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STUDIES ON ALDOSTERONE SECRETION IN MAN*

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Interest in the relation of adrenal cortical function to sodium metabolism was stimulated in 1933 by the studies of Loeb, Atchley, Benedict, and Leland, who described the excessive urinary sodium loss in adrenalectomized dogs, and by similar observations of Harrop, Soffer, Ellsworth, and Trescher (1933), who further suggested that one of the functions of the adrenal cortex was to assist the organism to preserve adequate volume and electrolyte composition within the extracellular compartment. Three years later Harrop, Nicholson, and Strauss (1936) reported that adrenal cortical extracts were capable of inducing sodium retention in dogs, and Thorn, Garbutt, Hitchcock, and Hartman (1936) demonstrated similar effects in normal human subjects as well as in patients with Addison's disease.

In 1937 Steiger and Reichstein announced the synthesis of 11-deoxycorticosterone (deoxycortone) acetate. The effectiveness of this substance in correcting the abnormalities of mineral metabolism in patients with Addison's disease was described by Thorn, Howard, and Emerson in 1939. Although synthetic deoxycortone acetate proved very effective as replacement therapy in such patients, there was no indication that this compound was secreted under normal circumstances until the recent findings of Farrell, Rauschkolb, Royce, and Hirschmann (1954), who were able to isolate and identify deoxycortone in the adrenal venous blood of the dog. However, the quantity found in these experiments appeared to be too small to account for any conspicuous biological action.

That the "amorphous fraction" of adrenal extracts contained a substance or substances of high sodium-retaining activity was suggested by Kendall in 1937, and indeed Hartman, Spoor, and Lewis (1939) postulated the existence of an adrenal "sodium factor" different from the life-maintaining fractions of the adrenal cortical extracts available at that time for clinical use, and possessing sodium-retaining activity greater than that of deoxycortone.

In 1937 Thorn and Harrop reported that not only did adrenal extracts, corticosterone and 11-dehydrocorticosterone induce sodium retention and increase potassium excretion in normal human subjects as well as in adrenalectomized dogs and in patients suffering from Addison's disease, but that sex hormones (oestrogens, progesterone, and testosterone), which, as steroids, possess a closely related structure, also decrease the renal excretion of sodium in normal dogs. Of these latter substances only progesterone appeared capable of prolonging the life of bilaterally adrenalectomized dogs (Thorn and Engel, 1938).

With the increasing clinical use of deoxycortone acetate, the occurrence of oedema, hypertension, and cardiac failure was reported during its administration (Ferrebee, Ragan, Atchley, and Loeb, 1939; Thorn and Firor, 1940). These complications were particularly prone to occur since it had become the rule to give patients with Addison's disease a diet rich in sodium chloride and poor in potassium. Early in the use of deoxycortone it became evident that supplementary sodium chloride was contraindicated and that the potassium intake should certainly not be restricted.

In contrast to the picture of excessive weight gain and oedema, another manifestation of deoxycortone overdosage was characterized by hypertension and hypokalaemia leading to episodes of weakness and polyuria. In 1940 Thorn and Firor reported muscular weakness and transient paralysis associated with hypokalaemia in a patient with Addison's disease treated for a short period of time with large quantities of deoxycortone and glucose infusions. This patient improved readily with a diet rich in potassium. These authors pointed out the similarity between the symptomatology observed in this patient with that of patients afflicted with familial periodic paralysis, and they emphasized the usefulness of potassium in both conditions. Kuhlmann, Ragan, Ferrebee, Atchley, and Loeb (1939) were able to induce in normal dogs, by the administration of excessive amounts of deoxycortone acetate, a picture characterized by hypokalaemia, muscular weakness, and a diabetes insipidus-like syndrome. It was readily apparent at this

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time, in both man and experimental animals, that supplementary sodium chloride combined with restriction of potassium intake intensified the undesirable side-effects of the salt-retaining steroid hormones, whereas sodium chloride restriction with added potassium salts minimized such effects.

During the succeeding decade many unsuccessful attempts were made to characterize the substance or substances responsible for the "salt-retaining" properties of adrenal cortical secretions. An important piece of indirect evidence was contributed by Greep and Deane in 1947. They reaffirmed the fact that the hypophysectomized animal required minimal sodium chloride supplementation in contrast to the adrenalectomized animal. They also pointed to the persistence of the zona glomerulosa in rats following hypophysectomy, in contrast to the involution and atrophy of the other zones of

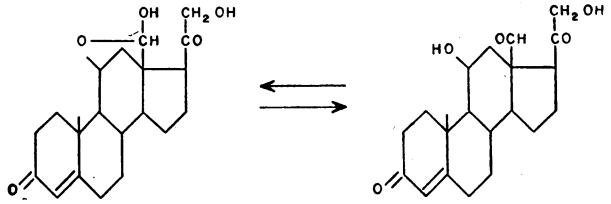

FIG. 1.—Formulae of aldosterone.

the adrenal cortex, and suggested that perhaps the "salt-retaining hormone" was secreted by the zona glomerulosa and was less dependent on adrenocorticotrophic hormone (A.C.T.H.) than the cells responsible for the secretion of 17-hydroxycorticosteroids.

In 1950 Deming and Luetscher were able to demonstrate by biological assay the presence of a sodium-retaining factor in the urine of patients with oedema. The potency of the material isolated suggested that it was not one of the known adrenocortical steroids. In 1952 Simpson, Tait, and Bush, employing chromatographic separation, were able to isolate a very potent sodium-retaining factor from adrenal venous blood. This they termed "electrocortin."

The collaboration of the Swiss team of Wettstein, Neher, von Euw, Schneider, and Reichstein with Simpson and Tait finally resulted (Simpson *et al.*, 1954) in the elucidation of the chemical structure of "electrocortin" as the 18-aldehyde of corticosterone (Fig. 1). It was accordingly given the name of "aldosterone."

Very rapidly there followed the isolation of crystalline aldosterone from extracts of the urine of patients with nephrosis (Luetscher, Neher, and Wettstein, 1954) and congestive heart failure (Luetscher, Neher, and Wettstein, 1956) in whom Luetscher and colleagues by bioassay had demonstrated an increased quantity of "sodium-retaining factor." In the meantime the synthesis of aldosterone had been achieved by Schmidlin, Anner, Billeter, and Wettstein (1955). The activity of aldosterone in man was first demonstrated by Mach, Fabre, Duckert, Borth, and Ducommun (1954) in two patients with Addison's disease. There remained only the identification and description of the clinical syndrome ascribed to hypersecretion of aldosterone as a primary factor, "primary hyperaldosteronism," which was reported by Conn (1955).

The studies which we propose to report at this time represent the efforts of our group directed at the investigation of the mechanisms involved in aldosterone secretion. As a preliminary step the methodological aspect of the problem is discussed briefly.

Measurement of Aldosterone in Urine

Aldosterone produced by the adrenal gland may be detected by reliance on its characteristic biological properties, using bioassay techniques such as those standardized by Simpson and Tait (1952), Singer and Venning (1953), or Johnson (1954). It can also be measured chemically after its isolation by means of a physicochemical method such as that proposed by Neher and Wettstein (1955). The results presented and discussed here were obtained by a method which is based upon that of Neher and Wettstein (1955). It consists essentially of acid hydrolysis of a litre aliquot of the total 24-hour urine sample, extraction with chloroform, chromatography on a "florisil" column to remove pigments and other contaminants, progressive isolation of aldosterone by two successive paper chromatographic fractionations (the propyleneglycol-toluene system of Zaffaroni, Burton, and Keutmann (1950) and the Bush (1952) "C" system), and final quantitative estimation by the blue tetrazolium reaction applied to the steroid eluted from the paper (Hernando, Crabbé, Ross, Reddy, Renold, Nelson, and Thorn, 1957).

To date, there is no simple specific and sensitive method available for the measurement of aldosterone in biological fluids. The concentration of aldosterone in urine may be less than one part in one hundred million. Reactions which are sensitive enough to detect aldosterone in microgram amounts are not specific for aldosterone only. It is therefore essential to separate this compound from other steroids which give the same reaction. This necessitates the employment of at least two chromatographic systems. Several tests have been applied to the material isolated from urine by this method to ensure its identity as aldosterone and its freedom from contaminants. Its chromatographic behaviour before and after acetylation and its properties in additional physicochemical tests indicate that this compound is identical with authentic aldosterone. In a few instances contaminants have been found, but the properties of these contaminants fortunately are such that the purity of the material isolated from paper is assured if the ultra-violet absorption and blue tetrazolium measurements agree. To ensure the purity of the material absolutely it is necessary to add a further chromatographic system, such as the E_2B system of Eberlein and Bongiovanni (1955).

The material was also assayed biologically by testing its effect on the urinary sodium/potassium ratio in adrenalecto-

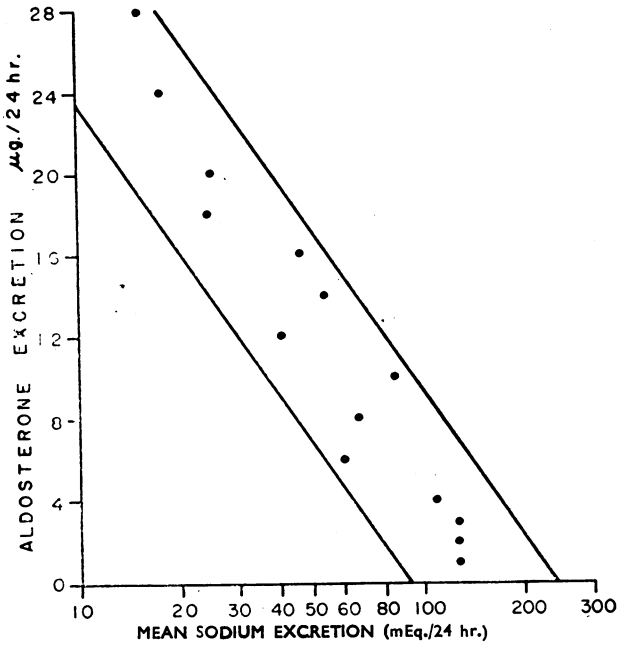

FIG. 2.—Relationship between aldosterone excretion and sodium excretion in the urine of normal subjects on different intakes of sodium. (Based on 201 individual determinations.)

mized rats. Maximum depression of this ratio was obtained with 0.025 to 0.05 μg. per rat (1 μg. is equivalent in this test to 25 to 50 μg. of deoxycortone). The potency of the material isolated from paper is thus consistent with that of d-aldosterone.

