Management of Primary Aldosteronism:

Evaluation of Potassium and Sodium Balance, Technic of Adrenalectomy and Operative Results in 24 Cases

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PRIMARY aldosteronism was first described by Conn over a decade ago.[5] Since then its protean manifestations have become well known, and much effort has been directed toward improvement in the methods of diagnosis. Little information is available, however, to indicate the most effective methods of preoperative preparation, operative management and postoperative care of patients with primary aldosteronism. Experiences with 24 patients with primary aldosteronism form the basis for the recommendations made in this report.

Materials and Methods

Twenty-four patients were diagnosed as having primary aldosteronism on the basis of hypertension, hypervolemia and increased secretion of aldosterone. All but one of these patients had hypokalemia while eating a diet containing 110 mEq. sodium per 24 hours. The one exception was a patient similar to those cases reported by Conn and associates[10] who had normokalemic primary aldosteronism. Despite the frequency of abnormal carbohydrate metabolism in these patients with primary aldosteronism, diabetes was never the initial complaint for which treatment was sought.[7] Although primary aldosteronism has been reported to affect more women than men,[9] there were 12 males and 12 females in our series.

All preoperative measurements of aldosterone were made while the patient ingested a diet containing 110 mEq. sodium per 24 hours. During the first 3 to 4 postoperative days, only electrolyte-free fluids were given until the patient was able to resume taking the preoperative diet, in order to obtain comparable conditions for measurement of aldosterone. The amount of aldosterone in the urine was measured by the double isotope dilution technic of Kliman and Peterson.[12] Urinary Porter-Silber chromogens were measured to assess the rate of cortisol secretion.[15]

Urine was collected for 24-hours periods and was analyzed for sodium and potassium by internal standard flame photometry. Serum electrolytes were measured by the same technic at appropriate intervals. Total blood, red cell, and plasma volumes were determined by the use of Cr^{51}-tagged red blood cells and predicted values were based on height and weight.[17]

In six cases blood was drawn at operation from the adrenal vein that drained the gland which contained an adenoma, and

Presented before the American Surgical Association, March 23–25, 1966, Boca Raton, Fla.

Supported in part by the United States Public Health Service Grant AM-06415 from the National Institute of Arthritis and Metabolic Diseases.

the concentration of aldosterone was determined by the same method used for measurement of urinary aldosterone.

Three patients were studied intensively during the first 3 postoperative weeks after unilateral adrenalectomy for primary aldosteronism and at later times to ascertain responsiveness of the remaining adrenal gland to various stimuli, including: 1) restriction of the intake of sodium to 10 mEq. per 24 hours for 5 days; 2) infusion of corticotropin, 25 units, over an 8 hour period; and 3) infusion of valine-angiotensin II amide over a period of 6 hours at a rate that would maintain an increase in blood pressure of 30 mm. Hg. systolic and 20 mm. Hg. diastolic (1 to 5 mμ./Kg./mm.).[11]

Preparation for Operation

During the early portion of this study, six patients underwent operation without preoperative replenishment of potassium stores. Potassium depletion, as reflected by the serum potassium concentration (2.5 to 3.6 mEq./L.) was moderately severe. One of these patients, who had known cardiac disease and a previous history of myocardial infarction, had a brief period of severe bradycardia during induction of anesthesia but was promptly resuscitated. Operation was abandoned and potassium was replenished. A unilateral adrenal adenoma was later removed and the postoperative course was uneventful. No complications occurred in the other five patients. However, it seems evident that one of the prime risks in operations upon patients with primary aldosteronism is ventricular fibrillation or other arrhythmias that may result from potassium depletion. Weakness of the respiratory muscles and subsequent respiratory insufficiency may also occur if curare-like agents are used for relaxation.[18] Preoperative repletion of potassium is now regarded as one of the most important steps in the proper preparation of the patient. Correction of potassium deficits also alleviates many of the metabolic complications of primary aldosteronism, such as: 1) loss of renal conservation of water, 2) impairment of carbohydrate tolerance and 3) interference with normal baroreceptor activity.[2]

Spironolactone, 1 gram given in four divided doses daily for 3 days, rapidly returned the serum potassium to normal in two patients who later underwent successful removal of unilateral adenomas. The spironolactone was discontinued one week before operation, after which normal serum electrolyte levels were maintained by restriction of sodium and administration of potassium. While no untoward effects were observed from the use of spironolactone, and despite its recommended use by some,[13] we no longer prepare patients with this agent. Spironolactone has not been needed since we have adopted the regimen described below.

