by this method is free cortisol (Peterson *et al.*, 1955). Dexamethasone, in doses up to 4 mg. daily, is not detectable in the plasma by this method. Patients receiving other steroids were changed to an equivalent dose of dexamethasone 24 hours before withdrawal whenever possible. In these patients plasma 17-O.H.C.S. concentrations while still on steroids were a measure of endogenous cortisol only. Unless otherwise stated blood was taken between 9 and 10 a.m. to avoid the normal diurnal variation in plasma cortisol levels, which can be large.

Cortisol-secretion rates were determined by the method of isotope dilution using 4-^{14}C cortisol (Cope and Black, 1958).

Results

Normal Plasma 17-O.H.C.S. Concentrations.—Plasma 17-O.H.C.S. concentrations in 30 hospital patients who had never been treated with steroids were measured between 9 and 10 a.m. Patients with endocrine, liver, and renal disease were excluded. None of these patients was under obvious stress at the time blood was taken. The mean plasma 17-O.H.C.S. concentration was 15.4 μg./100 ml., with a range of 6 to 24 μg./100 ml. These normal values are in good agreement with those of Peterson *et al.* (1957) and other workers.

Normal Response to Acute Adrenal Suppression.—Seven patients from the above normal group were subjected to acute adrenal suppression by the administration of 1 mg. of dexamethasone six-hourly by mouth for 24 hours. At the end of this time plasma 17-O.H.C.S. levels had fallen well below the lower limit of the normal range in all, indicating that endogenous steroid secretion had been well suppressed. The mean concentration observed was 2 μg./100 ml. In six of the seven patients the plasma 17-O.H.C.S. concentration had returned to normal levels within 24 hours after the last dose of dexamethasone, though the seventh case remained slightly subnormal. All seven were normal at 48 hours. The mean for the whole group was 10.7 μg./100 ml. at 24 hours and 16 μg./100 ml. at 48 hours.

Response of Patients with Hypopituitarism.—To establish the type of response likely to be encountered in subjects whose pituitary–adrenal axis had been severely damaged, a group of six patients who had previously undergone almost complete pituitary destruction by the implantation of ^{90}Yt (Fraser *et al.*, 1959) were also studied in a similar manner. Maintenance steroid therapy was temporarily withheld so that this could be done. Plasma 17-O.H.C.S. concentrations failed to rise to normal levels in any of these, and all developed early symptoms and signs of adrenal insufficiency. Plasma 17-O.H.C.S. levels were 1 μg./100 ml. or less during suppression and the mean was only 3 μg./100 ml. 24 hours after steroid withdrawal, falling slightly to 2.7 μg./100 ml. at 48 hours, and to 1.5 μg./100 ml. at 72 hours.

Response of Patients on Prolonged Steroid Therapy

The changes in plasma 17-O.H.C.S. concentration have been followed similarly in 13 patients after stopping steroid therapy which had lasted from one month to as long as three and a half years. Details of diagnoses and of steroid therapy are recorded in the accompanying Table. Patients 1 to 12 showed the same

Patients on Prolonged Corticosteroid Therapy

No.	Sex and Age	Disease	Corticosteroid Therapy		48 Hours Off Steroids	
			Duration (Months)	Drug	Plasma 17-O.H.C.S. (μg./100 ml.)	Cortisol Secretion Rate (mg./day)
1	M 36	Staph. pneumonia. Hypotension	1	Prednisone	19	23·8
2	F 51	Pulmonary fibrosis	1	,,	15	—
3	M 27	Serum sickness	1	,,	9	—
4	M 64	Infective hepatitis	2	,,	15	—
5	M 35	Idiopathic thrombo-cytopenic purpura	4	,,	6	12·8
6	M 31	Pancytopenia	4	,,	11	—
7	M 62	Asthma and chronic bronchitis	6	Methyl-prednisolone	26	—
8	F 72	Temporal arteritis	7	Prednisone	20	16·7
9	F 57	Rheumatoid arthritis	8	,,	12	
10	M 54	Polyarteritis nodosa	9	,,	21	14·2
11	F 76	Acquired haemolytic anaemia	9	Dexamethasone	15	12·0
12	F 68	Rheumatoid arthritis	18	Triamcinolone	19	—
13	M 62	Polyarteritis nodosa	44	Prednisone. Cortisone. Dexamethasone	3	1·8
				Normal range	6–24	5–25

