of the four adults who failed to respond, the maximum daily dosage of cortisone was only 100 mg., whereas in the series as a whole the maximum daily dosage was 200 to 300 mg. in more than half the cases.

This experience is rather more favourable than that reported previously: namely, 1952 report, partial or complete responses in 11 out of 16; 1951 report, partial or complete responses in 8 out of 14. The less favourable results of the earlier reports are probably partly due to the fact that smaller doses were being used; thus of five patients treated in 1951 who failed to respond to hormones, two received a maximum daily dose of 75 to 100 mg. of cortisone and one further patient received a total of 2,500 mg. of cortisone in 25 days.

Four patients were treated continuously with cortisone for six months or more. In two cases the patients remained well on 100 mg. a day but relapsed when given 50 mg. a day; both developed a mild Cushing syndrome. The other two patients remained well on 50 mg. and 75 mg. a day respectively.

Eight cases of non-thrombocytopenic purpura were treated in 1953-4, and six of these failed to respond to hormones. In five of these six dosage was adequate—namely, 200 to 300 mg. of cortisone a day for 12 to 20 days in three patients, and 100 mg. A.C.T.H. a day for 17 days in one patient. In the 1952 report, six patients were included, only one of whom responded to hormones.

Aplastic Anaemia, etc.

Sixteen patients with aplastic anaemia and two with refractory anaemia were treated. In three patients with aplastic anaemia the administration of cortisone appeared to check bleeding from the gums, etc., but otherwise no favourable effects were noted in any of the patients. This experience is similar to that mentioned in previous reports.

Leukaemia

Forty-nine children with acute leukaemia (25 lymphatic, 5 myeloid, 19 unclassified) were treated; 8 of these 49 died within 14 days of beginning hormone therapy; of the remaining 41, 34 had remissions following the administration of A.C.T.H. or cortisone; 13 of these remissions were classified as complete and 21 as partial. Eight of the 34 infants, in whom remissions were observed received aminopterin as well as hormones; many of these infants also received blood transfusions.

It must be emphasized that the remissions were not of long duration. Of 41 children who lived for more than 14 days after treatment had begun, the duration of life was known in 35 cases. Fifteen children died in less than three months; 10 more died between three and six months; seven more between six and twelve months; and only three lived for more than one year.

Fifty-two adults with acute leukaemia (23 lymphatic, 16 myeloid, 13 unclassified) were treated; 10 of these died within two weeks of starting treatment; of the remaining 42, 22 had a partial or complete remission; two of these patients received aminopterin as well as hormones.

Three adults with chronic lymphatic leukaemia were treated and showed a partial response; one adult with chronic myeloid leukaemia failed to respond. Four patients with reticulosis were given relatively short courses of A.C.T.H. (1-3 g. in 10 to 17 days) and showed no response.

Discussion

The present findings strongly reinforce the previous conclusion that among patients with blood disorders only those with acquired haemolytic anaemia and idiopathic thrombocytopenic purpura derive prolonged benefit from the administration of cortisone or A.C.T.H. It is apparent that patients with either of these two conditions can often be relieved of their symptoms for periods of months or even years by the continuous administration of hormones.

The only other condition in which favourable effects are observed is acute leukaemia. In this condition it now

appears that the administration of A.C.T.H. or cortisone may offer the most favourable means of inducing a remission (cf. Fessas *et al.*, 1954; Gasser and Cramer, 1953). However, it must be stressed that the prolongation of life is meagre. As reported previously (1952 report) few patients survive for more than a year after their first course of hormones, despite an initial good response.

Summary

In most patients with acquired haemolytic anaemia and idiopathic thrombocytopenic purpura remissions can be induced by the administration of A.C.T.H. or cortisone. The importance of adequate dosage is stressed. Remissions can often be maintained for long periods by continued administration of the hormones.

In acute leukaemia the administration of A.C.T.H. or cortisone induced temporary remissions in approximately half the patients treated, and this form of treatment compares favourably with others. Nevertheless few patients survive for more than one year.

In other haematological conditions the administration of A.C.T.H. and cortisone seldom produces any favourable effects.

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EFFECT OF 9 α -FLUOROHYDRO-CORTISONE ON ADRENAL HYPERFUNCTION IN CUSHING'S SYNDROME

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An interesting compound both for therapeutic use and for the investigation of many aspects of adrenal function was revealed when Fried and Sabo (1954) found that a halogen-substituted derivative of hydrocortisone, called 9 α -fluorohydrocortisone, had strong cortisone-like activity in the rat-liver glycogen test. Borman *et al.* (1954) have shown that this steroid has also strong sodium-retaining activity which has been estimated by Llauro (1955) to be about ten times that of D.C.A. and about one-tenth of the activity of aldosterone itself, the naturally occurring electrolyte controlling hormone. During the past year Goldfien *et al.* (1955) at Harvard have made a study of the pharmacology of this compound. They found it to be a potent substitute for cortisone in man. As a result of clinical trials in Addison's disease they came to the conclusion that the therapeutic potency of the halogen compound was about twenty times that of cortisone, and that it could be used for the successful maintenance of such patients.