Fourteen patients were prepared for operation by restriction of sodium intake to 10 mEq. daily and by oral administration of 6 Gm. of potassium chloride daily. In all of the patients, serum potassium returned to normal within 7 days, and in many cases by 5 days (Fig. 1). Sodium restriction decreases the filtered load of sodium and the availability of sodium ions in the exchange mechanism of the distal renal tubule, thus minimizing the usually excessive renal losses of potassium in primary aldosteronism.[3] This regimen is our current method of choice because of its ease of applicability and its consistent reliability. Repletion of potassium occurs despite the known effect of sodium restriction in increasing aldosterone output by the normal adrenal gland and despite the effect of potassium on increasing the aldosterone secretion by a tumor. That elevation of aldosterone secretion *per se* is not harmful is confirmed by the fact that administration of 15 to 20 mg. of desoxycorticosterone acetate daily fails to change serum electrolyte concen-

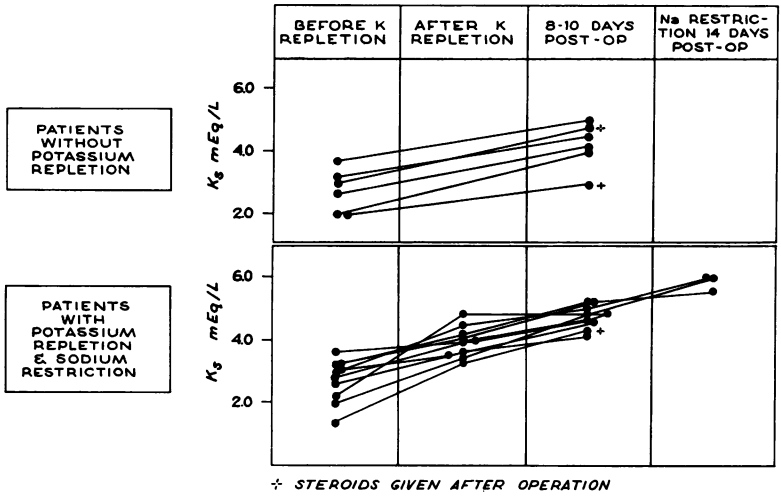

FIG. 1. Response of serum potassium to preoperative preparation and to surgical treatment of primary aldosteronism.

tration, urinary electrolyte excretion and blood pressure in patients with primary aldosteronism.[1]

Three patients were given hydrocortisone (300 mg.) beginning on the day of operation. Two of these patients had bilateral adrenalectomy and one had unilateral adrenalectomy. There is no valid reason to give steroids preoperatively since, should bilateral total adrenalectomy be necessary, steroids can be given intravenously in effective amounts while the patient is on the operating table.

The response of serum potassium to sodium restriction and potassium supplementation, and to the surgical treatment of primary aldosteronism, is demonstrated in Figure 1. Serum potassium concentration returned to or remained at normal levels by the eighth to tenth postoperative day whether or not the lowered body stores of potassium had been restored preoperatively. However, during the first 3 to 4 postoperative days, when only electrolyte-free solutions were given, serum potassium fell from 0.4 to 1.0 mEq./L. in ten patients without disturbances of cardiac rhythm. A decrease in serum potassium of this magnitude is of particular importance in patients in whom potassium is not replaced preoperatively; in two such patients the serum fell to below 2 mEq./L. Large doses of potassium, up to 100 mEq. daily, were required to combat these dangerously low levels of serum potassium. Thus, potassium repletion may provide some additional protection in the postoperative period.

Diuretic agents should always be withheld preoperatively since they accentuate the already profound urinary losses of potassium. Antihypertensive medications were discontinued in all patients for at least one month before operation and no untoward effects were observed. Furthermore, since antihypertensive agents may occasionally be associated with profound hypotension during anesthesia, they should not be given in the immediate preoperative period.

