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TREATMENT OF ADRENOCORTICAL DEFICIENCY STATES

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The treatment of adrenocortical deficiency states has been completely revolutionized since the advent of the new adrenocortical steroids. The discovery by Hench, Kendall, and others in 1949 of cortisone as a therapeutic agent marked an advance into a new therapeutic era. Now that adrenal substitution therapy is a practical measure, adrenalectomy for a variety of disorders has become increasingly popular. Total or subtotal adrenalectomy is now orthodox therapy for Cushing's syndrome, and total adrenalectomy has also been extensively used in the treatment of metastatic malignant disease and of malignant hypertension; it has also been empirically performed in the treatment of a number of disorders: diabetes mellitus, schizophrenia, and rheumatoid arthritis, to mention three. Substitution therapy has therefore become a day-to-day problem in the wards of many hospitals, and, as a natural sequence, the treatment of adrenocortical crisis has become more common than it used to be.

The tempo of practical therapeutics is now so rapid that by the time a new effective form of treatment is evolved and applied in medicine its probable successors are already on the scene, as yet incompletely studied and unproved clinically. This is particularly so in the adrenal-deficiency states, where steroid chases steroid across a constantly changing scene. We have passed from the time of high-salt treatment, through the cortical extract era, from the deoxycortone to the cortisone age, and are now in the happy position of having many practical tools, all of proved efficiency. In spite of this, many patients with adrenal deficiency still lag behind somewhere on this therapeutic pathway; to-day brown lethargic Addisonian patients, on deoxycortone alone, resemble the partially treated patients of the pre-1949 era. Such patients are by no means rare even at the time of writing.

The clinical material which forms the basis of this study consists of 150 patients, 5 adrenalectomized for malignant hypertension, 2 for Cushing's syndrome, and 143 for metastatic malignant disease. Details of these cases have been published by Sir Stanford Cade (1954, 1955). Of the metastatic cases, 65 have survived and have been followed-up for more than six months to September, 1956. The number of "survival years" of these 65 cases now totals 85.3. The two patients with Cushing's syndrome are in good health, four and one year after operation. Of the patients with malignant hypertension only one survives after two years; the others lived 10, 12, 19, and 12 months after operation.

The details of these five patients, all under the care of Dr. Swithin Meadows, have been reported by Van T'Hoff (1956).

Sodium Loss, Cortisone Deficiency, and Water Intoxication

The classical symptoms of adrenal deficiency are increasing weakness, lassitude, and inability to respond to any form of stress, followed by vomiting, diarrhoea, prostration, and finally coma. The blood urea rises as the serum sodium falls; the serum potassium rises steadily as the patient becomes depleted of salt and water. These symptoms are, however, found only typically in a minority of patients; in most cases the early signs and symptoms are more subtle and less easy to define.

In the adrenal-deficient subject, particularly in the adrenalectomized subject suffering from metastatic malignant disease, the variables with which the clinician has to contend daily are: (1) the salt-and-water balance; (2) the cortisone requirements; and (3) the activity of the underlying (malignant) disease process.

The clinical and biochemical picture may change rapidly overnight in these severely ill patients. Inter-current infection, extreme pain from involvement of a fresh structure by the neoplastic process, vagaries of appetite and thirst, and, particularly, gastro-intestinal upsets may all rapidly and thoroughly upset the delicate balance of the adrenalectomized subject. The symptoms and signs of imbalance in each of the above—water, sodium, and cortisone—may be very similar; symptoms due to neoplastic extension may also cause a similar clinical picture. To illustrate this point, apathy, anorexia, nausea, and vomiting may be due to water intoxication, sodium loss, cortisone deficiency (absolute from the usual dosage being omitted, or relative in the face of cross-infection or some other stress), or extension of the malignant process. If these symptoms are initiated by extension of the neoplastic process they may in turn cause sodium deficiency and/or water loss and/or hypocorticism (relative cortisone deficiency).

The commonest early symptoms of cortisone deficiency are, in our experience, apathy, lassitude, nausea, anorexia, and a general lack of well-being, followed later by vomiting. The blood urea usually rises, but not invariably at this early stage, and the blood pressure usually, but not always, drops. The pulse usually increases, and the pulse pressure lessens. Exactly the same symptoms and signs may herald sodium deficiency;

the two commonly go hand in hand, though by no means invariably, for a patient on a high dosage of cortisone may, for instance, lose large amounts of sodium in the urine and be overtreated with cortisone while still deficient in sodium and in negative sodium balance. Conversely, the patient may suffer cortisone withdrawal symptoms before electrolyte changes are manifestly apparent.

