A mechanism accounting for this observation is suggested.

A possible solution to the problem is discussed.

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TREATMENT OF ADRENAL CORTICAL INSUFFICIENCY

BY

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Prior to 1951 patients with Addison's disease could be maintained only with difficulty on the replacement therapy available. Since cortisone and hydrocortisone have been in use these patients have been able to lead normal lives, and it has also been possible to perform total adrenalectomy in selected cases of malignant disease and Cushing's syndrome. Addison's disease is a rare condition, and it is not surprising that there have been differences of opinion about the place of cortisone in its treatment in relation to deoxycortone and extra salt. However, the performance of total adrenalectomy has provided an opportunity for the study of a larger group of patients who have what is in effect severe Addison's disease. Detailed observations have been made on nine patients with Addison's disease and on 30 after total adrenalectomy. The former have been seen at regular intervals for up to seven years and the latter for up to three years. Particular attention has been given to the place of 9α-fluorohydrocortisone in the treatment of chronic adrenal insufficiency.

Hormones of the Adrenal Cortex

The two most important hormones produced by the adrenal cortex are hydrocortisone and aldosterone. Hydrocortisone is sometimes referred to as a "glucocorticoid" hormone because it stimulates gluconeogenesis; it has, however, other more important actions. If the level of circulating glucocorticoid drops abruptly, the blood pressure falls, renal function is impaired with reduction of glomerular filtration rate, and sodium tends to leave the extracellular fluid and enter the cells and possibly bone (Hills *et al.*, 1953; Mendelsohn and Pearson, 1955). Cortisone is not secreted by the adrenal glands, but there is interconversion of hydrocortisone and cortisone in the body and the actions of the two are similar. Aldosterone is the main "mineralocorticoid" hormone of the adrenal cortex. It maintains the body sodium by limiting renal excretion and has a less conspicuous effect in increasing potassium output. Cortisone and hydrocortisone have some mineralo-corticoid action, and in large doses may produce sodium retention and oedema or potassium loss and hypokalaemia.

The other hormones of the adrenal cortex are not necessary for maintaining life. Corticosterone (compound B) has mineralo- and glucocorticoid properties, but in humans it is produced in only very small amounts. In both sexes the adrenal cortex secretes significant quantities of androgens and traces of oestrogens.

Replacement Therapy Available

Hydrocortisone is the most important hormone secreted by the adrenal cortex, and tablets of hydrocortisone or cortisone acetate are essential for adequate replacement therapy. Maintenance of sodium equilibrium is less simple because aldosterone is not yet available. In many patients the weak mineralo-corticoid action of hydrocortisone or cortisone is sufficient provided the salt intake is high. There are two powerful salt-retaining steroids that can be used. Deoxycortone was introduced for the treatment of Addison's disease in 1937 (Simpson, 1938). It must be given by frequent intramuscular injection or implantation of pellets; the sublingual route has been used, but absorption is uncertain. Microcrystalline suspensions of deoxycortone trimethyl acetate may be given by injection at monthly intervals (Thorn *et al.*, 1953). The long-acting preparations (pellets and microcrystalline suspensions) have the disadvantage that their action is not constant throughout the intervals between implantation or injection. An important practical advance in salt-retaining steroids is the fluorine-substituted 9α-fluorohydrocortisone. Its glucocorticoid activity is twenty times that of the parent compound, whereas sodium-retaining power is increased more than one hundred times (Garrod *et al.*, 1955). Fluorohydrocortisone is readily absorbed from the alimentary canal.

Of the remaining hormones, androgens if indicated can be given in the form of methyltestosterone by the sublingual route. There is no evidence that corticosterone or oestrogen replacement is necessary.