Operation

Operative Findings. The relationship bebetween the weight of the adrenal tumor and preoperative excretion of aldosterone are shown in Table 1. There was no significant tendency for adenomas to occur on one side, although in much larger series the tumors were found twice as often on the left side.[9] Especially important from the standpoint of the surgeon, however, is

TABLE 1. *Correlation of Pathologic Findings and Aldosterone Excretion in 20 Patients with Primary Aldosteronism*

	Side of Tumor	Weight of Tumor (*Gm.*)	Weight of Remainder of Adrenal (*Gm.*)	Size of Adenoma (*cm.*)	Aldosterone Excretion (*μg./24 hr.*)
Unilateral adenoma					
I. M.	right	4.5	7.5	—	28
R. Y.	right	2.0	7.0	2 × 1.3 × 0.8	26
L. B.	right	8.4	7.6	—	30
C. T.	left	5.0	6.0	1.7	38
M. P.	left	9.8	7.0	3.5	43
C. H.	left	1.7	7.0	1.5	95
R. T.	left	4.5	13.0	—	40
R. G.	left	4.8	6.4	—	57
M. J.	left	2.3	3.7	2 × 2.3 × 1	55
M. S.	left	13.0	5.0	3.2 × 2.5 × 1.5	30
R. H.	left	1.2	14.5	1.2	35
N. G.	right	6.5	13.0	2.5	33
P. C.	right	6.0	—	4.0	35
M. K.	right	3.5	—	2.3 × 2.1 × 1.5	68
R. H.	left	0.5	5.0	0.6	30
Hyperplasia and adenoma					
V. M.	right	7.0	9.0	1.8 × 1.5 × 1	60
	left	—	16.0	two 5 mm. nodules one 1 cm. nodule	
Hyperplasia					
S. J.	right	17.2	—	—	53
	left	17.5	—	—	
R. V.	right	11.0 Total resection	—	—	38
	left	9.5 Subtotal resection	—	—	
G. W.	right gland removed	13.3	—	4 mm. nodule	28
Normal adrenal					
L. H.	left gland removed	6.5	—	several 2–3 mm. nodules	28

the fact that in our patients 70 per cent of the lesions were less than 3 cm., as has been found in other series.[9]

Contrary to expectation and despite suggestions in the literature,[14] we found no correlation between the *size of the lesion* and the severity of the aldosteronism as measured by the urinary excretion of aldosterone (Table 1). Nor was there any correlation between the *severity of the hypertension* or electrolyte abnormalities and the amount of urinary excretion of aldosterone. We did not find that atrophy of the contralateral adrenal gland was sufficiently obvious at operation to warrant practical use of this finding by the surgeon, although atrophy of the uninvolved adrenal gland has been reported.[14] Consonant with these observations is that the adrenal gland adjacent to the tumor was of normal weight except in patient M. J., an Indonesian (Table 1). Persons of Asiatic origin normally have adrenal glands of small size. In three patients the contiguous adrenal gland was enlarged (R. T., R. H., N. G.). Of interest is that all three had had vigorous treatment for hypertension for 5 to 15 years and had cardiac decompensation. The pa-

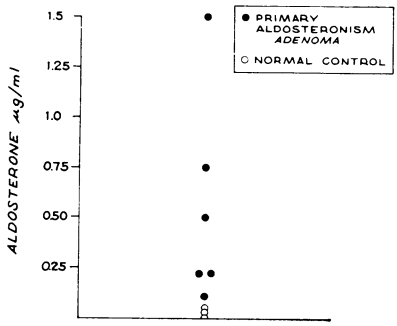

FIG. 2. Concentration of aldosterone in adrenal vein plasma. Comparison of six patients with primary aldosteronism caused by adenoma and three patients without aldosteronism.

tient with an adrenal gland or normal weight (L. H.) had only a few small cortical nodules but no obvious adenoma.

In one distressing case, a slightly larger than normal right adrenal gland was removed first after both glands had been thoroughly mobilized, inspected and palpated. The right adrenal gland proved to be normal and only when the entire left adrenal gland had been removed and thoroughly sectioned could a small encapsulated adenoma be found. In two other cases the adenoma could be seen on the posterior surface only after complete mobilization of the adrenal gland, yet the tumors could not be palpated. These experiences led to an investigation of possible methods for better preoperative localization of the lesion.

The concentration of aldosterone in the adrenal vein blood draining the gland that contains an adenoma, and that in normal adrenal-vein plasma, is shown in Figure 2. In each case, the concentration of aldosterone was from two to 30 times greater than that found in the adrenal venous blood of three normal patients without primary aldosteronism. Unfortunately, instantaneous determination of aldosterone concentration at operation is impossible. However, since the uninvolved contralateral adrenal in the case of an adenoma invariably excretes practically no aldosterone (see below), selective catheterization of the left renal vein and inferior vena cava might be of value in helping to determine the site of the lesion under certain circumstances.