pattern of response as was seen in the normal control group, and all these had normal plasma 17-O.H.C.S. concentrations 48 hours after stopping treatment. The mean values for these 12 patients were 1.4 μg./100 ml. during suppression, 6.4 μg./100 ml. at 24 hours, and 14.8 μg./100 ml. at 48 hours. The response of these patients is compared with that of the normals and the patients with hypopituitarism in Fig. 1. In 5 of these 12 patients cortisol-secretion rates were measured on the third day after stopping steroids. These were all normal, the mean for the five being 15.9 mg./day (see Table). The mean figure in healthy resting normals is about 14 mg./day.

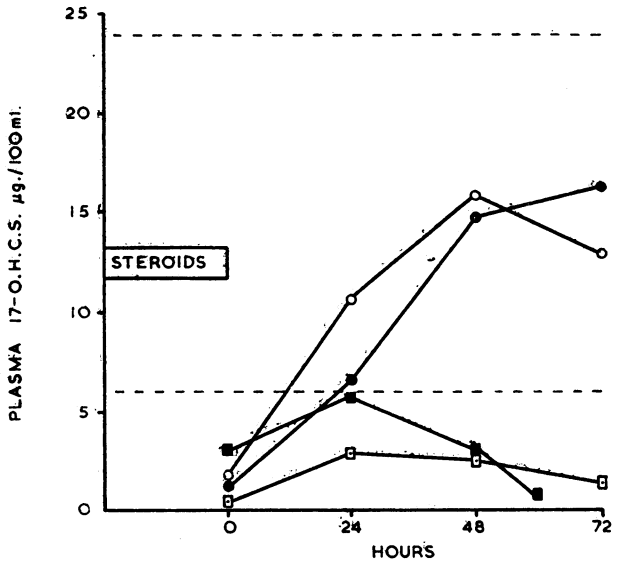

FIG. 1.—Mean free plasma 17-O.H.C.S. levels after stopping steroids. Open circles—7 normal subjects. Open squares—6 patients with panhypopituitarism. Closed circles—patients 1–12 after prolonged steroid therapy. Closed squares—patient 13 (see text). The horizontal broken lines show the limits of the normal range between 9 and 10 a.m.

Thus the difference from the normal group in ability of recovery of adrenal function was negligible. Integrity of the pituitary–adrenal axis was apparently unimpaired, as judged by this test, after periods of steroid therapy lasting as long as 18 months.

No opportunity to study the effects of surgery arose on any of these patients, but four other patients on long-term steroid therapy experienced a relapse of their disease within one month of steroid withdrawal. All these had plasma 17-O.H.C.S. levels which were raised to the extent to be expected in normal persons undergoing that degree of stress. The mean for the four was 35 μg./100 ml., the range being 29 to 45 μg./100 ml. There was thus good evidence that in 16 of the 17 patients studied the pituitary–adrenal axis had not been appreciably damaged by the period of steroid therapy.

Damage to Corticotrophin-release Mechanism due to Steroid Therapy

The remaining patient is excluded from the above generalization because his response was in sharp contrast to that of all the other patients. He is therefore considered in greater detail below, since he was the only patient of those studied who showed unequivocal evidence of severe damage to the pituitary–adrenal axis with resultant adrenal failure.

CASE 13

The patient was a 62-year-old man suffering from polyarteritis nodosa, which had been proved by biopsy. He had been maintained on steroids for the past three and a half years and had been on dexamethasone for the previous 18 months. For some months prior to study he had been taking 0.5 mg. twice daily. On this, as on most earlier therapy, his disease was fully suppressed and he was symptom-free and able to continue regularly at work. Even on this relatively small dose he had gained weight and developed some mooning of the face.

