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Selection of Patients and Operative Approach in Primary Aldosteronism

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A system for discriminating between adrenal adenoma and hyperplasia based on the levels of aldosterone production, plasma renin concentration, severity of electrolyte disturbances, plasma aldosterone patterns during recumbency and after assuming erect posture, and ^{131}I-19-iodocholesterol scan has been developed. Indicated for operation are patients with adenomas whose elevated blood pressure cannot be continuously controlled with usual doses of medication and patients with documented deterioration of target organ function. Adrenalectomy has been performed 83 times in 81 patients with a diagnosis of primary hyperaldosteronism. Results of excision of adrenal adenomas have been excellent with significant lowering of blood pressure in all cases and cure of hypertension in over 60%. Results of total or subtotal adrenalectomy for hyperplasia have been poor with almost all patients still requiring medication for hypertension. Adenomas have always been unilateral, and usually can be localized so that unilateral exploration is curative. Therefore, we have tried to distinguish preoperatively between adenoma and hyperplasia. Anterior transperitoneal adrenalectomy has been effective with few complications, and no postoperative hypocortisolism after unilateral adrenalectomy for adenoma. The unilateral extraperitoneal approach gives shorter morbidity and potentially fewer serious complications.

ALTHOUGH PRIMARY ALDOSTERONISM is a relatively rare disease, it is a significant cause of correctable hypertension, and therefore must be considered in the care of every patient treated for high blood pressure. Unfortunately, this disease takes many forms and only in primary aldosteronism due to adenoma, is surgical therapy truly effective in eliminating most or all manifestations of the disease. Therefore, after primary aldosteronism is diagnosed, a number of decisions remain before operation can be elected, and some decisions may remain to be made during the operative procedure.

We have studied over 115 patients with primary aldosteronism and have performed 83 operations on 81 patients during a 14-year period. The first 24 patients were previously reported to this Society by Silen and Associates in 1966.[13] Based on this experience we have formulated a system of categorization in which selection of patients for adrenalectomy is an important part.

For analytical purposes, we have categorized primary aldosteronism into five major categories: 1) Aldosterone-producing adenoma (APA); 2) Idiopathic aldosteronism due to bilateral adrenal hyperplasia (IHA); 3) Adrenocortical cancer; 4) Glucocorticoid-remediable aldosteronism, and 5) "interdeterminate aldosteronism," a group of patients whose signs, symptoms, and biochemical findings do not conform to any known category. Adrenal surgery has not been performed in these pa-

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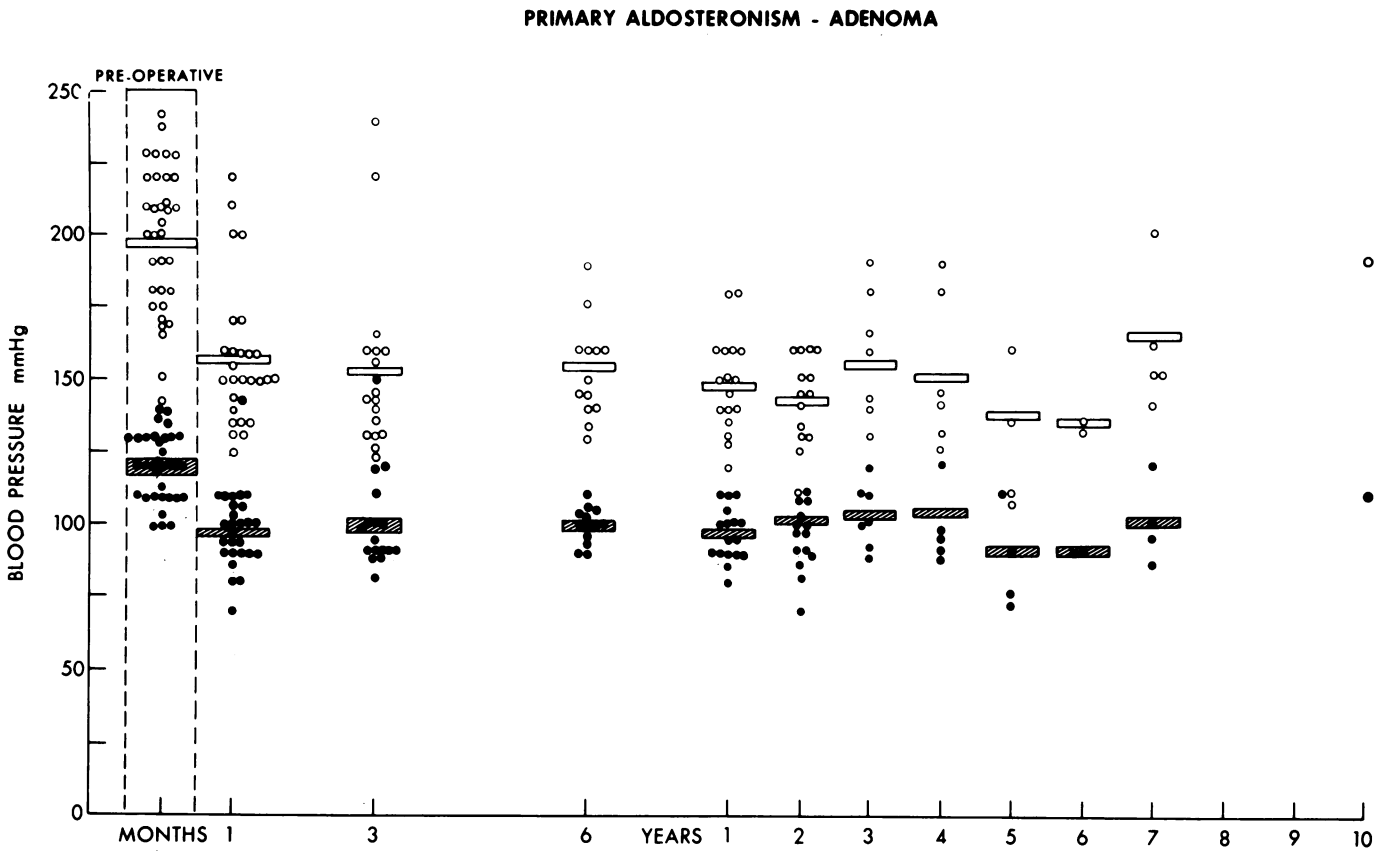