The surgeon who is operating on patients with primary aldosteronism must be prepared to deal not only with the solitary adenoma, but should also be aware of the possibility of multiple adenomata, carcinoma, and hyperplasia. In addition, normal adrenal glands have been found in this disease in as many as 6 per cent of the cases.[6] Primary aldosteronism resulting from adrenal cortical tissue in aberrant locations has not been reported, however. It is abundantly clear, therefore, that both adrenal glands must be thoroughly exposed, inspected and palpated. Exposure and inspection of only the anterior or posterior surface alone are not sufficient for proper evaluation since a small adenoma may readily escape detection. Both surfaces of each adrenal must be exposed, not only so that both aspects may be inspected, but also to permit bi-digital palpation.

Technic. We prefer the transabdominal approach and have used it in all our patients, usually through a bilateral subcostal type of incision, although in two patients with narrow costal angles, exploration was performed after a long midline incision was made. The right adrenal gland is exposed by excising a triangular flap of posterior parietal peritoneum at the extreme apex of the hepato-renal pouch of Morrison after the gallbladder is retracted cephalad and the duodenum caudally. A simple method of approach to the left adrenal gland consists of complete mobilization of the splenic flexure and left side of the transverse colon of the colon by division and ligation of the gastrocolic omentum and the splenocolic attachments. The inferior border of the body and tail of the pancreas is then readily visible even in

obese patients. Division of the thin avascular posterior peritoneal attachment of this inferior portion of the pancreas will allow mobilization of the pancreas superiorly and provides excellent exposure of the underlying left adrenal. This method of exposure obviates the necessity for mobilization of, and possible injury to, the spleen.

Beginning at the inferior border of each adrenal gland, the entire inferior, lateral, and superior margins are completely mobilized, and in addition, the posterior aspect of each gland is thoroughly exposed. This can only be carried out by meticulous ligation of each strand of tissue to the adrenal gland, usually with fine metallic clips. The hemostasis must be accurate and complete so that hematomata do not form and interfere with accurate assessment of the glands. After completion of the dissection, each adrenal should be attached only by its major vein and 4 to 5 mm. of tissue on either side of this vessel. Such extensive mobilization has not caused permanent adrenal insufficiency in our experience.

Further Considerations. Even if an obvious adenoma is found in the first gland to be inspected, the other adrenal gland must be thoroughly explored. Multiple adenomata have been found in as many as 15 per cent of the glands that have been removed.[6] We prefer total unilateral adrenalectomy to subtotal excision or simple excision of the obvious tumor in a patient with a single adenoma, especially because of the possibility of multiple lesions within the involved gland. None of our patients had carcinoma.

The most puzzling cases were the patients with either *hyperplastic or normal glands.* When a gland is clearly larger than normal (to make this judgment may take extensive experience in adrenal surgery), total adrenalectomy should be done. The specimen should be weighed and sectioned immediately; should the gland weigh more than normal or show cortical hyperplasia, the other gland should be removed *in toto.* Subtotal resection only subjects the patient to the possibility of recurrence of the aldosteronism should an excessive amount of tissue be left behind, or to the possibility of adrenal insufficiency in the face of stress, if not during normal activity. When no lesion is found in either gland, we prefer to remove the gland that seems somewhat larger or more suspect. If sectioning and weighing of this gland reveal hyperplasia, the contralateral adrenal is removed completely. If the first gland to be removed is of normal weight we prefer to leave the remaining normal-appearing gland in place, with the idea that removal of half of the bulk of adrenal tissue may ameliorate the aldosteronism. This procedure is certainly open to question and only further experience will prove its merit. Total adrenalectomy under these circumstances in a patient with clear-cut findings of primary aldosteronism could never be criticized, however. We chose this method because it conserves adrenal tissue and because the remaining gland can always be removed at a later date. Multiple subtotal resection of the adrenal glands has been advocated when an adenoma cannot be found and the adrenal appears to be normal.[14] We have found this procedure to be unsatisfactory because bleeding is difficult to control from the remnant of the adrenal gland, intraglandular hematoma is common, and even if one adenoma is found, others may also be present.