He was admitted to hospital for study in precisely the same manner as the other long-term therapy subjects. His initial plasma 17-O.H.C.S. level was 3.3 μg./100 ml. Twenty-four hours after stopping the dexamethasone this had risen to 5.7 μg./100 ml., but at 48 hours it had fallen to 3 μg./100 ml. On the evening of the third day of steroid withdrawal, 60 hours after the last dose of dexamethasone, he became febrile and felt ill, complaining of aching limbs and nausea. His cortisol-secretion rate measured on this day gave a figure of only 1.8 mg./day—that is, about one-eighth of the normal mean figure. He was thought to be developing acute adrenal insufficiency, and his plasma 17-O.H.C.S. concentration at this time had fallen to 1 μg./100 ml. He was given 100 mg. of hydrocortisone sodium succinate intravenously and 4 mg. of dexamethasone by mouth, with complete relief of his symptoms within an hour. His blood-pressure, which had begun to fall, returned to normal levels and his fever subsided. This sequence of events is shown in Fig. 2.

After recovery he was maintained once more on dexamethasone, 0.5 mg. six-hourly, and while still on this maintenance therapy was given in addition a course of intramuscular corticotrophin gel, 50 units 12-hourly, for five days. Good adrenal stimulation was obtained, as indicated by a steady rise in the plasma 17-O.H.C.S. level, measured five hours after the morning injection. By the fifth day this had reached 39 μg./100 ml., a figure about three times the normal mean.

When the corticotrophin and dexamethasone were both stopped together the plasma 17-O.H.C.S. level fell rapidly. In 24 hours it was down to normal, but had fallen to 4 μg./

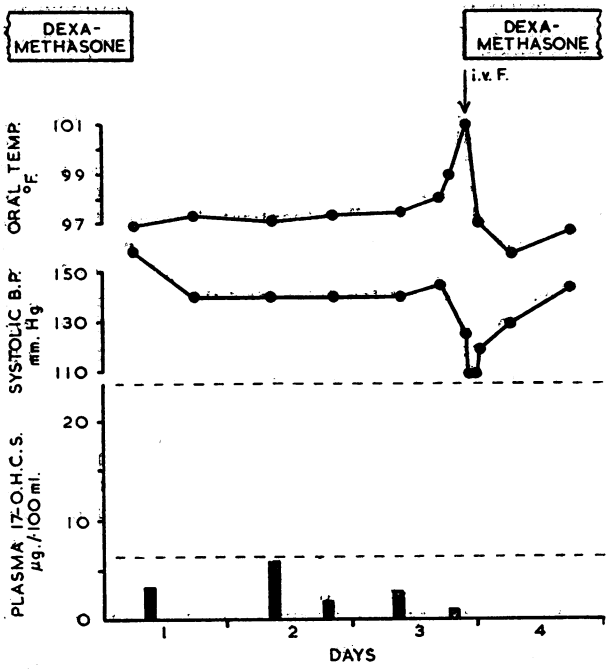

FIG. 2.—Case 13. Acute adrenal failure on the third day off steroids (see text). The horizontal broken lines show the limits of the normal range of free plasma 17-O.H.C.S. concentrations between 9 and 10 a.m.

100 ml. four days after the last injection of corticotrophin, and to 2 μg./100 ml. on the fifth day. This sequence of events is shown in Fig. 3. At this time he began to feel very lethargic though there were no significant changes in his blood-pressure, temperature, or pulse rate. As no spontaneous rise in plasma 17-O.H.C.S. level was occurring, it was thought desirable to restart the dexamethasone, and thereafter he has remained well on a dose of 0.5 mg. twice a day.