FIG. 1. Blood pressure response in patients followed for long periods after total or subtotal adrenalectomy for bilateral adrenal hyperplasia.

tients. Therefore, pathologic diagnosis is not available.

Extirpation of an APA will completely control the metabolic manifestations of aldosteronism, hypervolemia, potassium wasting, alkalosis, weakness, fatigue, and loss of sympathetic vasoactive reflexes. Hypertension is completely controlled in about 60% of patients and improved in the remaining 40% (Fig. 1).[4]

Unfortunately, patients who have had adrenal hyperplasia (IHA) have not responded well to adrenalectomy (Fig. 2). Control of the metabolic manifestations has often been achieved, but hypertension is rarely cured, and recurrence or persistence of metabolic alkalosis, sodium retention, and hypokalemia is frequent unless all or almost all adrenal tissue is removed. Therefore, we feel that it is not usually advisable to operate on patients with this form of the disease since operation, even total adrenalectomy, seldom offers a better quality of life than does medical therapy alone.[4,7]

Adrenocortical cancer manifesting itself as aldosteronism is rare and seldom surgically cured. It, too, has a wide spectrum of effects. We have experience with two such patients, and, fortunately, both are alive and essentially well at 2 and 9 years.

Treatment with cortisol completely cures the rare patient who has the glucocorticoid-sensitive form, and such patients never need operation.

Diagnosis and Categorization

The patient is diagnosed as having either primary or secondary aldosteronism by a series of tests including serum electrolyte concentration, urinary electrolyte excretion, urinary aldosterone excretion, plasma aldosterone concentration, plasma renin activity, and renal function tests. Chronic diuretic therapy and chronic licorice ingestion can mimic primary aldosteronism and must be avoided during this and subsequent phases of the investigation. A useful screening test is the measurement of serum and urinary potassium done while the patient has a normal or high sodium intake. This diet provokes hypokalemia in patients with primary aldosteronism. On rare occasions, aldosterone may have to be measured while the patient's serum postassium is relatively normal since potassium depletion can retard aldosterone production. If aldosterone concentration and excretion are elevated, 17 hydroxycorticosteroids are normal, plasma renin concentration is suppressed, potassium wasting is proved, and renal function is not severely impaired, primary aldosteronism is diagnosed.[2]

At this stage, the differentiation between IHA and APA can already be made with some accuracy. Quadric analysis of multiple variables[1] including aldosterone excretion level, serum potassium, plasma renin, hyper-