A compound with these properties might be expected to produce inhibition of natural adrenal activity, and in fact Goldfien *et al.* (1955) were able to demonstrate a fall in urinary excretion of 17-hydroxycorticosteroids, an important group of adrenal metabolites, during the administration of 9 α -fluorohydrocortisone to a man with normal adrenal function. In a case of adrenogenital syndrome with adrenal hyperplasia, these workers found that the high output of ketosteroids was progressively inhibited to below normal levels by 9 α -fluorohydrocortisone.

Such an inhibition could have been produced equally well by cortisone administration, since it is now well recognized that in the adrenogenital syndrome cortisone promptly inhibits the high ketosteroid output, provided that this is due to adrenal hyperplasia and not to a tumour. This effect has now become the basis of an important method of treatment and has led to a theory of the aetiology of the disorder.

It is not yet known whether cortisone therapy inhibits adrenal function similarly in the other type of adrenal hyperactivity, the so-called Cushing's syndrome, which is associated with excessive hydrocortisone production. This point has not hitherto been readily amenable to experimental investigation because adrenal activity is usually judged by the amount of hormone or of its breakdown products present in the blood or in the urine. Since the hormone and the excreted metabolites resulting from cortisone or hydrocortisone administration are essentially the same as those occurring naturally, any inhibition of the activity of the gland itself will be effectively masked, if blood hormone levels or excreted metabolites are used as a criterion of adrenal activity. Jailer *et al.* (1953) have produced evidence suggesting that 17-ketosteroid output is lowered by intramuscular injection of cortisone in subjects with Cushing's syndrome, but such a change does not necessarily indicate a reduction in hydrocortisone production.

The new halogen steroid 9 α -fluorohydrocortisone provides an opportunity to overcome this technical difficulty since the end-products of its metabolism are likely to be different from those derived from hydrocortisone. We have had the opportunity to study the effects of 9 α -fluorohydrocortisone on a typical case of adrenal hyperactivity of Cushing's type in which the histology of the adrenal gland has been determined.

Adrenal activity has been judged by the daily excretion rate in the urine of hydrocortisone and of some of its metabolites. Particular attention has been paid to the excretion of hydrocortisone itself, as this seems likely to provide the most sensitive and specific index of changing adrenal function.

Methods

Ketogenic steroids have been estimated by the method of Norymberski *et al.* (1953). 17-Ketosteroids have been estimated by the standard M.R.C. method (M.R.C., 1951). Hydrocortisone and other adrenal metabolites have been estimated by the method of Cope and Hurlock (1954), which includes the chromatographic separation of the individual steroids on paper. The free hydrocortisone has been determined by extracting the urine with chloroform at pH 1. Total (free + conjugated) hydrocortisone, tetrahydrocortisone, and tetrahydro-hydrocortisone have been determined on a chloroform extract of the urine made after hydrolysis. This hydrolysis of steroid conjugates has been effected by 1,000 Fishman units of beta-glucuronidase per ml. of urine acting for 48 hours at pH 4.5 and at 37° C. We are grateful to Dr. C. E. Sewell for help with these analyses.

Case History

The patient, a 25-year-old male press operator, was fit on discharge from the Army five years ago (1950) (Fig. 1); height 5 ft. 5 in. (165 cm.), weight 8 st. 8 lb. (54.4 kg.). Since then progressive weight gain has occurred—14 lb. (6.3 kg.) each year, until February, 1955, when he weighed 14 st. 12 lb. (94.3 kg.). During the ensuing three months he gradually lost weight, and in June weighed 12 st. 2 lb. (77.1 kg.); he has not dieted.

There has been temporal recession of hair with increased growth of hair on the trunk and upper parts of the limbs during the past three years; he has had no need to shave more frequently.

In April, 1955, he noticed painless red striae on his abdomen, thighs, and axillae, and during the past two months his skin has been easily bruised.

During the past three months carbuncles have occurred on the back of his neck and behind his right knee. There has been no change in energy; he does not tire easily, although he admits to a slight increase in breathlessness. Sexual impulses are normal, with no known loss of libido. There is no significant previous illnesses or past history.