With the use of a procedure consisting of as many steps as that currently employed for the determination of aldosterone one can anticipate an appreciable loss of material. Studies designed to test the recovery of aldosterone added to urine and exposed to the foregoing method indicate a recovery rate of 20 to 30%. Most of the loss occurs during the successive steps of paper chromatography, each system being about equally responsible. As the addition of a third chromatographic system (E_2B) will increase this loss it is not used as a routine procedure.

Such large losses obviously affect the reproducibility of results. For example, the aldosterone content of six aliquots from the same urine pool were determined. These six samples were run on six different occasions. The individual quantities of aldosterone isolated were 27, 26, 25, 18, 17, and 12 μg. The employment of radioactive cortisone added to urine as a test of reproducibility and degree of recovery is currently under investigation.

It can be seen from these observations that the method has serious limitations, that the interpretation of results must be tentative, and that the most reliable indication of altered urinary excretion (and, by implication, of adrenocortical secretion) of aldosterone will be derived from serial studies rather than from single isolated determinations. Therefore one is forced at the outset to accept the fact that the measurement of aldosterone, either by biological or by physicochemical methods, is at best an approximation at the present time. Furthermore, without a suitable method for determining the level of aldosterone in blood, the assessment of urinary aldosterone changes in terms of alterations in the secretion of aldosterone by the adrenal gland must be made with reservation.

Urinary Excretion of Aldosterone in Normal Subjects

In a total of 72 urine samples obtained from 17 normal adult subjects, males and females, the mean level of aldosterone excretion was 5.0 μg. in 24 hours (S.D. ±3.0) on an unrestricted diet. The observations in 16 of these subjects are recorded in Table I, in conjunction with the urinary sodium output on the day aldosterone was measured. In 10% of cases, normal subjects were found to excrete as much as 10 to 15 μg. of aldosterone in 24 hours without any apparent change in diet, electrolyte excretion, or clinical status. No correlation between the level of excretion of aldosterone and the quantity of sodium excreted in the urine was observed at levels of aldosterone excretion below 8 μg./24 hours. Above that level a correlation was found, as shown in Fig. 2.

TABLE I.—*Daily Urinary Excretion of Aldosterone, Sodium, and Potassium in Normal Subjects on Unrestricted Diet*

Males					Females				
Name	Urine Vol. (ml.)	Aldosterone (μg./24 hr.)	Na (mEq/24 hr.)	K (mEq/24 hr.)	Name	Urine Vol. (ml.)	Aldosterone (μg./24 hr.)	Na (mEq/24 hr.)	K (mEq/24 hr.)
A. F.	700	4	135	74	M.C.	1,050	8	134	62
J. B.	600	6	72	55	H.W.	930	8	99	—
L. H.	850	3	79	69	R. B.	490	2	59	—
E. R.	1,350	6	95	47	C. H.	1,400	2	129	—
D. N.	740	4	66	71	V. H.	1,840	5	165	—
S. Z.	1,110	4	205	—					
A. L.	1,166	4	235	—					
J. F.	2,000	10	220	—					
J. C.*	1,125	6	237	94					
R. A.†	2,130	5	97	60					
A. S.	1,860	5	111	—					

* Mean values from 10 determinations. † Mean values from 14 determinations

A study of diurnal variation in urinary aldosterone excretion in six normal male and six normal female subjects revealed a day-to-night ratio in excess of unity in 10 cases; in one subject the ratio was unity. In only one subject was the ratio less than unity (Fig. 3). The mean value for the day collection (3.9 μg.) was three times as high as that for the night collection (1.9 μg.).

Factors Influencing the Urinary Excretion of Aldosterone

To date, studies by a large group of clinical investigators suggest that the following factors exert an influence, although of varying importance, on the excretion of aldosterone: corticotrophin, fluid balance, sodium balance, and potassium balance.

The observations of our own group on factors influencing the secretion of aldosterone may be summarized as follows:

1. Effect of Corticotrophin

The effect on aldosterone excretion of 25 units of corticotrophin given intravenously over an eight-hour period on

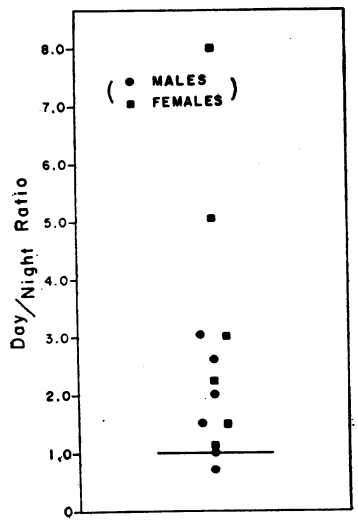

FIG. 3.—Diurnal variation in urinary output of aldosterone observed in normal subjects on an unrestricted diet. "Day" collection, 7 a.m. to 7 p.m. "Night" collection, 7 p.m. to 7 a.m.

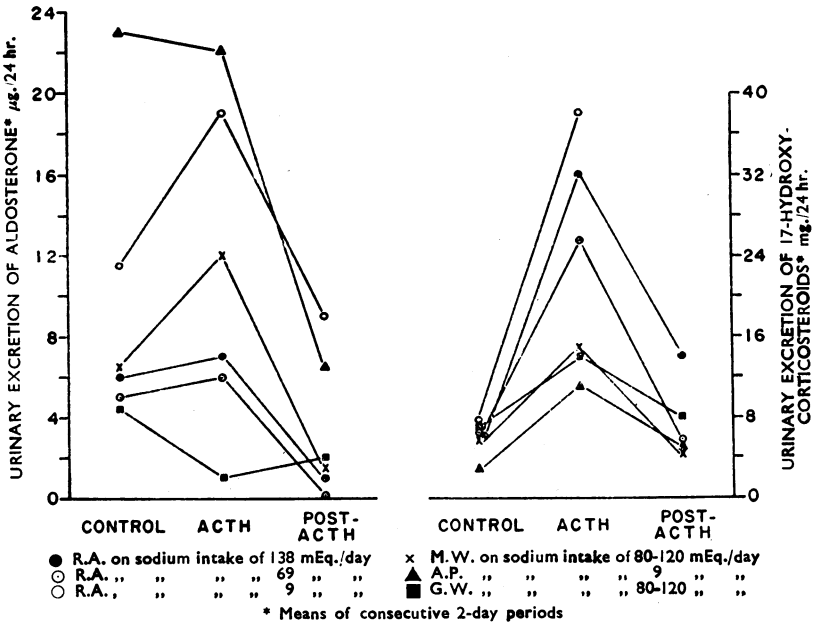

FIG. 4.—Effect of intravenous administration of corticotrophin on urinary excretion of aldosterone and 17-hydroxycorticosteroids.

two successive days was studied in 21 instances. The pattern of response was very irregular and there was no correspondence between the response of aldosterone and that of 17-hydroxycorticosteroids (see Fig. 4). However, in selected cases, in which the subjects were maintained on a low-sodium diet, there were indications of a clear-cut rise of aldosterone excretion in association with the administration of corticotrophin. Interpretation of data is made difficult under these circumstances because of the effect of dietary sodium restriction itself on the level of aldosterone secretion. A similar increased response of subjects on a low sodium intake compared with their response on a normal intake of sodium is to be seen in the papers of Duncan, Liddle, and Bartter (1956) and Muller, Riondel, and Manning (1956).

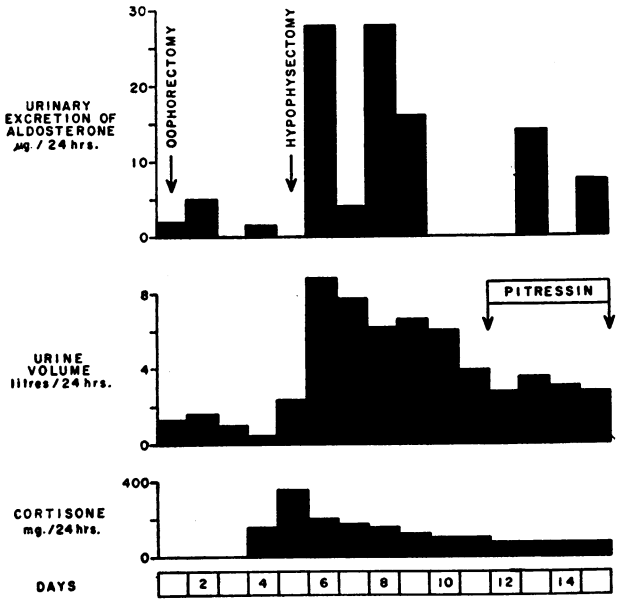

FIG. 5.—Case H. J. (F.) Urinary excretion of aldosterone following oophorectomy and hypophysectomy for breast cancer in a woman aged 38.