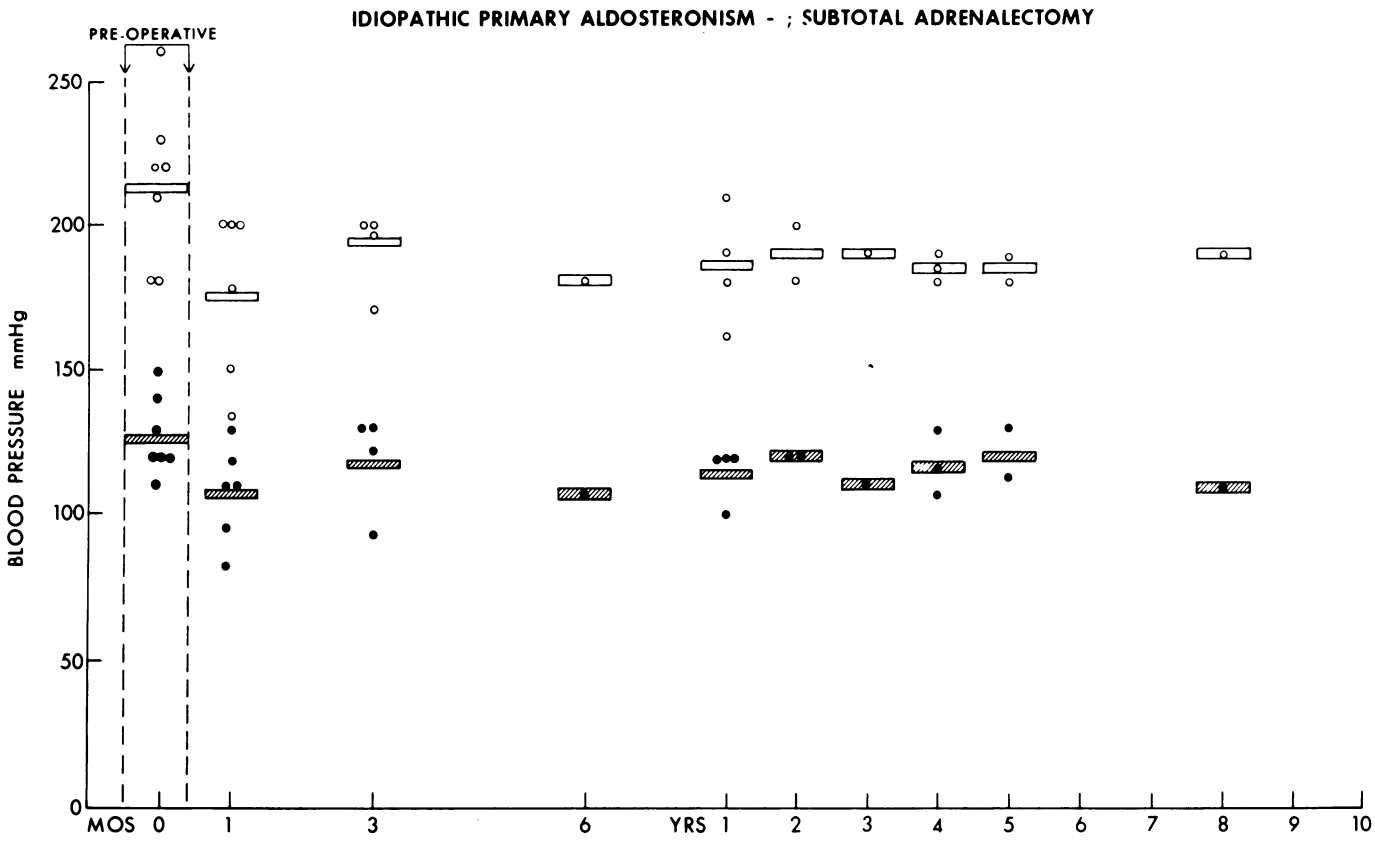

FIG. 2. Blood pressure response in patients after unilateral adrenalectomy for aldosterone-producing adenoma.

tension, age, and sex can be mathematically analyzed, and, in most cases, this analysis can distinguish between the two forms. Other forms of discriminants, such as linear discriminant analysis based on plasma renin concentration plotted against aldosterone excretion after DOCA treatment can be used.[3,5] In general, the more complete the syndrome, the more likely the patient is to have an APA.

Since none of the analyses of the total syndrome provide an exact differentiation between APA and IHA, we have sought more direct evidence to distinguish between the various forms. The introduction of tests based on diurnal variations of aldosterone production, and adrenal scanning with ^{131}I-19-iodocholesterol seem to have provided such evidence.[3,9]

In normal, recumbent patient the diurnal variation of aldosterone parallels that of cortisol, reaching a low in the evening and a high in the early morning. When the normal patient assumes the erect posture in the morning, however, plasma renin rises, followed by increased plasma aldosterone concentration. Aldosterone production in the patient with IHA is presumably still under the influence of renin since patients with IHA have normal diurnal variation during a 24-hour recumbent period, but their aldosterone level rises on standing. On the other hand, an APA has presumably become more autonomous, no longer responds to postural changes, but still follows the ACTH circadian rhythm. Patients with APA, therefore, have normal diurnal variation of plasma aldosterone while recumbent, but during standing the recumbent type of diurnal variation continues, and plasma aldosterone parallels cortisol concentration. As a result of these findings, plasma aldosterone concentration was measured after overnight recumbency and after 4 hours in upright posture in the 30 patients (Fig. 3). In the group of patients with APA whose aldosterone rose on standing, two of the "changes" were within the limits of error of the method, and two others (the largest changes) paralleled paradoxical changes of cortisol and thus were indeterminate tests. This test, therefore, is a most promising discriminator.[3]

Patients who have had adrenal carcinoma manifesting as hyperaldosteronism have had extremely high aldosterone secretion. One patient also had elevated cortisol and compound S. The other patient secretes only aldosterone at extremely high levels. Plasma aldosterone concentrations throughout the day are chaotic and without pattern in adrenocortical cancer.