On examination he was seen to be an afebrile, fat, very plethoric young man with typical florid Cushing's appearance (Figs. 2 and 3). He was mentally normal apart from shyness. He had gross "moonface"; the neck and trunk

FIG. 1.

FIG. 2.

FIG. 3.

were obese, while the extremities were not. There was a suggestion of a "buffalo hump" but no definite kyphosis. His cheeks were red with well-marked vessels, and the skin here felt thick and firm. The skin on the rest of the body, though well-padded, was actually thin. Hess's test was negative. Large vertical red-mauve striae were spread over the lower abdomen, thighs, and axillae; in the latter situation they were an especially vivid purplish colour. There was early frontal thinning of the scalp hair. Thick dark hair was abundant over the chest, abdomen, back, and upper part of thighs. His voice was normal. External genitals and scrotum were normal; no gynecomastia. Heart sounds were normal; blood pressure was 170/130; pulse 84 and regular.

Investigations.—Hb, 96% (14.21 g.); red cells, 5,000,000; white cells, 9,800 (neutrophils 80%, lymphocytes 14%, monocytes 6%, eosinophils less than 50); prothombin time, 13 sec. (normal); urea, 19 mg. per 100 ml.; serum chlorides, 98 mEq per litre; serum sodium, 148 mEq/l.; serum potassium, 4 mEq/l.; calcium, 5.44 mEq/l.; serum phosphorus, 1.7 mEq/l.; alkaline phosphatase, 9 King-Armstrong units per 100 ml.; alkali reserve, 28 mEq/l.; plasma proteins, 7.7 mg. per 100 ml. Glucose-tolerance test normal; no glycosuria. X-ray examination: chest normal; sella turcica normal; skeleton and hands, no evidence of osteoporosis; presacral oxygen insufflation revealed bilaterally enlarged adrenal shadows (Dr. I. Gilliland and Dr. R. S. Steiner).

Operation (Mr. N. C. Tanner).—Subtotal adrenalectomy was performed. The right adrenal weighed 8 g.; the left adrenal (subtotal) 6 g. was removed. The adrenal glands were not as large as the x-ray shadow had suggested, probably owing to periadrenal fat.

Histology (Dr. A. G. E. Pearse).—"Macroscopically the only abnormality is the presence in the right adrenal of a single adenoma measuring 7 by 5 mm. Microscopically the cortex of both glands is essentially similar, the chief feature being a widening of the zona fasciculata, which is filled with large pink presumably active cells, and a diminution of the other two zones. Cortical lipids are practically confined to the thin outer layer. There are no micro-adenomata such as are associated with recurring periods of activity and inactivity—the adenoma is of a peculiar pattern and it has arisen from the fasciculata rather than the outer layers of the cortex. The deep pink staining cells which compose it are arranged in acinar formation and there is mucin secretion into the lumen. It is not the usual pattern for an active cortical adenoma."

Results

The relevant steroid analyses in this patient are collected in the Table. The data of greatest interest are the excretion

Effect of 9 α -fluoro-hydrocortisone on Steroid Excretion (figures refer to daily output)

Day	9 α -Fl-F Dose (mg.)	17-Keto- steroid (mg.)	17-Keto- genic (mg.)	Hydrocortisone		Tetra- hydro- E (μ g.)	Tetra- hydro- F (μ g.)
				Free (μ g.)	Total (μ g.)		
1	—	11	40	402	409	2,700	1,940
6	—	13	—	485	—	—	—
7	2	11	—	514	—	—	—
8	2	—	—	531	—	—	—
9	2	—	—	536	—	—	—
10	5	—	—	230	—	—	—
11	5	—	—	282	—	—	—
24	—	33	309	624	3,120	1,060	—
25	—	14	51	468	4,200	1,536	—
26	10	—	333	562	3,200	1,220	—
27	15	14	51	258	3,312	1,594	—
28	15	17	51	70	2,830	970	—
29	—	—	—	212	—	—	—
30	—	—	—	333	—	—	—
31	—	22	64	393	704	4,350	1,300

rates of hydrocortisone itself. This was running at the high figure of 400 to 500 μ g. daily during the preliminary control period, the normal output by this method being between 40 and 200 μ g. a day. The output of hydrocorti-

sone was not affected by a small dose of 2 mg. daily of 9 α -fluorohydrocortisone given orally in four equal doses during the day. When the daily dose of halogen steroid was increased to 5 mg. similarly divided, a prompt reduction of hydrocortisone output by about 50% took place.