TABLE II.—*Endocrine Parameters in a Woman (Case A. V.) With Panhypopituitarism*

	Patient	Normal
Urinary 17-ketosteroids	3·3 mg./24 hr. 1·8 ,, ,,	(5–15)
,, 17-hydroxycorticosteroids	2·1 ,, ,, 0·2 ,, ,,	(1–10)
,, aldosterone	7·0 µg./24 hr. 6·0 ,, ,,	(0–8)
Serum protein-bound iodine	1·6 µg./100 ml.	(4–9)
Radioactive iodine uptake at 24 hr.	10%	(20–60)
Urinary follicle stimulating hormone	None detectable	

Adrenal indices improved with corticotrophin.
Thyroid indices improved with T.S.H.

Patients with long-standing panhypopituitarism may excrete normal or only slightly reduced baseline levels of aldosterone in the urine in contrast with the very low values of 17-hydroxycorticosteroids and 17-ketosteroids found in this disorder. An example of such a case is presented in Table II, in which the urinary aldosterone excretion of 7 µg. per 24 hours (a normal value) is contrasted with other endocrine parameters. However, when this patient was subjected to a low-sodium diet, weight loss and negative sodium balance occurred without any significant rise in urinary aldosterone levels, in contrast to normal subjects, who show a rather prompt increase under such circumstances.

In the period immediately following hypophysectomy for metastatic breast carcinoma, an increase in urinary aldosterone was observed in two patients (Fig. 5). This rise may be associated with the diabetes insipidus present in both cases.

Finally, a normal subject placed on a low-sodium diet and simultaneously given a large quantity (10 mg.) of 9 - alpha-fluorohydrocortisone daily showed essentially the same increase in aldosterone excretion in conjunction with weight loss as he had previously shown on a low-sodium regimen alone (Fig. 6). This observation suggests that the inhibition of endogenous corticotrophin release (evidenced by a sharp drop in urinary 17-hydroxycorticosteroid excretion) did not prevent the anticipated aldosterone response, although the latter was somewhat decreased in amplitude.

From these observations it would appear that the baseline secretion of aldosterone is not as intimately dependent upon corticotrophin as is that of adrenal hydroxysteroids and ketosteroids, and that a response to exogenous corticotrophin administration is variable in contrast to the consistent stimulation of adrenal secretion of glucocorticoids observed under similar conditions.

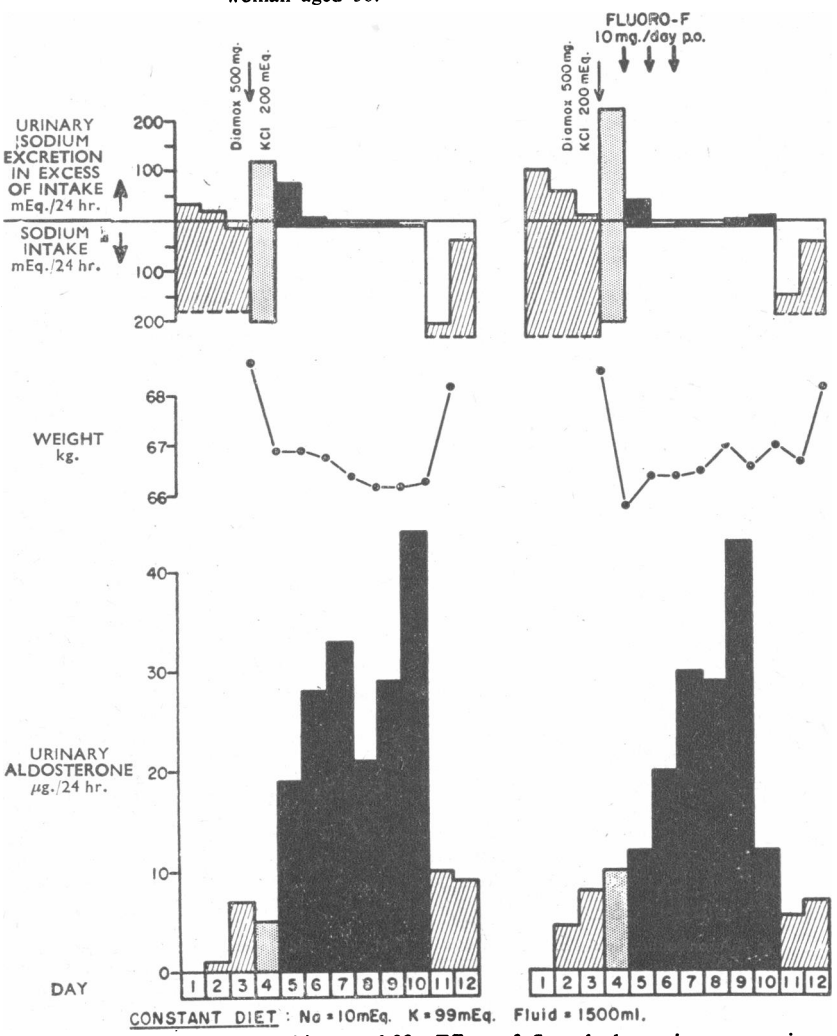

FIG. 6.—J. C. (M.) Normal subject aged 28. Effect of fluorohydrocortisone on urinary aldosterone rise due to restricted sodium intake.

Pituitary hormones other than corticotrophin have been administered and their effect on the level of aldosterone excretion has been observed. Beef growth hormone was not found to modify significantly the urinary levels

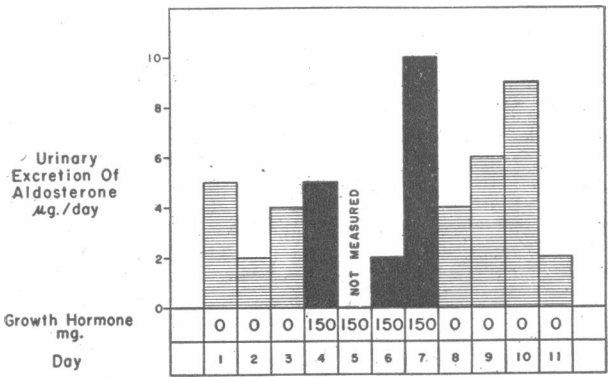

FIG. 7.—Case M. G. (M.) Urinary aldosterone levels in hypophysectomized man aged 45 during administration of beef growth hormone (Armour, lot D 728076).

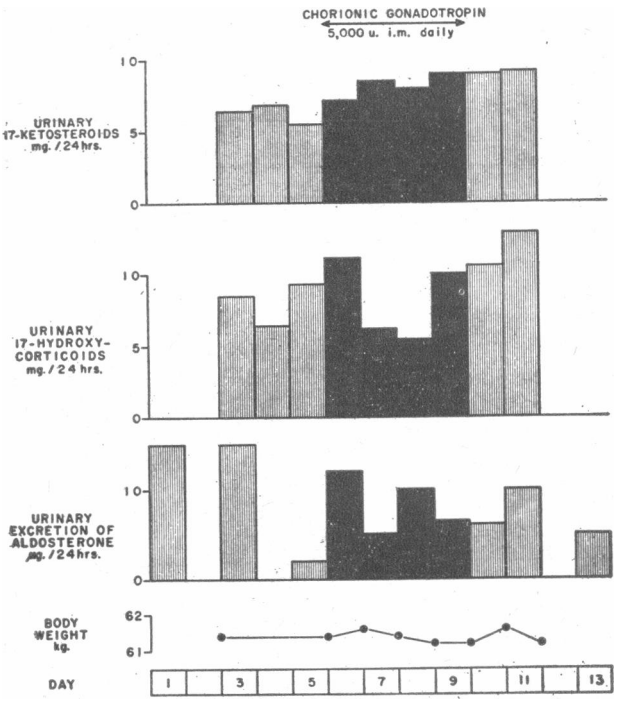

FIG. 8.—Case R. A. (M.) Effect of chorionic gonadotrophin administration on urinary steroids in man aged 42 with benign spinal tumour.

of aldosterone in man (Fig. 7). The relative ineffectiveness in man of growth hormone derived from other species is well known, hence the above experiment does not exclude a possible role of human growth hormone in aldosterone secretion in man. An increased excretion of aldosterone has indeed been noted in a pituitary dwarf during the administration of both human and monkey growth hormone (Beck, McGarry, Dyrenfurth, and Venning, 1957). However, studies of growth hormone in animals under conditions in which growth can be demonstrated give no clinical evidence of an excessive secretion of aldosterone.

Chorionic gonadotrophin was likewise devoid of effects on aldosterone excretion in man when administered for a period of four days (Fig. 8).

2. Effect of Changes in Fluid Balance

The effects of pitressin were followed in a patient with diabetes insipidus receiving a daily sodium intake of approximately 100 mEq and an unrestricted fluid intake. An increase in urinary aldosterone output from a mean value of 7 µg. to that of 12 µg. per 24 hours followed the withdrawal of pitressin. The loss in body weight and increased fluid output that took place as an immediate effect of cessation of pitressin administration were not accompanied by an appreciable increase in sodium excretion.

This increase in aldosterone excretion was thought to be mediated by the deficit of body water which developed under these circumstances. Beck, Dyrenfurth, Giroud, and Venning (1955) have studied the opposite situation and have shown that an expansion of total body water by the forced administration of water during pitressin injections was followed by a fall in aldosterone excretion.

3. Effect of Sodium Restriction

Normal subjects respond to a low-sodium diet with an increase in urinary aldosterone excretion (Fig. 9). Observations in 11 studies carried out on seven healthy male subjects are summarized in Fig. 10. It can be seen that in all instances increased values were observed; however, the variation in response is considerable. The greatest increases were observed in subject J. C. when acetazolamide ("diamox") (500 mg.) was taken on the day before the low-salt diet was instituted. There was no consistent relationship between body-weight loss (regarded as reflecting loss of extracellular fluid), the degree of urinary sodium concentration attained, and the increase in urinary aldosterone excretion. Weight loss and decreased urinary sodium concentration were observed repeatedly before any measurable increase of urinary aldosterone excretion occurred during these studies.