If the patient has a well developed primary aldosteronism syndrome, and responds to the erect posture with a fall in plasma aldosterone, an APA can be diagnosed with high accuracy. In our patients, APA has al-

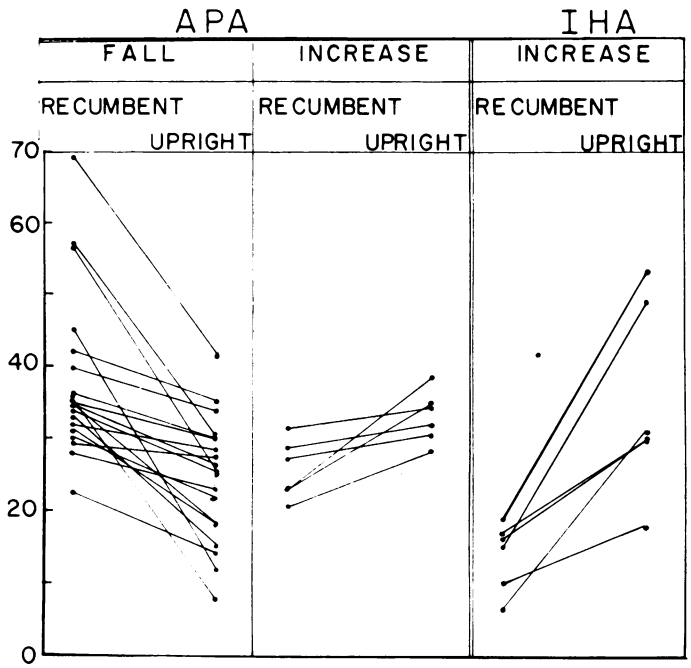

FIG. 3. Changes in plasma aldosterone during sustained erect posture after baseline early morning plasma aldosterone. See text for explanation of apparently anomalous results in center column. The two larger rises in APA cases both paralleled paradoxical elevations in cortisol and were thus nondeterminant.

ways been unilateral. Therefore, the next step is to localize the adenoma by performing a ^{131}I-19-iodocholesterol scan. This test has two functions: if the adenoma clearly localizes, not only is the diagnosis of adenoma confirmed, but the side for a unilateral operation is determined.[8]

Isotope studies have been performed on outpatients at the Donner Laboratory of the University of California in Berkley. Serial scintiphotographs of the adrenal area were obtained between the third and nineteenth days after injection (Fig. 4).

Thirty-one patients with suspected primary hyperaldosteronism were studied. Tracer lateralization was achieved in 10 patients, 8 of whom have been proved by operation to have adenoma on the predicted side. The two remaining patients have not yet had adrenalectomy. One patient who had equal, bilateral concentration of the isotope proved to have IHA. In the remaining patients (except the two with malignant disease) there was no lateralization, and no operation has been undertaken. The smallest adenoma diagnosed was 0.9 cm in diameter and became apparent only by computer analysis when scanning was continued through the nineteenth day. Smaller adenomas, therefore, may be difficult to localize.

Two patients, who were already thought to have carcinoma, had more difficult scans to interpret. One patient, whose tumor produced solely aldosterone, concentrated isotope on one side only and proved to have adrenal carcinoma on the side showing no function. The other patient, who secreted cortisol, compound S, and aldosterone, had an atrophic gland on the other side and visualized neither gland on scan. Both patients were explored through the abdomen and both sides were inspected for verification of diagnosis.

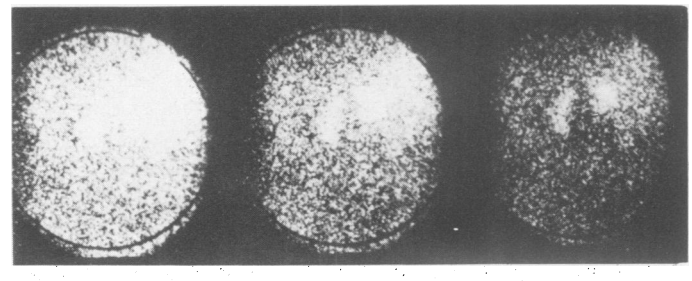

FIG. 4. ^{131}I-19-iodocholesteral scan showing adenoma in the right adrenal.