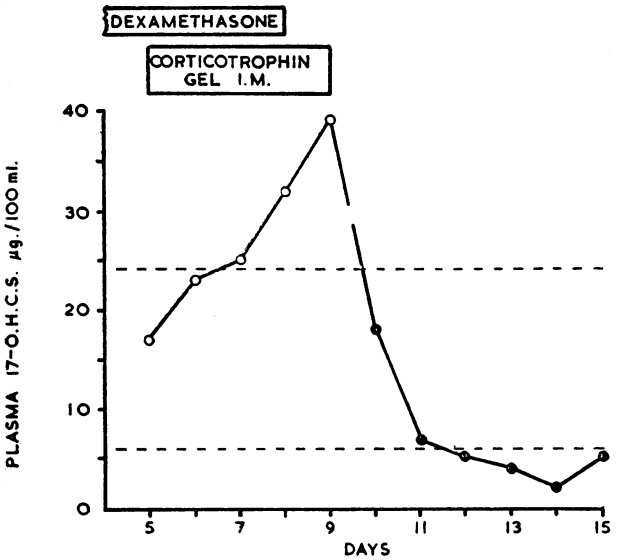

FIG. 3.—Case 13. Adrenal response to corticotrophin stimulation, and failure to maintain normal free plasma 17-O.H.C.S. levels when this was stopped. Open circles—five hours after morning corticotrophin injection. Closed circles—9 a.m. levels (see text). The horizontal broken lines show the limits of the normal range between 9 and 10 a.m.

Comment.—There was thus in this case, first of all, clear objective evidence of an inability to recover adrenocortical activity after the steroids were stopped. Secondly, there was clear evidence that this was not alone due to the adrenal atrophy, for when this was completely overcome by a course of corticotrophin the patient's own pituitary was unable to secrete enough endogenous corticotrophin of its own to maintain even a small part of the adrenal activity which had been stimulated. Insensitivity of the corticotrophin-releasing mechanism at some point was thus quite clearly demonstrated, and no other explanation of his steroid behaviour was possible. This case represents one of the relatively few well-authenticated cases of damage to the corticotrophin-release mechanisms produced by steroid therapy. His initial symptoms had been of bouts of fever with severe leg pains, and there was no clinical reason to suspect any arterial disease process in the neighbourhood of the pituitary gland or hypothalamus to account for this damage to its function.

Evidence of Adrenal Failure

The need for producing objective evidence of adrenal or pituitary–adrenal failure in such circumstances must be stressed, because many unwarranted assumptions have been made in the past on quite inadequate evidence.

Such an uncritical attitude was severely criticized by Francis D. Moore (1957) when he said: "There are several articles in the literature which mistake the generally beneficial effects of cortisone under a wide variety of toxic situations for evidence of adrenocortical insufficiency. Indeed these authors seem to accept a beneficial response as prima facie evidence of adrenal cortical insufficiency. This is a criterion by which most patients with rheumatic disease and poison ivy would be considered as suffering from cortical insufficiency."

We have in the course of this work encountered several examples of the truth of this statement; some of these cases had been on long-term steroid therapy and others had not had any steroids. Two illustrative examples are given.

Case 11.—A woman of 76 with acquired haemolytic anaemia had been treated with dexamethasone for nine months, the highest dose being 8 mg./day. Treatment was tailed off over a period of a week. On the third day after stopping dexamethasone she started vomiting and felt generally unwell. Her blood-pressure fell from 130/80 to 110/60. Her plasma 17-O.H.C.S. concentration at this time was 15 μg./100 ml. Her cortisol-secretion rate, which was being measured at the time, was 12 mg./day, which is within the normal range. Nevertheless there was complete relief of her symptoms when she was given intravenous hydrocortisone sodium succinate and her blood-pressure returned to its previous level.

