Cardiovascular Conferences of Howard University and Freedmen's Hospital, IV

Some Aspects of the Physiology of Aldosterone

JAMES O. DAVIS, Ph.D., M.D.

Laboratory of Kidney and Electrolyte Metabolism, National Heart Institute, Bethesda, Maryland

ALDOSTERONE (formerly known as electrocortin) is the naturally occurring sodium-retaining hormone of the adrenal cortex. For years it has been recognized that a very potent sodium-retaining substance is present in extracts of adrenal glands. During the early studies[1, 2, 3] it was found that after separation of all known compounds from an adrenal gland extract, there remained in the "mother liquors" a material which was highly active in maintaining life of adrenalectomized dogs. This residue was called the "amorphous fraction" because no crystalline material could be separated from it with available methods. Studies by Mason[4] of the effect of the "amorphous fraction" on electrolyte metabolism indicated that it was at least 5-10 times as active as desoxycorticosterone. Certain chemical properties of the active substance such as its high solubility in water as well as its potent effect on electrolytes distinguished it from desoxycorticosterone.

ISOLATION, CRYSTALLIZATION AND SYNTHESIS OF ALDOSTERONE

By application of new chromatographic methods, aldosterone was isolated and identified through the collaborative efforts of Simpson, Tait, Wettstein, Neher, Von Euw, Schindler and Reichstein in 1953.[5] Very important in the identification of aldosterone was the development of a highly sensitive bioassay by Simpson and Tait in 1952[6] for the detection of the sodium-retaining and potassium-excreting activity of aldosterone. Shortly after the report by Simpson, et al.[5] Mattox, Mason and Alpert[7] also crystallized aldosterone. The chemical structure of aldosterone was determined in 1954 by the same group of workers[8, 9, 10] who first isolated and crystallized it. Aldosterone is the 18-aldehyde of corticosterone (compound B of Kendall) or 11β-21-dihydroxy-3, 20-diketo-4-pregnene-18 aldehyde. Aldosterone exists in two tautomeric forms (Fig. 1); the hemiacetal form is shown on the left and the aldehyde on the right.

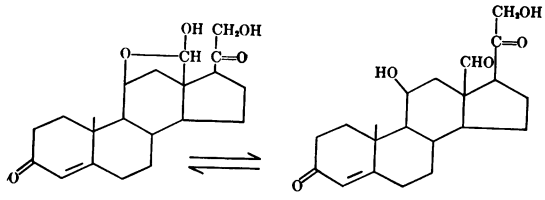

Fig. 1.—Chemical structure of the tautomeric forms of aldosterone.

Physiological studies of aldosterone have been greatly impeded by its scarcity since only a few milligrams have been available for research purposes. The best natural source of aldosterone has been urine from patients with cardiac failure, cirrhosis of the liver and nephrosis. The recent synthesis of aldosterone by Wettstein and associates should soon make aldosterone available in quantities adequate for research.

ZONAL ORIGIN OF ALDOSTERONE

For more than a decade studies have provided suggestive evidence that the adrenocortical hormones concerned with electrolyte regulation are secreted by the zona glomerulosa. In 1943, Sarason[11] found that prolonged administration of desoxycorticosterone produced cytological changes suggestive of inactivity of the zona glomerulosa in the rat. Hypophysectomized rats showed no change in the zona glomerulosa while the fasciculata and reticularis were atrophic. Since electrolyte balance was maintained in hypophysectomized rats[12], early reports suggested that the zona glomerulosa secretes the salt regulating hormone or hormones.

Later, Deane, Shaw and Greep[13] found that a low sodium diet or high potassium intake produced cytological changes in the zona glomerulosa

indicative of increased activity. More recently it was shown by Luetscher and Axelrad[14] that a low sodium diet resulted in increased urinary excretion of aldosterone. Liddle and associates[15] and Laragh and Stoerk[16] found that a high potassium intake increased aldosterone output. These studies on the influence of dietary electrolyte intake also suggest that the zona glomerulosa is the principal adrenocortical site for the origin of aldosterone.

