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Aldosteronism Associated with Adrenal Cortical Adenoma

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• **An electrolyte-regulating corticoid has been identified and given the name aldosterone. This hormone may be produced in amounts above normal in adrenal cortical tumors in hyperplastic adrenal glands and in normal appearing adrenal glands. Overproduction of aldosterone is accompanied by certain characteristic clinical manifestations which should suggest the diagnosis. The diagnosis may be supported by examinations available in most well equipped clinical laboratories. Bioassay of aldosterone in the urine and estimation of exchangeable body sodium and potassium, using radioactive salts, are necessary for confirmation of the diagnosis.**

Since the description of this salt-retaining hormone by Simpson and Tait and the discovery of its chemical structure by Reichstein in 1954, reports of 14 cases have been published. Surgical removal of the offending tissue gives spectacular relief from the very distressing symptoms.

TRUE ADENOMAS of the adrenal cortex are infrequently seen. Histologically they are composed of cells resembling one or more of the three types normally encountered in the adrenal cortex. Functional disturbances due to overproduction of specific hormones occur frequently in patients in whom cortical adenomas are found. It cannot be determined by histological examination if a given adenoma may produce any hormone in excess of normal. Overproduction of adrenocortical hormones may occur in the absence of adenoma with or without anatomic evidence of hyperplasia of the gland. The clinical manifestations will depend on the nature and quantity of hormones produced. Three classes of cortical hormones are recognized: (1) The sex hormones which influence the development of primary and secondary sex characteristics, (2) the corticoids which affect carbohydrate and protein metabolism, (3) the cortical hormones with pronounced effect on electrolyte and water metabolism.

In 1952, Simpson and Tait described a salt-retaining hormone secreted by the adrenal cortex, referring to it as "electrocortin."[10] In 1954, Reichstein announced the chemical structure of this hormone and named it "aldosterone."[11] In 1950, Deming and Luetscher isolated a substance with similar properties from the urine of patients with nephrosis and congestive heart failure.[6] Aldosterone is 20 to 30 times as potent as desoxycorticosterone acetate (DOCA) in reducing sodium excretion and it is five times as active as DOCA in enhancing potassium excretion.[7] The mechanism which regulates the production of aldosterone is not known. The secretion of aldosterone appears to be affected little by hypophysectomy and is not enhanced by the administration of corticotropin (ACTH).[8] The reverse is true of other corticoids.

Certain clinical conditions that are characterized by pronounced edema have been shown to be accompanied by increased excretion of aldosterone

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in the urine. These conditions include nephrosis with edema,[9] congestive heart failure,[12] decompensated hepatic cirrhosis,[1] and eclampsia.[2] Conn classified these conditions as examples of secondary aldosteronism.[3] Primary aldosteronism is a clinical syndrome which results from increased production and secretion of aldosterone by the adrenal cortex. This overproduction of salt-retaining corticoids may come from an adrenal cortical neoplasm or may come from the adrenal cortex of an hypertrophied adrenal gland or a normal-appearing gland.

The clinical manifestations of primary aldosteronism as described by Conn include periodic severe muscular weakness, intermittent tetany, paresthesia, polyuria and polydipsia, hypertension, and absence of edema.[4] The laboratory findings are hypokalemia, hypernatremia, alkalosis, normal blood calcium, and a low ratio of sodium to potassium in sweat and saliva. There is also an increase in the exchangeable body sodium and a decrease in exchangeable body potassium. Pronounced resistance to potassium repletion by oral or parenteral administration of potassium is characteristic. Another feature is hyposthenuria that does not respond to Pitressin (beta-hypophamine). The excretion of aldosterone in the urine is increased. The urinary 17-ketosteroids and the 17-hydroxycorticoids are normal and respond to corticotropin stimulation.

The cortical adenomas that produce excessive salt-retaining corticoids show no histological characteristics which help to distinguish them from other cortical adenomas. The cells are large and resemble those of the adrenal cortex. The cytoplasm is vesicular and is laden with lipid, and the nuclei are small and vesicular. The cells usually resemble those of the zona fasciculata, but there may be some cells resembling the other zones.

Conn described vacuolar changes in the renal tubular epithelium leading to focal necrosis and calcium deposit in some areas. He also noted a severe degree of renal arteriosclerosis in a biopsy specimen.