In the second observational period larger doses were given. During the first 24 hours 10 mg. of the drug given in four divided doses caused no fall in the hydrocortisone output, but two further days on a dose of 15 mg. caused a big fall in hydrocortisone output. When judged by the free hydrocortisone extracted from the urine at pH 1 there was a fall to about 20% of the initial level, but when judged by the total of free and combined hydrocortisone in the urine the fall in output was about 50%. On withdrawal of the drug there was a prompt return of the hydrocortisone output to its original level.

Several other points of interest may be noted in the Table. There was no inhibition of the 17-ketosteroid output, which was already rather low initially. There was no inhibition of the output of 17-ketogenic steroids, though these were raised well above the normal range, which in a man is from 9 to 20 mg. daily. There is no appreciable inhibition of tetrahydrocortisone excretion and the output of the closely allied tetrahydro-hydrocortisone shows only a slight reduction. With any of these latter criteria as indices of adrenal activity, therefore, no inhibition of function would have been revealed during such short periods of administration of the drugs as have been studied here.

Progress Report.—Six weeks after operation the patient is very well. His weight is now 10 st. 6 lb. (66 kg.), his blood pressure 122/82. Other metabolic studies and histochemical work on the adrenal glands will be the subject of a further communication.

Discussion

The impression gained is that under the influence of 9 α -fluorohydrocortisone an inhibition of hydrocortisone takes place but that this is very temporary and is promptly restored to its original level as soon as the drug is withdrawn. The fact that this halogen steroid reduces hydrocortisone output in the urine could possibly be explained in several ways. There might be an adverse effect on renal function leading to poor excretion. Renal-function studies were not made in this subject, but such an explanation is highly unlikely because the overall output of 17-ketosteroids and of ketogenic steroids was not affected. A specific blocking effect in the kidney affecting hydrocortisone excretion but not that of other steroid metabolites seems most unlikely. Interference in the analytical procedures by the presence of 9 α -fluorohydrocortisone is equally improbable. Although this steroid has some chemical properties similar to hydrocortisone, its rate of flow as the free alcohol on the chromatogram is only about half that of hydrocortisone and interference would not have occurred. The breakdown products of 9 α -fluorohydrocortisone are unknown, but it is most unlikely that they could interfere with the hydrocortisone estimation.

It must be concluded, therefore, that the hydrocortisone level in the blood was lowered temporarily by this drug. The most reasonable deduction is that adrenal production of hydrocortisone has been temporarily reduced.

That such an inhibition, even though temporary, has been produced in this manner in a proved case of adrenal hyperfunction raises points of great interest from the theoretical point of view. It shows that the hyperplastic adrenal is still susceptible to hormonal control. The inhibition of Cushing's hyperplasia by this drug may be compared with the inhibition by cortisone of the androgen-producing hyperplasia in the adrenogenital syndrome. In this latter condition the administration of cortisone has become an orthodox method of routine treatment. The response to cortisone has also become an important diagnostic tool, for it has been found that whereas the adrenogenital syndrome due to adrenal hyperplasia is inhibited by cortisone or hydrocortisone, that due to tumour, whether adenoma or carcinoma, is not (Jailer *et al.*, 1952, 1954; Segaloff *et al.*, 1955).

The finding that 9 α -fluorohydrocortisone can inhibit adrenal activity in Cushing's syndrome due to adrenal hyperplasia raises hopes that a diagnostic procedure may be developed in this condition similar to that used in the adrenogenital syndrome, and that Cushing's syndrome due to adrenal tumour may prove insensitive to inhibition by 9 α -fluorohydrocortisone. But opportunities to test such a possibility occur rarely and experience can only be accumulated by the reporting of individual cases as they are encountered.

It is unfortunate that this case of typical Cushing's syndrome could not be classified with complete certainty as due to either hyperplasia or adenoma. The adenoma present was small and atypical and it seems unlikely that it was the active source of the excess hydrocortisone, because the rest of the adrenal gland was hyperplastic rather than atrophic. The case was therefore probably one of adrenal hyperplasia with an incidental non-functioning adenoma.

While cortisone provides valuable treatment in the adrenogenital syndrome, it seems improbable that 9 α -fluorohydrocortisone will provide effective therapy in Cushing's syndrome. It is clearly desirable to determine to what extent the hyperplasia can be controlled, but it may prove that no endocrine benefit will be obtained, since a daily dose of 5 mg. of 9 α -fluorohydrocortisone would be equivalent to about 100 mg. daily of hydrocortisone. It is unfortunate that we had no opportunity in this case to study the effects of more prolonged administration of the drug.