In a study of hypophysectomized dogs with experimental ascites by Howell, Davis and Laqueur,[17] marked sodium retention was observed in the presence of a normal or nearly normal zona glomerulosa whereas the fasciculata and reticularis were severely atrophied. From more recent unpublished observations in our laboratory, it has been shown that increased urinary aldosterone excretion occurs under these cirumstances. The data suggest increased aldosterone secretion by the zona glomerulosa of an otherwise atrophic adrenal cortex.

Additional evidence of aldosterone production by the zona glomerulosa in rats has been reported from in vitro observations by Giroud, Stachenko and Venning.[18] When rat adrenal glands were incubated in vitro, aldosterone was released at a rate of 0.66 micrograms/100 mgm. of tissue/hour. Only negligible amounts of aldosterone were recovered from decapsulated rat adrenals; decapsulation removed principally the zona glomerulosa. Also, comparison of aldosterone production in decapsulated rat adrenals with aldosterone output from their capsules showed that most of the hormone was present in the capsular portion which contained the zona glomerulosa. All available evidence indicates, therefore, that the principal site of aldosterone secretion is the zona glomerulosa.

EFFECTS OF ALDOSTERONE ON ELECTROLYTE METABOLISM

One of the most important actions of aldosterone is its profound influence on electrolyte

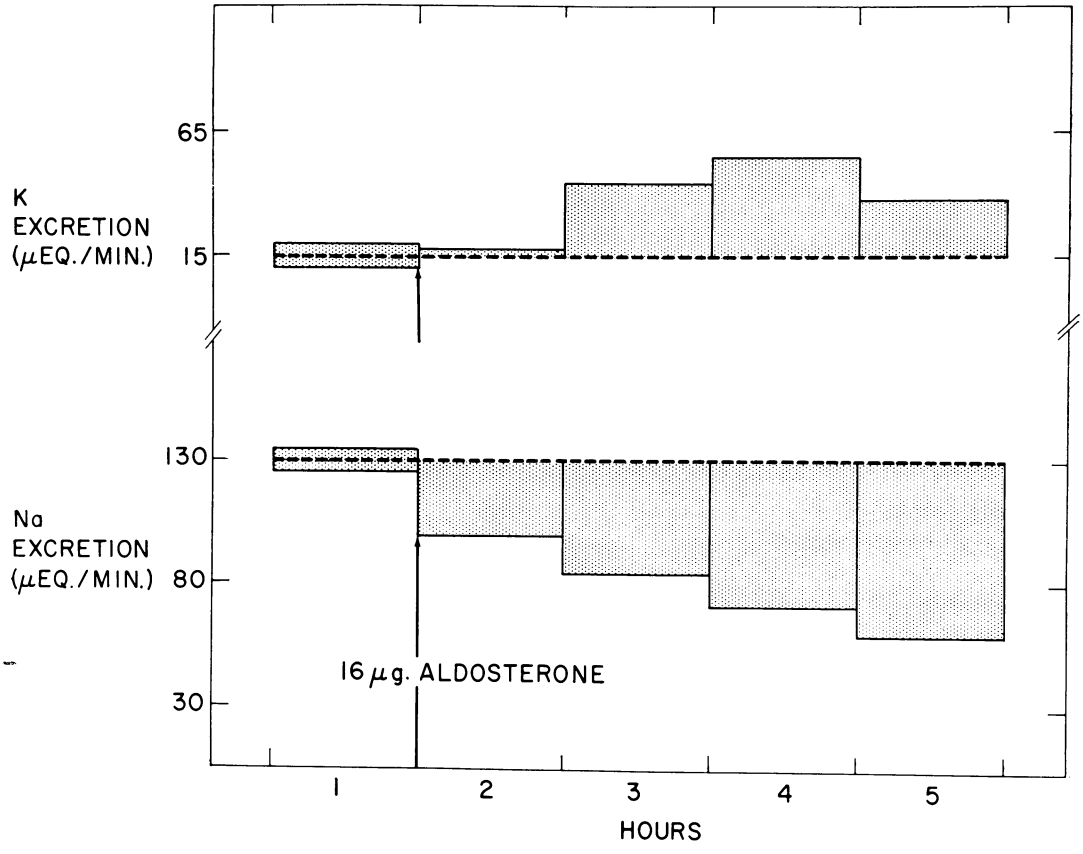

FIG. 2. Effects of the intravenous injection of 16 micrograms of crystalline aldosterone on the excretion of Na and K in an adrenalectomized dog. The dotted lines represent the control levels of Na and K excretion.

