

Primary Mineralocorticoid Excess Syndromes

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ALDOSTERONE

Primary Aldosteronism (Including Conn's Syndrome)
 Angiotensin II-Responsive Aldosterone-Producing Adenoma
 Primary Adrenal Hyperplasia
 Aldosterone-Producing Adrenal Carcinoma
 Glucocorticoid Remediable Aldosteronism

MINERALOCORTICOIDS OTHER THAN ALDOSTERONE

17 α -Hydroxylase Deficiency
 11 β -Hydroxylase Deficiency
 Deoxycorticosterone
 Corticosterone
 Congenital Apparent Mineralocorticoid Excess Syndrome

Acquired Apparent Mineralocorticoid Excess Syndromes
 Ectopic Adrenocorticotrophic Hormone Syndrome
 Glucocorticoid Resistance
 Essential Hypertension
 Exogenous Mineralocorticoids

ACTIVATING MUTATIONS OF THE MINERALOCORTICOID RECEPTOR

ABNORMAL RENAL TUBULAR IONIC TRANSPORT (OR DISORDERS OF THE RENAL TUBULAR EPITHELIUM THAT MIMIC PRIMARY MINERALOCORTICOID EXCESS) (PSEUDOALDOSTERONISM)

Liddle's Syndrome

CONCLUSIONS

Aldosterone, which is the most important mineralocorticoid produced by the zona glomerulosa, plays a vital role in normal sodium homeostasis. Excess production of aldosterone leads to sodium retention and potassium loss. By definition, disorders in which aldosterone excess is consequent to activation of the renin-angiotensin system are classified under secondary aldosteronism. This chapter focuses on primary abnormalities of aldosterone hypersecretion, on a variety of other conditions in which mineralocorticoids other than aldosterone produce similar clinical and biochemical syndromes, and on a syndrome associated with abnormal renal tubular ionic transport.

of 11 β -hydroxysteroid dehydrogenase (11 β -HSD) (e.g., licorice, carbenoxolone) or secretion of excess mineralocorticoid steroids other than aldosterone (e.g., deoxycorticosterone [DOC]).⁶

Primary aldosteronism is defined as aldosterone production that is excessive to the body's needs and relatively autonomous of its normal chronic regulator, the renin-angiotensin system, which is suppressed. In early series of patients, hypokalemia was used as a reason for further investigation and thus, not surprisingly, was thought to be present in the majority of patients. In more recent studies in unselected hypertensive patients, the majority with primary aldosteronism have been normokalemic. Very occasional patients are normotensive, and, in some cases, normal levels of plasma and urinary aldosterone have been found.^{7,8}

ALDOSTERONE

PRIMARY ALDOSTERONISM (INCLUDING CONN'S SYNDROME)

Conn's classic article¹ describing primary aldosteronism was published in 1955. The patient under study had hypertension, neuromuscular symptoms, and excessive renal potassium loss, associated with increased levels of a sodium-retaining hormone subsequently identified as aldosterone. The clinical and biochemical abnormalities were reversed after removal of a benign adrenal tumor. Over the next few years, many other investigators made similar observations. In 1964, Conn and colleagues² reviewed the features of a further 145 cases. The diagnosis was greatly facilitated by the development of methods for measurement of plasma renin activity (PRA), which was found to be suppressed in primary aldosteronism^{3,4} but elevated in secondary aldosteronism, as in malignant-phase or renovascular hypertension.⁵

Since the original description, it has become clear that the same clinical and biochemical picture can be found in patients without adrenal tumors. The spectrum of primary aldosteronism is listed in Table 128-1 together with estimates of the prevalence of the different subtypes. The patients with primary aldosteronism also should be distinguished from those taking exogenous mineralocorticoids (e.g., fludrocortisone) or drugs or substances previously thought to be mineralocorticoids but now known to act indirectly via inhibition

Prevalence

Conn⁹ originally thought that as many as 20% of patients with apparent essential hypertension might have the syndrome that he reported. This was thought to be a gross overestimate. Until recently, with the introduction of routine measurement of the aldosterone-renin ratio (see later), most authors have suggested that the prevalence of primary aldosteronism is less than 1% in an unselected hypertensive population.^{10,11} Lewin and colleagues¹² carried out limited investigations in 5485 participants in the stepped-care group of the Hypertension Detection and Follow-up Program and identified 3 patients with possible primary aldosteronism. A slightly higher prevalence was found in 3783 patients with moderately severe, nonmalignant hypertension attending the Glasgow Blood Pressure Clinic. Ten patients had primary aldosteronism (0.4%).¹³ Other investigators, however, have found a significantly higher prevalence when studying selected populations, especially when the aldosterone-renin ratio was applied to all patients with hypertension studied and not just those with hypokalemia (2%–12%).^{14–17}

Our own results are in keeping with this. A total of 254 consecutive patients attending a London hypertension clinic with a high percentage of nonwhites were studied. The patients were initially screened by measurement of plasma potassium concentration. If this was less than 3.5 mEq/dL,

Table 128-1 Primary Aldosteronism

Subtype	Approximate Prevalence (%)
Aldosterone-producing adenoma including All-responsive adenoma*	33
Idiopathic hyperaldosteronism†	63
Aldosterone-producing carcinoma	<1
Primary adrenal hyperplasia	<1
Glucocorticoid-remediable hyperaldosteronism‡ (FH-I)	0.5
FH-II	3-4
Ectopic aldosterone-producing adenomas and carcinoma	Very rare

*The Brisbane group finds that the angiotensin II-responsive form makes up approximately 50% to 60% of the adenomas that we remove.

†This condition is by convention included in the differential diagnosis of primary aldosteronism because, despite some evidence that it is a form of secondary aldosteronism, aldosterone secretion is at least partially autonomous, as judged by suppression testing in which aldosterone secretion continues despite marked renin suppression (see text).

‡This prevalence is based on testing all patients using the hybrid gene long polymerase chain reaction test.

FH-I, FH-II, familial hyperaldosteronism types I and II.

full evaluation of the renin-angiotensin-aldosterone axis was carried out. The initial screening was performed with the patients given antihypertensive therapy (95% were taking a thiazide diuretic). Drug therapy was then stopped in those patients with hypokalemia. In this group, full investigation of the renin-angiotensin-aldosterone axis was performed. The results are given in Table 128-2.

In this population, the prevalence of primary aldosteronism was 5.2%. Of interest was the observation that when diuretic therapy was stopped, 62% of the patients became normokalemic. Conn¹⁸ himself reported a 7.6% prevalence of normokalemic primary aldosteronism. It is thus important to appreciate that the prevalence of this condition is quite dependent on the population studied and the methods used. Not all patients are hypokalemic, but in those who are, diuretic therapy may either unmask or exaggerate the condition.

Relatively little has been published on the prevalence of primary aldosteronism in primary care populations. This has been examined by Lim and colleagues¹⁹ in a single-physician practice. In the practice population of 4400, 453 patients had been diagnosed with hypertension using standard guidelines. Of these, 200 were randomly selected and 135 agreed to take

Table 128-2 Screening London Hypertension Clinic for Prevalence of Primary Aldosteronism

254	Consecutive hypertensive patients on treatment
83	Plasma potassium <3.5 mEq/L ⁻¹
47	High plasma aldosterone
26	Low plasma renin activity
13	Low plasma renin activity standing
	High plasma aldosterone lying down
13	PATIENTS IDENTIFIED AS HAVING PRIMARY ALDOSTERONISM
	Trial of spironolactone
	1 patient unable to tolerate drug
	6/12 blood pressure <140/95 mm Hg
	Other 6 patients mean systolic blood pressure drop of 42 mm Hg (range, 25-64) and mean diastolic fall of 19 mm Hg (range, 14-27)
	CT scanning: 3/13 patients' scans indicated adrenal tumors
	4/13 had decrease in plasma aldosterone on standing, compatible with adenoma

CT, computed tomography.

part; treated patients continued on their medication. For various reasons, 10 patients were excluded. Of the remaining 75 (63 men, 62 women; mean age, 67), 18 (14.4%) had an aldosterone-renin ratio greater than 750, indicating a probable diagnosis of primary aldosteronism. These patients had significantly higher blood pressure and were taking more drugs than those with ratios less than 750. The authors suggested that taking the sensitivity of the ratio as being 93% (as judged by fludrocortisone suppression testing) in the prediction of primary aldosteronism, approximately 10% of the hypertensive population had primary aldosteronism. Of 350 unselected hypertensive patients attending primary care clinics in Singapore, 63 (18%) were reported by Loh and colleagues²⁰ to have elevated aldosterone-renin ratios. Only 13 (21%) of these were hypokalemic. Saline infusion testing was used to confirm the diagnosis among 56 of those with elevated ratios, with positive results in 16 patients, only 6 of whom were hypokalemic. These findings led the authors to estimate a prevalence of primary aldosteronism of at least 5% among the adult Asian population with hypertension. In a Chilean study, Fardella and associates²¹ used the ratio to screen for primary aldosteronism among 305 hypertensive patients and 205 normotensive patients recruited from a primary outpatient clinic hypertension program. Fludrocortisone suppression testing was used to confirm the diagnosis in patients with elevated ratios and was positive in 29 (9.5%) of the hypertensive and 3 (1.5%) of the normotensive subjects. None of these patients with primary aldosteronism were hypokalemic.

Etiology

The various causes of primary aldosteronism are listed in Table 128-1. With the exception of glucocorticoid-suppressible hyperaldosteronism (alternatively called dexamethasone-suppressible hyperaldosteronism or glucocorticoid remediable aldosteronism [GRA]), the precise molecular cause has not been determined. GRA is an autosomal-dominant disorder involving hypertension, variable hypokalemia (most patients are normokalemic), aldosterone excess with suppression of PRA, and excess production of 18-hydroxycortisol (18-OH-F) and 18-oxocortisol (18-oxo-F) (see later). The biochemical hallmark of this form of aldosteronism is that aldosterone secretion is primarily regulated by adrenocorticotropic hormone (ACTH) and can be suppressed by glucocorticoid therapy. Lifton and colleagues²² have shown that this results from ectopic expression of aldosterone synthase, an enzyme normally found only in the zona glomerulosa. The genes encoding aldosterone synthase and 11 β -hydroxylase (which is expressed in both the zona glomerulosa and zona fasciculata) are 95% homologous, and both lie on chromosome 8. Lifton and colleagues have shown in a large kindred linkage of GRA to a gene duplication arising from unequal crossing over, which has fused the 5' regulatory region of 11 β -hydroxylase (under ACTH control) to the coding sequence of aldosterone synthase (Fig. 128-1). Subsequent studies with 12 other pedigrees have shown similar mutations but with at least 5 independent breakpoints. In vitro work has indicated that all breakpoints should be within or to the left of exon 4. Hybrids that contained exons 1, 2, and 3 and up to mid-exon 4 coded for an enzyme that synthesized aldosterone. Hybrids containing exons 5, 6, and 7 did not result in aldosterone production. It is possible that the position of the breakpoint may have an influence on phenotype. Stowasser and Gordon²³ reported a greater likelihood of severe (versus mild) hypertension among affected members of families with relatively proximal breakpoints (resulting in a greater number of aldosterone synthase sequences). The fact that patients with GRA are frequently normokalemic despite clear aldosterone excess and suppression of PRA is in keeping with findings of recent studies involving patients with other forms of primary aldosteronism, the majority of whom have also been normokalemic. Because of the similarities between GRA and angiotensin-unresponsive

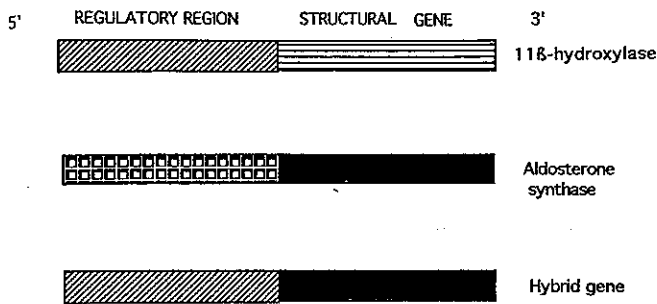


Figure 128-1 Molecular pathogenesis of glucocorticoid remediable hyperaldosteronism. Gene duplication from unequal crossover has resulted in a fusion of the 5' regulatory sequence of the 11 β -hydroxylase gene with the coding sequence of the aldosterone synthase gene. This results in a hybrid gene, which is then under dominant adrenocorticotropic hormone control.

aldosterone-producing adenomas (APAs) (primary regulation of aldosterone is by ACTH and increased production of 18-oxygenated cortisol compounds), investigators have tested whether the chimeric gene found in GRA is present in APA but have not found it to be so.²⁴ No abnormality of aldosterone synthase has been found in either APAs or idiopathic aldosteronism. Using an antibody specific for aldosterone synthase (i.e., one that did not cross-react with 11 β -hydroxylase), Ogishima and coworkers²⁵ showed this localized aldosterone synthase both in APA and in the adrenal of a patient with idiopathic hyperaldosteronism (IHA).

The cause of IHA has been the subject of considerable debate. The histology of the adrenals has been reported as being either normal or showing diffuse, micronodular, or macronodular hyperplasia. Considerable evidence suggests that the aldosterone excess is angiotensin II-responsive and may result from enhanced sensitivity of the zona glomerulosa to angiotensin II.^{26,27} The positive correlation between plasma aldosterone and plasma angiotensin II raises the possibility that this is a form of secondary rather than primary hyperaldosteronism. Padfield and associates²⁷ have suggested that IHA is part of a continuum with low renin essential hypertension (LREH). Against this argument, however, is the observation that aldosterone secretion in IHA is at least partially autonomous of the renin-angiotensin system, as demonstrated by failure of normal suppression during fludrocortisone or saline suppression testing (despite complete suppression of renin). Witzgall and colleagues²⁸ confirmed the exaggerated angiotensin II-induced aldosterone response in IHA and LREH. They then repeated the study with a simultaneous infusion of dopamine and in a separate experiment measured the aldosterone response to the dopamine antagonist metoclopramide. Dopamine impaired the aldosterone response to angiotensin II, and metoclopramide produced an exaggerated aldosterone increase in both IHA and LREH. They concluded that there was increased but ineffective dopamine inhibition of aldosterone secretion in these two conditions. Other authors have failed to confirm this.²⁹ Veglio and associates³⁰ found that metoclopramide stimulated aldosterone only in IHA and not in essential hypertension. Oral bromocriptine lowered plasma aldosterone in patients with IHA but not in patients with essential hypertension.