Adrenal venous catheterization with measurement of plasma aldosterone and cortisol is sometimes helpful. This technique has not usually been effective in our hands, because we are only infrequently able to catheterize both adrenal veins. If an APA is present, cortisol will be synthesized by both glands, and adrenal venous effluent cortisol concentration will be about the same on both sides. A step-up of three times the systemic aldosterone on one side localizes the APA. If only one vein can be catheterized, and the diagnosis of adenoma is not secure, a "step-up" on the one side catheterized can be misleading because it is consistent with aldosterone production from a hyperplastic adrenal gland. Our single operation in recent years for hyperplasia was occasioned by undue reliance on a catheterization of only one adrenal vein and insufficient reliance on a non-lateralizing adrenal scan. In this case, a recumbent-erect, diurnal variation study was, unfortunately, not done.

During adrenal venous catheterization, venography can be done in the hope of outlining an adenoma. Unfortunately, adrenal veins are easily ruptured, and destruction of normal adrenals has been reported.[6] We find this technique unduly complex and dangerous and have not performed it since iodocholesterol scanning has become possible.

Patients placed in the indeterminate group undergo periodic testing and medical therapy until they clearly fall into a determinate group. This risks an occasional complication of hypertension, but tends to reduce the risk of ineffective operation on adrenal hyperplasia. These patients as a group have responded well to spironolactone therapy, and operation has rarely been elected.

Indications for Operation

Adrenalectomy is not always required even when APA is unequivocally diagnosed. During the testing program, most patients have been given spironolactone. If a dose

of less than 150 mg/day completely controls hypertension, the metabolic syndrome, and the symptoms of fatigue, carpopedal spasms, and nocturia, adrenalectomy is not usually elected since side effects of spironolactone are rare at this dose level. Severe side effects may preclude this form of treatment. The response to spironolactone rather accurately has predicted the response to adrenalectomy for APA. Patients electing nonoperative management must be periodically re-evaluated. Any change in target organ function or difficulties in controlling blood pressure indicates adrenalectomy. Patients who obviously present a surgical risk are held longer on medical management. Young patients are encouraged to have the operation early.

An occasional patient from the interdeterminate or the IHA groups may be selected for operation because of the severity of his or her disease. We have undertaken such operations reluctantly, but despite the lack of effect on blood pressure, some patients have noted relief of hypokalemia and significant decrease in fatigue which is the paramount symptom of significant hyperaldosteronism.

Preoperative Preparation

The major objective of preoperative preparation is to have the patient normokalemic during operation. Most of our patients have been treated with antihypertensives up to several weeks before operation. However, if the patient has been severely hypertensive, we have continued alpha methyl DOPA up to the day of operation. Patients who are hypokalemic are admitted several days in advance and are treated with sodium restriction (up to 20 mEq/day) and potassium repletion up to 6-8 gm KCL/day in addition to diet. A positive potassium balance is achieved, but it is seldom possible or necessary to replete the total body potassium deficit.

More recently, patients have been treated up to the time of operation with spironolactone. In 10 such patients, we have found this an acceptable, sometimes preferable, alternative. It is important to understand, however, that the patients' postoperative needs have varied significantly according to the preoperative preparation (see /Postoperative Care).

Operative Approach

During the first years of our experience, we almost routinely approached the adrenals transperitoneally through an anterior bilateral subcostal incision. The left gland was approached using the "transligamentous" dissection in which the gastrocolic ligament is divided and the pancreas is mobilized anteriorly and superiorly by incising the posterior peritoneum at its inferior edge. This leads the dissection to the anterior surface of the left adrenal and tends to prevent damage to the spleen and splenic vein. Both adrenals were routinely exposed, and the diagnosis of IHA or APA made on inspection of both adrenals. With some experience, this is surprisingly easy to do. In fact, it is often easy to determine which gland contains an APA even before the adenoma can be seen or felt since in our experience, half of the glands containing an adenoma are also visibly hyperplastic while the contralateral gland is normal (see Pathology).

TABLE 1. *Operative Complications of 59 Operations Done Since 1965*

	Anterior transabdominal (42)	Posterior or flank (17)
Venous injuries	2	0
Pancreatitis	0	0
Splenic Injury	1	0
Liver Injuries	0	0
Wound Infection	1	0
Wound Hematoma	1	2
Pneumothorax	0	0
Atelectasis-minor	Frequent	Frequent
Atelectasis-lobar	0	0
Pneumonia	0	0
Pulmonary Embolism	0	?1
Hernia	0	0

Before the decision is made to remove adrenal tissue, both glands must be inspected carefully. The anterior and posterior surfaces should be freed of surrounding tissue, from the upper to the lower pole, and the medial surfaces partially freed. We have routinely practiced this extensive exposure; yet, we have had no remaining single adrenal gland fail to function adequately. The dissection is done with use of fine metal clips and electrocautery. The adrenal gland must never be grasped with instruments. If it is, a medullary hematoma will develop and confuse the identification of adenomas. If a hematoma does confuse the evaluation, it can be evacuated safely by piercing the cortex with a knife.