metabolism. The most extensive studies have been made on sodium and potassium excretion by the kidney. The effect of 16 micrograms of crystalline aldosterone on sodium and potassium excretion in an adrenalectomized dog is shown in Figure 2. The adrenalectomized dog was maintained on 200 m.Eq./day of sodium, 18m.Eq./day of potassium and 5 mgm./day of cortisone acetate given intramuscularly 18 hours before the injection of aldosterone. After a one hour control period, 16 micrograms of aldosterone were injected intravenously. A striking drop in renal sodium excretion occurred while potassium output increased. These data are similar to those reported by Liddle and associates.[19] These workers also showed that the qualitative response in sodium and potassium excretion was similar to that for desoxycorticosterone; the slopes of dose response curves for aldosterone and for desoxycorticosterone were nearly identical. Estimates of the comparative action of aldosterone and desoxycorticosterone on sodium and potassium showed that aldosterone was 30 times as potent as desoxycorticosterone.[19] Simultaneous measurements of the rate of glomerular filtration during electrolyte studies[20] demonstrated that doses of aldosterone (5-10 micrograms) adequate to produce sodium retention and increased potassium excretion exerted no detectable influence on glomerular filtration rate. Consequently, these data provide evidence that the effect of aldosterone is on electrolyte transport.

The effects of aldosterone on electrolyte metabolism are not limited to its actions on the kidney. On the contrary, aldosterone exerts widespread effects by acting upon salivary and sweat glands and the intestinal mucosa. Aldosterone also influences the electrolyte content of muscle but the effect may be indirect.

Mach and associates[21] reported that aldosterone depressed the sodium:potassium concentration ratio in saliva in normal subjects. This finding was confirmed by more extensive studies by Simpson and Tait[22] of saliva from normal humans. The depressed ratio was largely the result of a decrease in sodium rather than an increase in potassium. In patients with cirrhosis of the liver and with congestive heart failure, the sodium concentration was depressed both in saliva[23, 24, 25] and in sweat;[24, 25, 26] these changes were presumably the result of increased circulating aldosterone since excessive amounts of aldosterone are excreted in urine from patients with these clinical conditions. Also, in a patient with an adrenocortical adenoma and excessive urinary excretion of an aldosterone-like corticoid, Conn[27, 28] reported a reduction in the sodium and an elevation in the potassium concentration in both sweat and saliva. Although the corticoid described by Conn was not identified conclusively as aldosterone, the data were very suggestive. Muscle biopsies from this patient with the adrenocortical adenoma showed a great excess of intracellular sodium and a markedly decreased intracellular potassium content. Finally, in patients with congestive heart failure and decompensated hepatic cirrhosis it was reported by Berger and Steele[25] that the amount of sodium removed from the gut with cation exchange resins was considerably less than in normal subjects. This retention of sodium by the gut appears to be related to increased circulating aldosterone; in normal subjects and in patients with heart failure, Duncan, et al.[29] found that urinary aldosterone output and sodium uptake by resin were inversely related. Also, in the dog with thoracic inferior vena cava constriction and ascites* increased circulating aldosterone was found[30] and a very low ratio of sodium to potassium in the feces resulted from a drop in fecal sodium and an increase in fecal potassium output (Fig. 3). Following bilateral adrenalectomy and in the absence of hormone therapy, aldosterone excretion in urine disappeared[31] and the fecal sodium:potassium ratio returned to normal.[32] Further evidence of this relationship was obtained from observations of hypophysectomized dogs with thoracic caval constriction and ascites;[33] the low fecal sodium:potassium ratio was present only during excessive urinary aldosterone excretion.

In the patient with an adrenocortical adenoma described by Conn,[27, 28] a hypernatremia and a hypokalemic alkalosis developed. Also, polyuria and polydipsia were prominent symptons. A similar case was reported by Mader and Iseri.[34] Adrenal tumors were removed surgically from both patients. In the case of Conn,[27] removal of the tumor resulted in the return of serum electrolytes and water turnover to normal, a sharp sodium

* The dog with thoracic inferior vena cava constriction and ascites resembles very closely the patient with decompensated hepatic cirrhosis in regard to the physiology of electrolyte metabolism.