Thirteen cases of primary aldosteronism are referred to by Conn in a recent article, including one of the cases reviewed in this paper. The two cases here reviewed were studied by Crane and are being reported by him elsewhere.[5] In ten of the fourteen known cases, the patient was cured by removal of an adrenal cortical adenoma, and one was cured by bilateral adrenalectomy. The remaining three cases were recognized after an adrenal cortical adenoma was noted at autopsy.

Following is a brief review of two patients with the disease who were treated at the White Memorial Hospital and Clinic during 1954 and 1955.

CASE 1. A 32-year-old white man was admitted to the White Memorial Hospital on November 21, 1954, with complaint of headaches and dry mouth of ten months' duration. He had been told by a physician that he had high blood pressure. Drugs had been given for hypertension and for headache but neither was relieved. The patient had had two episodes of weakness and syncope with sweating within the previous four months. He had had sporadic weakness of the arms or legs or both, lasting hours to two days, for the past four or five months. He complained of urinary frequency—urination one or two times at night and four to five times during the day. The volume of urine was greater at night, he thought, than during the day. There was no dysuria. The patient had been on a low sodium diet.

Upon physical examination the patient was observed to be well-developed and well-nourished, in no distress, and appearing to be the stated age of 32 years. The blood pressure was 190/120 mm. of mercury. A regular sinus rhythm and a grade three apical systolic murmur were noted on examination of the heart. The chest was clear. No masses or other abnormalities were noted in the abdomen. No significant abnormalities were noted in the neurological examination.

The specific gravity of the urine was 1.007. A phenolsulfonphthalein test was done and 55 per cent of the dye was returned in two hours. A urine concentration test resulted in a specific gravity range from 1.010 to 1.027. The urine volume ratio was day : night as 2 : 3. At no time was albumin detected in the urine. The blood nonprotein nitrogen was 37 mg. per 100 cc., the serum sodium was 152 mEq. per liter, the serum potassium was 2.1 mEq. per liter, and the carbon dioxide combining power of the serum was 40 mEq. per liter. The hemoglobin content and the erythrocyte count were within normal limits, as was the differential of leukocytes.

A test with phentolamine was negative for pheochromocytoma. A sodium amytal test lowered the blood pressure from 200/120 mm. to 130/90 mm. of mercury, a decrease which was maintained for a two-hour period.

On diagnosis of essential hypertension, a left thoracolumbar sympathectomy was done November 23, 1954.

On the second postoperative day the serum sodium was 133 mEq. per liter, potassium 1.9 mEq. per liter, and calcium 9.1 mg. per 100 cc. Infrared recording of alveolar carbon dioxide was 47 mm. of mercury and the pH of arterial whole blood, determined at the same time, was 7.57. Because of the hypernatremia, hypokalemia and alkalosis at the time of the initial examination, attention was directed to adrenal function. A 24-hour specimen of urine contained 17.2 mg. of total 17-ketosteroids and 5.8 mg. of 17-hydroxycorticoids. Uropepsin excretion was 143 units in one hour.

The patient was released from the hospital on December 3 with prescription of 1 gm. of potassium chloride four times a day. He was readmitted to the hospital December 14, 1954, with complaint of palpitation on the slightest exercise and dryness of

the mouth. He had stopped taking potassium chloride two days before returning to the hospital. The blood pressure was 200/120 mm. of mercury and there was no change in the previously observed conditions on physical examination, nor significant change in results of blood examination or urinalysis since the previous hospitalization. The serum sodium was 146 mEq. per liter, the potassium content 2.1 mEq. per liter, and the carbon dioxide combining power was 40 mEq. per liter. A phentolamine test and a piperoxan test were negative for pheochromocytoma. The pulmonary carbon dioxide was 48 mm. of mercury and the arterial blood pH was 7.52.

On December 16, 25 mg. of corticotropin in 5 per cent glucose in 1,000 ml. of water were given by vein over an eight-hour period. The total 17-ketogenic steroids excreted in the urine in 24 hours increased to 64.4 mg. from the previous value of 5.8 mg. The circulating eosinophil count dropped from 699 per cu. mm. to 205, four hours after corticotropin was given. The urinary uropepsin excretion rate was 107 units in one hour (normal range, 15 to 40 units). On December 19, 1954, a right thoracolumbar sympathectomy was done and both adrenal glands were explored. The right adrenal gland appeared considerably enlarged. Approximately 80 per cent of the gland was removed. The specimen measured 6 x 3 x 2 cm. In a cross-section, a firm yellow circumscribed nodule 1 cm. in diameter was observed. The microscopic diagnosis was benign cortical adenoma of the adrenal gland.

