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THE PITUITARY AND ADRENAL CORTEX IN GENERAL MEDICINE*

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The rapid progress of medical research is leading inevitably to increasing specialization in ever-narrowing fields. Endocrinology is no exception, but at the same time it has become apparent that the hormones of the adrenal cortex and anterior pituitary gland are concerned in many medical and surgical conditions that are not primarily endocrine in origin.

In these lectures it is intended to review the role of the adrenal cortex in the response to stress, to discuss the importance of secondary aldosteronism in the production of oedema, to consider the non-endocrine indications for total adrenalectomy, and, finally, to discuss the pharmacology and dangers of high-dosage steroid therapy with cortisone and its newer synthetic derivatives.

The hormones of the anterior pituitary gland are complex polypeptides and it is proving difficult to isolate, purify, or estimate them. Progress in this field has been less spectacular than in the case of the adrenal cortical hormones, but there is evidence that growth hormone has some action in non-endocrine conditions.

Hormones of the Adrenal Cortex

The main hormones secreted by the adrenal cortex are shown in Fig. 1. Those on the left are produced under the influence of corticotrophin; aldosterone excretion continues in the absence of this pituitary

FIG. 1.—Principal hormones secreted by the adrenal cortex.

hormone. From the point of view of maintenance of life the two important hormones are hydrocortisone and aldosterone. Corticosterone is produced in comparatively small amounts, though it is of much greater significance in some animals (Bush, 1953). The adrenal secretes small quantities of oestrogens, and this may be important in women with breast cancer, or after the menopause or oophorectomy (Bulbrook *et al.*, 1958). Cortisone is not produced to any great extent by the adrenal, but there is considerable interconversion of hydrocortisone and cortisone in the body (Gold *et al.*, 1959) and their actions are essentially similar.

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Hydrocortisone and cortisone are often referred to as glucocorticoid hormones because by promoting gluconeogenesis and by reducing carbohydrate utilization they tend to raise the blood sugar. This is unfortunate because these hormones normally have only a minor role in the regulation of carbohydrate metabolism. Their most important actions are concerned with the distribution of water and sodium between the various fluid compartments of the body, and the maintenance of blood-pressure and renal function. These actions can be demonstrated by studying the changes produced by cortisone withdrawal in salt-loaded adrenalectomized patients. Fig. 2 shows the results of an investigation of this type undertaken in 1957 with the help of Drs. G. Walker and M. M. Martin.

The patient was normally controlled on 12.5 mg. of cortisone six-hourly; this was discontinued for a period of 72 hours and then 50 mg. of hydrocortisone (cortisol) was given intravenously. Sodium intake was 200 mEq/day and positive balance was maintained; the cumulative sodium balance and total exchangeable sodium were parallel, the latter being measured with ^{22}Na and an external body counter (Martin and Walker, 1957). In the second part of Fig. 2 it will be seen that there was little change of body weight, an increase of total body water (antipyrine), and a reduction of inulin space. The glomerular filtration rate (G.F.R.) fell, but this was corrected by intravenous hydrocortisone. The loss of diurnal rhythm of water excretion is also shown. Similar studies have been reported by Hills *et al.* (1953) and Mendelsohn and Pearson (1955). The former noted reduction of inulin space and increase of total body water, whereas Mendelsohn and Pearson reported that the inulin space increased without any change of total body water.

The essential physiological actions of hydrocortisone and cortisone may therefore be summarized as: (a) maintenance of distribution of water and sodium between the cellular and extracellular fluids; (b) maintenance of blood-pressure; (c) maintenance of G.F.R.; and (d) necessary for renal excretion of water.

Aldosterone has little action in these spheres in the amounts present in the circulation. It is concerned principally with sodium and potassium homeostasis, and exerts its effect through the renal tubule. At the same time it has some action on the sodium/potassium ratio of the saliva, sweat, and faeces (Thorn *et al.*, 1955).