Case A. B.—A man aged 46 with chronic pyelonephritis and old spinal tuberculosis had never been on steroid therapy. He was admitted to hospital with an acute urinary infection. He became shocked, drowsy, and hypotensive, his blood-pressure falling from 110/70 to 60/25. The combination of buccal and generalized pigmentation with a high plasma potassium (8.4 mEq/l.) and a low plasma sodium (123 mEq/l.) suggested the possibility of an Addisonian crisis. His blood-pressure was rapidly restored to normal levels within one hour of an intravenous injection of 200 mg. of hydrocortisone sodium succinate. His plasma 17-O.H.C.S. concentration just before the hydrocortisone was given was 61 μg./100 ml., an elevated level compatible with the stress of his illness. He died 10 days later of renal failure. At post-mortem examination his adrenals were of normal weight and appearance.

Discussion

Seventeen patients who had received corticosteroid therapy for periods varying from one month to three and a half years have been examined for evidence of damage to the pituitary–adrenal axis. In 16 of these there was good evidence that the functioning of this axis was not appreciably impaired, 12 showing a prompt spontaneous rise of plasma 17-O.H.C.S. to normal levels after withdrawing all steroid therapy, and the remaining four showing a good plasma 17-O.H.C.S. response to the stress of a relapse within one month of the cessation of steroid therapy.

The seventeenth patient, however, stands in sharp contrast to the rest. Not only was adrenal failure demonstrated in this patient, but this failure could be shown to be due to an inertia of the corticotrophin-releasing mechanism, and not to a primary defect in the adrenal gland itself. Furthermore, the discovery of such a patient in this manner indicates the clear clinical value of a relatively simple test which would seem to be devoid of serious risk, provided the patient is under close supervision in hospital during the period of deliberate steroid withdrawal.

Tests in which a stress is created by the use of an injected pyrogen introduce an added risk which may indeed be grave in a patient with non-responsive adrenals. Moreover, the reaction to such pyrogens is very variable and the response is difficult to standardize (Farmer *et al.*, 1961). These criticisms also apply to tests using insulin-induced hypoglycaemia (Amatruda *et al.*, 1960). Tests involving metopiron throw a greater

load on the pituitary–adrenal axis, but the result is the replacement of circulating cortisol by another steroid. Unless special chemical precautions are taken to estimate the amount of this abnormal steroid separately from the cortisol in either plasma, where it is compound S, or in the urine, where it is tetrahydro S, the effect will be evident only when adrenal activity rises above the normal range. It seems uncertain at present whether the metopiron tests will prove more sensitive in detecting inertia of the pituitary–adrenal axis than is the test used by ourselves in this study, which also depends on the same natural physiological stimulus to adrenal secretion.

Response to A.C.T.H. cannot be used to test the whole axis, because it only indicates the degree of adrenal atrophy and gives no information about the pituitary corticotrophin-releasing mechanisms.

Our finding of only one case in 17 in which damage to the pituitary–adrenal axis could be proved is in general conformity with the clinical impressions of some other investigators. Relatively few comparable studies have been so far reported. Holub *et al.* (1959) studied the response to metopiron of four patients who had been on long-term steroid therapy, using urinary 17-ketogenic steroids as criterion of response. One of these, who had had a particularly long period of steroid therapy (10 years), showed no reponse to the drug, although his adrenals were shown to be responsive to corticotrophin.

The response of 16 long-term steroid patients to metopiron was also studied by Meakin *et al.* (1960). Unfortunately they used a method of urinary steroid analysis which is relatively non-specific, but the impression gained was that five of these 16 gave a subnormal response.

Amatruda *et al.* (1960) studied the rise in plasma cortisol in response to insulin-induced hypoglycaemia. The patients studied were 10 with pulmonary tuberculosis who had received daily prednisone for at least six months, together with corticotrophin zinc on alternate days to minimize adrenal atrophy. They found a normal rise in plasma cortisol in all cases.

In the case found by Holub *et al.* (1959) a failure of the corticotrophin-release mechanism was probable but was not proved. In the other studies the data were insufficient to permit a conclusion being reached.