On December 30, eleven days after adrenalectomy, the arterial blood pH was 7.48, the carbon dioxide combining power 32 mEq. per liter, serum sodium content 144 mEq. per liter, and serum potassium 3.1 mEq. per liter. A month later the arterial pH was 7.41, the carbon dioxide combining power was 28 mEq. per liter, the serum sodium 135 mEq., and serum potassium was 5.1 mEq. The urinary uropepsin was 30 units in one hour.

All the previously noted symptoms and abnormalities abated promptly following removal of the cortical adenoma of the adrenal, and the patient remained well thereafter. The blood pressure at the time the patient was discharged from the hospital was 148/108 mm. of mercury. On return visits it ranged from 110/60 to 120/70 mm. of mercury.

CASE 2. A 43-year-old white woman was admitted to the White Memorial Clinic February 17, 1955, with complaint of weakness of the lower extremities for four years and of the upper extremities for one month. The onset of the weakness had been gradual and it had spread from the legs to the thighs and then to the arms. On several occasions during the preceding two years the weakness had been so severe that the patient was unable to walk. Once she fell, causing minor injuries. The usual duration of an episode was one week, and the periods seemed to be getting longer. At no time was there paralysis. Dull aching and soreness in the muscles had been noted in the lower extremities, but pain in the arms was minimal. During the preceding year the patient had had severe headaches which were relieved by vomiting. The headaches were not related to the episodes of weakness. There was a tendency for the ankles to swell toward the end of the day. At the age of 19 years the patient had been treated with iodine for goiter. For two years she had had hypertension but she believed that before that she had had low blood pressure. The patient said that she had had dry mouth and thirst for about six weeks before admittance and had been drinking 12 glasses of water daily. She urinated three to four times a night.

Upon physical examination the patient was observed to be well-developed, well-nourished, in no distress and appearing to be the stated age. The blood pressure was 170/100 mm. of mercury. The heart rate was in regular sinus rhythm and there were no murmurs. The size of the heart was normal. No abnormalities were noted upon examination of the abdomen or upon neurological examination. Examination of the blood on admission to the clinic (and again nine months later on admission to the hospital) showed the hemoglobin content, hematocrit, leukocyte content and differential of leukocytes all within normal limits. The specific gravity of the urine varied from 1.003 to 1.011 on five different visits. A concentration test gave a maximum specific gravity of 1.012. The dye return in a phenolsulfonphthalein test for renal function was 70 per cent in two hours. The protein-bound iodine was 5.2 micrograms per cent of serum. A phentolamine test was negative for pheochromocytoma.

The patient was seen about every two weeks in the clinic until her admission to the hospital on November 29, 1955. During that time the blood pressure ranged from 170/100 mm. to 220/120 mm. of mercury. With potassium hydrochloride taken by mouth, there were no more episodes of weakness, and thirst was almost completely relieved.

On eight specimens taken over a period of nine months the serum potassium averaged 3.2 mEq. per liter. The lowest was 2.7 mEq. and the highest 4.4 mEq. On the same specimens the serum sodium ranged from 149 to 152 mEq. per liter. The average of seven determinations of sodium-potassium ratio in the saliva was 0.21. On a normal subject the ratio was 1.64. On stimulation by chewing paraffin there was no increase in the concentration of sodium in the sputum. The sodium-potassium ratio in the sweat was 0.69 on one occasion and 0.42 on another. The serum chloride was 109 mEq. per liter. The alveolar carbon dioxide was 37 mm. of mercury and the simultaneous arterial pH was 7.44. The serum carbon dioxide combining power was 25 mEq. per liter. The exchangeable body sodium was 46.4 mEq. per kilogram of body weight (normal range 35.7 to 41.6), and the exchangeable body potassium was 31.6 mEq. per kilogram (normal range 38.5 to 54.4). These determinations were made with radioactive sodium and potassium.