There are two vital adrenal cortical hormones with different actions; it is therefore not surprising that two types of acute adrenal insufficiency can be differentiated (Lipsett and Pearson, 1956). In one there is an absolute

or relative lack of hydrocortisone, resulting from true deficiency or increased demand and exemplified by the patient just described, from whom cortisone was temporarily withdrawn. The second is due to lack of aldosterone, leading to sodium depletion, hypotension, and extrarenal uraemia with marked elevation of plasma potassium. This type of crisis is seen in some adrenalectomized patients treated with cortisone alone and in whom the sodium intake is inadequate: it comes on rather more slowly than the crisis of acute hydrocortisone deficiency. Differentiation between these two

excretion; the only clear responses were with boat-race crews, and the cox and coach were affected as much as the actual crew (Thorn *et al.*, 1953). The plasma level of hydrocortisone may be raised by emotional stress (Mason, 1959) or by taking amphetamine sulphate (Bayliss, 1955). Emotional factors may also result in increased aldosterone production (Venning *et al.*, 1957).

Serious illnesses like coronary thrombosis (Bayliss, 1955), cerebrovascular accidents (Oka, 1956), and fulminating infections (Melby and Spink, 1958) cause increased adrenal production of hydrocortisone. Pain

and shock are probably the two main factors responsible (LeFemine *et al.*, 1957). Tyler *et al.* (1953) have pointed out that to cause a marked elevation of the plasma hydrocortisone level it must be a "life-threatening" type of stress. They reported a patient in severe diabetic ketosis with a level of 51 $\mu\text{g.}/100\text{ ml.}$, falling to 8 $\mu\text{g.}/100\text{ ml.}$ three weeks later (Perkoff *et al.*, 1954). Patients who are dying (Sandberg *et al.*, 1956) and those in peripheral circulatory failure due to fulminating infections (Melby and Spink, 1958) have been found to have very high plasma levels. In these cases not only is there evidence of increased hydrocortisone production by the adrenal, but also the rate of hepatic conversion of free hydrocortisone to its inactive metabolites is reduced. It seems clear that in severe illness there is an increase of hydrocortisone production and that if it fails, or sometimes despite its occurrence, there may be severe hypotension and peripheral circulatory failure. The significance of these findings in patients with severe illnesses cannot yet be assessed. It is possible that if the level of circulating hydrocortisone were raised still higher in some of these shocked patients the circulatory status would be improved. This means higher than a normal adrenal can achieve, and

FIG. 2.—Effect of cortisone withdrawal in a woman aged 48 who had undergone total adrenalectomy for widespread metastatic carcinoma of the breast.

types of acute adrenal insufficiency is important because they do not respond to the same treatment. The hydrocortisone-deficient type responds well to intravenous hydrocortisone, and the sodium-deficiency type to intravenous saline with sodium-retaining hormone. The classical crisis of untreated Addison's disease is a combination of the two and needs treatment with hydrocortisone, intravenous saline, and sodium-retaining steroid.

The Adrenal and Stress

It is well recognized that patients with Addison's disease respond badly to the stress of an acute illness or infection or to a surgical operation. In these conditions the maintenance of blood-pressure, fluid distribution, and renal function require higher levels of circulating hydrocortisone than in the normal resting state. A considerable amount of work has been done to try to assess the types of stress that lead to increased hydrocortisone production. Thorn subjected a number of normal individuals to stressful situations and found that exposure in a cold room, anoxia, and emotional upsets were without effect on the urinary steroid

may be evidence in favour of giving intravenous hydrocortisone to shocked patients without invoking adrenal exhaustion or failure (DiRaimondo and Forsham, 1958).

There has been considerable interest in the last few years in the metabolic response to stress and the possible role of the adrenal cortex in the changes in electrolyte and nitrogen excretion. It is difficult to investigate this relationship in medical stress. Studies have been reported in which the metabolic and steroid changes after corticotrophin have been compared with those resulting from artificial fever produced by intravenous typhoid vaccine and other pyrogens; the results were inconsistent, and the metabolic changes could not be correlated with altered adrenal cortical activity (Conn *et al.*, 1954). Most of the studies of the metabolic response to stress have been made in surgical patients. It has been shown that the hydrocortisone level in the plasma may be raised before operation if there is anxiety (Franksson and Gemzell, 1955), and that a further rise follows induction of anaesthesia, especially if ether or cyclopropane is used (Hammond *et al.*, 1958). The very considerable increase during and shortly after the operation is due partly to increased adrenal cortical production

and partly to reduction of the rate of metabolism of the steroid by the liver (Tyler *et al.*, 1954), although studies with hydrocortisone infusion in the immediate post-operative period have given conflicting results (Murray *et al.*, 1958; Dudley *et al.*, 1959).