Others have suggested that the factor stimulating aldosterone secretion is one of the pro-opiomelanocortin-derived peptides. Previous work from our laboratory has shown that the aldosterone response by isolated perfused zona glomerulosa cells to ACTH was markedly enhanced by N-terminal pro-opiomelanocortin, which contains the γ -melanocyte-stimulating hormone sequence³¹ (Fig. 128-2). Griffing and colleagues³² measured plasma immunoreactive γ -melanocyte-stimulating hormone in nine patients with IHA and in seven found levels above normal. The levels were significantly

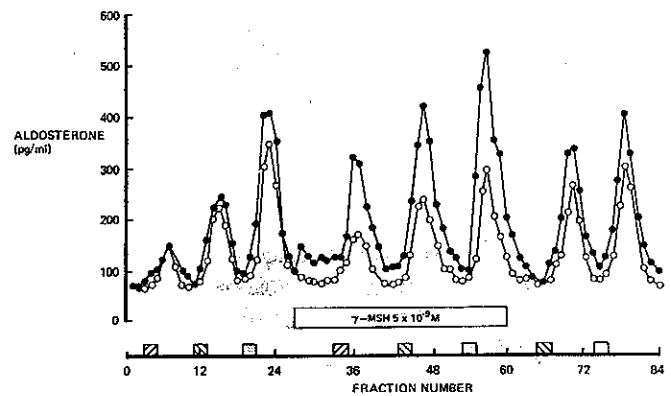


Figure 128-2 Aldosterone secretion by isolated perfused rat zona glomerulosa cells in response to pulses of adrenocorticotropic hormone (1-24) given before, during, and after infusion of γ -melanocyte-stimulating hormone (γ -MSH) precursor (5×10^{-9} mol/L). This precursor circulates in the plasma. Responses in the column infused with γ -MSH precursor (\bullet) are compared with those in a control column (\circ). Doses of adrenocorticotropic hormone (1-24) given were 1, 2.5, and 5 ng/L (\square). γ -MSH precursor was infused in the experimental column only between fractions 27 and 60.

higher than in APA and essential hypertension. In contrast, plasma ACTH and cortisol and urinary cortisol did not differ in the three groups. In a further study, they found that plasma β -endorphin levels were also elevated in IHA,³³ raising the possibility that there may be abnormal processing of pro-opiocortin in this condition. Lowry and colleagues³⁴ have shown that this molecule appears to be important in adrenal growth; it is interesting to speculate whether this may relate to the hyperplasia.

The role of angiotensin II in stimulating aldosterone secretion in IHA is supported by the effect of captopril or other angiotensin-converting enzyme (ACE) inhibitors in lowering plasma aldosterone in this condition (see later). The source of the angiotensin II is unclear, given the low PRA. This raises the possibility of an abnormality of the intra-adrenal renin-angiotensin system. Fallo and coworkers³⁵ examined the effect of captopril on the aldosterone response to potassium infusion in IHA and APA. Before captopril, potassium stimulated an increase in aldosterone in both groups. After captopril, the response was significantly blunted in IHA but not in APA. The authors suggested that this supported the hypothesis that the adrenal renin-angiotensin system played a role in the aldosterone response to potassium in IHA.

Klemm and colleagues³⁶ found renin mRNA levels to be elevated in angiotensin-responsive APAs (which biochemically behave similarly to IHA in that aldosterone production is responsive to angiotensin) but not in angiotensin-unresponsive APAs when compared with normal cortices. Renin mRNA levels were also elevated in some adrenal cortices surrounding angiotensin-responsive APAs, suggesting that the defect in tissue renin gene expression was not confined to the tumor.

It is interesting to relate these studies to work on the effect of dietary potassium and sodium on the accumulation of mRNA for aldosterone synthase in rat adrenals.³⁷ A high-potassium or low-sodium diet increased aldosterone synthase mRNA. These effects could be attenuated by captopril. This effect of captopril in inhibiting potassium induction of aldosterone synthase P-450 mRNA occurred despite the presence of low PRA. These investigators suggested that this implicated angiotensin II formed within the adrenal in the effect of potassium on aldosterone secretion. It would appear that this dependence might be abnormal or in some way altered in IHA.

To test for further evidence of opioid peptide control of aldosterone secretion in IHA, the opiate receptor antagonist naloxone has been given to patients with IHA and APA.^{35,38}

In APA, there was no significant effect. In IHA, naloxone after dexamethasone lowered plasma aldosterone but not naloxone alone. The significance of this is unclear.

Nothing is known about the cause of primary adrenal hyperplasia (PAH) in which either both or, more rarely, one adrenal gland shows either micronodular or macronodular hyperplasia and produces a clinical and biochemical picture very similar to that of angiotensin-unresponsive APA (for reviews, see Chen et al.³⁹ and Otsuka et al.⁴⁰).

Gordon and associates⁴¹ described a new familial form of primary aldosteronism with two affected members in each of three families. In some of the patients, APAs have been found. This new form has been called familial hyperaldosteronism type II (FH-II) to distinguish it from the glucocorticoid-suppressible type (FH-I). In the series of 159 patients with primary aldosteronism, FH-I was more common than FH-II (13 versus 3 patients). FH-II is not glucocorticoid suppressible. Although the molecular basis of FH-II remains unknown, linkage analysis in two kindreds has implicated a locus on chromosome 7p22.^{42,43}

Pathology

As already discussed, three major pathologic types are associated with primary aldosteronism: adenoma, hyperplasia, and carcinoma.

Adrenocortical Adenoma

This was once considered to be the most common abnormality, found in approximately two thirds of patients with the syndrome. However, investigators using widened approaches to screening have reported disproportionately greater increases in detection of IHA than APA, leading to IHA becoming the more common subtype. This is likely to reflect the less florid clinical and biochemical manifestations of IHA, and the ability of more sensitive screening methods to more readily detect these patients.

Adrenal adenomas occur more frequently in the left than in the right adrenal.^{2,44} They are usually less than 2 cm in diameter, with a golden yellow color (Fig. 128-3). On light microscopy, four cell types have been identified: small and large hybrid cells with features of both zona glomerulosa and zona fasciculata cells and others with either zona glomerulosa or zona fasciculata characteristics.⁴⁵ Ultrastructural studies have shown that most of the mitochondria possess tubular cristae similar to those found in the cells of the zona glomerulosa; in addition, if spironolactone therapy has been given, spironolactone bodies may be found.^{45,46} Interestingly, APAs are often present together with zona glomerulosa hyperplasia in the surrounding cortex.⁴⁵ In rare instances, multiple adenomas are found, as may an adenoma with associated

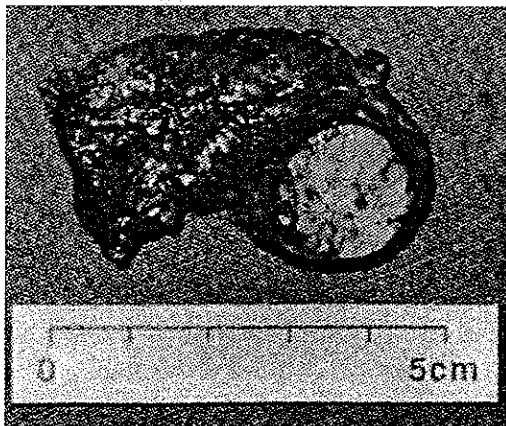


Figure 128-3 Typical Conn's adenoma removed from patient with 24-year history of hypertension poorly responsive to conventional antihypertensive therapy.

macronodular hyperplasia. These findings, which are reminiscent of those in the multiple endocrine neoplasia syndromes, have led some investigators to propose that genetic mutations affecting regulation of growth of adrenocortical cells may underlie at least some cases of primary aldosteronism.⁴⁷ One case of bilateral adenoma with two types of adenoma cell associated with both primary aldosteronism and Cushing's syndrome has been described.⁴⁸

Idiopathic Hyperaldosteronism

The zona glomerulosa in IHA usually shows either diffuse or focal hyperplasia with normal ultrastructure but may be apparently macroscopically normal.^{46,49} Associated nodules may be microscopic or as large as 2 cm in diameter. Their ultrastructure is typical of clear cells of zona fasciculata origin. In keeping with this, in vitro, the nodules produce cortisol and not aldosterone. Immunohistochemistry using an antibody against cytochrome P-450 11 β -hydroxylase showed that immunoreactivity was intense in cortical nodules, the inner zona fasciculata, and the zona reticularis in Cushing's disease but was also high in the zona glomerulosa and outer zona fasciculata in IHA. The compact cells in APA also stained with the antibody.⁵⁰ As previously mentioned, aldosterone synthase immunoreactivity has been found in both APA and IHA.²²

The pathologic features may be important in determining the outcome of unilateral adrenalectomy. Ito and colleagues⁵¹ studied 37 patients with primary aldosteronism treated in this way: 23 had unilateral solitary adenomas (group 1), 3 had unilateral multiple adenomas (group 2), and 11 had adenomas with multiple macroscopic or microscopic nodules (group 3). The mean age of group 3 was higher than that in the other two groups (47.8 years versus 42.8 and 42.7, respectively). Despite the fact that postoperative hormonal changes were similar, there were marked differences in the blood pressure response, with half of group 3 remaining hypertensive at 1 year. The authors suggested that the nodules might result from long-standing hypertension. Glands with nodules almost invariably show arteriopathy of the capsular vessels.⁵² It is suggested that this leads to focal ischemia and atrophy, with better perfused cells becoming hyperplastic, leading to nodule formation.

Adrenal Carcinoma

This is a rare cause of hyperaldosteronism. Histologically, it may be difficult to distinguish from an adenoma but usually the carcinomas are larger (>3 cm in diameter) with areas of necrosis and pleomorphic nuclei.⁴⁵ Calcification, which is commonly found in carcinomas, may be detected by computed tomography (CT) scanning or ultrasonography.

Ovarian Carcinoma

Very occasional cases of primary aldosteronism have been reported in association with malignant ovarian tumors.⁵³⁻⁵⁵ After excision of the tumor, the biochemical abnormalities and hypertension have either resolved or improved. Recurrence of the tumor produced a return of the syndrome.⁵³

Ectopic Aldosterone-Secreting Adenoma

This is an extremely rare cause of primary aldosterone excess.⁵⁶

Clinical Spectrum

The clinical features of this condition have been extensively reviewed.^{41,57-62} The majority of patients are asymptomatic. Some are discovered to be hypokalemic on routine investigation of hypertension, whereas others may have symptoms of hypokalemia such as muscle weakness; very occasionally muscle paralysis; more commonly polyuria, polydipsia (secondary to nephrogenic diabetes insipidus); paresthesias; and, rarely, tetany. Among Chinese patients, there is a high

incidence of periodic paralysis.⁶³ In a series of 50 patients with APA reported from Hong Kong, 21(42%) had periodic paralysis as a presenting feature.

Conn and colleagues⁶⁴ found an interesting sex difference in the incidence of paresthesias and tetany. Females were far more likely to complain of paresthesia or present with tetany than were males. Tetany results from the decrease in ionized calcium associated with the hypokalemic alkalosis. Plasma calcium levels are normal, and treatment is repletion with potassium and not administration of calcium.

It was originally believed that malignant hypertension did not occur in primary aldosteronism.² This is not true and many cases have been reported.^{65,66} The diagnosis in such cases may be missed because PRA may not be suppressed. Conversely, occasional patients with normotensive aldosteronism have been described.^{67,68} This is not infrequent among pedigrees with FH-I or FH-II in whom affected individuals have been detected at early, preclinical stages of the disease process through genetic or biochemical family screening programs.⁶⁹

In primary aldosteronism, the normal circadian pattern of blood pressure appears to be preserved with a nocturnal decrease,⁷⁰ but the magnitude of the decrease is reduced.⁷¹ There would appear to be decreased supine and standing blood pressure variability in primary aldosteronism compared with essential hypertension,⁷² probably due to a preservation of baroreflex function or a consequence of the salt-loaded state.

Incidence

Age and Sex

Primary aldosteronism has been described in patients of all ages, including childhood.⁷³ Growth failure may be the presenting feature as with other causes of hypokalemia such as Bartter's syndrome. Several groups have found that patients with classic angiotensin-unresponsive adenoma are usually younger than those with IHA.^{65,74} However, primary aldosteronism in children younger than 16 years of age is usually found to be due to adrenal hyperplasia. Of the eight reported children with adrenal adenoma causing Conn's syndrome, all but one were female.

Adenomas are more commonly found in females than in males.^{2,44} However, centers reporting high detection rates of the angiotensin-responsive form of APA have found these to be more common among males.⁷⁵ These patients also tended to be older than those with classic angiotensin-unresponsive APAs. IHA has been found by some to be as common in males as females⁴⁵ and by others to be more common in males.⁷⁴

Diagnosis

Special Clinical Presentation

The diagnosis of primary aldosteronism during pregnancy may present a problem because of high circulating levels of progesterone, which has been shown to inhibit the effect of aldosterone on sodium transport. Thus, aldosterone 500 µg given either as a single intravenous injection or infused over a period of 8 hours during the last month of pregnancy did not affect sodium or potassium excretion, whereas the same dose given after delivery produced marked sodium retention and increased potassium excretion.⁷⁶

Subtype Differentiation

As indicated in Table 128-1, once the diagnosis of primary aldosteronism has been made, APAs need to be differentiated from various forms of hyperplasia, rare aldosterone-producing carcinomas, and the very rare tumors responsible for ectopic production of aldosterone.