The lack of close correlation between the rapid fall in urinary sodium concentration and the response of urinary

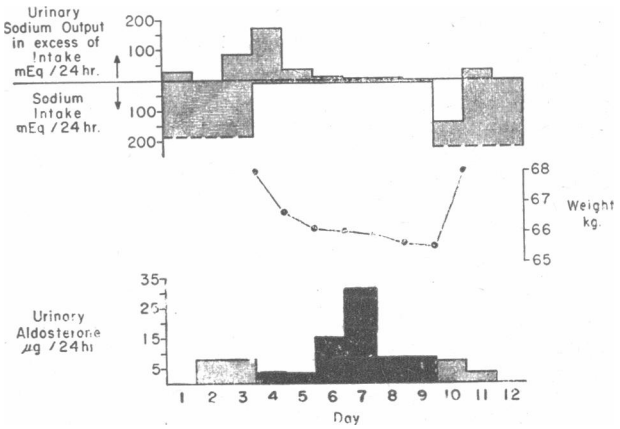

FIG. 9.—Case J. C. (M.) Normal subject aged 28. Effect of dietary restriction of sodium on urinary excretion of aldosterone.

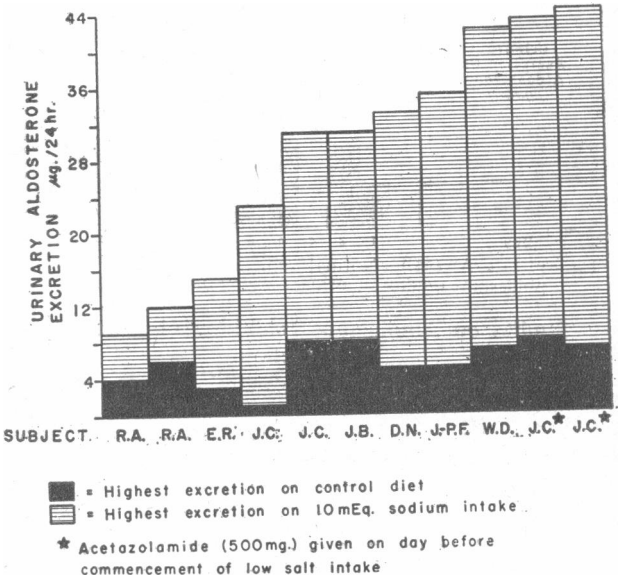

FIG. 10.—Effect of dietary restriction on urinary aldosterone levels.

aldosterone excretion is illustrated in Fig. 11. It will be noted that there is a very considerable fall in the urinary excretion of sodium before any rise of aldosterone excretion occurs.

In summary, there appears to be no doubt that aldosterone excretion is increased following sodium restriction. However, the majority of normal subjects will display a fall in urinary sodium concentration before we can observe an appreciable increase in aldosterone excretion. From this it appears that there are factors other than increased aldosterone secretion participating in the response of the kidneys to a decreased dietary intake of sodium.

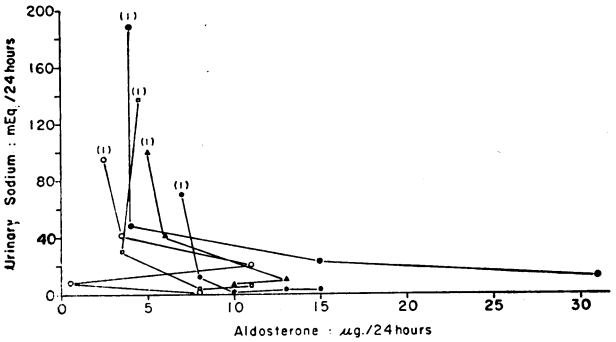

FIG. 11.—Urinary excretion of sodium and of aldosterone on successive days of a restricted sodium intake (9 mEq per day) in five normal subjects. The points marked (1) represent the first day of sodium restriction, successive points representing succeeding days of the low-sodium diet.

4. Effect of a High Potassium Intake

In normal subjects a moderate and short-term increase in the daily potassium intake in the presence of a normal or low sodium intake did not appear to alter aldosterone excretion significantly (Fig. 12). Small increases in aldosterone excretion have occasionally been observed by other investigators (Luetscher and Curtis, 1955; Bartter, 1956; Laragh and Stoerk, 1957), but in our experience potassium loading is certainly not as uniformly associated with increased excretion of aldosterone as is sodium deprivation.

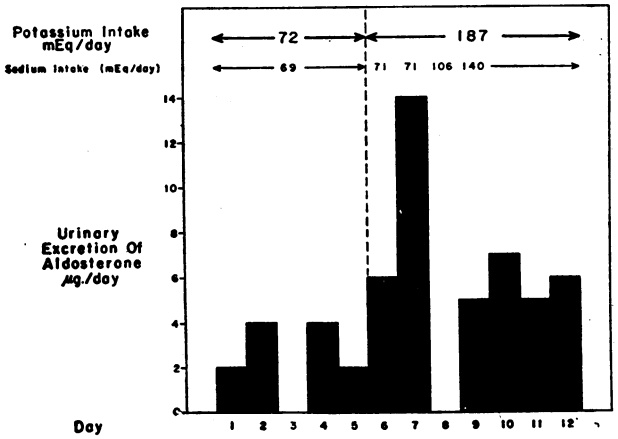

FIG. 12.—R. A. (M.) Normal subject aged 40. Effect of high potassium intake on urinary excretion of aldosterone.

Studies on Amphenone Inhibition of Aldosterone Excretion

Amphenone B (Fig. 13) exerts an immediate and marked inhibition of the secretion of steroids by the perfused adrenal cortex as shown by *in vitro* studies (Rosenfeld and Bascom, 1956); this inhibition has also been demonstrated in man (Thorn *et al.*, 1956; Hertz *et al.*, 1956; Gallagher *et al.*, 1956) (Fig. 14). Failure to recognize the interfering role of urinary metabolites of amphenone on the Zimmermann reaction used for the determination of 17-ketosteroids has resulted in some confusion in reports of the effectiveness of amphenone. Prolonged suppression of 17-hydroxycorticosteroid secretion with amphenone is seen in cases with secreting adrenal tissue which is unresponsive to corticotrophin (as in adrenal carcinoma) or in the presence of maximal corticotrophin stimulation, as during the administration of corticotrophin (Fig. 15). Little or no effect of amphenone on

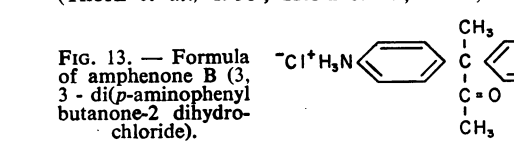

FIG. 13. — Formula of amphenone B (3, 3 - di(*p*-aminophenyl butanone-2 dihydrochloride).

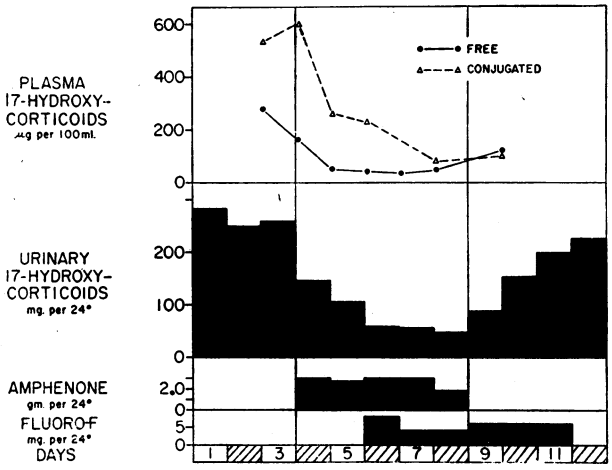

FIG. 14.—Case S. D. (F.) Effect of administration of amphenone B on blood and urine 17-hydroxycorticosteroids in woman aged 41 with adrenal cortical carcinoma.

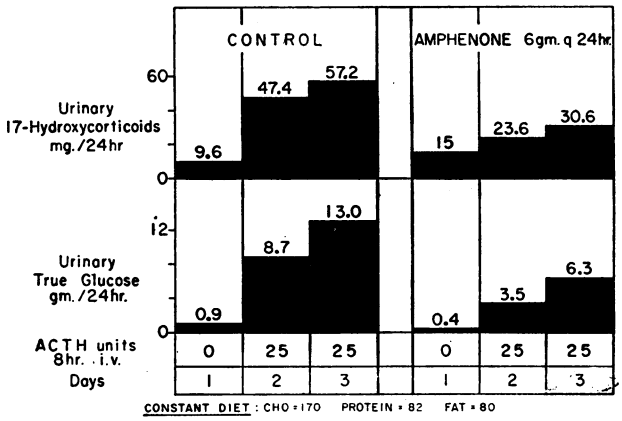

FIG. 15.—Case K. H. (M.) Modification of the response to corticotrophin caused by the simultaneous administration of amphenone B in man aged 22 with Cushing's syndrome due to adrenal hyperplasia.