This inhibition by 9 α -fluorohydrocortisone throws some light on the aetiology of Cushing's syndrome. It is best explained on the assumption that in this syndrome, as in the normal state, there exists a self-regulating mechanism by which any excessive production of hydrocortisone above the predetermined level leads to an inhibition and reduction of output. In Cushing's syndrome it would seem that this level is set at a much higher point than in the normal, but that the self-regulating mechanism is still capable of operation. The ingestion of the potent hormone 9 α -fluorohydrocortisone presumably increases suddenly the blood concentration of hydrocortisone-like substances and sets this self-regulating mechanism in operation, reducing the endogenous production of hormone to a point where the total of exogenous and endogenous hormone is not widely different from the production rate originally prevailing. Whether inhibition is mediated through a reduction in corticotrophin (A.C.T.H.) production cannot be positively stated. Subjects with Cushing's syndrome are often benefited by irradiation of the pituitary gland. They are also exceptionally sensitive to corticotrophin, their hyperplastic adrenals being readily stimulated to still greater hydrocortisone production (personal observation). This sensitivity suggests that endogenous corticotrophin production is not very excessive, but rather that the receptor, the adrenal cortex, is exceptionally sensitive to a steady but moderate corticotrophin stimulus. On such a basis the inhibition of the adrenal cortex in Cushing's syndrome by 9 α -fluorohydrocortisone becomes intelligible, but it must be stressed that at present such an explanation cannot be regarded as more than a working hypothesis requiring further proof.

No certain explanation can be offered for the failure to influence the output of ketosteroids, ketogenic steroids, or of the individual metabolites tetrahydrocortisone and tetrahydro-hydrocortisone. All these are metabolic breakdown products of adrenal steroid metabolism, and it seems probable that there is some lag in their response to changes in adrenal activity. If this be the explanation, then reduced excretion of all these fractions would be expected to follow a more prolonged period of adrenal inhibition by means of 9 α -fluorohydrocortisone. We have not yet had an opportunity to determine whether this occurs. Tetrahydrocortisone excretion is a relatively insensitive indicator of increasing adrenal activity. Under the stimulus of corticotrophin it increases much more slowly than does hydrocortisone excretion. 17-Ketosteroid excretion also seems to be less affected by corticotrophin than does hydrocortisone output,

which can readily increase ten to twenty times in a few hours. In the relative insensitivity and time lag of these indices of adrenal function may lie our failure to influence their excretion rates with this drug.

Summary

9 α -fluorohydrocortisone, a halogen-substituted derivative of hydrocortisone, is a potent substitute for cortisone in man; it has been used successfully as the sole maintenance therapy in patients with Addison's disease.

It is well recognized that cortisone promptly inhibits the high ketosteroid output in the adrenogenital syndrome, provided that this is due to adrenal hyperplasia and not to tumour. In the adrenogenital syndrome with adrenal hyperplasia the high output of ketosteroids can be inhibited by 9 α -fluorohydrocortisone.

In Cushing's syndrome, which is associated with excessive hydrocortisone production, it is not yet known whether cortisone inhibits adrenal function, because adrenal activity is usually judged by blood hormone levels or its excreted metabolites, which are essentially the same as those occurring naturally.

9 α -fluorohydrocortisone provides an opportunity to overcome this technical difficulty, since the end-products of its metabolism are likely to be different from those derived from hydrocortisone.

The effect of 9 α -fluorohydrocortisone on a typical case of Cushing's syndrome has been studied, particular attention being paid to the excretion of hydrocortisone, as this seems likely to provide the most sensitive and specific index of changing adrenal function.

Hydrocortisone excretion in this patient was high, 400–500 μ g. daily (normal 40–200 μ g. daily). 9 α -fluorohydrocortisone was administered in daily doses of 2, 5, 10, and 15 mg. An inhibition of hydrocortisone output in the urine was observed, which returned to normal levels as soon as the drug was withdrawn.

The finding that 9 α -fluorohydrocortisone can inhibit adrenal activity in Cushing's syndrome due to adrenal hyperplasia raises hopes that a diagnostic procedure may be developed in this condition similar to that used in the adrenogenital syndrome, and that Cushing's syndrome due to adrenal tumour may prove insensitive to inhibition by 9 α -fluorohydrocortisone.

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A total of 51 million people have been tested for tuberculosis and nearly 17 million vaccinated with B.C.G. since 1948, when India began her prophylactic programme, reported the Tuberculosis Association of India at their sixteenth annual meeting last April. Teaching and demonstration centres have been set up in Delhi, Patna, and Trivandrum to carry out preventive, diagnostic, and advisory work, and courses for doctors and nurses have been held at these institutions. Public education concerning the disease has been carried out by poster campaigns and broadcast talks, and films are in preparation. Government grants are available for the association's hospitals.