The urinary excretion of 17-ketosteroids and 11-oxysteroids was normal and responded normally to stimulation with corticotropin. There was pronounced diuresis of water and sodium following the third day of corticotropin administration. On July 11 a bioassay for aldosterone in the urine was done by Conn. He reported 100 microgram equivalents of desoxycorticosterone acetate in 24 hours, which is within the upper limits of normal. The result of a similar test on November 30 was 200 microgram equivalents in 24 hours.

Uropepsin excretion was 20 units in one hour on one occasion and 42 units on another (normal range 15 to 40 units in one hour). On November 30 the uropepsin excretion rate was 79 units in 24 hours and 106 units in 24 hours on two trials.

On November 30, 1955, both adrenal glands were explored. The one on the right appeared normal. A mass 3 cm. in diameter was found attached to the left adrenal gland. The mass and three-fourths of the gland were removed. Biopsy specimens were taken from the left kidney and the liver. A portion of the rectus muscle was taken for chemical analysis. On subsequent chemical analysis of the muscle the sodium content was found to be 39.5 mEq. per kilogram and the potassium was 42 mEq. per kilogram (normal, 31 and 93, respectively).

About twelve hours after the operation the blood pressure dropped to 65/40 mm. of mercury. Levarterenol bitartrate, cortisone and 4 gm. of potassium chloride were given intravenously in one liter of 5 per cent dextrose in saline solution. The blood pressure rose to 132/96 mm. within one hour. Once more during the postoperative period the blood pressure dropped, this time to 80/50 mm. Again it responded promptly to therapy and then fluctuated from 120/80 to 170/110 mm. until the day of discharge from the hospital when it was recorded as 124/90 mm. The blood pressure thereafter remained within normal limits.

During the week following the operation the excretion of sodium was in excess of the intake, the sodium-potassium ratio in the saliva changed from 0.21 before operation to 0.64 and the serum potassium returned to normal. At the time of the latest report, January 23, 1956, the serum potassium was 5.1. There was no change in arterial pH, in alveolar carbon dioxide or in the carbon dioxide combining power of the serum, all of which had been within normal limits ever since the patient first came under observation. Before operation the maximum specific gravity of the urine during concentration tests was 1.012. After removal of the tumor it rose to 1.020. At latest report on the uropepsin excretion rate (March 5) it was 15 units in one hour.

The patient no longer complained of dry mouth, polydipsia and polyuria. Saliva flowed more copiously and the patient perspired more freely. She gradually regained strength and when last observed felt quite well.

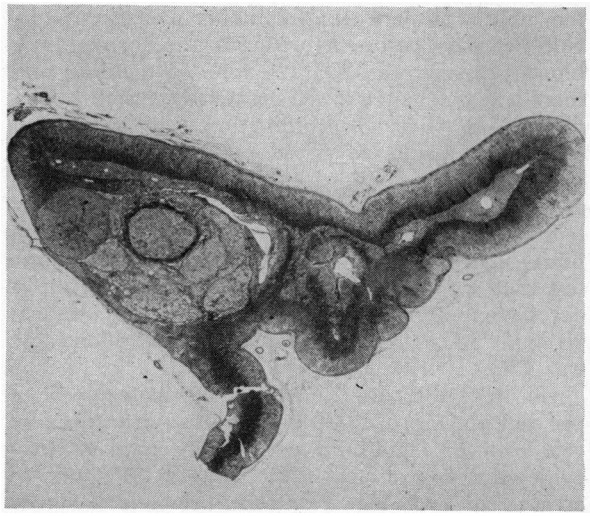

Figure 1.—Section of tumor in Case 1, showing encasement in fibrous capsule. (× 1.5)

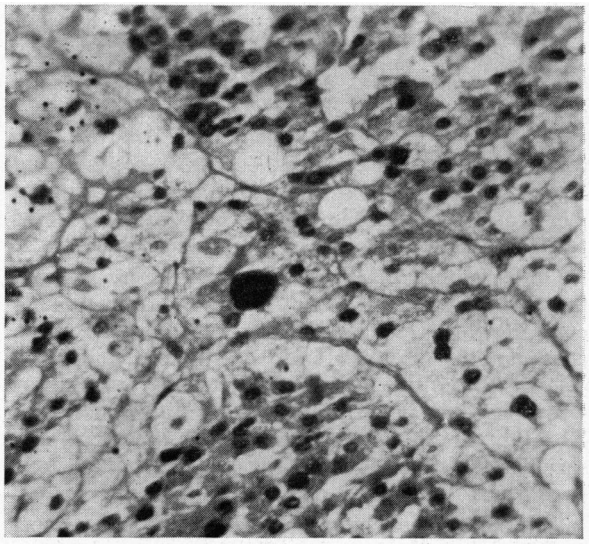

Figure 2. — Photomicrograph of section of tumor in Case 1. The cells resembled those of zona fasciculata in normal gland. (× 200)