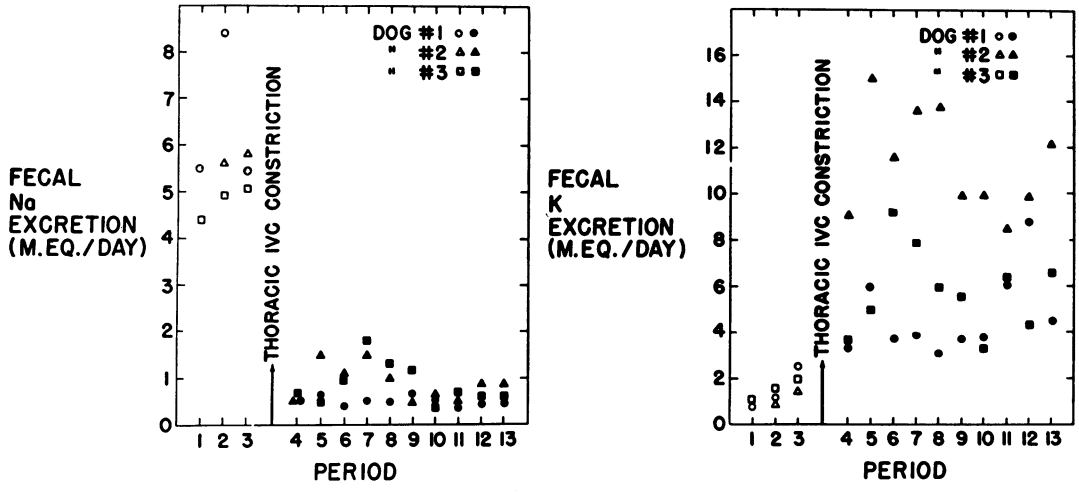

Fig. 3.—Fecal Na and K excretion in dogs before and following constriction of the thoracic inferior vena cava. Each collection period was 5-8 days in length. Ascites formation occurred throughout the experimental period and renal Na retention was almost complete.

diuresis, potassium retention and an increase in the concentration of sodium in sweat. Bioassays for urinary sodium-retaining activity gave normal values.

It is of considerable interest that all of these renal and extrarenal actions of aldosterone have been reported for desoxycorticosterone or one of its esters. For almost 20 years desoxycorticosterone and its esters have been the only potent sodium-retaining steriods available and desoxycorticosterone acetate (DCA) has served as the prototype for numerous studies on the physiological action of a sodium-retaining steroid. The early synthesis of desoxycorticosterone in 1937 by Steiger and Reichstein was an extremely important contribution. It made progress possible toward elucidation of the physiology of adrenocortical sodium-retaining hormones for almost two decades before aldosterone was identified.

Recently, Farrell and associates[35] have identified desoxycorticosterone in adrenal vein blood from dogs. They concluded that the amount of desoxycorticosterone secreted was too small for it to play an appreciable physiologic role, particularly in view of its low potency compared to aldosterone.

EFFECT OF ALDOSTERONE ON BLOOD PRESSURE

The relation of aldosterone to blood pressure is a subject of considerable importance because of the possible pathogenic role of aldosterone in hypertensive disease. The effect of aldosterone on blood pressure was demonstrated by maintenance of a normal arterial tension in adrenalectomized dogs[36] and in Addisonian patients.[37,38] The presence of hypertension in association with large quantities of a potent sodium-retaining corticoid (apparently aldosterone) in urine from a patient with an adrenocortical adenoma[27,28] and the return of blood pressure to normal following removal of the tumor suggest the possibility of a causal relation of aldosterone in some cases of hypertension. More recently, it has been reported by Genest and associates[39] that increased quantities of aldosterone were present in urine from patients with essential hypertension. This finding needs confirmation since dietary sodium was uncontrolled and two of the patients showed evidence of congestive heart failure which results in increased aldosterone output.

One of the first attempts to produce experimental hypertension by administration of aldosterone was unsuccessful by Gross, et al.[40] Forty micrograms/day of aldosterone were injected into adrenalectomized, unilaterally nephrectomized rats given 1 per cent sodium chloride to drink. However, in a more recent preliminary report[41] Kumar and coworkers described hypertension and its associated pathological sequelae during chronic administration of 0.5-1.0 micrograms per 24-48 hours in both intact and adrenalectomized rats. This dose was considerably less than that employed by Gross and associates. The explanation for the difference in the results of these two groups of workers is not clear.