The clinical picture in water intoxication may be very similar to that seen in hyponatraemia, the essential difference being that all blood constituents are diluted in water intoxication and oedema appears with increasing gain in body weight. The appearance of the patient is usually relatively normal in water intoxication (Wynn, 1956), while the sodium-depleted patient is haggard, with inelastic skin. The two conditions may not, however, be easy to differentiate, and hyponatraemia and water-loading may coexist. Cortisone in this water-intoxication syndrome in adrenalectomized subjects may act as a diuretic agent, and while fluid intake is reduced produces brisk diuresis. It is of interest that Pearson *et al.* (1953) found that as a result of experimental withdrawal of cortisone in adrenalectomized patients water intoxication occurred and was, in their opinion, an important feature of adrenal insufficiency. The danger of fluid overloading is a real one in such patients; Hollander *et al.* (1952) quote two instances where death from pulmonary oedema occurred as a result of excessive intravenous infusions.

Salt-retaining Agents

The only treatment for adrenal deficiency prior to the advent of cortisone in 1949 lay in increasing the salt intake in the diet and in giving drugs to cause salt retention; deoxycortone was the most effective agent in this respect. Cortisone and hydrocortisone, though relatively weak sodium-retaining agents, may prove adequate for some patients, but recently many new potent mineralocorticoid substances have been discovered. Aldosterone, for instance, exerts a physiological action in the transport of sodium, potassium, and hydrogen ions by renal tubular and other cells, and is of importance in the normal control of fluid and electrolyte balance. Its secretion is controlled by "a function of extracellular fluid volume, a function of potassium ions, and less importantly, by corticotrophin" (Bartter, 1956). It is a naturally occurring substance, and was isolated in 1952 from the active amorphous fraction of the adrenal cortex (Simpson and Tait, 1952). It has been found both in adrenal venous blood and in peripheral blood, in the urine, and in adrenal cortical adenomata. Its effect on renal sodium and potassium excretion is some 30 times that of deoxycortone. It is the most potent sodium-retaining potassium-eliminating hormone yet found in cortical extract, blood, or urine (Luetscher and Curtis, 1955).

In adrenalectomized man, however, Maclean *et al.* (1955) found that, on withdrawing cortisone, aldosterone given alone did not prevent signs of adrenal deficiency setting in acutely within 36 hours. They state: "The adrenal salt hormone (aldosterone) in man appears to be necessary for the prevention of sodium depletion during severe dietary restriction or excessive extrarenal loss. Its role, therefore, is minor in comparison with hydrocortisone, which is necessary for life maintenance."

In a search for analogues of cortisone and hydrocortisone 9 α -fluorohydrocortisone and 9 α -chlorohydrocortisone were found to be far more potent salt-retaining agents than hydrocortisone itself. It was later found that in steroids possessing an 11- β hydroxyl group (hydrocortisone and 9 α -fluorohydrocortisone) the addition of the 2-methyl group greatly enhanced sodium-retaining and potassium-losing activity; a most potent member of this series,

2-methyl-9 α -fluorohydrocortisone is said to be 90 times as potent as deoxycortone and three times as powerful as aldosterone (Byrnes *et al.*, 1956; Liddle *et al.*, 1956). The delta analogues, prednisone and prednisolone, on the other hand, are weaker in this respect than cortisone and are relatively stronger glucocorticoids and weaker mineralocorticoids. Most of these new substances are therefore too powerful or too weak salt-retaining agents for adequate substitution balanced therapy in the adrenal-deficient subject, and to date it is necessary to "load" cortisone or hydrocortisone slightly by adding small amounts of a mineralocorticoid—usually deoxycortone or 9 α -fluorohydrocortisone. The perfect substitution agent is still awaited; to-day cortisone or hydrocortisone comes nearest to being the ideal single replacement agent.

Deoxycortone

Deoxycortone (D.C.A.; desoxycorticosterone acetate) may be given by pellet implantation or by intramuscular injection. Deoxycortone trimethyl acetate is given as a crystalline "depot" injection, which, slowly absorbed, has a prolonged action over a period of two to three weeks, and the humble 1 mg. "linguette" is absorbed through the buccal mucosa. We used these preparations, particularly the last two, until two years or so ago, but now rarely use any except the sublingual form and very occasionally the intramuscular daily injection. The sublingual form has one great advantage: though a very weak preparation, it is rapidly absorbed, and its effect becomes apparent to the patient within a few hours.