Practical Experience

Hydrocortisone production in a normal subject may be assessed by studies with isotope-labelled steroid (Peterson and Wyngaarden, 1955), or by measurement of urinary glucocorticoid excretion (Moxham and Nabarro, 1956). The adrenal glands of a normal adult secrete 20–25 mg. of hydrocortisone a day, which is equivalent to about 25–37.5 mg. of cortisone acetate. Patients who have had total adrenalectomy and those with severe Addison's disease can usually be maintained on 37.5 mg. of cortisone a day. Because of its rapid absorption and conjugation after oral administration, cortisone should be given as evenly spaced doses of 12.5 mg. When adrenalectomy has been performed for malignant disease 50 mg. of cortisone a day is often prescribed, and the slight excess of glucocorticoid is undoubtedly beneficial in causing an increased sense of well-being and appetite. In some patients it may lead to excessive weight gain.

In many cases the cortisone will also maintain sodium balance provided the salt intake is high. If an excess of

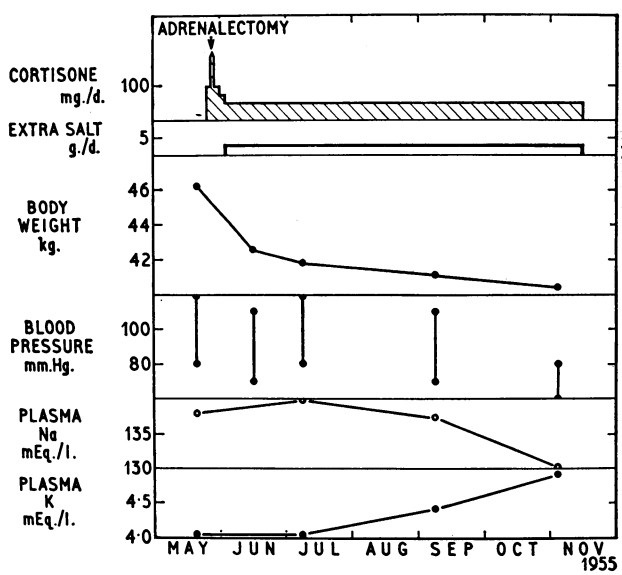

FIG. 1.—Case 1. Total adrenalectomy for carcinoma of breast. Development of sodium-depletion crisis.

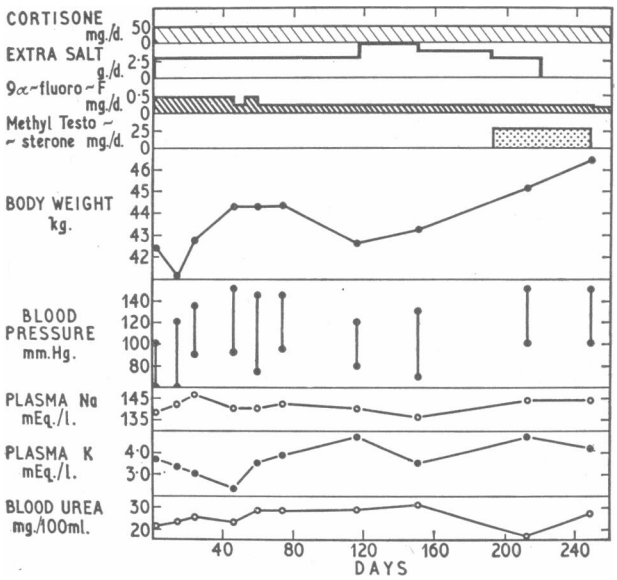

FIG. 2.—Case 1. Subsequent progress when 9α-fluorohydrocortisone given in addition to cortisone.

cortisone is given—for instance, 50 mg. a day instead of the physiological 37.5 mg.—with 3 g. of additional salt, sodium depletion is unusual, but it may occur.

Case 1.—A housewife of 49 had a radical mastectomy for carcinoma of the right breast in 1947. In 1953 there was evidence of diffuse involvement of the left breast, and this was treated by deep *x*-ray therapy. By April, 1955, she had a left pleural effusion and widespread skin infiltration over the left side of the chest. Oophorectomy and adrenalectomy were performed in May by Mr. J. H. Lees Ferguson. She was seen rather infrequently because she lived a considerable distance from the hospital, but her condition was satisfactory, the pleural effusion did not return after pre-operative aspiration, and the skin infiltration regressed. Six months after the operation her practitioner informed us that she was not well enough to attend, and he thought that she had developed visceral metastases. She was, however, brought up, and biochemical studies suggested that her extreme weakness and nausea were due to salt depletion (Fig. 1). Additional salt-retaining steroid was given, and it was found that to maintain sodium equilibrium she needed 0.25 mg. of fluorohydrocortisone and 3 g. of salt a day in addition to 50 mg. of cortisone. She lived for a further year after this episode (Fig. 2). It will be noted that she received 0.5 mg. of fluorohydrocortisone a day initially and after seven weeks had developed hypokalaemia (2.4 mEq/l.).