OCCURRENCE OF ALDOSTERONE IN DISEASE

The occurrence of increased aldosterone in urine from patients with certain diseased states led Conn[27] to propose the terms primary and secondary aldosteronism. Primary aldosteronism is the clinical syndrome in which the primary abnormality is increased secretion of aldosterone. The example described by Conn[27] was a patient with an adenoma of the adrenal cortex from which large amounts of aldosterone or an aldosterone-like substance were secreted. In secondary aldosteronism, the primary defect is not that of increased aldosterone secretion by the adrenal cortex; instead, the site of primary dysfunction is elsewhere. In heart failure the primary defect is in the myocardium whereas in decompensated hepatic cirrhosis an abnormality in the liver is present. Secondary aldosteronism is also observed in such conditions as toxemia of pregnancy, nephrosis and "salt-losing nephritis".

In addition to the difference in the primary defect, another striking dissimilarity between primary and secondary aldosteronism is the lack of edema in the former and its presence in many instances of the latter group. This finding may reflect the necessity of another factor in addition to increased circulating aldosterone for chronic sodium retention. In the dog with thoracic inferior vena cava constriction and ascites[42], an elevated venous pressure below the constricting ligature appears to be the additional factor necessary to produce marked sodium retention. No more than transient sodium retention occurred in the normal dog[43] or the adrenalectomized dog[44] during administration of large amounts of DCA, whereas the adrenalectomized dog with thoracic caval constriction retained sodium almost completely for long periods of time in the presence of 10-25 mgm./day of DCA.[32]

FACTORS INFLUENCING ALDOSTERONE SECRETION

The possible influence of the anterior pituitary gland on aldosterone secretion was one of the first factors considered. Indirect evidence on this relationship was obtained by Lane and de Bodo[45] and by Rolf, Surtshin and White[46] before aldosterone was discovered. Both groups of workers found that adrenocortical insufficiency failed to develop in the hypophysectomized dog on a low sodium intake. This finding suggested independence of adrenocortical salt regulatory function from the pituitary gland.

Also, administration of exogenous ACTH failed to produce sodium retention in both the dog[43] and the rat[47], and in the dog measurements of glomerular filtration rate demonstrated a striking increase. Augmented filtration rate promotes sodium excretion and, therefore, the increase which accompanied ACTH administration might have made a slight elevation in circulating aldosterone undetectable from studies of sodium excretion only. This interpretation of the early data is consistent with the slight rise in urinary aldosterone excretion observed during more recent studies following ACTH administration.[15] Also, Farrell, Rauschkolb and Royce[48] reported a slight increase in aldosterone secretion after administration of ACTH to hypophysectomized dogs; in contrast, a marked increase in secretion rate of 17-hydroxycorticosterone, corticosterone and 11-desoxycorticosterone resulted.

Additional evidence of the relationship of the pituitary gland to aldosterone production has been obtained from acute studies of the effect of hypophysectomy on aldosterone secretion in the dog. Farrell and co-workers[47] reported a drop in aldosterone secretion to 42 per cent of the control rate. Apparently, loss of factors other than ACTH resulted in the decrease since ACTH administration failed to return aldosterone secretion to the control level.

In pathologic states associated with the formation of ascites, the anterior pituitary gland is not essential for sodium retention. Hypophysectomized dogs with thoracic inferior vena cava constriction showed almost complete sodium retention when the venous pressure was sufficiently high[17]. As pointed out previously, during recent unpublished studies from our laboratory, increased urinary aldosterone excretion was observed in association with the marked sodium retention of the hypophysectomized dog with caval constriction.

Electrolyte intake is an important factor in the regulation of aldosterone excretion. A low sodium diet[14] or depletion of body sodium[49] leads to increased output of urinary aldosterone, and sodium loading decreases aldosterone excretion[49]. The rate of aldosterone excretion is also influenced by potassium intake;[15, 16] potassium loading promotes aldosterone output while a low potassium intake decreases aldosterone excretion. Furthermore, the

effects of a low sodium and a high potassium intake are additive[50]. It seems likely that these data on urinary aldosterone output reflect directional changes in the rate of aldosterone secretion. It has been reported[51] that a low sodium:potassium ratio of the blood perfusing the adrenal glands increased aldosterone output, but an alteration in the plasma sodium or potassium concentration does not appear to be the mechanism by which dietary electrolyte changes exert their effect on the adrenal cortex. This unknown mechanism remains an important unsolved problem.

