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

BY

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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 <i>et al.</i> * (1954)	5.0	13.0
Martin and Mills (1956)	3.6	2.5
Venning <i>et al.</i> (1957)	25.0	14.5
Koczorek <i>et al.</i> (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 pH 7, four times with 0.25 volumes of chloroform, removed the free cortisone and cortisol which interfere with the identification of aldosterone in the

paper chromatographic system used. After acidification to pH 1 the urine was left at room temperature and extracted four times with 0.25 volumes of chloroform over 48 hours to remove aldosterone as it was released from its conjugates. The combined chloroform extracts of the acidified urine were washed with N/10 sodium carbonate, water, and N/10 acetic acid and then evaporated. The residue was partitioned between benzene and water, and the water-phase re-extracted with chloroform (de Courcy, Bush, Gray, and Lunnon, 1953). After evaporation this residue was applied to a paper chromatogram in a band about 6 cm. wide and run at 37° C. in a benzene-methanol-water (2:1:1) system, using cortisone and cortisol as markers. The area containing the aldosterone between the two markers was eluted and a fraction of the eluate run again as a "spot" in the same system. The chromatogram was developed with methanolic soda and triphenyl-tetrazolium chloride. The quantity of aldosterone thus obtained was estimated by visual comparison of its fluorescence in ultra-violet light with that of cortisol standards. Neher and Wettstein (1955) have observed that aldosterone and cortisol have similar intensities of fluorescence in ultra-violet light.

In recent experiments the aldosterone specimens obtained by chromatography have been eluted, acetylated, and run in a benzene-toluene-methanol-water (10:10:7.5:2.5) system. Their R_f values have corresponded with that of pure aldosterone acetate.

At the time of the earlier experiments pure aldosterone was not available, and, to confirm the identity of the substance measured on the chromatogram, the sodium-retaining activity of most of the samples obtained by paper chromatography was assayed biologically, using a method based on that of Cope and Garcia-Llaurado (1954) and Llaurado (1956).

The test and standard substances were dissolved in 20% ethanol and administered intravenously, the standard at two levels, to groups of 8-12 adrenalectomized rats, each rat weighing 80-90 g. A control group was included in each assay, receiving 20% ethanol only. A salt-and-water load (4 ml. of normal saline) was administered to each animal intraperitoneally at the beginning of the experiment. The urine from each rat was collected for a three-hour period after the bladder had been emptied, and the Na/K ratio of each urine determined by flame-photometry. The reduction of this ratio in the experimental group was compared with that of the control group and expressed as a percentage which provided a measure of the sodium-retaining power of the

FIG. 1.—Aldosterone content of urine in normal and diabetic pregnancies (mean values).

substance administered. The standard used was 9 α -fluorohydrocortisone, which we found to have approximately one-third the potency of aldosterone.

Results

As pregnancy progressed there was an increase in the amount of urinary aldosterone from the non-pregnant level of 2-10 μ g./24 hours to a mean of 119.2 ± 27.3 μ g./24 hours at 32-40 weeks (Fig. 1), similar to results published by Venning *et al.* (1957) and Koczorek *et al.* (1957). Table II shows that in patients with hypertension and oedema the

TABLE II.—Aldosterone Excretion in Normal, Diabetic, and Toxaemic Pregnancies Between 32 and 40 Weeks

	No. of Cases	Mean Aldosterone in Urine μ g./24 Hours	S.E.	Range	Probability that Observed Figures are Different from Normal Pregnancy
Normal females (non-pregnant)	7	6.1	± 1.0	2-10	
Normal pregnancy	6	119.2	± 27.3	55-240	
Pre-eclampsia:					
(a) Hypertension + oedema	9	69.4	± 8.1	40-110	0.10-0.05
(b) Hypertension, + oedema, + proteinuria	10	34.7	± 35.9	0-120	0.01-0.001
Diabetic pregnancy	9	164.9	± 25.3	65-285	0.7
Diabetic pregnancy with hypertension, + oedema	4	38.8	± 2.4	35-45	0.05-0.02

mean excretion of aldosterone (69.4 ± 9.2 μ g./24 hours) was significantly lower than that of the normal pregnant subjects. The more severely affected patients with proteinuria in addition to hypertension and oedema excreted even less aldosterone—a mean of 35.0 ± 11.4 μ g./24 hours.