Morning nausea or vomiting can be a sign of sodium depletion, and if a sublingual tablet taken nightly or night and morning removes these symptoms better than promethazine-8-chlorotheophyllinate ("avomine") or chlorpromazine it points strongly to sodium deficiency as the cause. The sublingual tablet can be used in this way not only as a therapeutic weapon but also as a diagnostic pointer. To salt-losing Addisonian patients and adrenalectomized subjects, though a weak preparation, it is usually enough to control, or at least modify, the early symptoms of sodium deficiency if given with cortisone or hydrocortisone. The implant is too blunt a weapon and its control is too remote for the patient adrenalectomized for metastatic malignant disease, whose condition can fluctuate erratically from one day or week to the next. In such patients the intramuscular daily injection where dosage can be regulated daily is useful in acute salt-losing phases, but we now prefer the more powerful and more easily administered 9 α -fluorohydrocortisone.

9 α -Fluorohydrocortisone

9 α -fluorohydrocortisone was introduced by Fried and Sabo in 1954. It is a highly potent substance; Thorn *et al.* (1955) estimate that it is at least 50 times as active as hydrocortisone in its electrolyte-regulating capacity, some 20 times as active in its "organic-regulating potency." Used alone it has proved far too potent a salt- and fluid-retaining substance to be of practical use, though some severely ill salt-losing patients adrenalectomized for metastatic malignant disease have done well on it. Unless used in minute amounts the patients gain weight and become oedematous, and if the dosage is scaled down until this disadvantage is overcome signs of adrenal deficiency may appear; we have seen this occur on more than one occasion. The salt-retaining (mineralocorticoid) action being relatively weaker than the wider glucocorticoid effect, features of Addison's disease, such as weakness and repigmentation, may occur at a dosage level fully adequate for salt balance.

9 α -fluorohydrocortisone given in small amounts in conjunction with cortisone has proved in our hands and those of others (Garrod *et al.*, 1955) extremely useful in balancing adrenal-deficient, salt-losing patients. The tablet we commonly use contains 20 mg. of cortisone acetate plus 0.125 mg. of 9 α -fluorohydrocortisone. Experienced patients are often able to tell the signs of salt and/or cortisone deficiency (see Case 1), and we have found a useful general measure

is to give such patients three sets of tablets. They are instructed to take cortisone 25 mg. twice a day, and if mild symptoms of salt deficiency occur to take a fluorohydrocortisone-cum-cortisone tablet in place of a cortisone tablet every day, every other day, or every three to four days, depending on their symptoms. If, on the other hand, acute deficiency symptoms occur they are instructed to take a 1-mg. tablet of 9 α -fluorohydrocortisone for a few doses until symptoms are controlled. With this "three-tablet" scheme many patients are able to avoid the acute crises which previously took them to hospital, and only if vomiting makes oral therapy impossible or an acute crisis occurs in spite of the above treatment are other measures such as intravenous hydrocortisone needed. 9 α -fluorohydrocortisone, though not yet generally available, is an extremely useful additional substance in the treatment of those adrenalectomized subjects in whom cortisone given alone does not prevent the development of a negative sodium balance.

Liquorice Root and its Extracts

There is considerable evidence that liquorice and some of its extracts have, given orally, a deoxycortone-like action. Molhuysen *et al.* (1950) found that water, sodium, and chloride retention occurred with increase in weight and rise in blood pressure and an increase in potassium urinary excretion. Card *et al.* (1953) confirmed these effects on normal subjects and showed that glycyrrhetic acid had a similar effect. These workers demonstrated that, unlike deoxycortone, glycyrrhetic acid did not prolong the survival time of adrenalectomized rats. Groen *et al.* (1951, 1952) reported the successful control of two cases of Addison's disease treated by liquorice extract and glycyrrhizic acid, and a further case successfully controlled for over a year on liquorice extract alone is reported by Calvert (1954). Borst *et al.* (1953) made the interesting observation that some cases of Addison's disease did not respond unless a small dose of cortisone was added, and they concluded that cases of Addison's disease which respond to liquorice alone probably have some functioning adrenal cortical tissue left and that liquorice acts as substitution therapy only if small amounts of glucocorticoid are also present.