There is, however, in the literature one very well documented case showing that such damage to the corticotrophin-release mechanism is indeed a reality. The patient had not had long-term steroid therapy, but had Cushing's syndrome due to an adrenal cortical tumour which was eventually removed. As this tumour had been producing cortisol, similar conditions to those of long-term steroid therapy were created. The case was thoroughly investigated by Kyle *et al.* (1957). On three separate occasions in the year following removal of the tumour generous courses of corticotrophin were given which each time stimulated the adrenal cortex to give high plasma 17-O.H.C.S. levels. Yet after each of these, when corticotrophin was withdrawn, plasma 17-O.H.C.S. concentrations fell back again to near zero levels. The authors estimated that the recovery of the corticotrophin-release mechanism had not become complete until nearly two years after the removal of the tumour.

Our own case of post-steroid adrenal inertia is one in which a similar defect has been clearly demonstrated. Such cases are likely to be rare. It is probably not fortuitous that the only case in our series in which such damage was found was the one that had had the longest period of steroid therapy. The same was true of the case found by Holub *et al.* (1959). It is nevertheless important that such cases should be recognized before calamitous attempts to wean them from steroid therapy are made. To follow the plasma corticosteroid level during the three days after abrupt cessation of steroid administration would seem the simplest screening test to reveal such cases.

It is important to stress the fact that prompt recovery of a collapsed patient in response to intravenous hydrocortisone therapy is not evidence of adrenal failure at all, even if the collapse should occur in a patient who had received steroids. Our two cases are selected to illustrate this point, which, as stated earlier, was well made by Francis Moore (1957).

The more widespread use of plasma-corticosteroid estimations would do much to clarify many of these collapse cases. Thus Melby and Spink (1958) have investigated 22 patients with shock due to infection, in all of whom the period of hypotension lasted more than six hours. In none was the plasma 17-O.H.C.S. level below 30 μg./100 ml. Recent examples of diagnostic claims of adrenal collapse unsupported by any biochemical evidence are those of Stevens (1960) and of Capper and Moser (1960). Diagnosis of adrenal failure cannot reliably be made without chemical evidence. Yet Sampson *et al.* (1961) were able to claim that a case of collapse after six months of prednisone therapy observed by them was the first in which near zero plasma 17-O.H.C.S. levels had been reported. Our own Case 13 is another clear example of proved adrenal failure after steroid therapy.

Summary

Seventeen patients who had received long periods of corticosteroid therapy have been investigated to determine the integrity of the pituitary–adrenal axis. In 16 of these no evidence of damage to this axis was obtained. The other patient had developed adrenal inertia of severe degree which was shown to be due to damage to his corticotrophin-releasing mechanism.

Two examples are reported to emphasize the fact that prompt response of a collapsed patient to intravenous hydrocortisone cannot be regarded as evidence that the patient has experienced adrenal cortical failure.

Our thanks are due to Miss Jean Pearson and Miss Margaret Harwood for help in preparing reagents and in estimating the cortisol secretion rates.

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DEXAMETHASONE SUPPRESSION TEST IN DIAGNOSIS OF CUSHING'S SYNDROME

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In the diagnosis of endocrine disease suppression tests have proved useful for revealing minor and clarifying doubtful instances of glandular overactivity. The value of the thyroid suppression test as an aid to the diagnosis of thyrotoxicosis is already well established. In normal subjects the secretion of thyroid-stimulating hormone by the pituitary can be suppressed by the administration of thyroid hormone; while in thyrotoxicosis such suppression either fails to occur or is incomplete (Werner and Spooner, 1955). Suppression tests of adrenocortical function are less well established in clinical medicine, partly because of the lower incidence of adrenal disease, and partly because much of the early work was concerned with using such tests to try to distinguish between Cushing's syndrome due to adrenal tumours and that due to bilateral adrenal hyperplasia—for example, Jailer *et al.* (1954)—rather than to distinguish between patients with either type of Cushing's syndrome and those with normal adrenal function. In the same way as in the thyroid suppression test, suppression of normal adrenocortical function following the administration of exogenous corticosteroids occurs as a sequel to the suppression of adrenocorticotrophic hormone production by the pituitary.