Three patients were surgically re-explored because previous surgeons at adrenal exploration failed to recognize the pathology. One patient had bilateral hyperplasia and two had undiscovered adenomas in the upper pole of the right gland, the most difficult area of adrenal gland to expose.

Despite the apparent magnitude of the transperitoneal procedure, it has been extremely safe in our hands. Operative complications are listed in Table 1. There has been only one death in this series. This occurred in the early 1960's in one of the first patients to be operated upon and death was the consequence of postoperative bleeding at a renal biopsy site. Renal biopsies are no longer done except on special indication, and the succeeding 80 patients have been operated upon without mortality.

Since 1965, every operation has been done or super-

vised by one of the authors (T.K.H.) and complications are shown in Table 1.

Both venous injuries incurred in the anterior approach were caused by too vigorous retraction of tissues. One was avulsion of the inferior mesenteric vein from the splenic vein and one a partial tear of the right venal vein from the vena cava. Both were easily repaired.

The postoperative course was medically complicated by significant cardiac arrhythmias in two patients (one of whom had transient severe hypertension and oliguria) who had severe hypertensive cardiovascular disease preoperatively, and had relatively low K^+ at operation. Early in our experience, when we overestimated intraoperative fluid needs, bladder catheterization was often necessary. Now that fluid replacement is kept below about 1 liter, catheterization is rarely necessary.

In the last few years, localization of the APA has been accurate enough to allow the use of a unilateral posterior approach in many patients. Our method has been essentially that of Young.[10] In this approach, the 12th rib is resected after the paraspinous muscles are retracted medially, and the pleural reflection is identified by having the anesthesiologist give a large inspiration. The insertion of the diaphragm to the periosteum of the rib is identified and detached. The pleural space is occasionally entered, but the hole is easily sutured at the end of the operation with a small suction catheter in place. The catheter is then removed. No pneumothoraces requiring further treatment have resulted. Gerota's fascia is then incised and the adrenal gland is identified. A hip rest which allows the abdominal wall to fall freely downward is extremely helpful both to the surgeon and the anesthesiologist.

The posterior approach is better tolerated by the patient, as three patients who have had both types of operations have testified. Patients, in general, have eaten and ambulated freely about 2 days earlier after unilateral posterior operation.

One patient who was 6 feet 5 inches tall, and weighed over 300 pounds, was operated upon by a flank approach for removal of a right-sided adenoma.

Postoperative Care

It is rarely necessary to give blood during either operative approach. Only 5 patients received blood. A total of 8 units were given. Three were used in a bilateral reexploration. The average intraoperative fluid need is about 1 liter which is usually given as Ringer's solution.

Fluid needs after operation vary with the type of preoperative preparation. If the patient has been prepared without antihypertensives and with sodium restriction and potassium repletion, he is given 5% dextrose and water at an average of 2500 cc/day. No saline or potassium is given unless it is specifically indicated by clinical signs of poor perfusion, hypotension, excessive weight loss, or excessive postural hypotension. Patients prepared up to operation with spironolactone often required saline intraoperatively and postoperatively. This is rational since the spironolactone has reduced the hypervolemia of untreated aldosteronism, especially when an APA is the cause.[11]

No cortisol is given unless the patient has had a total or subtotal adrenalectomy. Bilateral adrenal exploration with the removal of one adrenal with an APA has not once required the use of cortisol in our practice. One patient with adrenal cancer producing excesses of both aldosterone and cortisol required cortisol postoperatively until the remaining, visibly atrophic, adrenal recovered its function.

Antihypertensives are rarely required postoperatively and are not routinely continued. Most patients with APA show a definite lowering of blood pressure within a week of operation, but the full effect of adrenalectomy is often not complete for several months (Fig. 1).

We have measured aldosterone postoperatively in most cases.[4] It usually falls almost to zero when an APA is removed. About 10% of patients who have a very low aldosterone postoperatively will continue to lose weight. If the serum K^+ rises to above normal range, and if postural hypertension and continued weight loss develop, sodium chloride is added to the diet, since the hypovolemia does not usually become troublesome until after the patient is eating. If the added salt is sufficient to reverse this syndrome, fludrocortisone is given. Nine patients transiently have required postoperative fludrocortisone support for a few weeks, but four patients who had a very long history of hypertension still require it years later.