Hudson *et al.* (1954) found that glycyrrhizin given alone was not enough to maintain three adrenalectomized subjects in health, but that given in conjunction with cortisone the dose of the latter substance could be reduced; on glycyrrhizin alone signs of hypoadrenalism came on gradually after one to two weeks. Mitchell (1956) quotes Hems as failing to find any glucocorticoid action when both glycyrrhizic acid and glycyrrhetic acid were tested by the rat-liver glycogen test. The general impression of most workers is that, while having a salt-retaining and water-retaining action these substances have either no glucocorticoid action or insufficient to maintain Addisonian patients in health.

Louis and Conn (1956) used ammonium glycyrrhizinate orally in man; in addition to its known action in inducing water, sodium, and chloride retention and producing a mild increase in urinary potassium they found that it consistently decreased excretion of urinary 17-ketosteroids and was capable of inhibiting pituitary release of melanocyte-stimulating hormone—that is, that it was capable of depressing endogenous production of both corticotrophin and M.S.H. in the pituitary. Galal (1955) concluded as a result of animal experiments that glycyrrhetic acid, given by any route, had an antidiuretic effect rather than a true deoxycortone-like one.

Used in adrenalectomized subjects in conjunction with cortisone, glycyrrhetic acid has proved in our hands a weak mineralocorticoid, causing some retention of sodium and chloride, but a stronger water-retaining substance. If dosage of glycyrrhetic acid be raised to 500 mg. daily the cortisone-treated patients will rapidly gain weight and become oedematous; we have twice seen, in our patients, water-loading occurring in the face of persistence of signs of salt deficiency. Galal suggests that this water-loading effect is not mediated through the posterior pituitary, but is

probably a direct effect on the renal tubules, stimulating reabsorption of water. The rather variable effects with various preparations of liquorice may well be because of batch variations, for many of these preparations are as yet far from being pure substances.

Addison's Disease

The reason for many of the failures to restore normality in Addisonian patients lies in an inadequate dosage of cortisone. Although small doses of 12.5 mg. with additional deoxycortone may enable the Addisonian patient to live in sodium balance, she will remain often lacking in energy, resisting infections indifferently, and remaining deeply pigmented. Since 1951 we have aimed at full physiological replacement—37.5–50 mg. of cortisone daily by mouth. The early-morning dose being the more important, it is common practice to give the larger dose, 25 mg., at this time, for it is in the morning that the patient feels the need of cortisone more particularly, and there is evidence that in the normal man adrenocortical secretion is highest at this time. On full dosage the patient improves remarkably, and gradually loses her abnormal pigment from skin and buccal mucosa. The change from the thin pigmented state to the plump pink one has a great psychological effect on the patient quite apart from the physical well-being that goes with it.

Cortisone alone in the above dosage may be enough to maintain the patient in good general health. Although it has only one-fiftieth to one-thirtieth the salt-retaining effect of deoxycortone, this seems to be enough for many patients, but there appears to be considerable variation in individual requirements in this respect. Some patients clinically normally balanced and symptom-free are found to be in negative sodium balance (Garrod *et al.*, 1955) when investigated more thoroughly, but in practice many do not appear to need a salt-retaining substance as a routine day-to-day measure. Case 2 is of interest in this respect.

Many potent sodium-retaining substances have been discovered in the last few years, and though deoxycortone acetate may still be used in its various forms we have far more potent substances in aldosterone, 9 α -fluorohydrocortisone, and 2-methyl-9 α -fluorohydrocortisone. None of these substances are as yet generally available for therapy, but we have used 9 α -fluorohydrocortisone extensively and are impressed by its usefulness. Our practice is to start the Addisonian patient on 37.5–50 mg. of cortisone acetate a day by mouth and only to add salt-retaining substances if the need becomes apparent. As with the adrenalectomized patients, pamphlets are given explaining the rationale of the therapy and the need for increased dosage in times of stress.

Adrenal Crisis

Adrenal crisis was once rare and almost confined to Addison's disease. In these days of more frequent adrenal surgery it is not uncommon. It may be seen in a variety of different forms (Hart, 1956): (1) during or after adrenalectomy if therapeutic cover is inadequate; (2) in Addison's disease; (3) rarely in Simmonds's disease; (4) in adrenal apoplexy (Waterhouse-Friderichsen syndrome); (5) in the face of severe stress after adrenalectomy—that is, relative cortisone deficiency; and (6) in the face of severe stress in non-adrenalectomized subjects whose adrenal cortices have been depressed by prolonged cortisone therapy, as in long-term therapy of rheumatoid arthritis.