The diabetic patients without hypertension and oedema had a mean aldosterone output of 164.4 ± 25.3 μ g./24 hours between weeks 32 and 40, a value greater than the normal; statistical comparison shows that the difference between the means is not significant. However, five of the nine diabetics during this period excreted aldosterone at rates greater than 150 μ g. daily, whereas this value was exceeded by only one of the six normal subjects. The diabetic women with hypertension and oedema had rates of aldosterone excretion similar to the other patients with pre-eclampsia—namely, a mean of 38.8 ± 2.4 μ g./24 hours.

Fig. 2 shows that the Na/K ratio in the patients' urine was related to the aldosterone content in five normal pregnant patients and seven patients with pre-eclamptic toxemia. Sodium retention, as indicated by a lower Na/K ratio, was greater in the toxæmic than in the normal patients with a similar excretion of aldosterone.

Discussion

There is conflicting opinion regarding the fate of sodium and water which have been shown by balance studies to be retained in considerable quantities during pregnancy (Coons, Coons, and Schiefelbusch, 1934; Hummel, Sternberger, Hunscher, and Macy, 1936; Chesley and Boog, 1943).

Chesley found an increase in the thiocyanate space in normal pregnancy and that this increase was particularly marked in pre-eclamptic toxæmia. He concluded that much of the sodium retention was the result of expansion of the extracellular fluid (E.C.F.) compartment. The thiocyanate method is based on the assumption that this ion does not penetrate in quantity into the cells before equilibrium takes place in the E.C.F. Should intracellular diffusion occur the volume of distribution will be greater than the actual E.C.F. volume.

Gray and Plentl (1954), using a sodium isotope dilution method, have shown that there is little change in the sodium space and total exchangeable sodium in normal pregnancy, confirming some earlier observations of Lambiotte-Escoffier, Moore, and Taylor (1953). However, they noted a total gain of 500 mEq of sodium in the last six months of pregnancy, which they thought could be accounted for in the products of gestation and the expanded maternal blood volume. The maintenance of a sodium space within the range found in non-pregnant patients indicates that, despite the rise in plasma volume, little change in the E.C.F. volume occurs in normal pregnancy. There is evidence that part of the storage of sodium in pregnancy takes place in the uterus; an increase in the sodium and a decrease in the potassium content per unit dry weight of uterine muscle has been observed (Cort and Cort, 1957; Hawkins and Nixon, 1957).

The absolute gain of sodium and water in the presence of a normal total-exchangeable sodium value and an increased thiocyanate space offers indirect evidence that in normal pregnancy there is an alteration in cell permeability (Chesley and Boog, 1943), associated with an increase in stored maternal intracellular sodium and water in addition to foetal needs. The increased intracellular storage of sodium in the mother, and the foetal requirements, are a drain on the salt content of the maternal E.C.F., which if uncorrected would cause a fall in the E.C.F. and plasma volumes. Bartter, Liddle, Duncan, Barber, and Delea (1956) have demonstrated that a reduction of the E.C.F. volume independent of its tonicity leads to a rise in aldosterone excretion. The rise in aldosterone output observed in normal pregnancy may thus be part of a homeostatic mechanism preserving the volume of the E.C.F. and meeting the loss of sodium from the E.C.F. into the maternal cells and foetal tissues by increased renal reabsorption.

That the E.C.F. is expanded in pre-eclamptic toxæmia is evident on clinical examination. Bartter *et al.* (1956) observed that expansion of the E.C.F. in normal persons produced a fall in the urinary output of aldosterone. The patients in our series of pre-eclamptic toxæmia excreted considerably less aldosterone than the normal patients between weeks 32 and 40 of pregnancy. In our view this fall in the aldosterone excretion is the result of the rise in the E.C.F. volume and the generalized oedema formation.

In the small group of toxæmic patients in whom we measured the urinary sodium and potassium, for a given Na/K ratio the output of aldosterone is less than in the normal group (Fig. 2). Sodium retention is maintained and even increased in pre-eclampsia despite the low aldosterone output. This suggests that a mechanism other than that of aldosterone secretion by the adrenal gland causes sodium retention in pre-eclamptic toxæmia.