Aldosterone excretion is often increased after operation (Llaurado *et al.*, 1956). This increase correlates poorly with changes in urinary sodium output (Venning *et al.*, 1958), and sodium retention can occur after operations on adrenalectomized patients (Forrest *et al.*, 1957) and Addisonians (Randall and Papper, 1958). Indirect evidence was given some years ago that post-operative sodium retention is the result of sodium deficiency (Flear and Clarke, 1955). More recently Hayes *et al.* (1959) have studied the problem and shown that the post-operative increase of urinary aldosterone is not an essential part of the metabolic response to surgery but the result of sodium depletion possibly from local immobilization of extracellular fluid at the operation site.

Metabolic Response to Surgery

The chief features that make up the metabolic response to surgery are an initial antidiuresis, a rather longer retention of sodium and chloride, and negative balances of potassium and nitrogen. In considering the possible causes of these changes there are the relative or absolute starvation that accompanies the operation, the increased production or circulating level of adrenal cortical hormones, and the effects of the operation itself—tissue damage, loss of blood, and local oedema. Attempts have been made, by keeping the adrenal steroid level and electrolyte intake constant, to eliminate these factors and ascertain the metabolic changes due to the stress itself (Mason, 1955; Robson *et al.*, 1955; Jepson *et al.*, 1957).

To keep the steroid level constant intramuscular cortisone in adequate, but not excessive, doses should be started 10–14 days before the operation. This will ensure a constant level of urinary excretion (Sprague *et al.*, 1950) but cannot compensate for any alteration in the rate of hepatic metabolism or for possible changes of steroid binding by plasma proteins which may reduce physiological activity (Sandberg *et al.*, 1957). The food intake must be kept absolutely constant if this factor is to be eliminated; it has been demonstrated that alterations of potassium and nitrogen intake may influence the sodium balance in the post-operative period (Krieger *et al.*, 1958). Between 1955 and 1957, with the help of Dr. G. Walker, a number of studies of this type were made. Most of the patients were undergoing total adrenalectomy under the care of Mr. D. H. Patey and Mr. L. P. LeQuene. Steroid levels were kept constant by giving intramuscular cortisone (100 mg. daily), starting 10–14 days before operation. Food intake was kept constant by giving a slow intragastric drip of an emulsified feed of identical composition with the diet; this was started a few hours after the end of the operation.

Cumulative balance figures showed that the metabolic response to surgery was reduced if steroid levels and food intake were kept constant. There was, however, reduction of urinary sodium and increased nitrogen excretion after operation. Potassium losses were much reduced if adequate intake was maintained. The results were similar to those of Abbott *et al.* (1959). There is general agreement that the overall pattern of the metabolic response to stress still occurs when the steroid

level is kept constant, but that the level required is much higher than normal. It has been demonstrated in adrenalectomized animals that the response does not occur in the absence of adrenal steroids (Ingle *et al.*, 1947). There is little evidence that the magnitude of the metabolic response is related to the degree of adrenal hyperfunction, although in studies of severe diabetic ketosis it has been shown that the negative nitrogen balance bears some relation to the 17-hydroxysteroid excretion (Nabarro *et al.*, 1952).

Aldosterone and Oedema

Chemists and clinicians studying the role of aldosterone in oedema are all agreed that the problems involved in measuring aldosterone production and excretion are considerable. Much of the early work done in this field can be criticized on grounds of unreliable methodology. Aldosterone production by the adrenal cortex amounts to about 0.2 mg./day in a normal subject and the level in the blood is very low. Little free aldosterone is present in the urine, but a measurable amount is excreted as an unusual conjugate hydrolysed by acid at room temperature, and there are also metabolites conjugated with glucuronic acid. There is no specific reaction for aldosterone; it can only be estimated by physical or chemical reactions that are also given by the very much larger quantities of hydrocortisone and other steroids present in the urine. Measurement of urinary aldosterone therefore involves several chromatographic purification procedures to free it from other steroids before the final estimation can be performed (Ayres *et al.*, 1957b). An important step forward is the use of tritium-labelled aldosterone. If this is injected into the patient and the urine collected over the next 24 hours a figure can be obtained for the rate of aldosterone secretion by the adrenal gland (Ayres *et al.*, 1957a).