Diagnostic Protocols

The approach to the diagnosis of primary aldosteronism differs widely. In some centers, the only patients investigated are

those with hypokalemia and hypertension. As already discussed, the majority of patients with this syndrome are normokalemic and thus a large number of patients will be misdiagnosed or undiagnosed if this approach is taken. In other centers, all hypertensive patients are screened for this diagnosis. The cost involved in doing so is small in comparison with the cost of life-long drug therapy, and the potential benefit to the patient is very considerable, especially if the cause of the primary aldosteronism is such that definitive therapy such as surgery could produce a cure. If this approach is thought to be too radical or too expensive, then the next best thing is to screen patients with hypokalemia together with young patients and those whose blood pressure is difficult to control. At the Mayo Clinic, an average of 12 patients per annum were diagnosed with primary aldosteronism from 1960 to 1991. However, with improved screening the number of patients with this diagnosis increased 10-fold over the subsequent 8 years.⁵⁷ The algorithms used by the Brisbane group are shown in Figure 128-4.

Historically, the key to the initial diagnosis in most patients has been measurement of plasma potassium. The presence of hypokalemia (plasma potassium <3.6 mEq/L) in an untreated hypertensive patient was taken as an indication for further investigation of the renin-angiotensin-aldosterone axis. As already discussed, it is also worthwhile investigating patients who have diuretic-induced hypokalemia. Plasma potassium levels may be elevated by red blood cell hemolysis and, to a lesser extent, by the use of a tourniquet with muscle pumping.⁷⁷ Another reason for normokalemia may be that the patient is on a low-sodium diet. This is because urinary potassium excretion is related to the distal nephron sodium load in

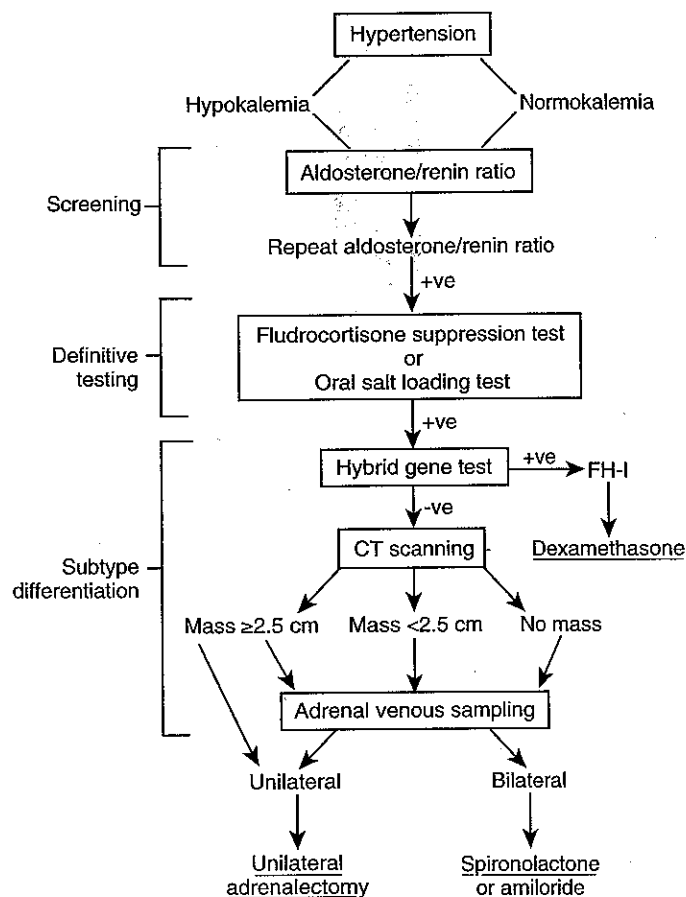


Figure 128-4 Algorithms used by the Brisbane group in the investigation of patients with suspected and confirmed (i.e., after fludrocortisone or oral salt-loading test) primary aldosteronism.

conditions in which there is primary mineralocorticoid excess.^{78,79} If the 24-hour urinary sodium is less than 100 mmol, most investigators would increase the sodium intake (e.g., NaCl 6 g/day for 5 days) and then repeat the plasma potassium measurement; some patients with normokalemic primary aldosteronism will then become frankly hypokalemic. In the pre-aldosterone-renin ratio measurement era, it was suggested that measuring plasma or serum potassium as a screening test for hyperaldosteronism had a sensitivity of 75% to 90%.^{14,80} The results from centers using aldosterone-PRA ratio screening suggest that this figure should now be revised downward and is probably less than 50%.

The precise prevalence of normokalemic primary aldosteronism in an untreated population is unknown but now appears to be much higher than previously thought. Many authors suggested that this was a rare entity if the patient had an adequate sodium intake. However, in the Bravo and associates⁸¹ series of 80 cases of primary aldosteronism, 22 patients (27.5%) had a normal serum potassium level. In another study,⁶⁵ 11% of the patients were normokalemic on multiple measurements of serum potassium. Other laboratories confirmed these findings.^{14,74} Thus, even before the introduction of the aldosterone-renin ratio as a screening test, between 7% and 38% of patients with primary aldosteronism were found to have basal serum or plasma potassium levels greater than 3.6 mEq/L. After the introduction of screening with the ratio, 60% to 70% of patients with primary aldosteronism have been reported to be normokalemic.

Hypokalemia secondary to mineralocorticoid excess is associated with inappropriate kaliuresis. The extent of this depends on potassium intake, but the excretion usually exceeds 30 mmol/24 hr. In addition, the enhanced sodium-hydrogen exchange leads to increased hydrogen ion excretion, commonly as ammonium ion, which is responsible for the usual mild metabolic alkalosis. For reasons that are unclear, some patients with GRA may have alkalosis but be persistently normokalemic. Plasma sodium levels are usually either in the upper part of the reference range or are frankly elevated in primary aldosteronism. As with other biochemical parameters, the abnormality may be more marked in patients with an adenoma than in those with hyperplasia.⁶⁵ Total exchangeable sodium has been found to be increased in patients with primary aldosteronism caused by an adenoma, although it is normal in those with idiopathic hyperplasia.²⁶ A similar distinction has been found for total exchangeable potassium, with significantly reduced levels in patients with an adenoma but not in those with hyperplasia.²⁶ However, whether similar distinctions occur between IHA and the angiotensin-responsive variety of adenoma (which biochemically mimics IHA in other ways, including responsiveness of aldosterone to angiotensin II and normalcy of "hybrid steroid" (18-OH-F- and 18-oxo-F) levels⁸²) has yet to be determined.

Measurement of Mucosal Potential Difference in Screening for Mineralocorticoid Excess

Sodium flux across the colon and rectum is stimulated by aldosterone. Thus, in both primary and secondary aldosteronism, there is a reduction of fecal sodium and an increase in potassium. The same is true of exogenous mineralocorticoid administration. The reabsorption of sodium is associated with an increase in the potential difference (PD) across the rectum and pelvic colon.⁸³ This has been used as a rapid screening test for aldosterone excess.⁸⁴ Unfortunately, rectal PD is affected by a variety of factors other than aldosterone; the value of the screening test is thus diminished. To overcome this situation, Skrabal and colleagues⁸⁵ introduced the concept of the subtraction PD. This is based on the finding that oral PD is altered by the nonsteroidal factors that affect rectal PD but is not mineralocorticoid responsive. Thus, by

measuring both oral and rectal PDs and subtracting the result of the oral from the rectal, it was possible to improve the precision and accuracy of the test (Fig. 128-5). Despite the fact that this work was carried out several years ago, it still remains the most rapid method of screening for mineralocorticoid excess and is especially useful when biochemical facilities are not readily accessible. More recent measurement of nasal PD in patients with Liddle's syndrome suggests that this may be a useful alternative to the measurement of rectal PD.⁸⁶

Assessment of the Renin-Angiotensin-Aldosterone Axis: Plasma and Urinary Aldosterone

The hallmark of primary aldosteronism is the excessive production of aldosterone, which is autonomous of the renin-angiotensin system and occurs in the face of renin suppression. Various factors, including antihypertensive drug therapy and the inhibiting effect of hypokalemia on aldosterone secretion, may affect this and thus make the diagnosis more difficult.

If plasma potassium is less than 3 mmol/L, potassium supplementation should be given before measurement of aldosterone.^{87,88} The same is true for measurement of subtraction PD.⁸⁹ However, even when hypokalemia is corrected, plasma aldosterone levels are still frequently within the normal range among patients with primary aldosteronism, even those with APAs. An alternative to plasma aldosterone is to measure 24-hour urinary aldosterone excretion. What is actually measured is aldosterone produced by hydrolysis at pH 1 of the acid-labile metabolite aldosterone 18-glucuronide.⁹⁰ It should be remembered that this reflects only approximately 15% of aldosterone secreted. Assays to measure 3 α ,5 β -tetrahydroaldosterone (15%–40% of metabolites) are used less commonly. As with the measurement of plasma aldosterone, urinary aldosterone excretion may be normal in primary aldosteronism, especially in severely hypokalemic patients.^{87,88} Other

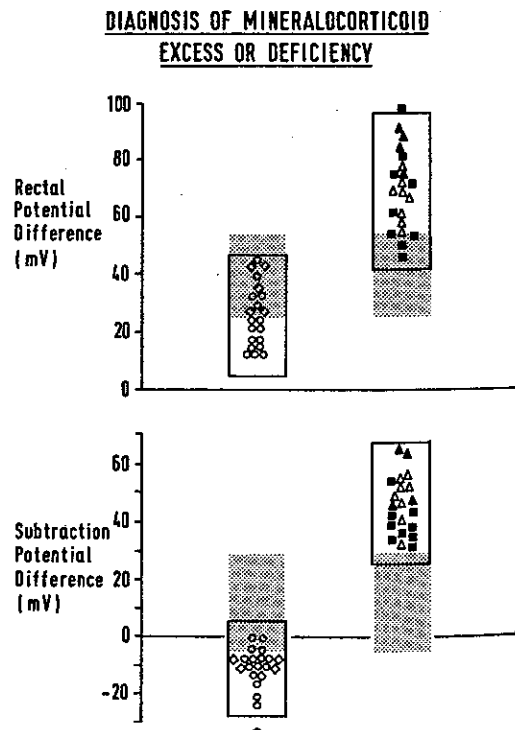


Figure 128-5 Comparison of the measurement of rectal potential difference (PD) and subtraction PD in patients with mineralocorticoid excess or deficiency. It can be seen that using rectal PD a considerable overlap exists with the normal reference range, but that this is not the case when subtraction PD is used.

reasons are an incomplete collection of urine or variability in rates of hepatic metabolism of aldosterone. Some patients have been described who have intermittent aldosterone hypersecretion, including some with apparent isolated DOC excess.^{91,92} An additional point is the recognition that urinary aldosterone excretion decreases with age.⁹³ It is therefore important to use an age-related reference range.

Plasma Renin Activity

The renin-angiotensin system is most commonly assessed by measuring PRA. This assay depends on the *in vitro* generation of angiotensin I, which is then measured by radioimmunoassay. The validity of the assay as an index of renin secretion depends on the adequacy of the renin substrate angiotensinogen. In primary aldosteronism, PRA is usually either low or undetectable in contrast to the elevated levels found in secondary aldosteronism. However, PRA lacks specificity as a screening test for primary aldosteronism because it will not distinguish primary aldosteronism from other low-renin forms of hypertension. Renin secretion is stimulated by assuming the erect posture or by volume or salt depletion (as occurs with diuretic treatment) and is suppressed in situations in which β -adrenergic input to the juxtaglomerular cells is impeded (as in β -adrenoceptor blocker treatment). Renin production is also reduced in patients with chronic renal failure, due partly to a reduction in functioning renin-producing cells and also to salt and water retention. Hence, it is necessary to know the patient's posture, medical treatment, renal function, and, if possible, sodium intake to correctly interpret PRA values.

Plasma Renin Concentration

This can be used instead of PRA in aldosterone-renin profiling.⁹⁴ This has the advantage that samples can be sent by mail. The automated measurement of active renin, using an immunometric assay incorporating an antibody directed against the active cleavage site, represents a more rapid, convenient approach that has demonstrated good correlation with PRA levels and has become popular among laboratories in recent times.

Aldosterone-Renin Profiling

The aldosterone-renin ratio is widely regarded as the most reliable means of screening for primary aldosteronism.^{47,95-97} As indicated previously, this approach has revealed a surprisingly large number of patients with primary aldosteronism. In our own series of 254 consecutive hypertensives (see Table 128-2), 13 (5.1%) had an aldosterone-renin ratio suggestive of primary aldosteronism, with four (1.6%) probably having APA. In the series of 348 patients with hypertension studied by Hiramatsu and colleagues,⁹⁵ nine patients (2.6%) had APA, confirmed by scintigraphy, venography, and surgical excision. Hiramatsu and colleagues found that in patients with APA, the aldosterone-PRA ratio (aldosterone, picograms per milliliter; PRA, nanograms per milliliter per hour) was always more than 400, whereas in 323 patients with essential hypertension, the ratio was less than 200. Six of these nine (67%) were normokalemic. In our series, 62% of the patients with primary aldosteronism were normokalemic off diuretic treatment, but all had plasma potassium levels of less than 3.5 mEq/L on thiazide therapy.

McKenna and associates⁹⁷ found that a single elevated aldosterone-renin ratio associated with an elevated or normal plasma aldosterone value correctly diagnosed primary aldosteronism in 10 patients, 5 with hyperplasia and 5 with APA. The only problem they had with false-positive results was in patients with chronic renal failure.⁹⁷ Secondary aldosteronism was characterized by elevated plasma aldosterone values together with a normal ratio.