The diagnosis, as mentioned below, must not be confused with that of water intoxication, where the patient has been overhydrated. In the acute form of this (water intoxication) syndrome marked mental disturbances occur, with disorientation, weakness, fits, and even coma; such cases can prove fatal and must be clearly differentiated from the true adrenal crisis before therapy is initiated. In the treatment of adrenal crisis hydrocortisone (free alcohol or hemisuccinate) may be given intravenously; Lundy (1955) has

reported on the use of water-soluble hydrocortisone. Cortisone acetate by mouth may be vomited, and by the intramuscular route is too slow in action. We usually give 100–300 mg. of a suitable preparation of hydrocortisone in a saline infusion over a period of some 6 to 24 hours, but it may be given in severely prostrated ill patients more quickly and in larger amounts than this. In severe salt-losing cases in crisis we have given 9 α -fluorohydrocortisone intravenously in one-twentieth the dose of cortisone given above with good results.

The Adrenalectomized Subject

The three groups of patients adrenalectomized for metastatic carcinomatosis, Cushing's syndrome, and malignant hypertension behave very differently as regards their subsequent balance on substitution therapy. In the case of the last-named (hypertensive) group, it has been our impression that the pre-operative and operative cover needed is greater than in the other two groups, for they seem to tolerate the operation less well and to need more cortisone in the first post-operative few days. Their subsequent day-to-day replacement therapy has been 50 mg. of cortisone acetate by mouth; no additional salt-retaining substance was given or apparently needed in any case. Dr. Van T'Hoff deliberately tried to lower at different times both salt and cortisone in an attempt to produce lowering of the blood pressure, which had remained unchanged at the previous high level after operation, without achieving this result. In these cases, all males, it proved impossible to render them normotensive without definite signs of cortisone and salt deficiency occurring. Although blood pressure was unchanged after total adrenalectomy, the patients nevertheless improved greatly; it was as though the malignant features were relieved and the patients suffered thereafter from simple essential hypertension. On 50 mg. of cortisone acetate daily no signs of sodium deficiency were apparent, and at this dosage level progress was relatively uneventful, salt rations not being severely restricted but largely left to the patient.

In Cushing's syndrome control has been achieved in these two cases by cortisone alone, no salt-retaining substance being given. In the second of these (Case 3) it appeared as though the patient needed some weeks to adapt gradually to a normal steroid level, her presenting signs and symptoms of hypocorticism being tachycardia, xeroderma, and lassitude. For a month post-operatively her daily requirement appeared to lie well above 50 mg. of cortisone; though low-grade wound infection may have been responsible there was never any sign of it. No such period of adaptation was apparent in the first case, which responded rapidly and effectively to normal dosage, and of the two cases of Cushing's syndrome this was the more severe and ill. Every new therapeutic substance has been tried in replacement therapy in this most co-operative subject; on 9 α -fluorohydrocortisone, 1 mg. twice daily, he became water-loaded at the same time as several features of Cushing's syndrome reappeared—moonface, lassitude, headache, and hypertension. All these rapidly disappeared within a few days of stopping this form of therapy. This gallant patient has been maintained on cortisone only—50 mg. daily for four years. At one time he was admitted in coma having inadvertently taken an overdose of a barbiturate—20 gr. (1.3 g.)—and having missed a day's cortisone therapy. On gastric aspiration and intravenous hydrocortisone he rapidly recovered. The hypertension present in these cases as part of Cushing's syndrome, unlike the cases of malignant hypertension quoted above, rapidly returned to normal and remained so after operation. In all the cases of malignant hypertension and in this case of Cushing's syndrome, the retinopathy previously present improved greatly very soon after operation.

These two groups—malignant hypertension and Cushing's syndrome—have been no great problem as regards substitution therapy after the first few weeks. The same cannot be said of the cases of metastatic malignant disease, for the

malignant process eventually recurs, the appetite disappears, and there is none of the day-to-day and week-to-week stability of the other two groups. Gastro-intestinal disturbances are common; one is dealing with a patient in whom activity of underlying malignant process, salt and fluid balance, and cortisone requirements are unknown daily variables. If episodes of cyclical vomiting occur before adrenalectomy in such patients, it is almost certain that they will also occur after this operation, and the use of a salt-retaining substance in addition to cortisone will probably be necessary from the start. Case 1 is interesting in this context.