Most of the methods used for aldosterone estimation depend on separation of the aldosterone from the urine after hydrolysis at pH 1. If this figure is to be of value it must represent a consistent proportion of the aldosterone produced each day by the adrenal. When tritiated aldosterone is given to the patient to measure the secretion rate, it is possible to determine the proportion of radioactivity secreted in the free state, as the acid hydrolysed conjugate and as glucuronide (Jones *et al.*, 1959; Peterson, 1959). This is shown diagrammatically in Fig. 3. Repeated estimations of secretion rates and distribution of urinary radioactivity in two patients have suggested that the urinary pH 1 extractable aldosterone may vary much more than the actual secretion rate (Hurter and Nabarro, 1960). Results

FIG. 3.—Distribution of radioactivity in a 24-hour collection of urine after injection of 1 μ g. of tritiated aldosterone.

TABLE I.—*Urinary Excretion of Radioactivity in a 24-Hour Period After Intravenous Administration of 1 µg. of 16 ³H-aldosterone. Four Estimations on a Patient with Congestive Cardiac Failure*

Date	Secretion Rate µg. 24 hrs.	Percentage of Radioactivity	
		In pH 1 Hydrolysate	As Glucuronide
August 8 ..	1,430	6.3	17.3
" 12 ..	1,560	6.0	20.4
" 16 ..	940	10.6	30.2
" 20 ..	1,340	14.7	20.7

of four determinations in a patient with cardiac failure are shown in Table I.

The control of aldosterone secretion in experimental animals and normal subjects has been clarified considerably in recent years by the work of Bartter and his group, and by Farrell. Farrell (1959) has obtained evidence that aldosterone secretion is controlled by a tropic hormone, "glomerulotropin," released from an area of the posterior diencephalon and pineal body. Bartter *et al.* (1959) have studied the various factors that influence aldosterone secretion. These include reduction of the intravascular volume in certain parts of the body and, to a less extent, potassium levels and corticotrophin. The intravascular volume operates in two areas; reduction of flow through the carotid artery stimulates increased production of aldosterone; removal of the arterial constriction does not necessarily allow aldosterone production to return to normal—there is a separate "turning off" mechanism. This has been located in the right auricle, distension of which tends to lower aldosterone secretion. These centres operate via the sinus and vagus nerves respectively.

Even before aldosterone had been isolated, potent salt-retaining substances had been detected in the urine of patients with the nephrotic syndrome (Deming and Luetscher, 1950). This has been shown to be aldosterone (Luetscher *et al.*, 1954), and an excess of aldosterone has also been found in patients with cirrhosis with ascites and oedema (Dyrenfurth *et al.*, 1957), cardiac failure (Luetscher *et al.*, 1956), episodic oedema (Luetscher and Lieberman, 1958), and oedema due to increased capillary permeability (Thorn *et al.*, 1957). In these cases it is important to consider what part the increased secretion of aldosterone plays in the production or maintenance of the oedema. Experimental administration of large amounts of aldosterone does not produce oedema in a normal subject; after a period of retention of sodium and water an "escape" from the aldosterone effect is seen and the patient comes back into sodium balance (August and Nelson, 1959). In patients with secondary hyperaldosteronism there must be some factor at work interfering with the escape phenomenon.

Muller (1959) has reviewed some of the factors involved in oedema production in uncomplicated nephrosis in children and in congestive cardiac failure. He has suggested that in nephrotic children lowered plasma osmotic pressure allows escape of oedema fluid from the capillaries, and this in turn reduces plasma volume. The carotid mechanism of aldosterone regulation is stimulated and significant overproduction results. The sodium that is retained, however, does not remain in the circulation but escapes through the capillaries, and hence the stimulus to increased aldosterone production persists. In cardiac failure the secretion rates of aldosterone are not nearly so high as in nephrosis, and Muller has suggested that there is failure of the "turning off" mechanism. Until there is more detailed informa-

tion available about the site of origin of the right-auricular impulses it is not possible to evaluate this hypothesis.

Aldosterone levels of oedematous patients vary with the salt intake, but an oedematous patient does not reduce aldosterone excretion in response to a salt load nearly as well as a non-oedematous subject (Duncan *et al.*, 1956). Diuretics tend to raise the aldosterone levels unless they result in improvement in the cardiac condition, in which case there may be reduction (Muller, 1959). Venesection acts similarly. Removal of the ascitic fluid from a cirrhotic patient results in striking increases of aldosterone levels (Wolff *et al.*, 1958). These studies are interesting but do not clarify the relationship between secondary aldosteronism and oedema.