DISCUSSION

The clinical manifestations in these two patients were almost identical and were remarkably similar to those in the case reported by Conn. Both complained of headache, dry mouth, episodes of weakness, and polyuria. One patient had no edema, the other had minimal edema of the ankles at the end of the day. Both had hypertension with systolic pressures around 200 mm. of mercury. Serum potassium levels ranged from 2 to 3 mEq. per liter with an occasional finding higher. Serum sodium determinations were in the upper normal range or slightly higher. The urine volume was increased and the specific gravity was low in both, but in the first

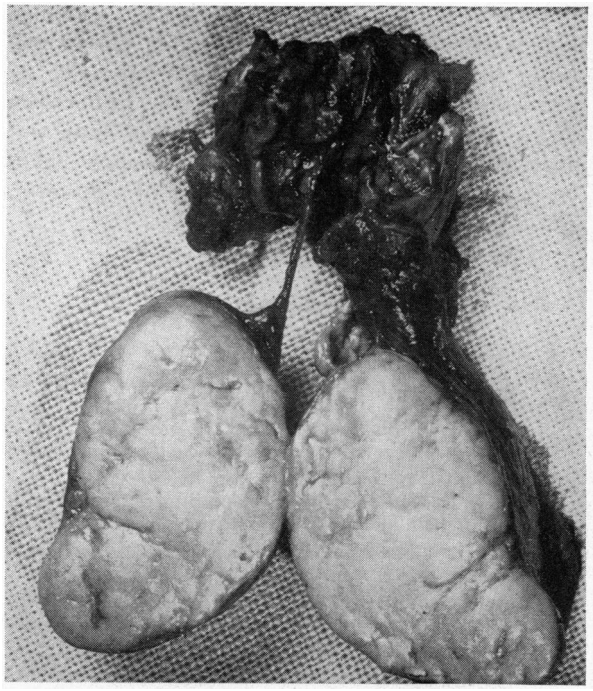

Figure 3.—Sectioned surfaces of tumor in Case 2 showing thin-walled capsule and attachment to adrenal gland by narrow pedicle. (× 1.5)

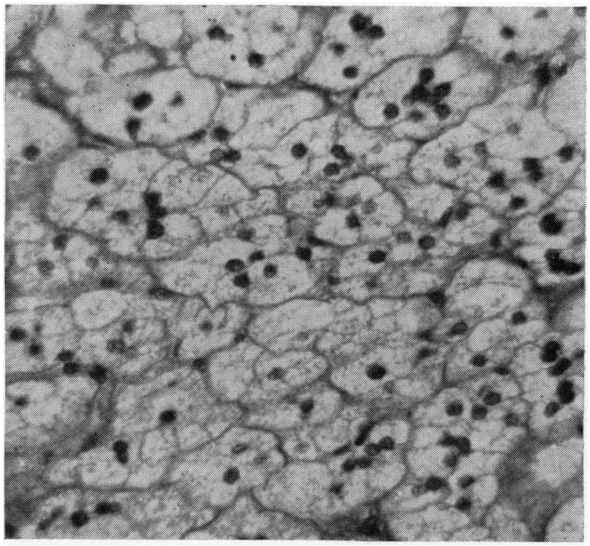

Figure 4. — Photomicrograph of section of tumor in Case 2. Cells bore striking resemblance to those seen in zona fasciculata. (× 200)