Although metastatic involvement of the adrenal cortex was common in these metastatic patients, occurring in some 60% of cases (Cade, 1955), in no instance did it produce complete destruction and the clinical picture of Addison's disease. Addison's disease due to metastatic carcinomatosis is indeed very rare; in 354 proved cases of metastatic adrenal involvement (Sahagian-Edwards and Holland, 1954) only four clinical cases were seen.

Most of our adrenalectomized malignant cases have initially needed only cortisone; 50 mg. a day by mouth proved sufficient for almost all patients at first, but in the course of time, and particularly as the underlying malignant process exacerbated and spread and food and salt intake diminished, many cases needed a salt-retaining substance in addition. There was obviously a great individual variation; some patients, dying two years or more after operation, remained adequately balanced on cortisone alone, others soon became salt-deficient. Our practice was to maintain the patient on 50 mg. of cortisone daily, increasing the dosage in the face of stress of any sort and giving to each patient a pamphlet explaining the rationale of such increases. Should signs and symptoms of sodium lack become apparent deoxycortone and latterly 9 α -fluorohydrocortisone was used as described above. In these adrenalectomized patients we were not impressed by any altered response to analgesics or hypnotics, and pain-threshold tests performed by Dr. C. J. M. Clark remained unaltered. Blood pressures were little changed and increasing pigmentation of Addisonian type was not observed. Intensive deep x-ray therapy, however, or radioactive gold greatly upset such patients; these forms of therapy appeared to act as a severe protracted form of stress, and cortisone dosage had to be greatly increased. There seems to be a very real risk in using these agents in patients deprived of their adrenal glands.

Case 1: Adrenalectomy for Metastatic Malignant Disease

A woman aged 45 had metastatic carcinomatosis from a malignant left breast, removed in 1948. Subsequently she was given teloradium therapy to a small hard gland in the supraclavicular fossa. Her condition deteriorated in 1953 and she developed multiple metastatic deposits in most of her bones and sustained pathological fractures of three ribs, a hilar gland mass, and paresis of the left phrenic and recurrent laryngeal nerves. From the end of June to the end of December, 1953, she was given testosterone therapy, a total of 2,550 mg. A bilateral oophorectomy was performed by Mr. Andrew Jessiman in March, 1954, and a two-stage adrenalectomy by Sir Stanford Cade the following month. Before this operation she had had occasional bouts of cyclical vomiting, and in the ensuing nine months she was readmitted on three occasions for rebalancing.

It rapidly became apparent that cortisone alone was not enough and that on it she became salt-deficient. She could be kept in good health on 50 mg. of cortisone daily by mouth, full salt rations, and one or two deoxycortone linguettes daily. She volunteered the interesting information that a deoxycortone linguette at night would prevent her feeling sick in the morning better than chlorpromazine, which had no effect. If this evening dose was omitted nausea recurred within 24 hours. She sustained a Colles fracture in January, 1955, which was dealt with without mishap

under a general anaesthetic and on increased cortisone dosage. When she was transferred to cortisone with minute amounts of 9 α -fluorohydrocortisone her balance remained entirely satisfactory, but in November, 1955, an Addisonian-like episode occurred out of the blue without any obvious cause. Hydrocortisone (free alcohol), 200 mg. intravenously, restored her to normality and she was subsequently maintained on compound cortisone and fluorohydrocortisone tablets.

She observed that when she became salt-deficient her mouth was dry and somewhat sore, her tongue raw and red, and she felt limp and short of breath, with nausea in the early morning proceeding to vomiting if left untreated. Dryness and soreness of the mouth, increasing dyspnoea, and anorexia she took as the earliest warning signs of salt deficiency. She knew when she was "getting overloaded," as her abdomen swelled and she felt heavy. In her case this abdominal swelling appeared as the earliest sign of overdosage with 9 α -fluorohydrocortisone, followed on one or two occasions by her shoes feeling tighter on her feet and her ring tight on her finger.

In many other cases ankle-swelling has been the earliest sign of fluid overloading; where previous mastectomy had led to oedema of one arm, patients frequently noted an increased swelling in this arm as an additional and early sign of fluorohydrocortisone overdosage.

When symptoms of salt deficiency occurred this patient could usually dispel them rapidly either by sublingual deoxycortone or by 9 α -fluorohydrocortisone, 0.125 mg., once or twice daily.