Wedge biopsies of the kidneys should be obtained under direct vision with good hemostasis in patients with either normal or hyperplastic adrenal glands to ascertain the status of the juxtaglomerular apparatus. The only death in this series occurred after uncontrollable renal hemorrhage from a needle biopsy of the kidney performed under direct vision at operation. Unfortu-

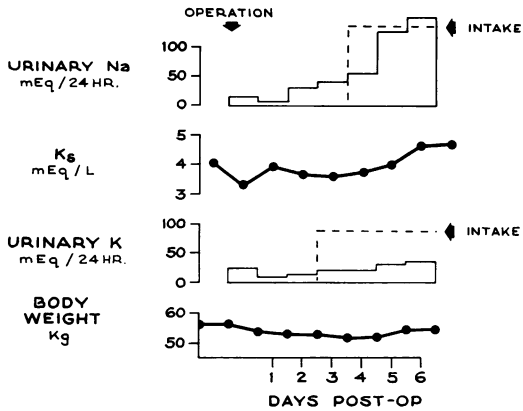

FIG. 3. Sodium and potassium balance during the first week after removal of a unilateral adenoma for primary aldosteronism. (Patient P. C.)

nately, nephrectomy was performed too late to save the patient.

Bilateral posterior paravertebral incisions performed simultaneously by two teams with the patient in the prone position, may provide better exposure of the adrenal glands than a transabdominal approach, especially in an obese patient.[16] There is no quarrel with the surgeon who wishes to use the posterior approach so long as both glands are thoroughly mobilized and examined before any procedure is done to either one. Our preference for the abdominal incision stems from long experience with this approach when treating patients with far-advanced carcinoma of the breast. The single upper abdominal incision is comfortable and strong.

Postoperative Observations and Management

In all patients urinary aldosterone fell to less than 5 μg./24 hours and in many instances to less than 1 μg./24 hours during the first two postoperative weeks (normal 5 to 20 μg./24 hours). This decrease is even more remarkable considering that sodium intake was zero during the first four postoperative days, and this response can be considered confirmatory evidence of the diagnosis of primary aldosterone. Aldosterone secretion gradually returned to normal although in some instances severe reduction persisted for 7½ months. Urinary Porter-Silber chromogens (17 hydroxy corticoids) fell about one third for about a week but later returned to previous basal levels. No glucocorticoid deficiency was apparent. The patient with an adrenal of normal size, but with some nodularity of the cortex (Case L. H.) was indistinguishable postoperatively from the patients who had had unilateral adrenalectomy for adenoma. Although hypertension still persists in this patient 18 months postoperatively, it is less severe than before operation and is much more easily managed. Serum electrolytes have remained within the normal range without supportive therapy in this patient and aldosterone excretion has remained within normal limits. Only subsequent observation will reveal whether contralateral adrenalectomy will be necessary. Should this be required, our plan of unilateral adrenalectomy in such cases may need to be altered to total bilateral adrenalectomy. Although one patient (G. W.) had unilateral adrenalectomy for an enlarged adrenal and the remaining gland may be hyperplastic, his postoperative course was identical to that of patients with unilateral adenoma. His serum electrolytes and aldosterone excretion are normal and his hypertension is much less severe than it was preoperatively.

Sodium and potassium balance in two patients during the first postoperative week after removal of unilateral adenomas are shown in Figures 3, 4. Sodium and potassium conservation is apparent with little change in body weight. The explanation for the early sodium retention despite the virtual absence of aldosterone excretion by the remaining adrenal gland is not completely apparent. It is possible that the preoperative restriction of sodium in both patients may be partly responsible for this finding. A slight but definite fall in serum

potassium occurred immediately postoperatively in both patients.

Our investigations of contralateral adrenal function after unilateral adrenalectomy for adenoma were prompted by the development of profound mineralocorticoid deficiency with weight loss, extreme weakness, hypotension, marked natriuresis and potassium retention in one of our patients (N. G.) following sodium restriction during the second postoperative week. In two subsequent patients sodium restriction resulted in the same phenomena when carried out after the first postoperative week. Sodium restriction during the second postoperative week in these three patients caused a cumulative deficit of 250 to 350 mEq. of sodium in 3 to 4 days with the clinical findings noted above.