Gordon and others^{47,98} carried out two reviews of their experience with this screening test. In the first of these,⁴⁷ published in 1992, they indicated that they had diagnosed

48 patients as having primary aldosteronism in the previous 12 months (15 with APA and 9 awaiting surgery). This compared with 90 patients with primary aldosteronism diagnosed in the period 1970 to 1990. Of the 48 patients, 34 (71%) were normokalemic on presentation (14 of 24 with APA, 58%). Since 1991, Gordon and others have measured the ratio in all hypertensive patients. Among 199 normokalemic hypertensive patients referred without any suspicion of primary aldosteronism, the incidence of this diagnosis as confirmed by the fludrocortisone suppression test was at least 8.5%.⁹⁸ The authors expressed plasma aldosterone concentration in nanograms per 100 mL and PRA as nanograms per milliliter per hour. If the ratio was less than 20, primary aldosteronism was unlikely, and if the ratio was greater than 30, then primary aldosteronism was likely. Because of the arbitrary nature of the cut-off point, they usually measured several ratios. It is important to take into account the effect of antihypertensive drugs on the ratio (see later).

In 1983, Swales⁹⁹ wrote an article entitled "Primary Aldosteronism: How Hard Should We Look?" He concluded that persistent severe hypokalemia (serum potassium <3 mEq/L) occurring in either treated or untreated hypertensive patients was worth investigating. Milder hypokalemia (serum potassium 3.0-3.5 mEq/L) in untreated patients was probably worth investigating. However, he thought that substantially fewer benefits were likely from investigating patients with inconsistent hypokalemia or hypokalemia in those taking thiazide diuretics. The results of the aldosterone-renin ratio studies suggest that this approach using potassium as the sole guide to the need for further investigation is inappropriate.

The sensitivity of the ratio is greatest when blood is taken in the morning hours when ACTH levels are still relatively high. The collection of samples from upright (sitting) patients increases sensitivity in those with angiotensin-responsive forms of primary aldosteronism (angiotensin-responsive APA and IHA). The Brisbane group therefore measures the ratio at 9:00 to 10:00 A.M. after at least 2 hours of upright posture,⁹⁸ as does the Mayo Clinic.⁵⁷ Patients are encouraged to maintain a liberal dietary sodium intake while undergoing screening to prevent stimulation of renin (and a false-negative ratio) induced by dietary sodium restriction.

Effect of Drug Therapy on the Renin-Angiotensin-Aldosterone System in Suspected Primary Aldosteronism

It should be recognized that several drugs may affect the secretion of aldosterone and renin and thus alter the aldosterone-PRA ratio (Table 128-3). Patients on diuretics (including spironolactone), especially if used for several weeks, cannot be properly investigated without stopping these drugs, usually for 6 weeks. β -Adrenoceptor blocking drugs, renal impairment, and old age can produce false-positive ratios, whereas diuretics, ACE inhibitors, angiotensin receptor blockers, and dihydropyridines produce false-negative ones. Prazosin (Minipress) or other α -adrenoceptor blockers, hydralazine, slow-release verapamil, and bethanidine (Esbatal) have minimal effect on the ratio in patients with primary aldosteronism and can thus be used. Slow-release verapamil (given as 120 mg twice daily) is usually well tolerated (unless constipation develops). Side effects from hydralazine are rare if low doses (e.g., 12.5 mg twice daily) are used initially, increasing stepwise in a gradual fashion (e.g., after 2 weeks) as required, and combination treatment with slow-release verapamil prevents the reflex tachycardia that can occur with "unopposed" use of this agent. Bethanidine can be used at a starting dose of 10 mg three times daily and prazosin at 0.5 mg two to three times daily. As with other adrenergic neuron blocking agents, postural hypotension may be a problem. With the above agents, it is usually possible to control severe high blood pressure satisfactorily off other drug therapy during the diagnostic workup process.

Table 128-3 Drugs Affecting Investigations of the Renin-Angiotensin-Aldosterone System

Drug	Effect	Action
Spironolactone	↑ PRA ↓ PRA ↑ Aldo/PRA ratio especially in idiopathic hyperplasia	Stop 6 weeks before tests
Estrogen	↑ Plasma renin substrate	Stop 6 weeks before tests
ACE inhibitors and Ang-II receptor blockers	↑ PRA ↓ aldosterone ↑ Aldo/PRA ratio in idiopathic hyperplasia and secondary aldosteronism	Stop 2 weeks before tests
Diuretics other than spironolactone	↑ PRA ↓ Aldo/PRA ratio	Stop 2 weeks before tests
Nonsteroidal anti-inflammatory drugs	Retain sodium ↓ PRA ↑ Aldo/PRA ratio esp in idiopathic hyperplasia	Stop 2 weeks before tests
β-Adrenoceptor blocking drugs	↓ PRA ↑ Aldo/PRA ratio	Stop 2 weeks before tests
Calcium-channel blocking agents	↑ PRA ↓ Aldo/PRA ratio	Stop 2 weeks before tests

ACE, angiotensin-converting enzyme; Aldo, aldosterone; PRA, plasma renin activity; ↑, increase; ↓, decrease.

Nonsteroidal anti-inflammatory drugs, by promoting salt and water retention (thereby suppressing renin) and hyperkalemia (which in turn stimulates aldosterone secretion), are frequently associated with false-positive ratios and should be withheld for several weeks before testing if possible.

Dynamic Tests of the Renin-Angiotensin-Aldosterone Axis in Suspected Primary Aldosteronism

As with most other endocrine conditions, the diagnostic value of single plasma samples or 24-hour urinary collections can be enhanced by dynamic tests. A wide variety of tests have been used. They are listed in Table 128-4.

Salt-Loading Tests These tests can be carried out by increasing dietary sodium intake, infusing saline, administering exogenous mineralocorticoid, or a combination of these. The rationale behind the tests is that, in normal subjects, volume expansion with saline will suppress PRA and plasma aldosterone, whereas in primary aldosteronism, further volume expansion does not have the same suppressive effect on aldosterone secretion. Although this is true in APAs, patients with IHA may show partial suppression. Hence, this test has been used not only to make the diagnosis of primary aldosteronism but also to distinguish between APA and IHA.

In 1967, Biglieri and associates⁹¹ showed that DOC acetate administration for 3 days resulted in a failure of suppression of urinary aldosterone excretion in APA but in suppression in normal subjects and in two patients with primary aldosteronism in whom no tumor was found at operation (i.e., presumed idiopathic hyperplasia). This suggested that the test might be of value in both diagnosis and differential diagnosis. However, subsequent studies showed that some patients with IHA also showed a failure of suppression.^{14,100} Salt loading

with a combination of a high-sodium diet and oral fludrocortisone, administered over 4-day period, is widely regarded as the most reliable means of definitively confirming or excluding the diagnosis of primary aldosteronism, but again it will not differentiate adenoma from hyperplasia.^{101,102} Reliability, however, depends on the maintenance of normokalemia by potassium chloride supplementation (otherwise hypokalemia may result in a fall in aldosterone levels and a false-negative test) and the demonstration of adequate suppression of PRA (to <1 ng/mL/hr). Further details regarding the fludrocortisone suppression test have been published elsewhere.^{103,104}

The failure of suppression of urinary aldosterone excretion in patients on a high-sodium diet (>200 mEq/d) has been used as a simple test of primary aldosteronism.^{57,81,105} After 3 days on this intake, a normal person will suppress aldosterone excretion to less than 12 µg/24 hr (33 nmol) in contrast to patients with primary aldosteronism, who will not normally show suppression. This is provided that potassium levels are maintained in the normal range by potassium chloride supplementation during the salt-loading period; otherwise, urinary aldosterone levels may fall to less than 12 µg/24 hr in patients with primary aldosteronism.¹⁰⁶

An alternative approach has been to measure plasma aldosterone levels after intravenous saline infusion. This has been used to discriminate between patients with essential hypertension and those with primary aldosteronism. Those patients with essential hypertension showed suppression of plasma aldosterone to less than 8 ng/dL and those with primary aldosteronism did not. The normal protocol for this test is to take a recumbent basal plasma sample at 8:00 A.M. and then, after infusing 1.25 to 2.0 L of normal saline over 90 minutes, another plasma sample is taken. A refinement is to measure cortisol and 18-hydroxycorticosterone (18-OH-B) in

Table 128-4 Dynamic Tests of the Renin-Angiotensin-Aldosterone Axis in Suspected Primary Aldosteronism

Test	Normal Subjects		Non-All-Responsive Aldosterone-Producing Adenoma		Angiotensin-Responsive Adenoma		Idiopathic Adrenal Hyperplasia		Primary Adrenal Hyperplasia		Dexamethasone-Suppressible Hyperaldosteronism	
	PRA	ALDO	PRA	ALDO	PRA	ALDO	PRA	ALDO	PRA	ALDO	PRA	ALDO
Salt loading	↓	↓	→↓	→	↓	↓	→↓	→↓	→↓	→	→↓	→
Effect of upright posture and time	↑	↑	→	↓	↑	↑	↑	↑	→	↓	→	↓
Angiotensin-converting enzyme inhibitor	↑	↓	→	→	↑	↓	↑	↓	→	→	→	→
Angiotensin II	↓	↑	→	→	↓	↑	→↓	↑	→	→	→	→
Infusion Dexamethasone suppression	→	→	→	→	→	→	→	→	→	→	↑	↓

All, angiotensin II; ALDO, plasma aldosterone; PRA, plasma renin activity; ↓, decrease; →, unchanged; ↑, increase.

addition to plasma aldosterone.¹⁰⁰ In patients with IHA, the aldosterone-cortisol ratio or 18-OH-B-cortisol ratio after the infusion is less than 3, whereas in those with APA, ratios are greater than 3. The reason for this is that in IHA, the plasma aldosterone and 18-OH-B are more angiotensin II dependent and the volume expansion caused by the saline produces a further reduction in renin and angiotensin II because these are less suppressed in IHA than in APA.

Coruzzi and coworkers¹⁰⁷ have investigated the value of central volume expansion by head-out water immersion in APA and IHA (i.e., isotonic, iso-oncotic expansion). In APA, PRA and plasma aldosterone levels did not change significantly, and there was no suppression of plasma aldosterone below 10 ng/dL. In patients with IHA, PRA and plasma aldosterone invariably decreased (aldosterone to <10 ng/dL) with immersion.

Effect of Posture and Time

In normal subjects, assumption of erect posture activates the renin-angiotensin system and elevates plasma aldosterone. Different patterns of response have been found useful in determining the differential diagnosis of primary aldosteronism (see Table 128-4). This test is normally carried out by taking a recumbent, basal plasma sample at 8:00 A.M. followed by sitting or standing or walking for 2 to 4 hours, and then another blood sample is taken.^{108,109} The samples are measured for plasma aldosterone, plasma cortisol, and PRA.

In angiotensin-unresponsive APA, it might be thought that there would be no change in plasma aldosterone. In fact, plasma aldosterone levels often fall because in these patients the APA is ACTH dependent. During the course of the morning, ACTH levels fall as part of the normal circadian rhythm, hence the decrease in plasma aldosterone. If, however, the patient is stressed by the test, the reverse may happen. This is most readily appreciated by measuring plasma cortisol. In Figure 128-6, the effects of time and posture on plasma aldosterone levels in patients with APA are shown. It can be seen that in one patient with angiotensin-unresponsive APA, there was an increase in plasma aldosterone between 8:00 A.M. and noon. In this patient, the plasma cortisol also increased, indicating that the individual had been stressed. When the test was repeated, both plasma aldosterone and plasma cortisol levels fell during the course of the morning. In patients with idiopathic hyperplasia, the adrenal usually demonstrates sensitivity (and sometimes hypersensitivity) to angiotensin II. Assumption of the erect posture results in a small increase in angiotensin II and hence an increase in plasma aldosterone (see Fig. 128-6). Similar changes are found if plasma 18-hydroxydeoxycorticosterone (18-OH-DOC) levels are measured in patients with APA or IHA.

In addition to the effect of stress on this test, there are other reasons why the results should be interpreted with caution. In GRA, similar results are found as in APA (see Table 128-4). In both conditions, the aldosterone-secreting cells are very responsive to ACTH. Gordon and colleagues^{103,104,110} have reported that at least 50% of APAs in their experience are responsive to angiotensin II and thus may respond with an increase in plasma aldosterone when the patient stands. Patients with unilateral zona glomerulosa hyperplasia may be thought on CT or magnetic resonance imaging (MRI) to have an adrenal tumor. These patients usually show an increase in plasma aldosterone on standing.

Angiotensin-Converting Enzyme Inhibition

In normal subjects who are not salt loaded, administration of an ACE inhibitor such as captopril will reduce plasma aldosterone levels. This reduction is not normally found in patients with primary aldosteronism. This difference has been exploited as a test to diagnose primary aldosteronism.