It is not easy to detect the patients with Addison's disease or following adrenalectomy who are unable to maintain sodium balance on a programme of cortisone and extra salt. The chief symptoms of sodium depletion—weakness and loss of weight—may be masked if 50 mg. a day of cortisone is being given; or if the patient has carcinoma they may be attributed to its progress. Reduction of blood pressure may be a useful guide, but most important are rises of the blood urea and plasma potassium. It could be argued that if the patient feels well there is no need to undertake biochemical studies or to modify replacement therapy on account of a raised blood urea or plasma potassium. We cannot agree with this, because two of our patients, who appeared to be still in remission following operation, died at home after a very brief illness. Their recent biochemical tests had not been completely satisfactory, and it would appear that chronic mild sodium depletion makes the patient more liable to develop acute adrenal insufficiency if any intercurrent illness arises.

When a patient develops clinical or biochemical evidence of sodium depletion the additional salt is increased to 6 g. and, if necessary, to 9 g. a day. Intakes in excess of this are apt to cause troublesome thirst and polyuria. The question of absorption of the extra salt is also considered. Most patients prefer the 1-g. enteric-coated tablets to capsules, but in one case we found that they were not digested (Nabarro *et al.*, 1956). If the patient has been taking tablets a change to capsules may be tried, but when a modest increase of salt intake fails to correct the clinical or biochemical abnormalities 9α-fluorohydrocortisone should be given.

Case 2.—A married woman aged 55 had a radical mastectomy performed in June, 1955. There was evidence of involvement of the internal mammary glands and, a few months later, of the paratracheal glands. In September Mr. D. H. Patey performed oophorectomy and adrenalectomy. She has remained very well since these operations and there has been no further progress of the malignant disease. Changes in weight and blood chemistry are shown in Fig. 3. The rising blood urea was partly controlled by increasing the salt intake, but fluorohydrocortisone proved more effective and allowed the cortisone dose to be reduced to 37.5 mg. a day. This patient is now receiving 37.5 mg. of cortisone and 0.2 mg. of fluorohydrocortisone but no salt tablets.

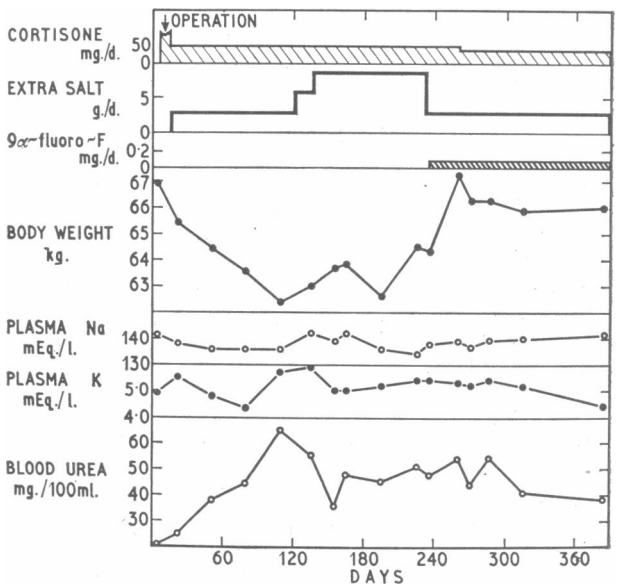

FIG. 3.—Case 2. Sodium depletion after adrenalectomy while receiving cortisone (50 mg. a day) and extra salt (3 g. a day). Partial response to increased salt intake; further improvement on fluorohydrocortisone.