A number of the diabetic pregnant women excreted more aldosterone than most of the normal patients. The greater weight of the foetus of the diabetic mother and the increased volume of the amniotic fluid (hydramnios) (Lawrence and Oakley, 1942; Pederson and Jorgenson, 1954) presumably result in an increased demand for sodium and water over and above that of normal pregnancy. The raised output of aldosterone beyond the normal range in these individuals may well be a response to the greater requirement of sodium and water.

It is of interest to consider whether the hypothesis that a redistribution of salt and water in the body may influence the rate of aldosterone excretion can be applied to other con-

ditions. Conn, Louis, Fajans, Streeten, and Johnson (1957) have shown that in familial periodic paralysis, in which increased rates of aldosterone excretion occur during the attacks, there is an associated rise in the intracellular sodium and a fall in potassium in voluntary muscle.

High levels of aldosterone have been observed in the urine of patients suffering from hepatic cirrhosis and ascites (Deming and Luetscher, 1950; Wolff, Koczorek, Jesch, and Buchborn, 1956). In this condition one has to distinguish between the effect of the loss of sodium and water into the ascitic fluid (particularly after repeated paracenteses) and the effect of the fall in plasma albumin and its influence on the E.C.F. volume. Although the E.C.F. volume may be expanded as a result of a fall in plasma albumin and the colloid osmotic pressure of the blood, the new equilibrium of the E.C.F. volume is, we think, maintained by a raised aldosterone output in the face of sodium and water loss into the ascitic fluid. Under these conditions the administration of sodium chloride may produce oedema and a marked increase in ascitic fluid with a fall in aldosterone output (Duncan, Liddle, and Bartter, 1956).

The foregoing conditions illustrate how a redistribution of sodium and water in the body may effect an alteration in aldosterone excretion and add support to the hypothesis that a similar mechanism operates in pregnancy.

Summary

Urinary aldosterone was measured at four-weekly intervals in six normal and three diabetic pregnancies and on one or more occasions between weeks 28 and 40 of pregnancy in 19 patients with pre-eclamptic toxæmia and in 10 other diabetic patients.

A considerable rise was observed in the amounts of aldosterone recovered from the urine of normal pregnant women as pregnancy progressed.

It is suggested that this rise in output is a physiological response by the adrenal cortex to maintain the extracellular fluid volume in the face of loss of sodium and water into the maternal cells and into the products of conception.

A number of diabetic patients were observed to have a considerably greater output of aldosterone from week 28 of pregnancy onwards than that of a normal group. It is thought that this is due to the greater demand for sodium and water by the tissues of the larger foetus and by the increased volume of amniotic fluid.

A gross reduction in the urinary aldosterone was found in pre-eclamptic toxæmia. It is concluded that an agency other than aldosterone is responsible for the further sodium retention and oedema in pre-eclamptic toxæmia.

The effect on aldosterone excretion of a redistribution of sodium and water in the body in certain conditions other than pregnancy is discussed.

Mr. J. H. Peel and Mr. S. G. Clayton, of the department of obstetrics, and Dr. R. D. Lawrence and Dr. W. Oakley, of the diabetic department, have kindly allowed us access to their patients. Professor C. H. Gray has been most generous with laboratory facilities, materials, and advice. Professor Reichstein kindly supplied a small sample of pure aldosterone. We appreciate very much the co-operation of the patients, sisters, midwives, and nurses of King's College Hospital. Miss Marjorie Sandiford has contributed considerable time and skill in the care of the animals; and Miss Mary Pickett and Dr. Peter Dixon provided invaluable laboratory assistance.

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PANCREATIC ISLET ADENOMATOSIS WITH HYPOGLYCAEMIC EPISODES

BY

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The clinical manifestations of endogenous ("spontaneous") hypoglycaemia were probably first described by Porges (1910), of Vienna, in a patient with Addison's disease; in 1912 Harvey Cushing described several more examples in patients suffering from pituitary chromophobe adenoma. As a result of the discovery of insulin in 1921 the clinical picture of exogenous hypoglycaemia in the form of "insulin reactions" soon became familiar, and Seale Harris (1924) described five cases in which the patients had experienced similar attacks of hunger, anxiety, weakness, and sweating which were correlated with low blood-sugar levels; in this way he introduced the term "spontaneous" hypoglycaemia, suggesting that this may result from hyperinsulinism produced by overaction of the pancreatic islet cells.