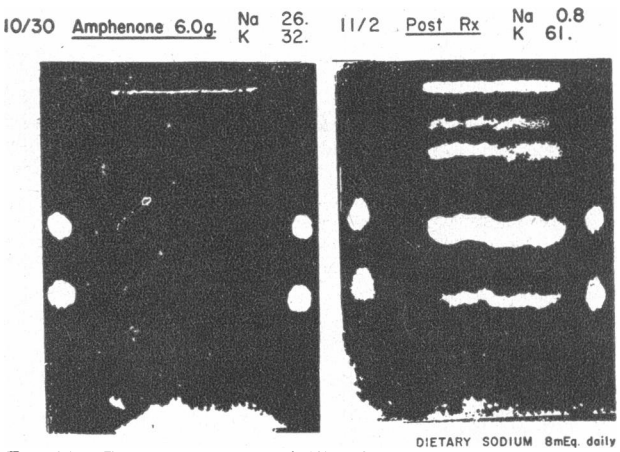

FIG. 16.—Case M. U (F., aged 40). Chromatogram (Bush "C" system) showing absence of aldosterone and other steroids from the urine during amphenone administration and their return in above-normal quantities on cessation of amphenone.

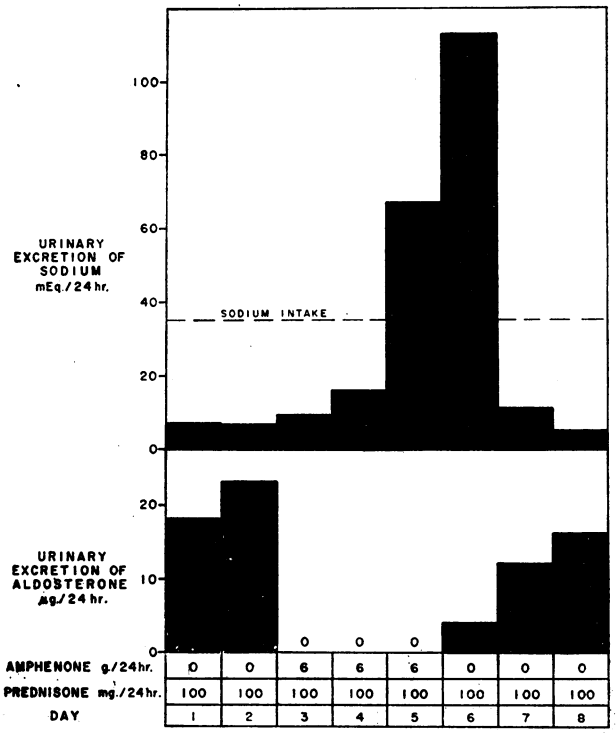

FIG. 17.—Case M. L. Response of urinary excretion of sodium and aldosterone to administration of amphenone in a woman aged 39 with generalized oedema.

the level of 17-hydroxycorticosteroid excretion has been noted in subjects excreting quantities of this steroid within the normal range. Rosenfeld and Bascom (1956) state that the site of block is at the level of the adrenal cell and suggest that this compound interferes with 11, 17, and 21 hydroxylation.

Since it appears that the production of steroids by the adrenal gland is decreased by amphenone because the latter substance exerts an inhibiting effect of steroid synthesis, it might be anticipated that aldosterone secretion would also be affected by this drug. This presumption was supported by the observation that a sodium diuresis often accompanied the administration of amphenone. This sodium diuresis has not been observed in patients with Addison's disease or following bilateral adrenalectomy (Renold *et al.*, 1957).

The disappearance of aldosterone from the urine during amphenone administration is shown in Fig. 16. The fall in urinary aldosterone excretion and the concomitant rise in urinary sodium excretion observed in a patient with oedema and increased urinary aldosterone values is illustrated in Fig. 17. It appeared from these studies that amphenone might be a useful agent to assess the pathogenetic significance of increased urinary aldosterone values in patients exhibiting evidence of excessive sodium retention as in nephrosis, cirrhosis, and congestive cardiac failure. It might be anticipated that patients with excessive fluid retention and high urinary aldosterone levels would respond to amphenone administration with a rise in urinary sodium excretion, if hyperaldosteronism were essential for the genesis or maintenance of the excessive sodium and water retention.

In a patient with late-stage severe heart failure the elevated levels of aldosterone were reduced to normal without a concomitant rise in urinary sodium concentration (Fig. 18). These clinical observations suggest that hyperaldosteronism was not the major factor, at the time of study, in perpetuating the marked state of oedema seen in this patient. The failure to observe a rise in urinary sodium concentration despite a fall in aldosterone levels in a patient with cirrhosis and ascites is illustrated in Fig. 19, whereas the response to mercuhydrin is readily apparent. In a second patient with

	Urinary Sodium mEq / 24 hr.	Urinary Aldosterone * micrograms/24 hr.
CONTROL	2.2	29
"	0.8	23
"	0.3	33
AMPHENONE 4 gm. day 1	2.8	4
" " " 2	1.8	3

Dietary Sodium : < 9 mEq / 24 hr.

* NORMAL RANGE : 0 – 8

FIG. 18.—Case A. P. Absence of sodium diuresis during amphenone administration despite suppression of aldosterone excretion in a man aged 31 with rheumatic heart disease, congestive heart failure with oedema, and cardiac cachexia.

cirrhosis and ascites an appreciable sodium diuresis accompanied the reduction in aldosterone excretion during amphenone administration. Perhaps in this patient the presumed secondary hyperaldosteronism was pathogenetically important in the excessive accumulation of sodium.

Thus in three patients with "secondary" hyperaldosteronism as evidenced by anasarca and elevated values for aldosterone in the urine, amphenone reduced the aldosterone excretion to normal in all three,

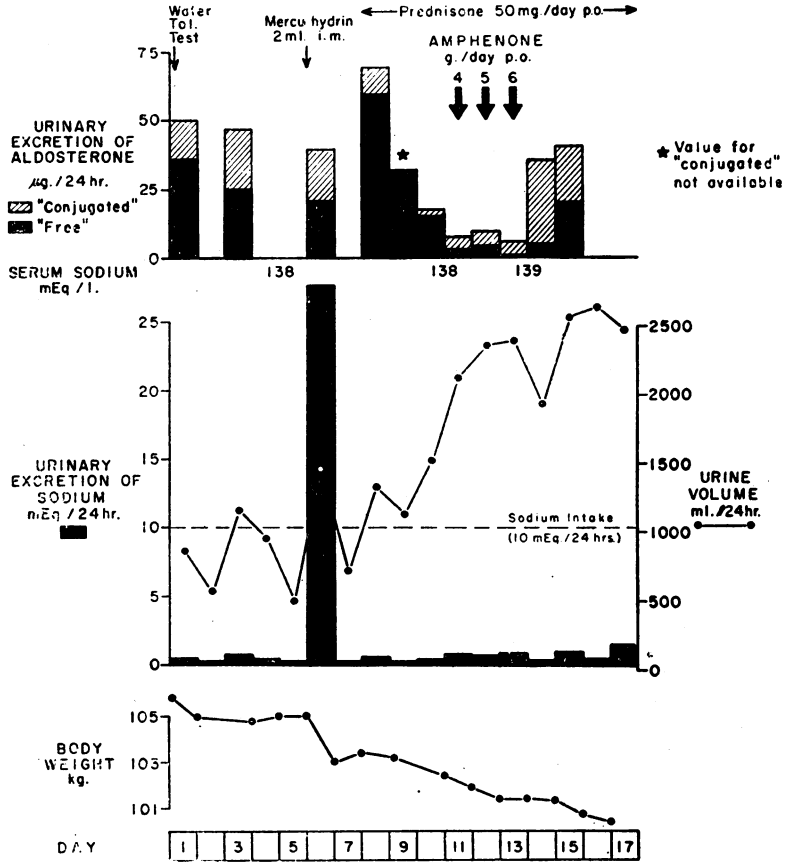

FIG. 19.—Case J. O'B. Influence of amphenone on urinary excretion of aldosterone and sodium in man with cirrhosis of liver and ascites. Sweating was profuse during period of study.

but in only one was a significant sodium diuresis observed. These studies need to be pursued before a final evaluation of the clinical usefulness of amphenone as a diagnostic agent can be established. The results of a study of the effects of amphenone in patients with cardiac and renal oedema might be helpful in depicting those occasional cases of hypertension and cardiac failure that have responded so successfully in the past to total adrenalectomy.

Secondary Hyperaldosteronism? Case Report

An unmarried female nurse aged 39 has been observed over a period of more than 10 years with generalized oedema. All investigations have failed to reveal any underlying cardiac, renal, or hepatic disease. The serum protein level was normal. Both pleural fluid and the oedema fluid draining from Southey tubes showed evidence of an elevated protein concentration, since they contained approximately 2.5 g. of protein % without evidence of inflammatory reaction. The intravenous administration of salt-poor albumin first resulted in a rise in serum albumin level and then in an appreciable increase (up to 3.4%) in the protein level in the fluid draining from Southey tubes. Ten days later the protein level returned to a value of 1.9 g.%. It was therefore concluded that a major factor in this patient's incapacitating oedema was a disorder of capillary permeability which permitted an excess of protein to escape from the vascular compartment (Emerson and Armstrong, 1955). For several years all possible means of inducing a sodium diuresis in this patient failed or had been of only transient usefulness.

When methods for measuring aldosterone became available, this patient was found to excrete large amounts of this hormone, the 24-hour urinary values often exceeding 100 μg. (Table III). Such levels are definitely well above those found in normal subjects maintained on a low sodium intake. In this patient on three separate occasions the administration of amphenone resulted in an immediate and sharp decrease in urinary aldosterone levels and a significant rise in urinary sodium excretion (Table IV). At no time in her 10-year history did this patient exhibit hypertension, hypokalaemia, alkalosis, or polyuria.

It is probable that secondary hyperaldosteronism existed in this patient as a result of the long-continued oedema and the vigorous therapeutic efforts to relieve the condition. In view of the high levels of aldosterone excretion and also of the sodium diuresis obtained as a result of amphenone administration, it was considered that total adrenalectomy might improve the oedematous condition by decreasing the renal reabsorption of sodium.