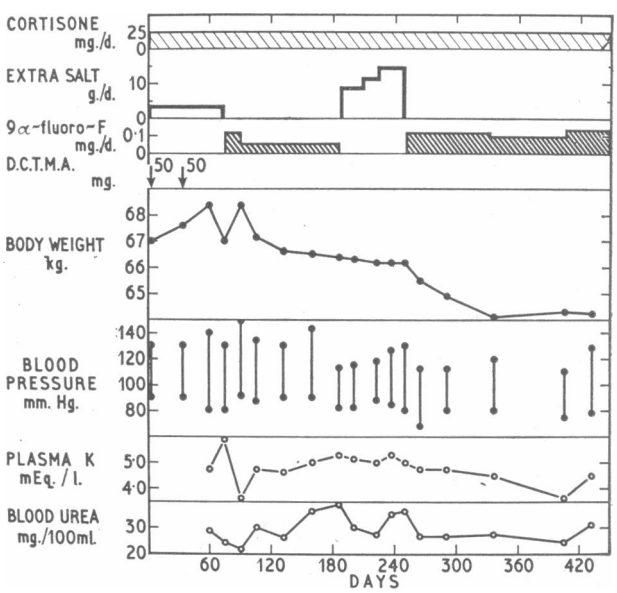

FIG. 4.—Married woman aged 52 treated for Addison's disease. Attempt to substitute a greatly increased salt intake for fluorohydrocortisone. (The steady loss of weight in this period was the result of dieting.)

We have studied one patient who had had Addison's disease for 18 years.

This patient had been receiving 25 mg. of cortisone a day and monthly injections of deoxycortone trimethyl acetate (Fig. 4). Fluorohydrocortisone was substituted for the latter, but the dose given (0.0625 mg. a day) was barely adequate. An attempt was made to replace the salt-retaining steroid by a greatly increased salt intake, but although the dose reached 15 g. of additional salt a day the results were disappointing. The patient subjectively was much less well and had thirst and nocturia. She is now well balanced on the same dose of cortisone and 0.125 mg. of fluorohydrocortisone a day.

Tables I and II show the most satisfactory replacement therapy in nine patients with Addison's disease and 30 who had undergone total adrenalectomy. In the case of the adrenalectomized patients it will be noted that, of those receiving 37.5 mg. daily of cortisone, two out of seven needed salt-retaining steroid; of those receiving 50 mg. a day it was two out of 23. In the smaller group of patients

TABLE I.—*Replacement Therapy in Addison's Disease*

Cortisone Dose (mg./day)	Extra Salt (g./day)	Salt-retaining Steroid*
25 mg. (3 patients)	3–5 g. (2)	Nil
	Nil (1)	F.F. 0·2 mg./day
37·5 „ (6 „)	3 g. (1)	Nil
	10 „ (1)	„
	Nil (4)	F.F. 0·1–0·2 mg./day (3)
		D.C.T.M.A. 50 mg. every 2 months (1)

* F.F. = 9α-fluorohydrocortisone. D.C.T.M.A. = Deoxycortone trimethylacetate.

TABLE II.—*Replacement Therapy in Total Adrenalectomy*

Cortisone Dose (mg./day)	Extra Salt (g./day)	Sodium-retaining Steroid
37·5 mg. (7 patients)	3 g. (4)	Nil
	6 „ (1)	
	Nil (2)	F.F. 0·2 mg./day
50 „ (23 „)	3 g. (18)	Nil
	6 „ (3)	
	Nil (2)	F.F. 0·2 mg./day

Indications for adrenalectomy—disseminated carcinoma of breast (21 cases), of prostate (3 cases); malignant hypertension (2 cases); Cushing's syndrome (4 cases).

with Addison's disease, five out of nine were better with sodium-retaining steroids in addition to cortisone. When fluorohydrocortisone is given it is usually possible to stop the extra salt tablets. The dose varies between 0.1 and 0.2 mg. a day; bigger doses have resulted in hypokalaemia (Case 1), and two other patients complained of excessive weight gain and headache while taking 0.25 mg. a day.