The usual test involves giving captopril 25 mg orally to recumbent subjects and then measuring plasma aldosterone

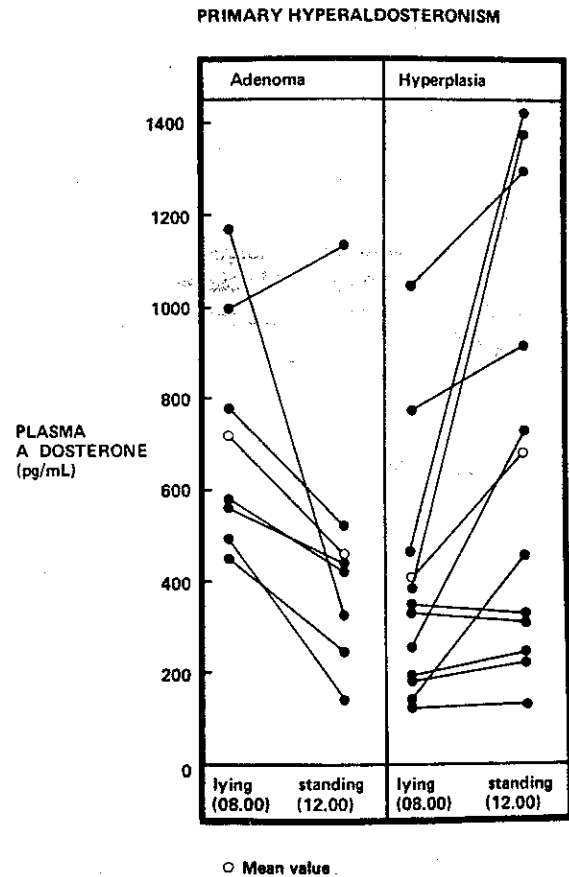


Figure 128-6 Measurement of effect of posture and time on plasma aldosterone levels in patients with aldosterone-producing adenomas and in those with idiopathic hyperaldosteronism with hyperplasia. (For details, see text.)

levels 2 hours later. In patients with primary aldosteronism, the 2-hour level has remained in excess of 15 ng/dL in contrast to the decrease in normal subjects.^{111,112} Not all authors have found this valuable.^{113,114} Muratani and colleagues¹¹⁴ studied 19 patients with primary aldosteronism and 72 with essential hypertension. Captopril was given after overnight recumbency. The test was 93% specific and had a 79% predictive value. However, a higher specificity (97%) and predictive value (90%) were found from analysis of the precaptopril plasma aldosterone-PRA ratios.

The effect of sodium intake on the captopril test was investigated by Naomi and coworkers.¹¹⁵ They used a higher dose of captopril (50 mg) and found that the results of the test were unaffected by altering the sodium intake. They looked at the plasma aldosterone (nanograms per deciliter)-PRA (nanograms per milliliter per hour) ratio in the blood sample taken 90 minutes after oral captopril given at 9:00 A.M. after 1 hour lying down. Using a ratio greater than 20 for the diagnosis of primary aldosteronism, they found that the test had 95% sensitivity and 92% specificity.

Angiotensin II Infusions

In both LREH and IHA, responsiveness or hyperresponsiveness of aldosterone to infusions of angiotensin II occurs.^{116,117} This, coupled with the positive correlation of angiotensin II with plasma aldosterone found in IHA (in contrast to the negative correlation in APA),²⁶ led Padfield and colleagues²⁷ to propose that IHA has more in common with LREH than with primary aldosteronism. However, this argument is weakened by the fact that similar responsiveness to angiotensin II occurs in angiotensin-responsive APA.¹¹⁰

In both APA and GRA, aldosterone levels are not normally affected by angiotensin II. However, in a subset of patients with APA, the tumor is angiotensin II responsive.^{59,110,118,119} The prevalence of this type of tumor is unknown but may be as high as 50% of all APAs.^{103,110,120} In the series of Irony and coworkers,¹¹⁸ less than 5% of the tumors were in this category; of 154 patients with primary aldosteronism, 12 were thought not to have either APA or IHA. Of these 12, 8 had nodular adrenocortical hyperplasia with results similar to angiotensin-unresponsive APA (i.e., nonangiotensin II responsive) and 4 had unilateral tumors with results as found in IHA (i.e., angiotensin II-responsive tumors). The nodular hyperplasia group was thought to have PAH. Both groups benefited from unilateral adrenalectomy, with improvement in blood pressure, elevation of plasma potassium, and normalization of aldosterone production.

Two patients have been described in whom the angiotensin II-responsive adenoma produced cortisol in addition to aldosterone.¹¹⁹ In both patients, cortisol levels could not be suppressed with dexamethasone. These results have been confirmed in a larger group of patients from the same center. Cortisol levels in five of six patients with angiotensin II-responsive adenomas could not be normally suppressed with dexamethasone in contrast to the normal APA.

Dexamethasone Suppression

Patients with GRA respond to dynamic tests of the renin-angiotensin-aldosterone axis in a manner similar to that of patients with angiotensin-unresponsive APAs (see Table 128-4). These two conditions can be distinguished by the patient's response to exogenous glucocorticoid. An upright morning plasma aldosterone level below 5 ng/dL after overnight dexamethasone administration (1.0 mg at midnight and 0.5 mg at 6:00 A.M.) has been suggested as a cut-off point to separate patients with GRA from those with either IHA or APA.¹²¹ The distinction between GRA and other forms of primary aldosteronism becomes more obvious with long-term glucocorticoid therapy. Long-term dexamethasone (e.g., 2 mg/d for 3 weeks) in GRA (but not in other forms of primary aldosteronism) leads to recovery of the suppressed renin-angiotensin system, normalization of plasma potassium and plasma aldosterone, reduction of blood pressure, and restoration of responsiveness of the zona glomerulosa to angiotensin II.¹²²⁻¹²⁴

The need for dexamethasone suppression testing in GRA has now been obviated by the introduction of genetic testing, which is 100% sensitive and specific.^{22,125}

Measurement of Steroids Other Than Aldosterone in the Diagnosis of Primary Aldosteronism

Deoxycorticosterone and 18-Hydroxydeoxycorticosterone
Plasma DOC levels are commonly elevated in patients with angiotensin-unresponsive APAs but are usually normal in IHA, GRA, and angiotensin II-responsive adenomas.¹²⁶ The levels in PAH are similar to those in angiotensin-unresponsive APA. Isolated DOC excess may present with a clinical and biochemical picture very similar to that of primary aldosteronism.⁹² It has been suggested that such patients may have intermittent primary aldosteronism. Certainly, aldosterone levels were not suppressed in these patients as would have been anticipated if the normal aldosterone control mechanisms were intact. Measurement of 18-OH-DOC has not proved to be useful in either the diagnosis or the differential diagnosis of primary aldosteronism.

Corticosterone (Compound B) and 18-Hydroxycorticosterone
In contrast to the measurement of corticosterone in primary aldosteronism in which the plasma levels are of little diagnostic value, the assay of 18-OH-B has been reported to be useful. Patients with APA have higher levels of 18-OH-B than do normal subjects or those with IHA.¹²⁷ In the Kem and colleagues¹²⁷ series of 34 patients with primary aldosteronism,

22 of 23 who had APA had plasma 18-OH-B levels greater than 100 ng/dL. In nine patients with IHA, the levels were less than 100 ng/dL. There were two patients with unusual macromicronodular hyperplasia in whom the 18-OH-B levels were in the APA range. One might suspect that these patients had PAH. In our experience, however, and in that of others, the measurement of plasma 18-OH-B has not been a completely reliable method of distinguishing between APA and IHA.^{127,128}

18-Hydroxycortisol and 18-Oxocortisol (18-oxo-F)
18-OH-F was first identified by Ulick and Chu¹²⁹ and has been found to be the most abundant free steroid in the urine of patients with primary aldosteronism. The levels in both plasma and urine are significantly higher in patients with angiotensin-unresponsive APA than in normal subjects or patients with IHA (Figs. 128-7 and 128-8). In addition, patients with GRA usually have levels that are even higher than those found in APA.¹³⁰⁻¹³³ In contrast to the normal angiotensin II-unresponsive APA, the levels of 18-OH-F are not elevated in angiotensin II-responsive APA.¹³² There appears to be little difference in usefulness between the measurement of 18-OH-F and that of 18-oxo-F.¹³² Stowasser and colleagues¹³⁴ examined the role of ACTH in the secretion of 18-oxo-F in subtypes of primary aldosteronism. They looked at 24-hour urine 18-oxo-F, aldosterone, and cortisol levels in 11 patients with FH-I, 11 with angiotensin II-unresponsive APA, 11 with angiotensin II-responsive APA, and 10 with bilateral adrenal hyperplasia before and after 4 days of dexamethasone. Aldosterone levels were consistently suppressed to zero in FH-I. 18-oxo-F levels were suppressed by at least 60% in all patients except those with angiotensin II-responsive APA.

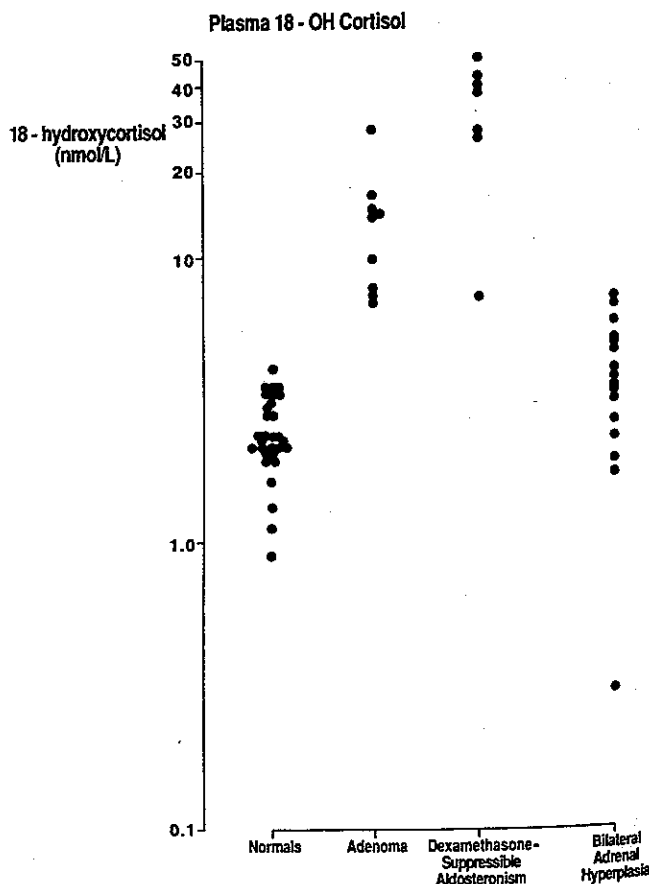


Figure 128-7 Plasma 18-hydroxycortisol levels in normal subjects and in patients with aldosterone-producing adenomas, dexamethasone-suppressible aldosteronism, and idiopathic adrenal hyperplasia.

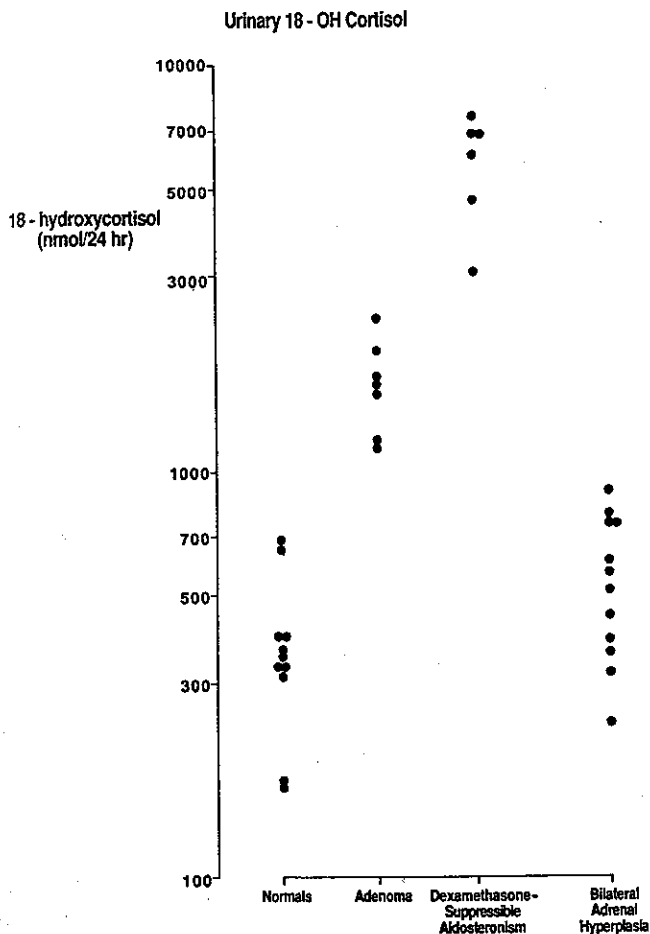


Figure 128-8 Urinary 18-hydroxycortisol excretion in normal subjects and patients with aldosterone-producing adenomas, dexamethasone-suppressible hyperaldosteronism, and idiopathic adrenal hyperplasia.

Until the introduction of genetic testing, our own practice was to use the measurement of plasma or urinary 18-OH-F as a simple screening test in patients with primary aldosteronism. Very high levels raise the possibility of GRA or APA. Normal levels make these diagnoses very unlikely, the exception being cases of angiotensin II-responsive APA. This approach is useful when deciding whether dexamethasone suppression or genetic testing is indicated. It is important to recognize that 18-OH-F levels may be markedly elevated in secondary aldosteronism and hence the need to verify that the patient has primary aldosteronism before an attempt is made to interpret the result of 18-OH-F assays.

Localization of Aldosterone Production

Adrenal Venography and Adrenal Vein Sampling Adrenal vein catheterization is technically difficult; even an experienced radiologist may be unable to enter the right adrenal vein. Complications can occur (especially adrenal hemorrhage or extravasation of contrast medium into the adrenal, which can lead to loss of function of the corresponding adrenal), but these are uncommon if adrenal venography is avoided. For this reason, it is unusual nowadays for adrenal venography to be performed and indeed many radiologists believe that it is contraindicated. When it was done, it was useful for identifying tumors larger than 1 cm in diameter, but these can now be found easily with either CT or MRI. Many authors, however, continue to regard adrenal vein sampling (AVS) as the gold standard for localization of aldosterone overproduction and recommend that it be performed in cases in which there is doubt about the differential

diagnosis on biochemical testing or when the CT or MRI scans are equivocal or normal and yet the biochemistry indicates APA.