In an attempt to study the effect of a sodium load on aldosterone excretion in this patient, a total of 700 mEq of sodium was given orally over a period of five days; the patient retained almost quantitatively the ingested sodium and gained more than 4 kg. in weight. Her urinary sodium excretion failed to increase above 5 mEq a day and aldo-

TABLE III.—*Aldosterone Excretion on Five Consecutive Days in a Woman (Case M. L.) With Anasarca*

	Urinary Sodium mEq/24 hr.	Urinary Sodium/ Potassium	Urinary Aldosterone* μg./24 hr.
Day 1	12	0·4	87
„ 2	6	0·13	123
„ 3	3	<0·1	66
„ 4	2	<0·1	70
„ 5	1	<0·1	98

Serum Na: 138 mEq/l. K: 4·6 mEq/l. Salivary Na/K ratio: <0·2.
* Normal range: 0–8.

TABLE IV.—*Effect of Administration of Amphenone on Urinary Excretion of Aldosterone and Sodium in a Woman With Generalized Oedema*

Course No.	Dose of Amphenone and Duration of Administration	Period *	Mean Aldosterone Excretion (μg./24 hr.)	Sodium Excretion † (mEq/24 hr.)
1	6 g./day (5 days)	Control	75	3·4
		Experimental	8·7	13·6
		Control	77	7·1
2	8 g./day (2 days)	Control	108	2·8
		Experimental	9	30·0
		Control	78	3·8
3 ‡	6 g./day (3 days)	Control	75	2·6
		Experimental	9	101·3
		Control	103	13·3

* The control periods before and after the experimental periods are equal in length to the experimental period.
† Sodium intake 9 mEq daily throughout.
‡ Prednisone (100 mg./day) was administered through this course.

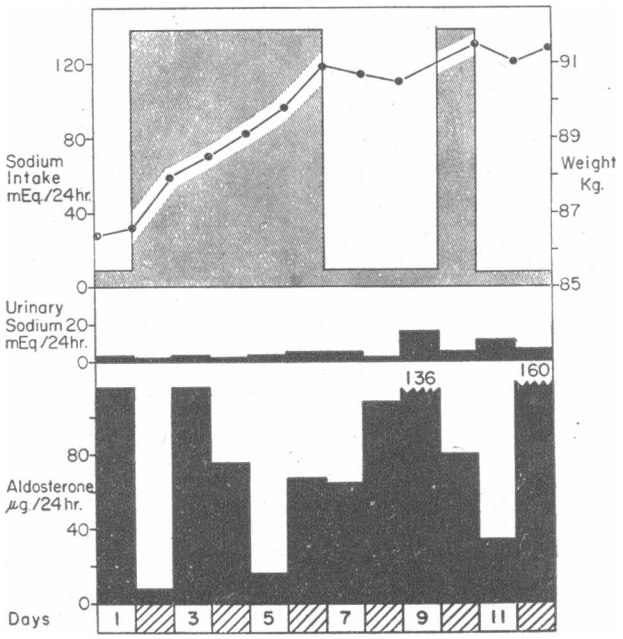

FIG. 20.—Case M. L. (F.) Showing absence of response with respect to urinary excretion of sodium and of aldosterone during a sodium load in woman aged 39 with anasarca and secondary hyperaldosteronism.

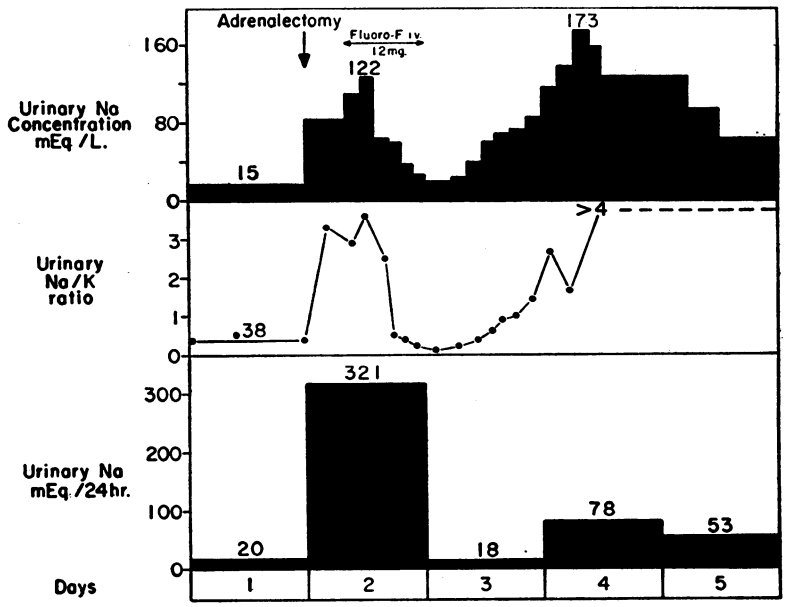

FIG. 21.—Case M. L. (F.) Showing the sodium diuresis which followed the removal of an adrenocortical adenoma in a patient aged 39 with generalized oedema.

sterone values decreased only slightly (Fig. 20). These studies suggested that the structure responsible for the increased aldosterone output was relatively insensitive to a large and rapid gain in total extracellular sodium and water.

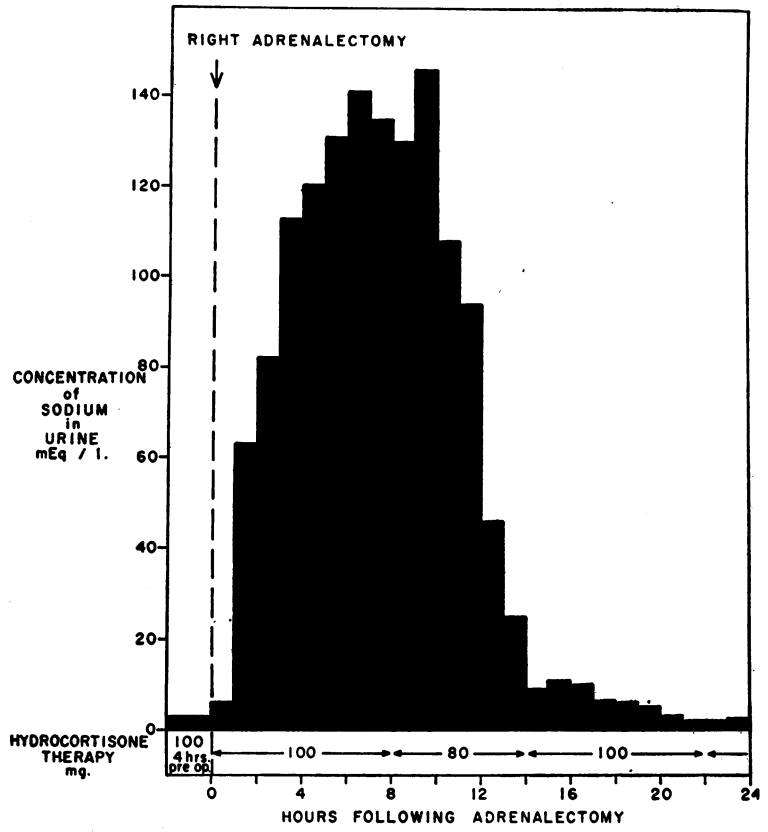

FIG. 22.—Case M. L. (F.) Sodium diuresis following right adrenalectomy in a woman aged 39 with hyperaldosteronuria. Left adrenalectomy had been done seven months previously.

In April, 1956, a left adrenal exploration was carried out by Dr. J. H. Harrison, and a small adenoma weighing 2 g. was found in the adrenal gland. This gland was removed completely. The other side was not explored. Physicochemical analysis of the adenoma revealed aldosterone to be present in a concentration of 3 μg. per g., whereas none was found in the remaining non-adenomatous part of the gland. The removal of this adrenal gland was followed on the day of operation by an immediate and intense sodium loss in the urine which necessitated supportive therapy with sodium chloride and salt-retaining hormone (Fig. 21). The intravenous administration of corticotrophin a week after operation revealed a functioning right adrenal gland as judged by the increase in the urinary excretion of 17-hydroxycorticosteroids and 17-ketosteroids.

Over the subsequent six weeks the sodium balance in the patient did not exhibit any dramatic deficit and her weight decreased by only 3 kg. despite a sodium intake of only 10 mEq. During a period of normal sodium intake (80 mEq a day approximately, for one month) a total of eight determinations of aldosterone averaged 5 μg. for the 24-hour period (range: 0 to 18 μg.). On a low sodium intake the mean urinary aldosterone level for nine determinations was almost identical—5 μg. (range: 0 to 16 μg.). Subsequently a negative sodium balance was induced by therapeutic means which had been ineffective prior to the adrenalectomy —namely, acetazolamide and prednisone. There ensued a weight loss of 10 kg. in two weeks. The urinary aldosterone excretion was 8 μg. per 24 hours at that time (range of 12 determinations: 0 to 29 μg.).