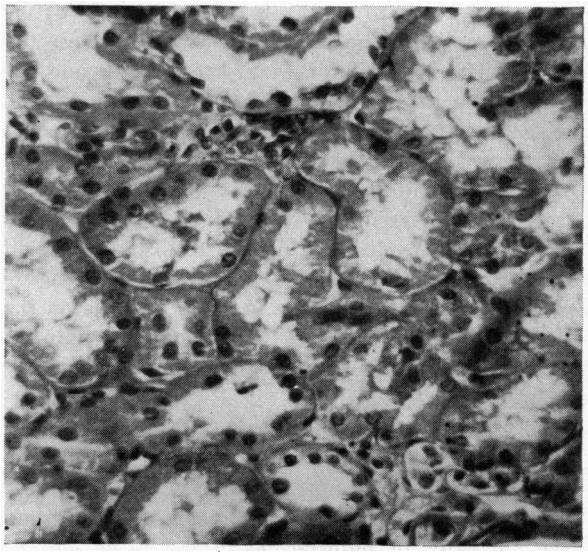

Figure 5.—Photomicrograph of biopsy specimen taken from left kidney in Case 2. (× 200)

case the specific gravity responded normally to the concentration test. In the second case the maximum specific gravity was 1.012 in the concentration test. The uropepsin excretion rate was increased in the first case, but in the second was normal on the first occasion and increased in a later test. There was metabolic alkalosis in the first case but not in the second.

Under corticotropin stimulation the excretion of 17-ketogenic steroids was increased. There was also a normal response in the total eosinophil count. The aldosterone excretion was not determined in the first case. Bioassay of urinary sodium retaining corticoids was done twice on the second patient. The first result was near the upper limit of normal, the second nearly twice normal.

Determinations of total body sodium and potassium were done only in the second case. There was a definite increase in exchangeable body sodium and a decrease in exchangeable body potassium. There was also a lowering of the sodium-potassium ratio in the saliva and sweat. There was an increase in sodium and a decrease in potassium in the muscle.

The prompt return to normal of all the clinical manifestations and laboratory findings following removal of the tumors indicates that these tumors were producing a hormone which was the cause of the disturbances.

The tumor in the first case was 1 cm. in diameter, embedded within the adrenal gland and was well defined by a fibrous capsule. Arranged in small groups and columns, the cells were large with clear cytoplasm and distinct boundaries. They had dark nuclei which varied considerably in size. The cells resembled most closely those of the zona fasciculata of the normal adrenal gland (Figures 1 and 2).

The tumor in the second case was 3 cm. in diameter and was attached to the adrenal by a narrow pedicle. It was covered by a thin capsule. The cut surface was yellow. The tumor cells were arranged in small groups separated by narrow fibrous septa. It was composed of large polyhedral cells with well

defined cell boundaries. The cytoplasm was clear with large vacuoles. The nuclei were small and very uniform in size and staining characteristics. These cells bore a striking resemblance to those seen in the zona fasciculata (Figures 3 and 4). Figure 5 is a photomicrograph of the biopsy specimen from the left kidney in Case 2.

Patients with symptoms of hypertension, muscle weakness, thirst and polyuria should be studied with special attention to mineral metabolism. Clinical laboratories are generally equipped to make determinations of sodium and potassium on blood serum, urine, sweat and saliva. Serum calcium should be determined to differentiate weakness due to hypercalcemia. Tests for alkalosis should include carbon dioxide combining power and pH of arterial blood. To exclude respiratory alkalosis, alveolar carbon dioxide should be determined at the moment the arterial blood is drawn for the pH determination. Alveolar carbon dioxide can be easily determined with the infrared carbon dioxide analyzer which is available in pulmonary function laboratories.

It is desirable to check on other functions of the adrenal gland in the laboratory study of these patients. Urinary excretion of 17-ketosteroids and 11-oxysteroids and total eosinophil counts should be determined before and during the administration of 50 mg. of corticotropin twice a day for five days. All urine should be collected for the 24-hour period preceding the administration of corticotropin and each 24-hour period during the test. There should be a drop in the eosinophil count within four hours and a pronounced increase in these steroids on the fifth or sixth day after starting the corticotropin. In aldosteronism, pronounced diuresis of sodium may occur.

To rule out a pheochromocytoma as the cause of the hypertension, phentolamine, piperoxan hydrochloride and sodium amytal tests may be helpful.

For confirmation of the diagnosis of aldosteronism, bioassay of aldosterone in the urine can be done. It may be necessary to repeat this test if the first result falls in the normal range. The exchangeable body sodium and potassium can be determined, using radioactive sodium and potassium salts. An increase in the excretion of aldosterone in the urine and an increase in exchangeable body sodium with a decrease in exchangeable body potassium should be demonstrated before a diagnosis of aldosteronism is considered confirmed.

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