On the side of the tumor, aldosterone-cortisol ratios measured in blood collected from the adrenal vein are significantly higher than those found in a peripheral blood sample, whereas on the contralateral side, the zona glomerulosa is suppressed and hence the aldosterone-cortisol ratios are no higher than peripheral^{118,119,121,122,135,136} (Fig. 128-9). Because of the problems involved in adrenal vein catheterization, it is important to measure both aldosterone and cortisol to determine whether the catheter is in the adrenal vein. Some authors have given ACTH to try to improve the test.⁷⁴ This overcomes the problems of intermittent aldosterone secretion and differences in endogenous ACTH when left and right adrenal vein samples are being taken. Others, however, have found that ACTH infusion leads to overproduction of aldosterone by the contralateral gland in addition to stimulating the APA and thereby lead to a false diagnosis of IHA. Even if it is not possible to enter the right adrenal vein, the measurement of aldosterone-cortisol ratios in the left adrenal vein and in the inferior vena cava can still sometimes enable correct lateralization of an adrenal adenoma.¹³⁷

Young and coworkers¹³⁸ have reviewed their experience at the Mayo Clinic with adrenal venous sampling. In a prospective study of 34 patients with primary aldosteronism 15 had a normal CT scan or minimal thickening of one adrenal limb, 6 had unilateral microadenomas, 9 had bilateral nodules, and 4 had atypical unilateral macroadenomas. Both adrenal veins were catheterized in 33 of 34 patients. Six (40%) of the patients with normal or minimal thickening on CT scan had unilateral adrenal aldosterone production. All 6 patients with microadenomas had unilateral production. Four of nine patients with bilateral masses had a unilateral source of aldosterone, as did three of the four with atypical macroadenomas. These results, if corroborated by operative pathologic findings and the therapeutic benefit of unilateral adrenalectomy, suggest that a very significant number of patients would have erroneous diagnoses if based entirely on CT findings.¹³⁸ Young et al. have also suggested that the age of the patient be taken into account when considering the need for AVS⁵⁷ (see Fig. 128-4). Thus, if there is a unilateral hypodense nodule on

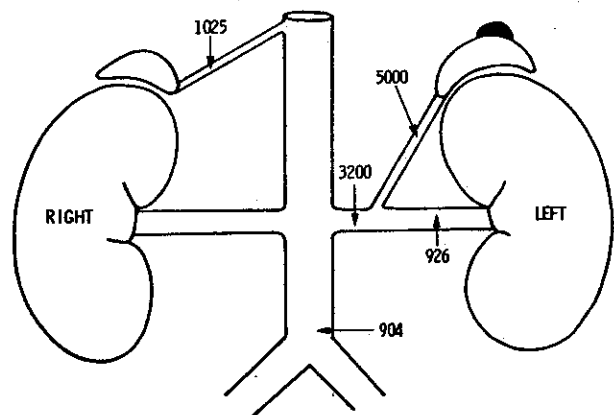


Figure 128-9 Adrenal venous catheterization study showing high levels of aldosterone in the left adrenal vein (5000 pg/mL) with a gradient into the inferior vena cava (3200 pg/mL in proximal left renal vein, 926 pg/mL in distal left renal vein). The level in the right renal vein (1025 pg/mL) is similar to that in the distal inferior vena cava (904 pg/mL), indicating suppression of the right zona glomerulosa. At surgery, a left adrenal adenoma was found. (The absolute level of aldosterone on the contralateral side is often higher than in the peripheral. It is the aldosterone-cortisol ratio that is always suppressed to peripheral levels or lower.)

CT scanning in a patient with confirmed primary aldosteronism and the patient is younger than 40 years old, the Mayo Clinic would proceed to surgery. If, however, the patient is older than 40, AVS would be considered.

Patients with PAH pose a particular diagnostic problem because CT, MRI, and isotope scanning may be either unhelpful or misleading, and yet unilateral adrenalectomy may be curative. The results of such a case are shown in Figures 128-10 (adrenal catheterization), 128-11 (selenocholesterol scan), and 128-12 (resected left adrenal). This patient was an 18-year-old boy found to have severe hypertension and hypokalemia with elevated plasma aldosterone and suppressed PRA. Adrenal vein catheterization indicated that the major source of aldosterone was the left adrenal, but the right adrenal was not suppressed. (This case was investigated before the introduction of routine measurement of cortisol in addition to aldosterone. In many cases of unilateral adenoma, blood collected from the nontumorous side shows higher aldosterone levels than in the periphery, but the aldosterone-cortisol ratio is either lower or the same as the periphery. It is suggested that this is because ACTH and potassium prevent the contralateral gland from switching off completely.) The scintiscan suggested a right adrenal lesion. Resection of the left adrenal showed macromicronodular hyperplasia and resulted in normalization of plasma aldosterone and PRA. Within 2 years of surgery, blood pressure had returned to normal and remained down. The unusual feature of this case is that, unlike the usual pattern of response found in PAH (see Table 128-4), the posture response was more typical of IHA or an angiotensin-responsive APA.

Adrenal Scintigraphy Either ^{131}I -labeled or ^{75}Se -6-selenomethylnorcholesterol can be used to image the adrenals and to distinguish between APA and IHA (Fig. 128-13). Dexamethasone pretreatment and an improved scanning agent, $[\beta\text{-}^{131}\text{I}]\text{iodomethyl-19-norcholesterol}$, have heightened the accuracy of diagnosis compared with that of the initially used $[\text{I}^{131}]\text{19-iodocholesterol}$.¹³⁹⁻¹⁴² It is important to know that previous treatment with spironolactone may vitiate the test (this medication should be stopped for 6 weeks). The dose of dexamethasone used has usually been greater than that required to suppress ACTH (i.e., 1 mg four times daily). Lugol's iodine solution or potassium iodide should be given before the iodocholesterol to block thyroid uptake.

The criteria used to make the distinction between APA and IHA appear to be important. In one study of 30 patients with APA and 20 patients with IHA, the authors looked at $[\beta\text{-}^{131}\text{I}]\text{iodomethyl-19-norcholesterol}$ uptake at 5 days and

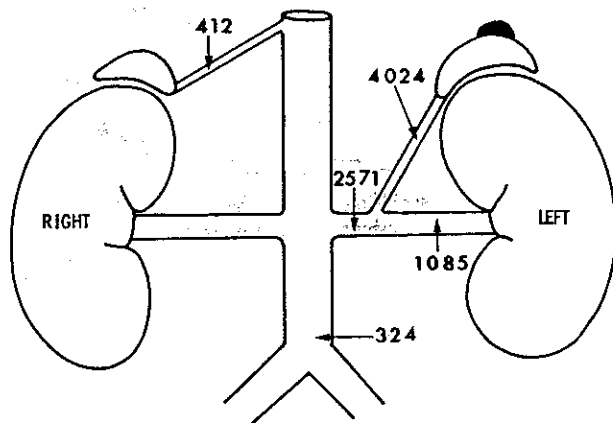


Figure 128-10 Adrenal venous catheterization study in an 18-year-old boy with severe hypertension, hypokalemia, elevated plasma aldosterone, and suppressed plasma renin activity. (See text for details.)

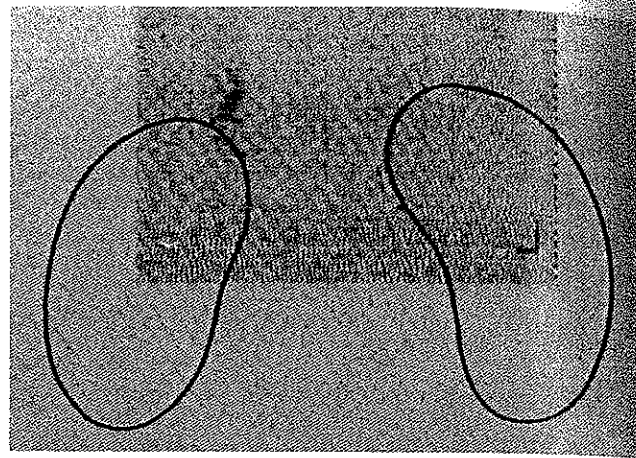


Figure 128-11 Adrenal scintiscan in a patient with primary adrenal hyperplasia showing uptake in the right adrenal (i.e., the gland contralateral to that which the catheter study suggested was the major source of aldosterone).

found that nearly one half of the patients with APA had bilateral uptake and that nearly one fourth of patients with IHA had marked asymmetric uptake.¹³⁹ Thus, this single measurement would not have been useful in distinguishing APA from IHA. The authors suggested that it was necessary to look at the pattern of adrenal imaging and that, on dexamethasone, early unilateral or early bilateral (i.e., <5 days) uptake was the best indication of the diagnosis.¹³⁹

In reviewing the literature, Young and Klee¹⁴³ suggested that the accuracy (i.e., percentage of correct diagnoses) of iodocholesterol scintigraphy was 72% versus 73% for CT scanning and 95% for AVS in which both adrenal veins were sampled. In other series, however, less satisfactory results were reported. Pagny and coworkers,¹⁴² in a series of 160 patients with primary aldosteronism, found that scintigraphy was accurate in only 27 (53%) of 51 examinations, whereas CT scanning was accurate in 70 (82%) of 85 examinations. However, it is important to recognize that scintigraphic scanning has a potential, if not always realized, advantage over CT scanning of correlating function with anatomic abnormality.

In adrenal carcinomas causing Cushing's syndrome, it is common to find that there is a failure of uptake of iodocholesterol, by either the tumor or the suppressed adrenals. In mineralocorticoid excess associated with adrenal carcinoma, uptake of iodocholesterol has been reported in both the primary tumor and in metastases.¹⁴⁴

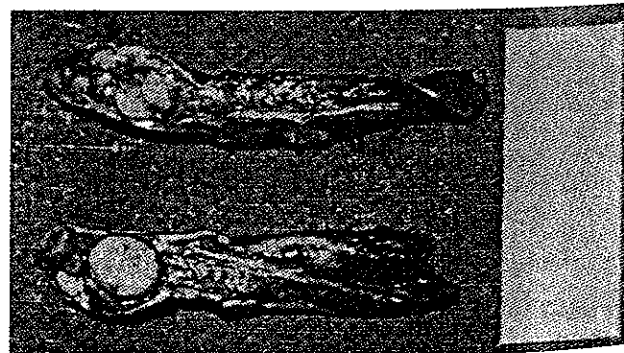


Figure 128-12 Resected left adrenal in patient with apparent primary adrenal hyperplasia. Histology confirmed macronodular and micronodular hyperplasia. (For details, see text.)

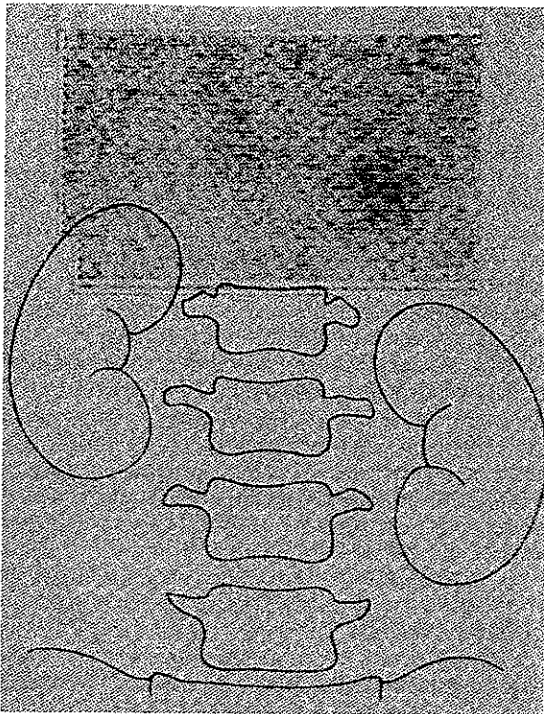


Figure 128-13 Adrenal scintigraphy with ^{75}Se -cholesterol in patient with left adrenal adenoma showing uptake in the region of the left adrenal but no uptake on the right.

Computed Tomography and Magnetic Resonance Imaging of Adrenals In many institutions, either CT or MRI is used at an early stage in an attempt to determine the differential diagnosis in a patient with diagnosed primary aldosteronism. It is important to recognize that the early CT scanners with their poor resolution missed many small tumors. With modern CT and 3-mm contiguous sections, it is possible to accurately diagnose tumors down to 7 mm in diameter.¹⁴⁵⁻¹⁴⁸ The historical changes in CT scanning in primary aldosteronism were studied by Balkin and associates.¹⁴⁵ They reviewed the value of CT in 34 patients with primary aldosteronism who were divided into two groups: those undergoing CT between 1977 and 1980 (group 1) and those undergoing CT between 1981 and 1983 with a high-resolution GE-8800 scanner (group 2). The results of CT scanning were compared with those of other diagnostic methods, including AVS, findings at surgery, and response to unilateral adrenalectomy. Overall, CT was not sensitive (48%) but was very specific (91%) (i.e., few false positives but many false negatives). In a comparison of group 1 with group 2, the results in the latter showed no significant improvement in specificity (92%) but a definite improvement in sensitivity (58%) (group 1: sensitivity, 42%; specificity, 90%). Despite the improvement, it is clear that a significant number of tumors can still be missed even with modern CT scanning.

There have been few direct comparisons of CT and MRI results in identifying adrenal lesions.^{142,145,147} In the Paris series, CT scanning gave a correct diagnosis in 82% of cases of APA and MRI in 100%.¹⁴² However, there was no direct comparison between the two techniques. Ou and colleagues¹⁴⁶ compared retrospectively five methods of localization in 22 patients with operative confirmation of APA. Correct localization of the lesion was obtained in 95% (20 of 21) by CT, 100% (7 of 7) by MRI, 80% (12 of 15) by dexamethasone suppression- ^{131}I -19-cholesterol scintiscan, 100% (6 of 6) by AVS, and 78% by venography (7 of 9). The authors advocate CT of the adrenals as the first means of localizing an adenoma, on the basis of comfort, safety, and cost. They suggested that AVS

should be reserved for patients in whom the biochemical findings suggest an APA but for whom CT, MRI, and scintiscans are inconclusive.