The patient was discharged from hospital on a programme which included a low-sodium diet, prednisone, potassium chloride, and intermittent administration of acetazolamide. On this regime her weight decreased from 91 kg. to 70 kg. At this weight level, however, she became weak, nauseated, and had muscle cramps, similar to the symptoms of which she had complained in the past when receiving intensive cation exchange resin therapy. These symptoms were believed to be secondary to excessive sodium loss, and she was allowed to increase her sodium intake and regain some weight. She was then readmitted to hospital. Renal function studies were still normal (C_{inulin}=110 ml./min.; C_{PAH}=415

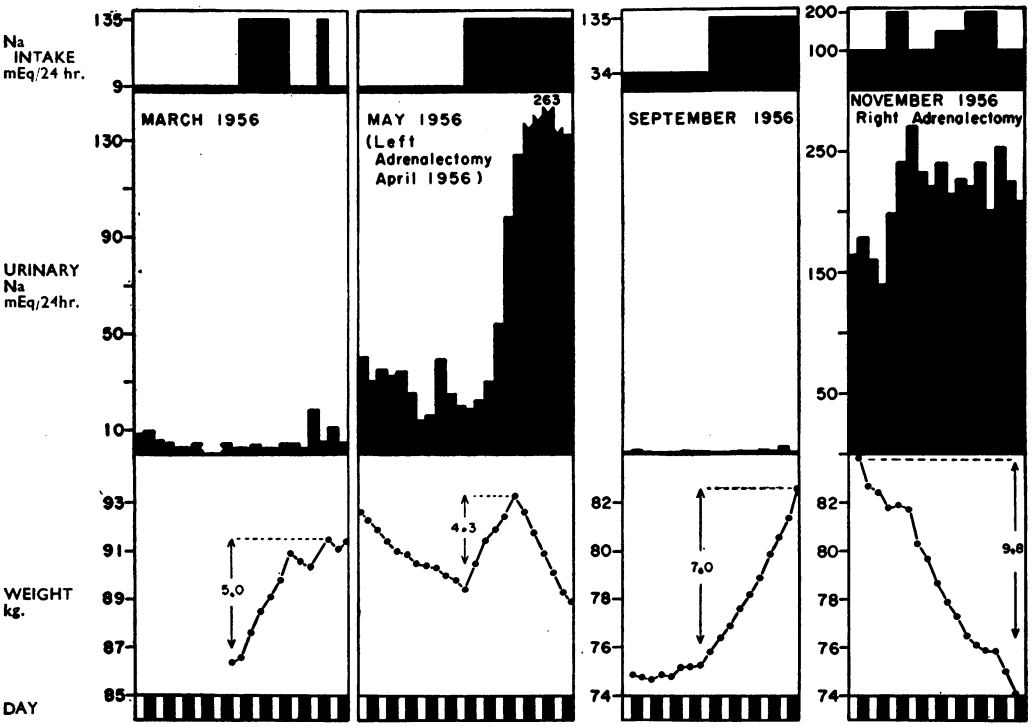

FIG. 23.—Case M. L. (F.) Showing the response to sodium loading with respect to the urinary excretion of sodium in a woman aged 39 with generalized oedema, before and after operative removal of the left and right adrenal glands.

ml./min.). During this period she was retaining sodium maximally, excreting less than 1 mEq a day despite a sodium load of up to 130 mEq daily. This almost quantitative retention of sodium was not modified by large doses of prednisone, acetazolamide, or mannitol, nor by the administration of corticotrophin. Amphenone was the only drug which consistently induced a sodium diuresis, as it had done before the left adrenalectomy. The sodium diuresis was again associated with the disappearance of aldosterone from the urine. The values of urinary aldosterone, averaging 49 μg. per 24 hours after admission, fell to a mean of 22 μg. when salt was given, but rose to a mean of 34 μg. when prednisone was administered while the high salt intake was maintained.

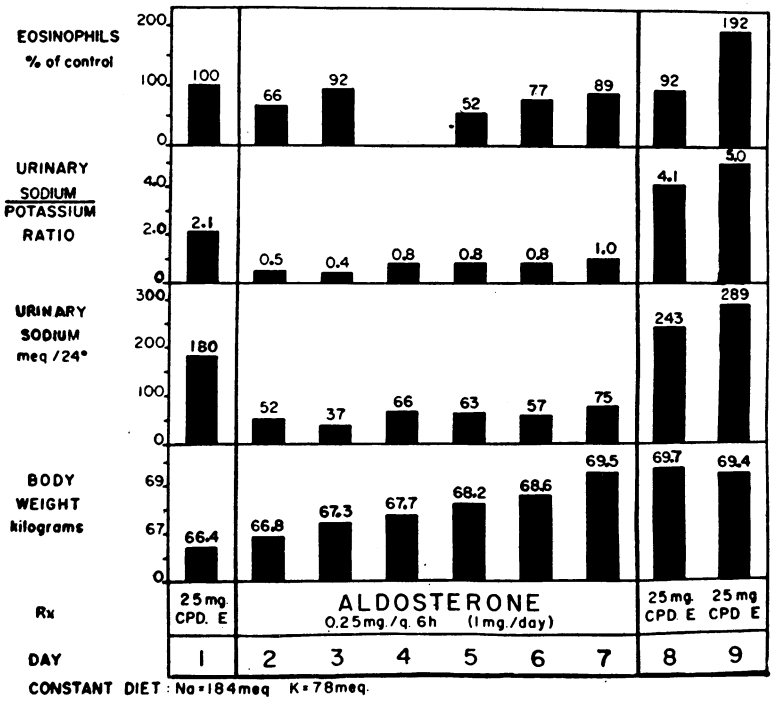

FIG. 24.—Case W. G. (M.) Metabolic effect of aldosterone in man aged 37 with Addison's disease (0.25 mg. administered intramuscularly every six hours).

A right adrenalectomy was performed in November, 1946. Macroscopically the gland appeared normal. Histologically, the cortex was composed chiefly of zona fasciculata, with cells resembling those forming the previously removed adenoma. Following this operation there again occurred an immediate and profound sodium diuresis (as shown in Fig. 22) within four hours of removal of the remaining adrenal tissue. As expected, aldosterone disappeared from the urine and the patient lost weight. On this occasion she was able to tolerate large amounts of sodium in her diet while still losing weight, and a sodium load revealed no limitation in the renal handling of sodium (Fig. 23). The patient's clinical condition also showed great improvement and she was able to tolerate a diet containing 12 g. of sodium chloride without evidence of sodium retention. When her weight approached 70 kg., however, she again exhibited symptoms suggestive of sodium depletion. It is apparent that the underlying primary factor responsible for her oedema still exists.

It would appear that the continued attempts to reduce salt intake and to induce sodium excretion in this patient by vigorous diuretic therapy had resulted in secondary hyperaldosteronism, in which both adrenal glands should have been involved. The interesting features of this case are the presence of a functioning adenoma and the probability that aldosterone was secreted by this structure only. This is suggested by the fact that the removal of the adenoma resulted in a prompt sodium diuresis with disappearance of aldosterone from the urine. Furthermore, aldosterone was demonstrable in the tumour and not in the surrounding adrenal tissue. Subsequently the right adrenal gland became the site of increased aldosterone production and the syndrome recurred, with an intractable tendency to accumulate oedema. In this patient secondary hyperaldosteronism was not accompanied by hypertension, hypokalaemia, hypochloraemia, or alkalosis, and in this respect the syndrome contrasts markedly with that ascribed to primary hyperaldosteronism.

Hyperaldosteronism and Potassium Deficiency

The classical manifestations of primary hyperaldosteronism as described by Conn (1955) consist of arterial hypertension, polyuria refractory to pitressin, and episodes of muscular weakness associated with hypokalaemia, hypochloraemia, and alkalosis, with an alkaline urine and decreased sodium/potassium ratio in saliva, sweat, and stools. Most of the clinical phenomena and the biochemical changes pertaining to this syndrome reflect the intense potassium deficiency induced by excessive aldosterone secretion.

The absence of oedema in primary hyperaldosteronism has not been satisfactorily explained. This is of particular interest in view of the fact that when aldosterone was given to a patient with Addison's disease (Thorn *et al.*, 1955) a rapid retention of sodium chloride and water took place, resulting in a weight gain of over 3 kg. in six days during the administration of aldosterone in doses of 1 mg. a day (Fig. 24). There would appear to be little doubt that clinical experience with aldosterone, when it becomes readily available, will indicate that oedema is an early complication of excessive administration. Whether or not an increase in endogenous aldosterone secretion in patients with otherwise normal adrenal secretion could facilitate potassium loss without excessive sodium retention remains to be seen. Some of these considerations have been summarized in Fig. 25, in which the sequence of metabolic alterations attendant upon potassium depletion are listed.

It appears essential to distinguish between potassium deficiency as produced by hyperaldosteronism and that encountered more frequently in general medicine and surgery. Under the latter circumstances severe potassium depletion

Effect On Potassium Metabolism

EXCESSIVE RENAL EXCRETION OF K (Alkaline Urine)
↓
POTASSIUM DEPLETION
↓
MUSCULAR WEAKNESS OR PARALYSIS
TETANY DESPITE NORMAL SERUM Ca
CHANGES IN ECG
NEPHROPATHY LEADING TO POLYURIA (ADH resistant) AND ALBUMINURIA IN SOME CASES
METABOLIC ALKALOSIS WITH HYPOKALAEMIA

Effect On Sodium Metabolism

ABSENCE OF RENAL RETENTION OF SODIUM WHEN ON NORMAL SODIUM INTAKE
ABSENCE OF OEDEMA

FIG. 25.—Sequence of events consequent upon the long-continued excessive secretion of aldosterone in Conn's syndrome (" primary hyperaldosteronism ").

TABLE V.—*Protocol of a Woman (Case B. M.), Aged 44, Admitted With Complaints of Three Attacks of Weakness and One Attack of Carpopedal Spasm*

Admission to Eastern Maine General Hospital, February, 1957 (Dr. Laura Weed)

Serum Na	139–147 mEq/l.
K	2·5–3·0 ,,
Cl	86–98 ,,
CO_2	30–41·5 mMol./l.
Ca	11·1–11·8 mg./100 ml.
P	2·0 mg./100 ml.
N.P.N.	26–34 mg./100 ml.
Blood pressure	150–180/90–110 mm. Hg

When serum K was 2·5 mEq/l. she excreted 40–50 mEq of K daily when on an intake of 70 mEq of K.