A more direct approach has been the use of amphenone, a compound which inhibits many enzyme systems of the body including those needed for synthesis of steroids (Hertz *et al.*, 1956). The effect of giving amphenone and inhibiting aldosterone synthesis in patients with oedema has been investigated in a number of centres, and the results of some of these studies are shown in Table II. It is clear from these

TABLE II.—*Effect of Amphenone on Sodium Excretion in Patients with Secondary Hyperaldosteronism*

Underlying Condition	Urinary Aldosterone before Amphenone (µg./Day)	Urinary Sodium (mEq/Day)	
		Before Amphenone	On Amphenone
C.C.F. ..	10	5	10
	14	5	70
	33	<1	3
Nephrosis ..	74	5	5
	23	1	20
Cirrhosis ..	43	1	105
	43	1	1
	26	5	13
Abnormal capillary permeability	89	1	28

results that stopping the secretion of aldosterone in oedematous patients does not necessarily result in a diuresis. Recent studies have shown that an analogue of amphenone, 2-methyl-1,2 bis-(3-pyridyl)-1-propanone (SU 4885), also interferes with aldosterone synthesis and gives similar results (Coppage *et al.*, 1959).

Another approach to the problem is to use the newly developed spiro lactone series of compounds. They have little effect on sodium and potassium excretion in adrenalectomized dogs in the absence of sodium-retaining steroids; they will, however, block the action of aldosterone on the renal tubules (Slater *et al.*, 1959b). In intact humans it has been shown that 1 mg. of spiro lactone (SC 8109) will partially neutralize the action of 0.5 µg. of aldosterone (Ross and Bethune, 1959). In an adrenalectomized dog given the 7α-thioacetoxy derivative (SC 9420) by mouth and a continuous infusion of aldosterone intravenously we have shown that 30 mg. of spiro lactone will partially inhibit the action of 21.5 µg. of aldosterone. The inhibition starts about two hours after the spiro lactone is given and continues for more than eight hours. 50 mg. given by mouth completely inhibits the action of 5 µg. of aldosterone given as a single intravenous injection.

In practice the responses to these compounds are variable. Fig. 4 A shows an excellent response in a

patient with cirrhosis, ascites, and oedema. His aldosterone secretion rate at this time was 205 $\mu\text{g./day}$, very low for a patient on a low-sodium diet. Studied later after a haematemesis, at a time when his aldosterone secretion rate exceeded 1 mg./day, the response to spiro-lactone alone was disappointing. The additive effects of chlorothiazide, spiro-lactone, and mersalyl are shown in Fig. 4 B. Subsequently, prolonged administration of spiro-lactone had little effect on sodium output, although there was a fall of the urinary excretion of pH 1 extractable aldosterone (Fig. 4 C). The mechanism of this is unexplained; we have noted it previously in patients responding poorly to spiro-lactone. In this case it was not accompanied by a corresponding fall of the aldosterone secretion rate. Our results in this and other patients suggest that when the aldosterone levels are very high the response to spiro-lactone alone is likely to be disappointing. This may be because the amount of spiro-lactone given has been inadequate. Alternatively, it may be that when the aldosterone levels are very high they play a comparatively small part in the oedema, and that, when they are lower, inhibiting just this one factor in sodium retention allows a diuresis to occur.

There are unexplained differences between primary and secondary hyperaldosteronism. Oedema is very common in the secondary variety but unusual in Conn's syndrome; on the other hand, potassium depletion and hypokalaemic muscular paralysis are often features of primary aldosteronism but rare in the secondary type. In a normal subject aldosterone causes initial sodium retention followed by an "escape" and return to sodium balance (August and Nelson, 1959). The aldosterone causes expansion of the extracellular fluid, increase of plasma volume, and elevation of the glomerular filtration rate. This results in increased sodium excretion, but it may not be the only factor in the escape phenomenon (Relman *et al.*, 1958). Admittedly patients with Conn's syndrome often have a low G.F.R., but there is a considerable fall after operation followed by a gradual rise (Hewlett *et al.*, 1957; Milne *et al.*, 1957). The low G.F.R. before operation may be due to potassium depletion (Schwartz, 1955). In secondary hyperaldosteronism sodium retention does not expand the plasma volume, because the sodium retained leaks out into the tissues and aggravates the oedema. The absence of potassium depletion in the secondary variety has been attributed to the very small amounts of sodium in the distal renal tubules and hence inability to exchange potassium for sodium. Patients given salt-retaining steroids do not have a potassium diuresis if they are on low-sodium diets (Relman and Schwartz, 1952). An additional factor may be that patients with Conn's syndrome rarely have adenomata producing exclusively aldosterone (Lieberman *et al.*, 1958), and the combination of aldosterone with other steroids like corticosterone may increase the potassium loss (Ross, 1960).