Androgens have been used in a few patients in this series. Four men are included in the Addisonian group; all have been tried on methyltestosterone (5–10 mg. a day), but only one has felt any benefit. A few of the women adrenalectomized for carcinoma have been given methyltestosterone if severely troubled by hot flushes or where there was evidence of further progress of the growth. The results were disappointing.

Discussion

The findings in these patients confirm that cortisone acetate in "physiological" amounts (25–37.5 mg. a day) is suitable replacement therapy for patients with chronic adrenal insufficiency. It is, however, clear that some of these patients require a very high salt intake if they are to remain in sodium balance. When a patient with Addison's disease is becoming sodium-depleted there will be weakness, loss of weight, hypotension, and biochemical abnormalities. Increasing the dose of cortisone has little influence on the sodium depletion and by stimulating cellular catabolism may aggravate the biochemical disturbances. Increasing the salt intake may lead to some improvement, but additional sodium-retaining steroid in the form of oral 9α-fluorohydrocortisone has proved most satisfactory. Our results in cases of severe Addison's disease and in patients who have undergone total adrenalectomy suggest that about one-third of those receiving 37.5 mg. of cortisone daily and one in ten of those receiving 50 mg. daily are benefited by additional fluorohydrocortisone.

Adrenalectomized patients treated with cortisone who develop the "salt-depletion syndrome" seem to do so between three and six months after the operation. The earliest definite evidence is a rise of the blood urea, and we have found it advisable to see all patients who have undergone total adrenalectomy at monthly intervals for the first twelve months. In addition to the usual clinical examination, weighing, and blood-pressure recording, the plasma sodium and potassium and the blood urea are estimated. As well as taking these precautions against the development of a sodium-depletion crisis, we advise the patients or their doctors about the need for extra cortisone if any intercurrent infection occurs. The patients are all given cards similar to those carried by diabetics taking insulin but stating that the patient has undergone total adrenalectomy and must have regular replacement therapy.

Summary

The hormones produced by the adrenal cortex and the preparations available for replacement therapy in adrenal cortical insufficiency are reviewed.

Experiences with nine cases of Addison's disease and 30 patients who had undergone total adrenalectomy are described.

Oral cortisone acetate, 37.5 to 50 mg. daily, was the basis of replacement therapy. It was found that about one-third of those on 37.5 mg. and one-tenth of those on 50 mg. a day became sodium-depleted.

The addition of oral 9α-fluorohydrocortisone, 0.1 to 0.2 mg. a day, was found to be an effective way of correcting this salt depletion.

Attention is drawn to the importance, following total adrenalectomy, of making regular biochemical examinations for the detection of sodium deficiency.

We thank the following surgeons for allowing us to study their patients: Mr. D. H. Patey, Mr. R. S. Handley, Mr. J. H. Lees Ferguson, Mr. L. P. LeQuesne, and Mr. B. J. Harries. Many of the biochemical estimations were performed in the routine laboratories of the Courtauld Institute of Biochemistry, and we are grateful to them for their help. We are indebted to the Medical Research Council and E. R. Squibb and Sons, London, for supplies of 9α-fluorohydrocortisone, and to Mr. V. K. Asta for the charts. We thank the Clinical Research Committee of the Middlesex Hospital for the provision of laboratory facilities and for a personal grant to one of us (J. D. N. N.).

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Three new films have recently been presented to the B.M.A. film library. They are: "Allergic Diseases in Man," by Dr. C. J. C. Britton (presented by C. L. Bencard Ltd.); "Haemorrhoids or Piles," by Mr. A. Lawrence Abel (presented by William R. Warner & Co. Ltd.); and "The Medical Witness," by the American Medical Association and the American Bar Association (presented by Riker Laboratories Ltd.). The first two are in colour, and are suitable for undergraduate and postgraduate audiences. "The Medical Witness" deals with conditions in an American court in an interesting and entertaining way. All the films have a sound track. The films may be hired on application to the Secretary of the Association, B.M.A. House.