Rossi and coworkers¹⁴⁷ carried out a prospective comparison of CT and MRI in 27 patients with suspected primary aldosteronism. They found 13 patients with unilateral APA (11 on the left, 2 on the right). The diagnosis was confirmed at surgery and by pathologic examination. MRI correctly identified all cases of APA but gave false-positive results in five cases (one with idiopathic hyperaldosteronism with bilateral nodular hyperplasia and four with essential hypertension of whom two had nonfunctioning adenomas). The sensitivity of MRI was thus 100%, the specificity was 64%, and the overall diagnostic accuracy was 81%. In comparison, CT correctly recognized only 8 of 13 APAs and gave false positives in 3 patients with essential hypertension including the 2 with nonfunctioning adenomas. The sensitivity of CT was thus 62%, the specificity was 77%, and the overall diagnostic accuracy was 69%. These results underline the dangers of relying totally on a morphologic approach that may miss small tumors or produce false positives in patients with nonfunctioning adrenal tumors. Because such tumors may be present in approximately 20% of patients with essential hypertension, the risk is not inconsiderable.

In a series of 29 patients reviewed by Dunnick and associates,¹⁴⁸ the sensitivity of CT scanning was 82% (14 of 17 APAs detected). Their view was that if the CT scan in a patient with primary aldosteronism showed a focal mass, ipsilateral adrenalectomy could be performed. If no mass was found, AVS should be performed. However, Stowasser and colleagues¹⁰⁴ found CT scanning to detect an adrenal mass lesion in only 56 (50%) of 111 patients with surgically proven APA diagnosed with primary aldosteronism (PAL) between 1992 and 1999, and in only one fourth of those with APAs less than 1 cm in diameter, which accounted for almost half of APAs removed. CT was also frankly misleading in 12 patients in whom CT demonstrated a definite or probable mass lesion in one adrenal but who showed lateralization of aldosterone production to the other on AVS. The inability of CT to distinguish APAs from most apparently nonfunctioning "incidentalomas" is not surprising given that these lesions may be indistinguishable on gross and histopathologic examination. For these reasons, the Brisbane group advocate AVS in all patients with primary aldosteronism (other than those found to have GRA by genetic testing), regardless of CT findings.

In addition to the morphologic diagnosis, attempts have been made to use CT attenuation values to distinguish adenomas from other lesions such as metastases, adrenal carcinoma, and pheochromocytoma. Korobkin and colleagues¹⁴⁹ showed that the mean attenuation value of unenhanced CTs of adenomas was significantly lower than in nonadenomas.

Treatment

Treatment depends on the cause of the primary aldosteronism, the medical condition of the patient, and various other factors such as adverse drug effects. In general, patients with APA and PAH are recommended to have surgical treatment, whereas medical treatment with aldosterone antagonists and other drugs is offered to patients with IHA.

Surgical Treatment

In a patient who is fit for surgery and who has APA, the usual treatment is unilateral adrenalectomy. Treatment of patients before surgery with spironolactone is often worthwhile because patients tend to have a smoother perioperative course with respect to control of blood pressure and plasma potassium levels, and treatment can result in significant improvements in clinical status (including reductions in left ventricular mass and improved left ventricular function) and fitness for surgery. Relatively low doses (12.5–50 mg daily) are

usually sufficient for reducing blood pressure, provided weeks or months are given to allow a maximal response. Such doses are much less likely to induce side effects (gynecomastia, reduced libido, menstrual irregularity, and hyperkalemia) that were common among patients treated with the much higher doses used previously.

Transperitoneal laparoscopic adrenalectomy is now the standard approach for the removal of adrenal tumors (see also Chapter 131). Terachi and colleagues¹⁵⁰ reported on a series of 100 such operations (APA, 41 patients; Cushing's syndrome, 15; nonfunctioning adenoma, 22; myelolipoma, 3; pheochromocytoma, 7; complicated adrenal cyst, 3). The mean \pm SD operative time was 240 ± 76 minutes. Only three operations had to be converted to open surgery. The authors concluded that laparoscopic adrenalectomy via the transperitoneal anterior approach can be equivalent to open surgery but has a shorter convalescence.¹⁵⁰ Similar results have been reported by Rutherford and associates¹⁵¹ from Brisbane in a series of 67 successful adrenalectomies, but operation times were considerably shorter (124 ± 47 minutes).

Nakada and colleagues¹⁵² have compared unilateral adrenalectomy with enucleation of the adenoma (22 unilateral versus 26 enucleation). Both methods had similar effects on blood pressure, plasma potassium, PRA and plasma aldosterone, cortisol, and ACTH. However, 5 years after surgery, the enucleation group showed significantly greater PRA and plasma aldosterone responses to sodium deprivation and diuretics than the patients who underwent unilateral adrenalectomy. On this basis, they suggest that enucleation is to be preferred. However, this approach has the potential to result in suboptimal correction of primary aldosteronism because it relies on the assumption that the removed adenoma is the correct and sole source of aldosterone excess.

After surgery, the blood pressure usually decreases progressively over a period of weeks to months. In the series of Itoh and associates¹⁵³ of 60 patients with primary aldosteronism, 36 (60%) were normotensive at 1 month after surgery and 46 (76%) by the second year. By the fifth year, 42 (70%) remained normotensive. This is very similar to the 69% long-term cure rate for unilateral adrenalectomy for APA based on 694 cases from 20 reports. Itoh and associates found that the best predictor of blood pressure at 2 months was the duration of hypertension before surgery; at 6 months and 1 year, the adrenal histology was predictive. By year 5, the most important predictor was whether there was a family history of hypertension.¹⁵³ Comparison of surgery with treatment with long-term spironolactone suggests that surgery for APA is more likely to lead to normalization of blood pressure.¹⁵⁴ Furthermore, patients undergoing surgery for APA consistently report marked improvement in quality of life to a degree that is more apparent than with treatment with spironolactone.

Medical Treatment

Not surprisingly, a diet with less than 80 mEq of sodium per day is a useful adjunct to other therapy. After starting spironolactone treatment, blood pressure control may take several weeks in contrast to hypokalemia correction, which is rapid. The most common adverse effects of spironolactone are impotence, gynecomastia, and menstrual dysfunction. The adverse endocrine effects may relate to the metabolism of the drug. The metabolites are divided into those that contain sulfur (such as the main metabolite 7α -thiomethylspironolactone) and those that do not (e.g., canrenone). It has been suggested that the effects such as gynecomastia are due to cross-reactivity of the sulfur-containing metabolites with sex steroid receptors. The response of the renin-angiotensin-aldosterone axis to treatment with spironolactone may help in difficult cases to distinguish between APA and IHA. In patients with APA treated with spironolactone, there was reported to be no increase in plasma or urinary aldosterone even though normalization of plasma potassium and an

increase in PRA occurred.¹⁵⁵ In contrast, in IHA, there was a two- to threefold increase in plasma and urinary aldosterone levels. In patients developing adverse effects on spironolactone, the drug of choice is amiloride (2.5–20 mg daily). This is an inhibitor of renal tubular ionic transport rather than an aldosterone antagonist. The antihypertensive effect is generally less potent than that of spironolactone, and in some patients a combination of each drug in low doses is a useful approach.

Patients with IHA should be treated medically. In 99 patients with IHA treated by either unilateral or bilateral adrenalectomy, only 19 (19%) were cured.¹⁴³ It is unclear how many who were in this category did not have IHA but rather had PAH. The usual approach to medical treatment of IHA is to start with spironolactone or amiloride. Despite improvement in electrolyte status, the blood pressure response is often suboptimal and additional drugs are required. Several have been used, including calcium-channel blocking agents such as nifedipine and ACE inhibitors.

The effects of calcium-channel blocking drugs have been reported in both APA and IHA. In 10 patients with primary aldosteronism (5 with APA, 5 with IHA), nifedipine, both acute and long-term (4 weeks) treatment, lowered blood pressure, normalized serum potassium, and reduced plasma aldosterone in both groups.¹⁵⁶ These results contrasted with those of nitrendipine given to three patients with APA and three with IHA for 4 weeks (40–60 mg/d).¹⁵⁷ In three patients with APA and two with IHA, there was a significant reduction in blood pressure, but no change in serum potassium, PRA, or aldosterone. However, in one patient with IHA, there was a marked effect with normalization of blood pressure and biochemistry. It was not clear why results in this patient differed from those in the others. Opocher and colleagues¹⁵⁸ studied the effect of verapamil infusion on aldosterone levels in 11 patients with primary aldosteronism (5 with IHA, 6 with APA). They found that aldosterone levels fell in IHA but not in APA. This lack of effect of calcium-channel blocking drugs in APA on aldosterone has been found by others.¹⁵⁹

The mechanism of action of calcium-channel blocking drugs in primary aldosteronism is unclear. Given the sensitivity of the adrenal zona glomerulosa to angiotensin II in IHA and the key role of an angiotensin II-induced increase in intracellular calcium in stimulating aldosterone secretion, it might be anticipated that the drugs might affect aldosterone secretion in IHA. Kramer and associates¹⁶⁰ suggested an alternative mechanism that could be relevant to both IHA and APA. Extracellular fluid volume expansion leads to the secretion of an endogenous inhibitor of Na^+/K^+ -ATPase; high levels have been found in primary aldosteronism. Ouabain, a known inhibitor of Na^+/K^+ -ATPase, when given to normal volunteers not only inhibits the enzyme but also increases peripheral vascular resistance. They found that this effect could be blocked by nifedipine.

ACE inhibitors have been shown to be effective in IHA. Enalapril lowered blood pressure and aldosterone secretion and improved plasma potassium levels.¹⁶¹ As already discussed, this effect may relate to blockade of the intrarenal renin-angiotensin system in IHA.

Drugs that block the synthesis of aldosterone have also been investigated. Trilostane, an inhibitor of 3β -hydroxysteroid dehydrogenase (3β -HSD), has been shown to lower blood pressure in both APA and IHA.¹⁶² However, there is very little experience with the long-term use of this compound. The adrenolytic drug mitotane is of value in aldosterone-secreting carcinomas.¹⁶³

In GRA, exogenous glucocorticoid is highly effective in controlling hypertension. It is not necessary to completely suppress ACTH to achieve normotension, and the lowest dose that maintains normal blood pressure should be given.¹⁶⁴ Treatment leads within 2 weeks to a return of plasma potassium, aldosterone, and PRA levels to normal with reduction of

blood pressure. Spironolactone, amiloride, and triamterene are alternatives.

ANGIOTENSIN II-RESPONSIVE ALDOSTERONE-PRODUCING ADENOMA

As discussed, angiotensin II-responsive APA is now recognized as an important subgroup of APA.^{110,116-118} It may account for as many as 50% of cases. The importance of the condition is that it may be confused biochemically with idiopathic adrenal hyperplasia (e.g., elevation of plasma aldosterone on standing). This confusion may result in a failure to diagnose an adenoma that could have been surgically resected.

PRIMARY ADRENAL HYPERPLASIA

The separate identification of PAH from IHA has been an important advance.^{39,40,60} The hyperplasia in PAH may be either bilateral or unilateral. Tests are indicative of an adenoma (see Table 128-4), but CT scans either suggest bilateral or unilateral hyperplasia. Basal plasma aldosterone levels are higher than in most patients with IHA and fail to decrease with saline infusion. The 18-OH-F and 18-oxo-F levels are higher than in IHA but lower than with most tumors. Spironolactone therapy is often effective not only in normalizing plasma potassium but in reducing blood pressure. In contrast to IHA, surgery by unilateral, subtotal, or bilateral adrenalectomy may be curative.⁶⁰

ALDOSTERONE-PRODUCING ADRENAL CARCINOMA

Aldosterone-producing carcinoma is a relatively rare cause of primary aldosteronism, with a suggested incidence of approximately 3% to 5% of aldosterone-producing tumors.¹⁶⁵ However, it would seem likely that these figures are a gross overestimate given the recent evidence of the much higher than expected prevalence of primary aldosteronism.^{163,166-169} The prognosis is poor, with a median survival rate of 14 months and a 5-year survival rate of 24%.¹⁷⁰ The diagnosis may be suspected from the clinical presentation because the tumors may secrete cortisol or adrenal androgens, or both, in addition to aldosterone. However, supine plasma aldosterone, the plasma aldosterone response to standing, and plasma cortisol taken at 9:00 A.M. may be similar to those found in patients with APA.¹⁶⁵ However, the 24-hour urinary free cortisol may be elevated, as may urinary 17-oxosteroids, reflecting the increased adrenal androgen secretion. The diagnosis may first be suspected on CT or MRI scanning. The presence of an adrenal tumor greater than 3 cm in diameter with associated biochemistry of primary aldosteronism should alert the clinician to this diagnosis. APAs are rarely larger than 2 cm in diameter. As discussed in the section on pathology, the presence of calcification in an adrenal tumor should be regarded with suspicion because this is not found in APA.¹⁶⁵ Unlike cortisol-secreting adrenal carcinomas, aldosterone-producing carcinomas may take up the labeled cholesterol adrenal scanning agent [β -¹³¹I]iodomethyl-19-norcholesterol, which may also localize metastases.¹⁴⁴

Treatment is with adrenalectomy, which is not curative but may be palliative. Mitotane has produced some benefit.¹⁶³

GLUCOCORTICOID-REMIABLE ALDOSTERONISM

GRA, first described by Sutherland and coworkers,¹⁷¹ has an autosomal-dominant mode of inheritance. The condition is rare; in a 1990 review, Fallo¹⁷² noted that only 51 cases had been described in the literature. However, it is likely that this is a gross underestimate and that many cases have remained undiagnosed. The most common feature of the syndrome is hypertension, often found in asymptomatic young people.