Pathology and Choice of Operation

Sixty-two of the 81 patients had unilateral adenomas. Eleven patients had bilateral hyperplasia without a dominant adenoma. Current controversies exist in other fields of endocrine surgery about the vague distinctions between hyperplasia and adenoma. There are analogous features in hyperaldosteronism. Four patients had bilateral hyperplasia with an obvious encapsulated adenoma in one gland. Twenty-one of 43 patients with dominant unilateral adenomas operated upon since 1965 have had clear evidence of hyperplasia as well as adenomas in the involved gland. Biopsies as well as inspection of the contralateral gland in 5 of these cases showed no visible or microscopic evidence of hyperplasia. The significance of this relationship between hyperplasia and adenoma in the same gland is unknown. This relationship probably accounts for a number of case reports of multiple adenomas in the same gland since hyperplasia often takes the form of multiple small nodules. The confusion atten-

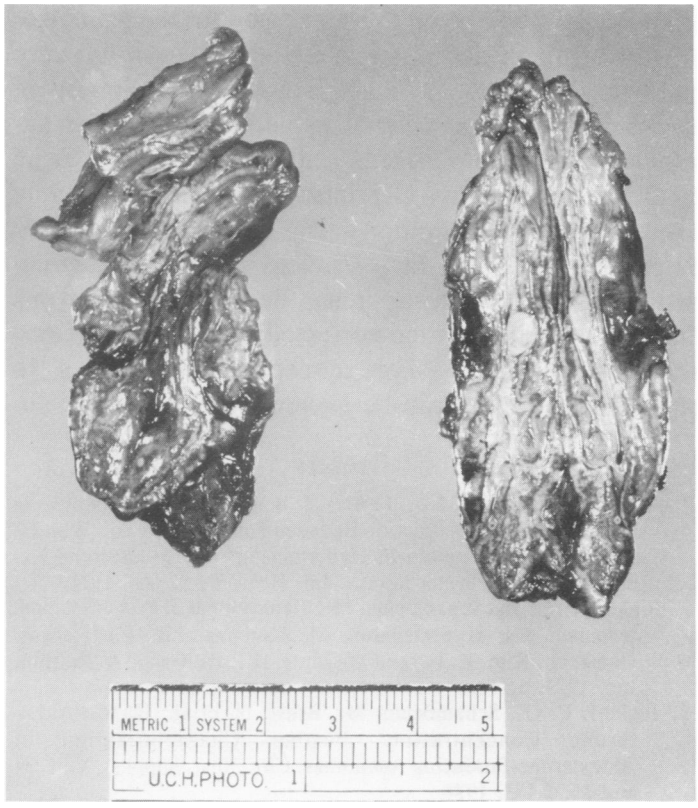

FIG. 5. Adrenal with florid hyperplasia. The other adrenal in this patient was similarly involved.

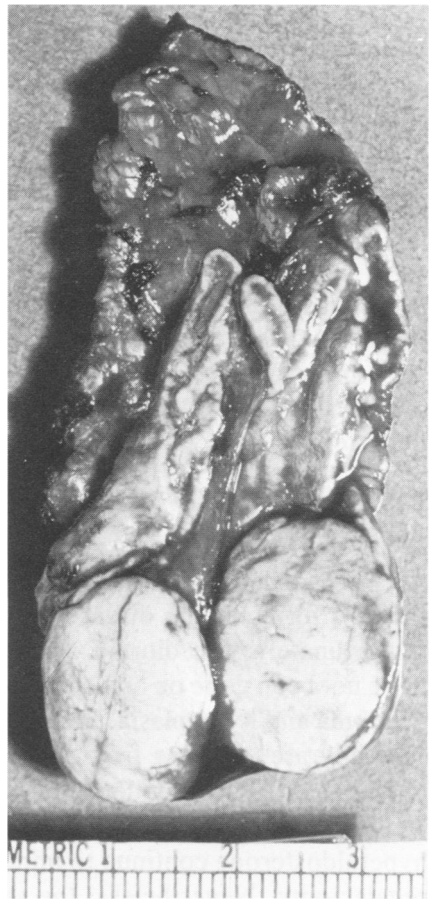

FIG. 6. Adrenal adenoma. Note the hyperplastic nodulation of the remainder of the gland.

dent upon the diagnosis of hyperplasia may also account for some cases of bilateral adenomas since hyperplastic nodules can brow as large as 5 mm (Figs. 5 and 6).

Because hyperplasia and adenoma often coexist, we would caution against partial adrenalectomy to remove adenomas since this may leave hyperplastic adrenal tissue in place. However, whether such tissue would actually have functional significance is unknown.