The first example of a pancreatic islet adenoma recorded in the literature was described by Nicholls in 1902, but this was an incidental necropsy finding and the clinical details are not available. The first successful surgical removal of such a tumour was carried out by Roscoe Graham (Howland, Campbell, Maltby, and Robinson, 1929); by 1950 Howard, Moss, and Rhoads were able to analyse the findings in almost 400 cases of islet-cell tumour previously recorded in American medical writings. The rare condition in which there is widespread diffuse adenomatosis of the pancreatic islet cells was first discovered by Lang in 1925, and the relevant literature was reviewed in 1955 by Bickerstaff, Dodge, Gourevitch, and Hearn, who described the first example seen in Great Britain and the seventh in the world. In this the surgically resected body and tail of the pancreas showed very numerous adenomata varying in diameter from 0.2 to 7 mm., together with many hyperplastic islets, though there had been no corresponding visible or palpable abnormality at operation. The

following case report relates to the first example of islet-cell adenomatosis seen in the General Infirmary at Leeds, and appears to be the second example in Great Britain and the eighth in the world.

Case Report

A schoolmistress aged 49 suffered from "attacks" which started in 1949 and occurred about once a week but later became irregular, with free periods of several months, though sometimes there were as many as six in a fortnight. She was of above average intelligence and her previous medical and psychiatric history was non-contributory. It was, however, difficult to elicit an accurate account of her symptoms, but the attacks were apparently all similar in pattern, starting with sudden diplopia in all directions and often associated with tingling round the lips, followed by disturbance of consciousness which varied in severity from a lack of concentration to drowsiness or sleep, though she was probably never in a completely unrousable state and she never had a convulsion; they lasted from 15 minutes to about two hours, and often occurred before lunch or in the evening. During many attacks she continued to walk about but was unsteady and talked nonsense, so that she was often thought to be drunk, and she always had total amnesia for the whole episode except the aura. Soon after the onset a general physician made a diagnosis of hysteria. In 1952 I was consulted and considered (with reserve) that this was "idiopathic" psychomotor epilepsy; at this time the electroencephalogram (E.E.G.) was normal (Fig. 1). In 1953 she was sent to a neurosurgeon, who investigated her condition fully, including air-encephalography, with negative results.

During 1956 the attacks became more frequent, and consequently she was admitted to the neurological department of Pinderfields Hospital, Wakefield. Routine physical examination was repeatedly negative, and during several days of observation she had no attack. A glucose-tolerance test (by the Hagedorn-Jensen method using capillary blood) gave the following results: Fasting blood sugar, 65 mg./100 ml.; blood sugar $\frac{1}{2}$ hour after 50 g. glucose, 75 mg.; at 1 hour, 45 mg.; at $1\frac{1}{2}$ hours, 55 mg.; at 2 hours, 60 mg.; at 3 hours, 65 mg.; at 4 hours, 45 mg.; at 5 hours, 30 mg.; at 6 hours, 35 mg. Urine tests were not recorded.

After this test had been pursued for five hours, consciousness was seriously disturbed, so that she was only just able to swallow glucose, which produced a rapid return to her normal mental state.

The patient was then transferred to the General Infirmary at Leeds, where a second glucose-tolerance test (by a modification of the Folin-Wu method using venous blood) was carried out after 24 hours' starvation; during the fifth hour of the test there was a similar disturbance of consciousness though the blood concentrations were higher (Table I).

A simultaneous E.E.G. by Dr. M. J. Parsonage (during which the patient was very drowsy, with evidence of a cold, clammy sweat) showed a comparatively small amount of alpha rhythm in the parieto-occipital and posterior temporal regions which was frequently interrupted by irregular, diffuse, slow activity of mixed theta and delta frequencies. The record was indicative of a diffuse disturbance of cortical activity compatible with a hypoglycaemic state; there were no precise localizing signs, but at times the slow activity appeared to be maximal in the right temporal region (Fig. 2).

Laparotomy was performed by Mr. A. J. Latchmore on

TABLE I

	Blood Sugar (mg./100 ml.)	Urine
Fasting	60 mg.	No sugar
50 g. glucose orally:		
$\frac{1}{2}$ hour	80 "	
1 hour	60 "	" "
$1\frac{1}{2}$ hours	60 "	
2 "	50 "	" "
3 "	50 "	
4 "	50 "	
5 "	50 "	