Total Adrenalectomy in Non-endocrine Conditions

Total adrenalectomy has been undertaken in a number of non-endocrine conditions (Table III).

TABLE III.—Indications for Total Adrenalectomy

Cushing's syndrome (adrenal cortical hyperplasia)	..	Removes source of excess hydrocortisone
Carcinoma of breast	..	Removes source of oestrogens
" " prostate	..	Removes source of androgens
Cirrhosis with ascites	..	Removes source of aldosterone
Intractable oedema	..	..
Malignant hypertension	..	? Removes source of aldosterone
Diabetes with complications	..	?

The commonest indication for the performance of this operation is disseminated cancer of the breast. Reports of long-term follow-up have been published by Dao and Huggins (1957) from Chicago, and from the Sloane Kettering Cancer Research Institute in New York

FIG. 4.—Man aged 63 with cirrhosis of the liver, ascites, and oedema. A, November, 1958. Aldosterone secretion rate 205 $\mu\text{g./day}$, good response to spiro-lactone (SC 8109) intramuscularly. B, June, 1959. Aldosterone secretion rate >1,000 $\mu\text{g./day}$, effect of spiro-lactone (SC 9420), 400 mg./day by mouth, with chlorothiazide and mersalyl. C, July, 1959. Effect of prolonged administration of spiro-lactone.

(Fracchia *et al.*, 1959). A large series of cases have been described in this country by Stanford Cade (1957). Remissions are obtained in about 40% of cases and may last as long as five years. The most promising cases are those with multiple bony metastases appearing several years after the treatment of the primary tumour. Cases with liver involvement usually fail to respond. Because only 40% of patients respond, attempts have been made to devise effective methods for the selection of suitable cases. The operation is indicated in patients with tumours stimulated by oestrogens, and, if the history shows that the patient has had a good response to oophorectomy, response to adrenalectomy may also be anticipated. It is more difficult to assess the response to irradiation of the ovaries or administration of androgenic hormones. Emerson and Jessiman (1956) have suggested stimulation and suppression tests using oestrogens and cortisone. These tests are difficult to apply, and it is generally necessary to rely on a clinical assessment.

The results of total adrenalectomy for malignant hypertension were reported by Thorn *et al.* (1952). There was often improvement in the appearance of the optic fundi, but to lower the blood-pressure it was necessary to keep these patients on the fringe of adrenal insufficiency, renal function was often further impaired, and the plasma potassium tended to rise rather alarmingly. To control this it was necessary to give additional salt-retaining steroid, and the blood-pressure went up

again (Morse *et al.*, 1959). Another group of cases have been followed in Philadelphia, but here the adrenalectomy was usually subtotal and often combined with sympathectomy (Jeffers *et al.*, 1953). Three groups of cases have been reported in this country; the effect of the operation on the blood-pressure has usually been disappointing, but there was no doubt that the papilloedema and appearance of the optic fundi improved (Arnott *et al.*, 1957; Hanley, 1957; van't Hoff, 1957). The operation carries an appreciable mortality, the difficulties of post-operative care are considerable, and with improvement of hypotensive drugs its performance can seldom be indicated for hypertension.

The rationale for undertaking total adrenalectomy for diabetes with retinitis and vascular disease is not entirely clear. Two series of cases have been reported (Wortham and Headstream, 1954; Malins, 1956). In the first series, three died and two of the other four showed slight improvement. In the second there was one death, one case showed improvement in the retinitis, and four showed no change or were worse.