These observations also call into question the practice of unilateral adrenal exploration. Preoperative diagnosis is now so accurate that we expect to find pathology in every unilateral exploration, but there is then no way to visually assess the other gland. Retrospective analysis of unilateral adrenalectomy done for bilateral hyperplasia (4 patients) shows clearly that unilateral adrenalectomy is not as good therapy for IHA as is subtotal (80%) or total adrenalectomy (10 patients). However, only a few patients have been so treated. Four of our patients have had bilateral hyperplasia with adrenal adenoma on one side. Unilateral exploration therefore poses a risk that a hyperplastic adrenal may be left behind. This is not necessarily, however, a severe problem since the chance of curing such a patient, even with total adrenalectomy, is relatively small, and a second operation can be elected if further study shows continued disease and further target organ deterioration occurs. When an adrenal remnant is preserved, it is far preferable to have the remnant on the left since reoperations on the right gland are hazardous because the remnant adheres to the vena cava.

The total evidence suggests that posterior unilateral exploration is the procedure of choice for a patient who has a high probability of unilateral adenoma based on the various discriminants between APA and IHA and with unequivocal localization with iodocholesterol scan and/or complete bilateral adrenal vein catheterization data. When doubt exists, the bilateral approach, while a larger operation, is safe and potentially more effective.

The left adrenal is involved in 60% of patients, and women continue to outnumber men with primary aldosteronism (3 to 2). There continues to be no association between the size of the adenoma and the severity of the disease. There seems to be no relation between this disease and the multiple endocrine disorders. One patient, after adrenalectomy, was found to have a parathyroid adenoma. No other patients with multiple endocrine adenomas have been found.

The two patients with adrenocortical cancer were correctly diagnosed preoperatively. One patient, a 32-year-old woman with a large (15 cm in diameter) malignancy which secreted aldosterone, cortisol, and compound S has, by previous experience of others, a poor prognosis. Nevertheless, she remains well at 2 years on no medical therapy. The other patient, a 58-year-old woman, has an aldosterone-secreting tumor of low malignant potential which has been present for 9 years. Her extremely high

aldosterone excretion halved when we removed about half of her widely scattered tumor nodules. Her symptoms are now relatively well controlled on spironolactone.

Two patients had apparently normal adrenals removed. One was operated upon early in the series when assay techniques were not as accurate as they are now. The other was operated upon a year before plasma renin activity assay became available. Retesting of this patient when the assay became available showed an extremely high plasma renin and a renin-secreting tumor was localized in the right kidney and removed with cure of his hypertension.[12]

Discussion

There is, as yet, no explanation of why adrenal hyperplasia behaves differently than adenoma or whether the two forms of the disease are even causally related. Unfortunately, the diurnal variation and postural tests have not been done on any of the 4 patients who had both adenoma and hyperplasia. We assume that these patients basically are suffering from bilateral hyperplasia.

The accumulated evidence of most reported series indicates that efforts to discriminate among the types of hyperaldosterone continue to improve the efficacy of adrenalectomy. Nevertheless, the safety of operative procedures in experienced hands contraindicates excessive efforts to avoid operation.

There seems relatively little difference in safety between the anterior, lateral, and posterior operative approaches. Each has its indications. The anterior approach in which both glands can be seen easily is particularly helpful in patients with suspected IHA, indeterminate primary aldosteronism, and patients with cancer. The surgeon who deals with this disease should be familiar with all three approaches to the adrenals. This is especially important when reoperations in the adrenal area are contemplated as was the case in three of our patients. These operations have been facilitated by using an approach opposite to the previous one so that the adrenals can be reached through unscarred tissue.

As our experience has developed, and testing procedures have become more sophisticated, the efficiency and safety of adrenalectomy has increased. It seems possible to approach the ultimate cooperation between endocrinologist and surgeon: perfection in diagnosis, absolute localization of disease, and surgery with minimal complications, no mortality, and excellent results. It is tempting for the surgeon to claim credit for the paucity of operative complications in this series. However, it is very plain that some of the major reasons why surgery of aldosteronism is far safer than adrenalectomy for advanced cancer or Cushing's disease is because the metabolic abnormality of primary aldosteronism can be overcome prior to operation and associated problems can be minimized. When the physiology of the operated patient is as predictable as it has become for us in this disease, problems can be corrected before they become serious; and excessive therapeutic reactions to physiologic changes can be avoided.

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Discussion

Dr. William Silen (Boston): In 1966, as Dr. Hunt mentioned, we reported with Dr. Biglieri before this society a group of 24 patients with hyperaldosteronism. We suggested, on the basis of differential levels of aldosterone determined on blood taken from the inferior vena cava and directly from the adrenal vein at operation in a small number of patients, that preoperative catheterization might be of value in determining the side of the lesion. Since then we have found that indeed such determinations are in most cases correctly predictive and enable the surgeon to confine his activities to the side of the lesion.

Therefore, whereas we had in 1966 advocated transabdominal bilat-