This gallant lady died of metastatic disease two and a half years after total adrenalectomy.

Case 2: Addison's Disease

On December 12, 1952, a married woman aged 35, with a three-months history of this disease, was admitted to hospital under my care in Addisonian pre-crisis, deeply pigmented, hypotensive (blood pressure 75/50), and vomiting. She was subsequently maintained on deoxycortone trimethyl acetate injections fortnightly for some six months, but on transferring to 37.5 mg. of cortisone acetate daily by mouth she improved greatly, had much more energy, withstood cross-infections better, increased in weight, and began to lose her abnormal pigmentation. On this dose she remained well, taking an occasional extra 12.5 mg. in the face of major stress; for instance, very hot summer days would necessitate an increase to 50 mg. cortisone daily over the period of the heat-wave. She remained perfectly well and was doing full household duties in spite of constantly lowered serum sodium and chloride figures until January, 1956, when she felt dizzy and nauseated and started to vomit. She came to hospital by ambulance. There were no signs of an acute infection; blood pressure was 120/80, her usual figure. She had taken extra cortisone tablets with no effect. On 75 mg. of cortisone daily and 0.125 mg. of 9 α -fluorohydrocortisone and two 1-mg. deoxycortone linguettes she improved, returning after two months to her usual cortisone dosage, stopping all other preparations. After a further two months, however, the symptoms returned and she was restarted on small additional amounts of fluorohydrocortisone. She remains well on 50 mg. of cortisone acetate daily with an additional 0.125 mg. of fluorohydrocortisone by mouth every third day, and with a very occasional additional dose of fluorohydrocortisone if symptoms recur.

Comment.—This patient improved dramatically on being changed from deoxycortone to cortisone therapy in 1953, and remained perfectly fit and well, leading a normal life, for 2½ years on cortisone alone in spite of constantly low serum sodium levels throughout this period. After this time small amounts of 9 α -fluorohydrocortisone have become necessary to prevent symptoms of salt deficiency. It is of interest that at all times throughout this study she could be rapidly changed from negative to positive sodium balance by small amounts of fluorohydrocortisone or by

1–2 mg. of deoxycortone given sublingually, but it took 30 months for symptoms of salt deficiency to appear when treated on cortisone alone.

Case 3: Cushing's Syndrome

A married woman aged 30 had a two-stage bilateral total adrenalectomy performed by Sir Stanford Cade on March 29 and April 5, 1956. Her blood pressure before operation was 140/100. A pre-operative course of glycyrrhetic acid had no effect on the elevated 17-ketosteroid, but appeared to produce a slight reduction in the hydroxysteroid urinary excretion. At operation both glands showed simple hyperplasia, the left more than the right. The operations were carried out uneventfully, but it became rapidly evident that her post-operative cortisone requirements were in excess of the usual; a reduction to 75 mg. or less daily was quickly followed by tachycardia and marked general malaise and feelings of exhaustion. She had the dry skin and scaly rash often seen after adrenalectomy in this condition. She was finally discharged to convalescence on May 8 on 25 mg. of cortisone three times a day. Five days later nausea, vomiting, and diarrhoea began. These symptoms were accompanied by a marked tachycardia, for which digitalis was given under the mistaken impression that the patient had paroxysmal tachycardia. Vomiting worsened and she was readmitted on May 17. It was clear that she was suffering from adrenal insufficiency in spite of receiving 75 mg. of cortisone daily by mouth; no significant abnormalities were seen in her electrocardiogram. The blood pressure was 80/50 and the skin dry and scaly. Blood chemistry: serum sodium, 132 mEq/l.; potassium, 4.3 mEq/l.; chlorides, 87 mEq/l.; serum urea, 23 mg. per 100 ml. No signs of wound infection were found and the condition responded to increased dosage of cortisone and occasional 1-mg. doses of 9 α -fluorohydrocortisone by mouth. Since then she has remained well and has been doing full household duties on 50 mg. of cortisone acetate daily by mouth.

Comment.—Some points of interest have been brought out in a study of this case. The dry, scaly skin seen soon after total adrenalectomy is the reverse of the moist "oily" one characteristic of Cushing's syndrome; the rapid swing from one extreme to the other is occasionally striking. A second feature of interest was the marked tachycardia. This, a sign of cortisone deficiency, was interpreted by an outside practitioner as a bout of paroxysmal tachycardia; the digitalis given probably aggravated the pre-existing nausea, anorexia, and vomiting. A third point of interest is that although clearly in Addisonian pre-crisis on her second admission her blood urea remained at a normal level.