In Cushing's syndrome the basic abnormality is an excessive secretion of cortisol, the secretion rate of which can be measured by isotopic means (Cope and Black, 1958). Among the urinary steroid measurements probably the next best method for revealing oversecretion is the measurement of free cortisol (Cope and Black, 1959), which is estimated after chromatography. The most widely used urinary steroid estimation is that of the basal excretion of 17-ketogenic steroids (17-KGS) or of 17-hydroxycorticosteroids (17-OHCS). Others have used the levels of plasma steroids for the diagnosis of Cushing's syndrome (Grumbach *et al.*, 1955). The measurements of the cortisol-secretion rate, urinary free cortisol, or plasma steroids all require special techniques which are not within the scope of many hospital laboratories. The disadvantage of the measurement of the basal values of urinary 17-KGS is that there is a considerable overlap between values found in normals and those found in cases of Cushing's syndrome (Cope and Black, 1959). Liddle (1960) has described the use of an adrenal suppression test in the diagnosis of Cushing's syndrome in which he estimated the urinary 17-OHCS after the administration of corticosteroid and found that the degree of suppression of the urinary 17-OHCS by the second day of steroid administration provided a good distinction between normal subjects and cases of Cushing's syndrome. We have also assessed the adrenal suppression test in the diagnosis of Cushing's syndrome, and our results confirm his in finding it valuable for this purpose. Like Liddle, we have used as suppressing agent 16α-methyl-9α-fluoroprednisolone (dexamethasone), and we have determined its effect on the urinary excretion of 17-ketogenic steroids (17-KGS) as well as 17-ketosteroids (17-KS), these estimations being available routine procedures in most hospital laboratories.

Method

The *standard test* consisted of the collection of two 24-hour urine specimens, after which dexamethasone was given for a week and two more 24-hour urines were collected on the sixth and seventh days. Toluene was used in the bottles to prevent bacterial overgrowth. The standard dose of dexamethasone used was 0.5 mg. six-hourly, but in some a higher dose of 1 mg. six-hourly was also used.

Subjects Studied.—(1) Nine normal subjects, who consisted of volunteer doctors and nurses and one patient convalescent from a non-endocrine condition; (2) seven patients suffering from idiopathic hirsutism and four with menstrual disorders; (3) twenty-four subjects finally diagnosed as cases of "simple" obesity; and (4) six patients with Cushing's syndrome. Three of the patients with menstrual disorders had irregular periods and infertility, for which no adrenal or ovarian cause could be found, and the fourth had a congenital absence of the vagina. Assessment of the degree of obesity of the obese patients by the Kemsley (1952) standards indicated a mean excess weight of 73% above the normal for subjects of the same age and sex. The six patients with Cushing's syndrome all had the typical clinical picture, and the diagnosis in four of them was confirmed by the estimation of the cortisol secretion rate (by Dr. C. L. Cope); in one of the other two patients the 24-hour urine cortisol level was measured and was raised (170 μg./24 hours). Radiography in all these patients after perirenal oxygen insufflation did not reveal evidence of an adrenal tumour, and they were all thought to be suffering from bilateral adrenal hyperplasia. One patient (D. J.), whose clinical details have already been published (Joplin and Fraser, 1961), had ocular signs suggesting an invasive tumour of the pituitary. All the patients were treated by pituitary implantation of ^{198}Au (Joplin *et al.*, 1961).

Procedures.—The 17-KS and the 17-KGS were estimated by the methods of Norymberski (Norymberski *et al.*, 1953). Basal collections on two separate days were obtained from 21 of the subjects with hirsutism or menstrual irregularities or obesity. The mean day-to-day variation in 17-KGS excretion was 2.3 mg., with a range of 0–7 mg. The precision of the