Discharged on low-Na diet with supplementary KCl (8 g./day).

Admission to Peter Bent Brigham Hospital, March–April, 1957

Serum Na	134–140 mEq/l.
K	3·0–4·5 ,,
Cl	97–111 ,,
CO_2	16·4–28·9 mMol./l.
Ca	5·3 mEq/l.
P	1·2 mMol./l.
Blood urea	20–38 mg./100 ml.
Arterial *p*H	7·51
,, pCO_2	41 mm. Hg
,, CO_2 content	27 mMol./l.
Urine *p*H	6·3–6·9

Urine contained protein on two occasions, with granular and hyaline casts.

Salivary Na/K ratio	0·37–0·78
Stool Na/K ratio	0·02

Ammonium chloride reduced urine *p*H from 6·3 to 5·5.

12-hour water deprivation—overnight volume 800 ml., osmolarity 737 mOsm./l.

Water load (20 ml./kg.)—67% excreted in four hours.

Creatinine clearance—71 ml./min.

Aldosterone excretion in urine—5 μg./24 hours (normal sodium intake).

At operation (April 27, 1957) three adrenocortical adenomata were found in left adrenal gland; the gland was excised.

usually occurs in conjunction with large losses of gastro-intestinal secretion—for example, vomiting, diarrhoea, draining fistula, intubation of the bowel. Occasionally one encounters the syndrome in elderly patients on the basis of nutritional deficiency or in cardiac patients after the protracted use of mercurial diuretics. The prolonged administration of large doses of corticosteroids can also induce clinically apparent potassium depletion. Cases of "potassium-losing nephritis" in which the clinical picture is dominated by an inability on the part of the diseased kidney to handle potassium properly are indicated by evidence of pyelonephritis and the presence of an acidosis. However, cases of primary hyperaldosteronism may present serious diagnostic difficulties, particularly when the clinical picture is accompanied by normal values for urinary aldosterone excretion (Chalmers, FitzGerald, James, and Scarborough, 1956). The protocol of such a case is shown in Table V.

A comparison between the syndrome of "potassium depletion" as seen in medicine and surgery and that of potassium depletion secondary to hyperaldosteronism is summarized in Table VI. Of particular interest is the presence of large quantities of potassium in the urine of patients with hyperaldosteronism coincident with hypokalaemia, whereas the cases of potassium depletion due to most other causes have low urinary potassium levels and an acid urine.

Secondary hyperaldosteronism can usually be differentiated from the primary form by the tendency of these patients to exhibit oedema, a low concentration of sodium in the urine, and no evidence of severe potassium depletion. Because of the difficulty encountered in aldosterone determination by either the chemical or biological methods it was hoped that a low salivary sodium/potassium ratio might provide a satisfactory initial screening test which, if positive, would then justify the more prolonged and costly process of measuring aldosterone in the urine. Although it is true that the salivary sodium/potassium ratio tends to be low in both primary and secondary hyperaldosteronism, it does not appear at this time that, in random specimens, there is a close relationship between this ratio and the quantitative value for urinary aldosterone. Studies such as that illustrated in Fig. 26 indicate that, although the salivary sodium/potassium ratio tends to fall as the urinary aldosterone level rises, the correlation at any given point may not be good and the final figure achieved may vary widely for a given urinary aldosterone value.

TABLE VI.—*Comparison of Laboratory Values Found in Experimental Potassium Depletion and Those Found in Conn's Syndrome ("Primary Hyperaldosteronism")*

	Experimental Potassium Depletion	Primary Hyperaldosteronism
Na in serum	Normal	Normal or slightly elevated
Na in urine	,,	Normal
K in serum	Reduced	Reduced
K in urine	*Reduced*	*Increased*
Na/K ratio in saliva or sweat	*Normal or increased*	*Reduced*
Urine *p*H	*Acid*	*Alkaline*

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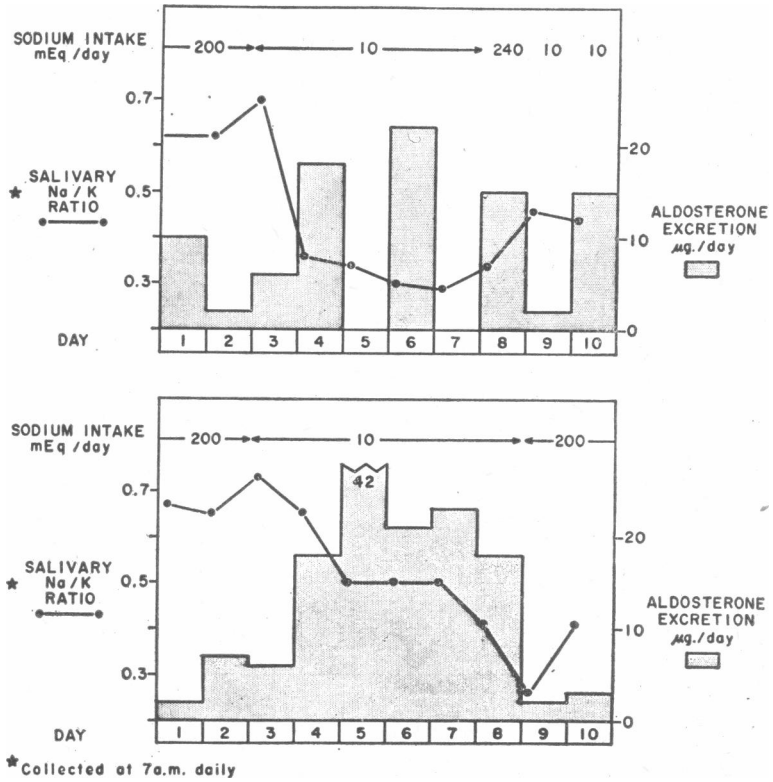

FIG. 26.—Showing (above) the presence and (below) the absence of correlation between the salivary sodium/potassium ratio and urinary aldosterone excretion in two normal subjects placed on a low-salt diet.

Hospital. The hypophysectomized patients were studied in collaboration with Dr. Andrew Jessiman, department of surgery, Peter Bent Brigham Hospital.

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The Hospital Personal Aid Service for the Elderly has published a second detailed account of its work, this report covering the period to December 31, 1956. Established in 1951 by the King Edward's Hospital Fund, the service co-operates with the four Metropolitan Regional Hospital Boards, each of which contributes £500 annually towards the cost, the Fund paying the balance. The service visits, on behalf of hospitals, elderly patients awaiting admission whose medical condition does not involve admission to acute wards. The main objects of the service are to suggest to the hospital the priority of those awaiting admission; to inform the hospital of the home circumstances in support of the suggested priority and as a guide when discharge is considered; to suggest suitable alternatives to admission wherever possible; to ensure that the waiting-list is a "live" one. The service acts only at the request of the hospital staff, who then discuss each case with the general practitioner concerned. Details of the service are obtainable from the secretary, c/o New Cross General Hospital, Avonley Road, London, S.E.14.

FUNCTION OF ALDOSTERONE IN THE METABOLISM OF SODIUM AND WATER IN PREGNANCY

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The recent discovery of aldosterone (Grundy, Simpson, and Tait, 1952) has provided a fresh tool for the study of sodium and water metabolism in pregnancy. Previous observers have recorded an increased renal excretion of aldosterone or sodium-retaining substances in the later months of pregnancy; in pre-eclampsia the excretion was either the same as, or slightly less than, that found in normal pregnancy (Gordon, Chart, Hagedorn, and Shipley, 1954; Martin and Mills, 1956; Venning and Dyrenfurth, 1956; Venning, Primrose, Caligaris, and Dyrenfurth, 1957; Koczorek, Wolff, and Beer, 1957; see Table I).

TABLE I.—*Mean Aldosterone Levels in Urine During Pregnancy and Pre-eclamptic Toxaemia*

Author	Normal Pregnancy µg./24 Hours	Pre-eclamptic Toxaemia µg./24 Hours
Gordon *et al.** (1954)	5·0	13·0
Martin and Mills (1956)	3·6	2·5
Venning *et al.* (1957)	25·0	14·5
Koczorek *et al.* (1957)	59·3	40·8

* Calculated on the basis 1 µg. of aldosterone=30 µg. of deoxycortone in biological assay.

We have studied 38 patients during pregnancy as well as seven normal non-pregnant women. The aldosterone excreted in the urine was estimated at four-weekly intervals from 12 to 16 weeks of pregnancy until term in six normal and three diabetic pregnancies. On one or more occasions similar measurements were made between weeks 28 and 40 of pregnancy on 19 patients suffering from pre-eclamptic toxaemia. Of these patients, 9 had hypertension (greater than 140/90 mm. Hg) and oedema, while 10 had proteinuria in addition. Ten other diabetic pregnant women were investigated during the 28th–36th weeks of pregnancy, and four of these were observed to have hypertension and oedema.

The normal patients were eating unrestricted diets, but those with toxaemia had diets modified only by restriction of table salt.

In five normal pregnant subjects and seven with pre-eclamptic toxaemia the concentrations of sodium and potassium were estimated in 24-hour specimens of urines.

Methods

Urinary excretion of sodium and potassium was determined with an EEL flame photometer, using external standards.

For the estimation of aldosterone in the urine 24-hour specimens were collected without preservative, and extraction was begun within eight hours of completion.

A preliminary extraction at *p*H 7, four times with 0.25 volumes of chloroform, removed the free cortisone and cortisol which interfere with the identification of aldosterone in the