Bleeding stimulates the adrenal cortex to secrete increased quantities of aldosterone[52]. This effect of hemorrhage may be related to loss of body sodium, a decrease in blood volume or to some undetermined factor. In an unpublished study from our laboratory, loss of body sodium alone was adequate to account for the increase in urinary aldosterone-like activity. In dogs bled daily, it was found that the magnitude of the increased aldosterone-like activity in urine was duplicated in normal dogs by reducing sodium intake to the same extent as the net sodium intake during bleeding.

Expansion of the extracellular fluid volume or some other consequence of water retention has been reported to influence aldosterone excretion in urine. By injection of pitressin tannate in oil during forced water administration, it was found that sodium excretion increased in both normal subjects[15, 49, 53, 54] and normal dogs.[55] In man, the natriuresis was associated with decreased urinary aldosterone output;[15, 49] aldosterone studies on urine from normal dogs were not conducted. Bartter[49] has postulated that this decline in urinary aldosterone excretion was effected by the expanded extracellular fluid volume which influenced the rate of aldosterone secretion. The cranial cavity is a site where small changes in volume might influence a receptor, but an attempt by Fishman[56] to detect such a receptor by altering intracranial venous pressure and the volume of cerebrospinal fluid yielded negative evidence. Regardless of the mechanism whereby water retention influenced aldosterone excretion in normal man, the effect on aldosterone output was in the opposite direction to explain the altered aldosterone secretion during cardiac failure. In congestive failure the extracellular fluid volume is usually expanded and the rate of aldosterone secretion is increased.[30] In this connection it should be pointed out, however, that the response in dogs with thoracic caval constriction and ascites to pitressin and forced water intake was different from that in normal dogs in that the adrenal cortex of the dogs with ascites was apparently stimulated further to secrete additional amounts of a sodium-retaining hormone.[55]

Many attempts have been made to elucidate the mechanism whereby the adrenal cortex is stimulated to secrete aldosterone during congestive heart failure. Several years ago it was suggested by Peters[57] that the extravasation of fluid and electrolytes from the blood stream in some unknown manner stimulated the adrenal cortex to secrete a sodium-retaining hormone. The data from our laboratory have been consistent with this hypothesis. A high venous pressure and hypoproteinemia both favor filtration of fluid from the capillaries into the tissue spaces. An elevated venous pressure appeared to initiate the sequence of events leading to sodium retention in dogs with caval constriction[42], and in the dog with right heart failure[58] sodium retention was always associated with a mean right atrial pressure of 8-10 cm. or more above normal. Ascites formation also leads to hypoproteinemia which favors the further filtration of fluid and electrolytes from the blood stream. The precise factors associated with this internal rearrangement of water and electrolytes and their relation to adrenocortical stimulation remain undetermined.

QUESTIONS AND ANSWERS

Is aldosterone available commercially? Aldosterone is not available commercially. In fact, aldosterone has not as yet been available in adequate quantities for research. Wettstein and associates of Ciba Pharmaceuticals are now synthesizing several grams of aldosterone which should soon be ready for distribution. This supply will, however, be available only for research purposes. It should be emphasized that DCA can be completely substituted for aldosterone as far as its physiologic and therapeutic values are concerned. Aldosterone, however, is needed for studies of its metabolism.

Have attempts been made to obtain a dose response curve with ACTH for the rate of aldosterone secretion? As far as I know, no such data are available. Farrell and associates have observed the response in aldosterone output to ACTH at one dose level only; only a slight increase in the rate of aldosterone secretion occurred.

Is there a quantitative relation between the level of venous or right atrial pressure and the rate of aldosterone

secretion? This is one of the features of the aldosterone problem in which we have been very interested. We have never observed increased aldosterone excretion in urine or increased aldosterone secretion by the adrenal cortex during experimental cardiac failure unless the mean right atrial pressure was elevated 8-10 cm. of water or more above the control level. We have studied the rate of aldosterone secretion at various levels of right atrial pressure during experimental cardiac failure, but we were unable to demonstrate a positive correlation. This result may be a reflection of the inadequacy of available methods for measuring aldosterone. Until a better method for measuring aldosterone is obtained, we cannot answer this question.