Summary

In the maintenance of the adrenocortical-deficient subject in health cortisone (or hydrocortisone) is now the most important single therapeutic substance. Doses of 37.5 to 50 mg. daily are necessary for full substitution therapy; deeply pigmented patients with persistent symptoms of weakness and lassitude on smaller amounts reflect inadequate dosage.

Of the salt-retaining substances, 9 α -fluorohydrocortisone is perhaps at the moment the most useful form of therapy, as, given orally in small amounts, it is more effective than deoxycortone; several other more powerful substances have recently been reported. In crisis intravenous hydrocortisone or fluorohydrocortisone is the method of choice, but the use of fluorohydrocortisone and cortisone orally in adequate dosage at the first sign of adrenocortical deficiency has greatly reduced the incidence of such crises.

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cortisone was donated by the Medical Research Council. Since this article was written we have learnt that Messrs. Squibb have made 9 α -fluorohydrocortisone available to hospitals in tablets of 1-mg. and 0.1-mg. strength.

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USE OF MECAMYLAMINE IN THE MANAGEMENT OF HYPERTENSION

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The discovery by Stone *et al.* (1956) that mecamlamine ("inversine"), a secondary amine, has pharmacological properties in many ways similar to those of the quaternary ammonium compounds, which are tertiary amines, is of interest not only in relationship to the properties of the substance itself but also because other secondary amines as yet untested may prove to be more satisfactory as ganglion-blocking drugs than any of those now available.

On the basis of both animal (Ford *et al.*, 1955; Stone *et al.*, 1956) and clinical studies (Ford *et al.*, 1955; Freis, 1955; Freis and Wilson, 1955, 1956; Moyer *et al.*, 1955) it is evident that mecamlamine causes blockade of both sympathetic and parasympathetic ganglia. It differs from the methonium compounds, however, in being readily and completely, or almost completely, absorbed from the alimentary canal. It has also been reported (Freis and Wilson, 1955, 1956) that, contrary to the invariable course of events with the methonium compounds, the continued administration of mecaml-

amine leads to little or no drug toleration, a point of great practical and theoretical interest. The structural formula of mecamlamine (3-methylamineisocamphane hydrochloride) is here shown.

The present study describes our experiences with the use of mecamlamine in the management of 40 cases of hypertension treated for from four to eight months.

Method

Mecamlamine was administered by subcutaneous or intravenous injection and by mouth. The blood pressure was measured by the method recommended by the Committee for the Standardization of Blood Pressure Readings (1939) in order to maintain uniformity with observations published previously on hexamethonium, pentolinium ("ansolysen"), and chlorisondamine ("ecolid") (Restall and Smirk, 1950; Smirk and Alstad, 1951; Smirk, 1953; Smirk and Hamilton, 1956).

Over a period of from four to eight months (average 4.6) 40 patients (20 males, 20 females) have received a trial of mecamlamine. Fundal gradings were or had been grade IV (Keith, Wagener, and Barker, 1939) in five cases, grade III in nine, and grades II or I in the remainder, most of whom had other severe manifestations such as congestive cardiac failure. Twenty-five patients had had treatment with other ganglion-blocking agents previously. In the remainder treatment was instituted with mecamlamine.

Drug Toleration

Before comparing the potencies of mecamlamine and other ganglion-blocking drugs it is necessary to consider whether mecamlamine causes drug toleration. At an early stage it became evident that toleration either did not occur or was present to a comparatively minor degree following the repeated administration of mecamlamine. Indeed, if drug toleration does develop it must do so early in the course of administration of gradually increasing doses; for once a fully effective dose has been discovered there is no consistent change in the dose needed to reproduce the same fall of blood pressure. In some instances the requisite dose has increased somewhat after several weeks or months of treatment; in other instances, somewhat less frequently, the requisite dose has decreased. In Fig. 1 is shown the

Fig. 1.—Effect on blood pressure of identical doses of mecamlamine given intravenously. I.V. (1) shows effect of an initial dose of 14 mg. of mecamlamine given slowly over the period shown, in the posture indicated. I.V. (2) shows effect of the same dose given in the same manner after two weeks of oral therapy, during which time the patient received 14 mg. of mecamlamine twice daily.