Adrenalectomy may be effective in cases of intractable fluid retention. Good results have been reported in cases of cirrhosis of the liver with ascites (Marson, 1954; Giuseffi *et al.*, 1957; Baronofsky *et al.*, 1960), and in a patient with oedema due to abnormal capillary permeability (Thorn *et al.*, 1957). A number of the diabetics with vascular disease and proteinuria reported by Wortham and Headstream (1954) lost their oedema after adrenalectomy. In hypertensive heart failure loss of oedema may benefit the patient (Thorn *et al.*, 1952). The effect of adrenalectomy in one patient with episodic oedema has been described—the oedema was improved but the patient's underlying psychological difficulties remained (Thorn *et al.*, 1956). In these cases it would seem that aldosterone removal is the operative mechanism, and if the spiro lactone group of aldosterone-blocking drugs prove effective, surgery will not be necessary.

We have made observations on operative cover and post-operative replacement therapy on 68 patients undergoing total adrenalectomy. Seven of these were for Cushing's syndrome and 61 for non-endocrine conditions (carcinoma of breast 56, prostate 3, hypertension 2). The steroid cover that we are at present using when the operation is performed for carcinoma is shown in Table IV. The use of intramuscular cortisone in these doses results in excellent sodium conservation in the post-operative period. It is not necessary to give additional salt-retaining steroid or extra salt. Intravenous hydrocortisone has been used to cover the operation in a few cases, but sodium conservation may then be much less effective (Fig. 5) and sodium-retaining steroid should be used. By the sixth day after operation the dose of cortisone is usually down to 12.5 mg. q.d.s.

TABLE IV.—Steroid Cover for Total Adrenalectomy in Cases of Carcinoma of the Breast or Prostate

4-days pre-op. . .	Cortisone 100 mg. daily i.m.	
D—Op. . .	Cortisone 100 mg. i.m. pre-op.	I.V. isotonic saline 500 ml.
	Cortisone 50 mg. i.m. 6-hourly post-op.	Subsequently 5% dextrose. Blood if required
D +1 . .	Cortisone 50 mg. 8-hourly i.m. or oral	
D +2 . .	Cortisone 50 mg. 8-hourly oral	
D +3 . .	Cortisone 25 mg. 6-hourly oral	
D +4 } . .	Cortisone 25 mg. 8-hourly oral	
D +5 } . .	Cortisone 12.5 mg. 6-hourly	
D +6 onwards	Fludrocortisone 0.1 mg. daily	

Plasma Na and K and blood urea estimated before operation and 10 days after. If the latter is abnormal adjustment of fludrocortisone dose is indicated.

FIG. 5.—Total adrenalectomy for carcinoma of breast. Urinary sodium excretion and cumulative sodium balance. Left: woman aged 51—routine steroid cover with intramuscular and oral cortisone. Right: woman aged 46—steroid cover with intravenous hydrocortisone and oral cortisone.

and the administration of 0.1 mg. of fluorocortisone a day is started (Table IV). We have come to the conclusion that 50 mg. of cortisone a day with extra salt is not always adequate as replacement therapy for the totally adrenalectomized patient. A sodium-depletion type of Addisonian crisis may be produced, and the use of a small dose of fludrocortisone with the cortisone is now recommended as a routine procedure (Nabarro and Walker, 1957).

[The second part of the Oliver-Sharpey Lectures will appear in next week's issue.]

"At this point you must allow me a very brief digression on the subject of pastoral diets. As I imagine most of you know, the milk of the camel, as compared with cow's and goat's milk, is deficient in mineral salts, particularly those of calcium. As a result, the physique of the camel man is a very slight one; indeed, compared with the camel-owning desert Somali, the cattle-owning savannah country Masai is a percheron to a racehorse. But not only is the camel man light-boned, he is also extremely excitable and volatile. His temperament can be described in the terms used by Lavater of Fuseli: 'His look is lightning, his word a storm, his jest death, his vengeance Hell—at close quarters he is rather trying.' All this is attributable I suppose to mineral deficiency. A distinguished old man, the head of his clan, who owned large herds of both cattle and camels, once told me that it was a tradition amongst the noble families of his tribe to insist that the young men who were later to take over the leadership of the people should spend their formative years with the cattle rather than with the camels. Understandably, he did not explain the custom in terms of the mineral salt content of various milks or of the assimilation of calcium but just said that he found that the young men raised in this way seemed to have more sense than those who spent their time with the camels." (Speech by Sir Richard Turnbull at opening of Scientific Conference on Malnutrition, Dar es Salaam, 1960. *E. Afr. med. J.*, May, 1960.)