During the first month after unilateral adrenalectomy the remaining adrenal gland did not respond with an increase in secretion of aldosterone after stimulation by sodium restriction, ACTH or angiotensin infusion despite elevation of the Porter-Silber chromogens after ACTH (Fig. 5). Subsequently, however, the capacity to respond to these stimuli returned in several months.[4] In all instances, the addition and liberal use of sodium chloride in the diet was the only therapy necessary to prevent

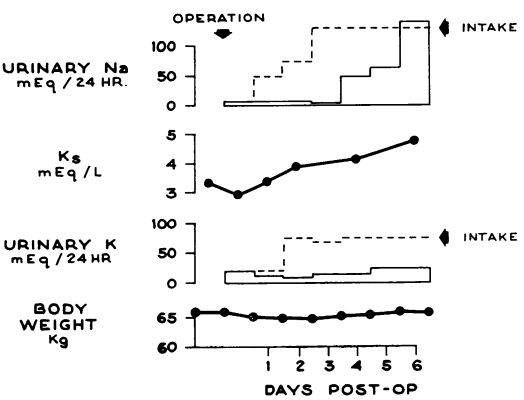

FIG. 4. Sodium and potassium balance during the first week after removal of a unilateral adenoma for primary aldosteronism. (Patient N. G.)

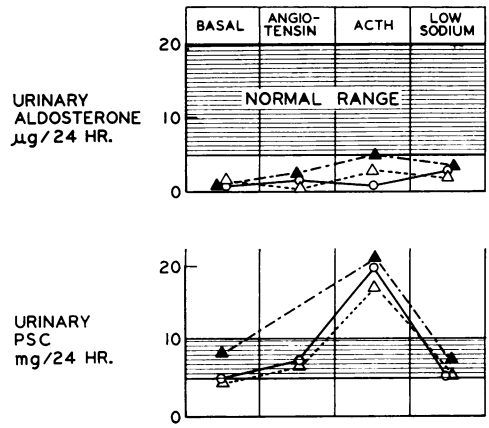

FIG. 5. Aldosterone and Porter-Silber chromogen excretion in three patients after unilateral adrenalectomy for adenoma causing primary aldosteronism. Basal excretion is compared with response to various stimuli.

the manifestations of mineralocorticoid deficiency.

Although postoperative restriction of sodium has been suggested in order to stimulate the production of renin, we believe this practice to be quite dangerous. Adrenal replacement therapy was required only in the two patients who had total adrenalectomy. Inability of the remaining adrenal gland to secrete aldosterone after unilateral adrenalectomy despite considerable stimulation is probably due to the fact that the chronic hypervolemia of primary aldosteronism suppresses the secretion of renin by the kidney. Increased pressor sensitivity to angiotensin observed in our patients postoperatively[4] supports the observation of others[8] that little or no renin is present in the peripheral plasma of patients with primary aldosteronism.

Results of Operation

Serum electrolytes returned to or stayed at normal levels in all patients. Blood pressure returned to normal by the fourth or sixth postoperative week although one patient did not become normotensive for a year. Even in the two patients whose blood pressure did not return to normal (Cases

G. W. and L. H.), hypertension was much more readily controlled with antihypertensive medication postoperatively than before.

Although it has been suggested that long-term spironolactone therapy be used instead of operation in patients with primary aldosteronism, we prefer the more lasting effects of surgical treatment, and supplemental medication is usually unnecessary. The rare occurrence of carcinoma as a cause of this syndrome provides another reason for the more definitive operative approach. Even though these patients usually do not have the malignant form of hypertension, the vascular sequelae of chronic hypertension and the increased susceptibility to renal infection should be corrected as quickly as possible.

Summary

Twenty-four patients with primary aldosteronism are reported. Preoperative correction of potassium depletion is mandatory and is best accomplished by combining sodium restriction with supplemental potassium intake. An extremely thorough exposure and evaluation of both adrenal glands is essential. Unilateral adrenalectomy is recommended for adenoma and bilateral total adrenalectomy for hyperplasia. After unilateral adrenalectomy for adenoma, sodium restriction is to be avoided because the remaining adrenal is unable to secrete aldosterone in response to this stimulus for at least one month and sometimes longer. Cortisol secretion of the remaining adrenal is normal after adrenalectomy for adenoma. Electrolyte abnormalities of primary aldosteronism are invariably corrected by surgical therapy and hypertension is relieved completely in 90 per cent of the patients.

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