What is the best index of aldosterone activity to use in a biological assay? We have used an index which combines mathematically the drop in sodium excretion and the rise in potassium output. Doctors Liddle and Cornfield at the National Institutes of Health arrived at this index, which they have designated the aldosteroid index, by a mathematical analysis of their assay data. The aldosteroid index gives considerably more precision in distinguishing between two dose levels of a sodium-retaining steroid than does the use of the sodium:potassium ratio of urinary excretion or the rate of sodium excretion alone.

What mechanisms explain the presence of edema in a patient with cardiac failure who is digitalized? This is a difficult question to answer without more information about the patient. I assume that digitalis had been "pushed" to the point of tolerance. If under these circumstances venous pressure remained elevated, an elevated pressure could explain the increased secretion of aldosterone and edema. If venous pressure was normal, then the possibility of other factors such as hypoproteinemia should be considered. According to the well-known Starling equilibrium, a low level of plasma protein favors filtration of fluid from the capillaries and, thereby, contributes to the formation of edema. Also, hypoproteinemia may increase aldosterone secretion, since Bartter found that administration of albumin to a hypoproteinemic patient decreased aldosterone excretion in urine .

What is the role of the central nervous system in the regulation of aldosterone secretion? This is a very important question about which very little is known. In a preliminary report, Farrell suggested from observations on dogs with different brain lesions that the hypothalamus is essential for normal aldosterone secretion. In contrast, in preliminary studies in our laboratory we have placed lesions in the hypothalamus in dogs with experimental ascites but no effect on urinary sodium and aldosterone excretion has been observed. Also, Laragh and associates constricted the thoracic inferior vena cava in dogs with diabetes insipidus; ascites accumulated at the same rate as in control dogs with thoracic inferior vena cava constriction and an intact endocrine system. More studies are needed to clarify the relationship of the hypothalamus to aldosterone secretion and to determine the relationship of other parts of the central nervous system to the secretion of aldosterone.

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EXPERT ADVISORY COMMITTEE FOR NURSE TRAINEESHIP PROGRAM

The Public Health Service has announced the appointment of 12 leaders in nursing, hospital administration, and medicine to an Advisory Committee for a new nurse training program. Surgeon General Leroy E. Burney said the Committee will advise the Service on administration of the new three-year program which provides funds to enable graduate nurses to get advanced training in supervision, administration and teaching. Since the establishment of the program last August, 553 traineeships amounting to nearly $2 million have been awarded through 56 schools of nursing and public health throughout the United States and Puerto Rico.

The Committee will be called the Expert Advisory Committee for the Professional Nurse Traineeship Program. Members are: Dr. Robert Berson, Vice-President in Charge of Medical Affairs, University of Alabama, Birmingham; Mr. Lawrence J. Bradley, Director, Genessee Hospital, Rochester, New York; Miss Ann Burns, Chief, Division of Nursing, Ohio State Health Department, Columbus, Ohio; Rev. John J. Flanagan, Executive Director, Catholic Hospital Association, St. Louis, Missouri; Miss Ada Fort, Dean, School of Nursing, Emory University, Atlanta, Georgia; Miss Frances Frazier, In Charge of Graduate Program in Public Health Nursing, Teachers College, Columbia University, New York, New York; Mrs. Lulu W. Hassenplug, Dean, School of Nursing, University of California, Los Angeles, California; Miss Katherine Hoffman, Assistant Dean, School of Nursing, University of Washington, Seattle; Miss Helen Nahm, Director, Department of Baccalaureate and Higher Degree Programs, National League for Nursing, New York, New York; Miss Agnes Ohlson, President, American Nurses' Association and Chief Nursing Examiner, State Examining Board, Hartford, Connecticut; Miss Marguerite Paetznick, Director Nursing Service, Denver General Hospital, Denver, Colorado; Mrs. Margaret Filson Sheahan, Director, Nursing Service, University of Chicago Clinics, Chicago, Illinois.