The diagnosis has often been made on evaluation of patients with hypertension refractory to usual antihypertensive therapy. The presence of hypokalemia has suggested the possibility of mineralocorticoid excess. However, it is now clear that many patients with this syndrome are normokalemic despite marked aldosterone excess with suppression of the renin-angiotensin system.^{22,173,174} The reason for this is unknown. This situation is not unique to GRA, however, in that it has become apparent that the majority of patients with other forms of primary aldosterone excess are also normokalemic. As might be expected, total body exchangeable sodium and potassium in milder cases are also not typical of the picture found in Conn's syndrome.¹⁷⁵

The pathophysiology of the syndrome has already been detailed. The condition results from a chimeric gene that combines the regulatory sequences of the 11 β -hydroxylase gene with the coding region of the aldosterone synthase gene²² (see Fig. 128-1). This results in the expression of aldosterone synthase in both the zona fasciculata and zona glomerulosa and produces a novel ACTH control system. Thus, in contrast to the normal zona glomerulosa, which is suppressed by chronic ACTH excess (e.g., as in 17 α -hydroxylase deficiency), ACTH is the dominant control mechanism of aldosterone secretion in GRA. Thus, chronic exogenous ACTH given to patients with GRA results in persistent elevation in aldosterone secretion.¹⁷⁶

The diagnosis, differential diagnosis, and treatment of GRA have been considered in the section on primary aldosteronism. An International Registry for Glucocorticoid-Remediable Aldosteronism has been established at Brigham and Women's Hospital at Harvard Medical School. This offers a 7-day genetic screening test for the condition that is 100% sensitive and 100% specific. It would seem that this will result in a significant increase in the diagnosis of this important condition. Further to the introduction of the original test, a polymerase chain reaction-based method has now been introduced and allows very rapid diagnosis, even in neonates.¹²⁵

MINERALOCORTICOID OTHER THAN ALDOSTERONE

17 α -HYDROXYLASE DEFICIENCY

17 α -Hydroxylase deficiency is an autosomal-recessive condition that is a rare cause of mineralocorticoid hypertension. It was first described by Biglieri¹⁷⁷ in 1966. Impairment of cortisol biosynthesis results in increased ACTH secretion and stimulation of excess production of DOC and corticosterone. In the classic form, aldosterone secretion is suppressed, but in a new variant, aldosterone secretion was found to be increased.^{178,179}

Lack of 17-hydroxylase and 17,20-desmolase activity results in deficient formation of sex steroids with consequent absence of secondary sex characteristics (primary amenorrhea in females and pseudohermaphroditism in males). Hypertension, hypokalemia, and primary amenorrhea in a female are thus highly suggestive of the diagnosis. In a male, the lack of sex steroids results in hypospadias with very small testes. The plasma steroid profile is characteristic, with elevated DOC, 18-OH-DOC, corticosterone (B), and 18-OH-B and low levels of 17 α -hydroxyprogesterone, 11-deoxycortisol, cortisol, and aldosterone. Elevated DOC levels retain sodium and thus suppress the renin-angiotensin system. In the urine, 19-nor-DOC levels are markedly elevated (see "11 β -Hydroxylase Deficiency"), and this steroid may play a pathogenic role as a mineralocorticoid. The combination of hypertension, hypokalemia, low PRA, and low plasma aldosterone means that this condition must be distinguished from Liddle's syndrome, congenital or acquired 11 β -HSD type 2 enzyme (11 β -HSD2) deficiency, exogenous mineralocorticoid administration, 11 β -hydroxylase deficiency, and isolated DOC or corticosterone excess. In adults, this is easy because

of the association of mineralocorticoid excess with gonadal failure. In children, the clinical picture may be less obvious, and further investigation is required. Children with 11β -hydroxylase deficiency can, however, be distinguished by the excess production of adrenal androgens with consequent virilization.

Treatment consists of giving a glucocorticoid dose sufficient to suppress ACTH secretion and hence DOC and corticosterone secretion. Dexamethasone is commonly used in doses ranging from 0.25 to 1.5 mg/d. This dose is often split, with a larger dose being given just before going to bed (e.g., 0.5 mg at night and 0.25 mg in the morning) to more effectively suppress the morning "surge" in ACTH release. It is important to recognize that suppression of DOC is rapid but that the renin-angiotensin-aldosterone system may take months or years to recover. Glucocorticoid therapy may thus produce mineralocorticoid deficiency that may require treatment acutely. In the majority of patients given glucocorticoid therapy alone, the renin-angiotensin-aldosterone axis recovers.

Sex hormone replacement therapy is usually also necessary. In the older woman, there is debate about estrogen replacement therapy because of the associated psychological and menstrual changes. Also, surprisingly, osteoporosis does not seem to be a problem despite the low levels of gonadal steroids.¹⁸⁰ In the male with no signs of virilization, bilateral orchidectomy, surgical creation of a vagina, and estrogen replacement therapy are options.

The hypertension usually responds to glucocorticoid replacement therapy. However, in the older patient with long-established hypertension, the blood pressure may not be adequately controlled and additional therapy with drugs such as calcium-channel blocking agents (e.g., nifedipine) may be required. The molecular genetics of this syndrome are detailed in Chapter 124.

11 β -HYDROXYLASE DEFICIENCY

As with 17α -hydroxylase deficiency, 11β -hydroxylase deficiency is a rare cause of mineralocorticoid hypertension. The deficiency results in a failure of the normal conversion of DOC to corticosterone (B) and of 11-deoxycortisol to cortisol. The latter activates negative feedback control of ACTH, which stimulates an increase in DOC and adrenal androgen production. The most common form of congenital adrenal hyperplasia results from 21 -hydroxylase deficiency. In contrast, 11β -hydroxylase defects contribute only approximately 8% to 16% of cases.¹⁸¹

The clinical features of the condition are mineralocorticoid hypertension associated with hyperandrogenism. However, the expression of the features is very variable with mild, moderate, or severe virilization and blood pressure levels that can be normal or severely elevated.¹⁸² In an early series of patients, hypertension was a common feature (80%), but in a more recent series, only 40% were hypertensive.¹⁸¹ This may relate to age at diagnosis because there is a significant correlation between this and systolic blood pressure. Although the hypertension is thought to result from DOC excess, the mechanism is not clear. The level of blood pressure does not correlate with plasma DOC levels. This might suggest that a metabolite rather than DOC itself is responsible. One possibility might be 19-nor-DOC, which was isolated by Gomez-Sanchez and colleagues.¹⁸³ This is a potent mineralocorticoid that binds with a high affinity to the mineralocorticoid receptor (MR). In normal subjects, this steroid is found in the urine and not in the plasma; it is thought to be synthesized in the kidney from a circulating precursor, 19-oxy-DOC. Surprisingly, even though 19-nor-DOC is markedly elevated in the urine of patients with 17α -hydroxylase deficiency (40 times normal), this does not seem to be the case in 11β -hydroxylase deficiency, in which levels are either normal or only modestly elevated.¹⁸⁴

Unlike in 17α -hydroxylase deficiency, the diagnosis may be suspected at an early age either because of virilization of the female with clitoromegaly or pseudoprecocious puberty in boys. The immediate distinction between 11β -hydroxylase and 21 -hydroxylase deficiency is most readily made by measurement of PRA, which is suppressed or low in 11β -hydroxylase deficiency and elevated in 21 -hydroxylase deficiency. Serum potassium is usually reduced. Plasma cortisol and corticosterone are low with elevated levels of 11-deoxycortisol. Plasma DOC levels are often approximately 150-fold higher than normal.

Treatment is with an adequate dose of glucocorticoid; the doses and preparations used are detailed in Chapter 124. As with 17α -hydroxylase deficiency, glucocorticoid therapy may result in a salt-losing crisis because the zona glomerulosa is atrophic. However, with chronic glucocorticoid therapy, the renin-angiotensin-aldosterone axis recovers. Similar to the results of treatment in 17α -hydroxylase deficiency, hypertension normally responds well to adequate glucocorticoid therapy. However, the dose has to be carefully monitored because excess glucocorticoid may cause hypertension as well as suppress growth. The molecular basis of the syndrome has become clear with the separate identification of 11β -hydroxylase and aldosterone synthase.^{185,186} These two enzymes have 88% homology in the DNA coding regions but only 52% homology in the 5' flanking region, in keeping with their very different transcriptional control mechanisms. The molecular genetics of this syndrome are detailed in Chapter 124.

DEOXYCORTICOSTERONE

The administration of DOC in the form of DOC acetate has long been used in animal models of salt-dependent hypertension.¹⁸⁷ Elevation of endogenous DOC induced by administration of the 11β -hydroxylase inhibitor metyrapone can also produce mineralocorticoid hypertension in dogs.¹⁸⁸ However, chronic metyrapone administration in humans does not usually produce mineralocorticoid hypertension.¹⁸⁹ In contrast to aldosterone, DOC is under predominant ACTH control; however, there is evidence suggesting that a pituitary factor other than ACTH may control DOC secretion.⁶⁴ The circulating levels of DOC are similar to those of aldosterone, but its mineralocorticoid activity is significantly less and its protein binding greater. DOC overproduction causing mineralocorticoid excess in humans may be either primary or secondary to ACTH excess. Primary deoxycorticosteronism may be caused by an adrenal adenoma, malignancy, or hyperplasia.⁶⁰ The syndrome should be suspected in patients with hypertension, hypokalemia, suppression of the renin-angiotensin-aldosterone axis, or increased excretion of 17-deoxycorticosteroids. Plasma DOC levels are often very high. If the syndrome is secondary to ACTH excess, then high levels of 17-hydroxycorticosteroids will also be produced.

In patients with primary aldosteronism due to an adrenal adenoma, plasma DOC levels are not uncommonly elevated. In a series of 44 patients with APA studied by Biglieri,¹²⁶ the mean plasma DOC level was approximately four times normal. The plasma DOC levels in PAH were also often elevated in compared with the normal levels found in most patients with IHA.

In patients with "pure" DOC-producing adenomas, plasma and urinary aldosterone levels have been found to be suppressed.¹⁹⁰ These patients otherwise have all the typical clinical and biochemical features of primary aldosteronism.^{191,192} The investigation and treatment of the patients is the same as for patients with suspected primary aldosteronism except that diagnostic criteria are based on DOC rather than aldosterone levels. Spironolactone is given before surgery, and unilateral adrenalectomy with removal of the adenoma has produced long-term cure.^{190,191} After surgery, Irony and colleagues¹⁹² have reported that DOC production by the contralateral

adrenal cannot be stimulated by ACTH, in contrast to cortisol. This is part of the evidence suggesting that there may be a factor other than ACTH controlling DOC.

Adrenal carcinomas producing DOC exclusively are uncommon. The patients usually have hypertension and hypokalemia but may present because of the symptoms associated with a rapidly enlarging adrenal mass or metastases.^{190,193,194} Aldosterone and renin levels are low. If there is associated corticosterone excess, plasma ACTH and cortisol may be low. As with other forms of adrenal carcinoma, the prognosis is poor, but long-term benefit from adrenalectomy has been reported.^{194,195}

Isolated DOC excess has been reported in some apparent LREH.¹²⁶ In these patients, aldosterone was not suppressed. DOC secretion may be increased in all types of Cushing's syndrome.

CORTICOSTERONE

Isolated corticosterone excess is a rare cause of mineralocorticoid hypertension. Corticosterone-producing adrenal tumors are usually carcinomas.^{196,197} Because of sodium retention and suppression of the renin-angiotensin system, aldosterone levels are low. As already discussed, corticosterone levels are elevated in patients with 17 α -hydroxylase deficiency; 18-OH-B levels are elevated in some with classic APA and PAH but rarely in IHA or angiotensin II-responsive APA. It has been suggested that some other steroids derived from corticosterone (18-hydroxy-19-norcorticosterone and 18,19-dihydroxycorticosterone) possess mineralocorticoid and hypertensinogenic activity and may play a pathogenic role.¹⁹⁸ These steroids appear to be produced *in vitro* by APAs.

CONGENITAL APPARENT MINERALOCORTICOID EXCESS SYNDROME

In 1979, Ulick and associates¹⁹⁹ described two children with hypertension, hypokalemia, and suppression of the renin-angiotensin-aldosterone system. In addition, the pattern of urinary steroid excretion indicated impairment of the conversion of cortisol to cortisone. This suggested that there might be a deficiency of the enzyme responsible for the conversion, 11 β -HSD (now known as 11 β -HSD2). Bioassays of plasma and urine failed to identify any excess mineralocorticoid. The investigators coined the expression apparent mineralocorticoid excess (AME) syndrome to highlight the enigma and thus drew attention to the difference between the clinical and biochemical pictures and the negative assays for known mineralocorticoids or mineralocorticoid activity. AME syndrome can be defined based on the association of hypertension, hypokalemia, suppression of the renin-angiotensin-aldosterone system, and defective inactivation of cortisol in mineralocorticoid target tissues.

Prevalence

AME syndrome is very rare with fewer than 50 cases in the world literature^{62,200} of the type originally described (i.e., with defective 11 β -HSD2 activity as assessed by the pattern of urinary steroid excretion). Even rarer is the type 2 variant of the syndrome in which there is the same clinical picture and basic biochemistry but in which the ratio of urinary cortisol to cortisone metabolites is normal.^{201,202}

Etiology and Pathophysiology

The molecular basis of AME syndrome is now known to be due to loss-of-function mutations in the gene coding for 11 β -HSD2. Its importance lies in the insight that it has provided into the tissue-specific role of 11 β -HSD.

Our studies with congenital and acquired (see "Licorice and Related Drugs") 11 β -HSD deficiency led us to conclude that the enzyme might play an important role in the protection of

the mineralocorticoid receptor (MR).^{203,204} Previous work by Krozowski and Funder²⁰⁴ had shown that the purified MR (otherwise called type I receptor) was nonselective and did not distinguish between cortisol, corticosterone, and aldosterone. Similar results were published by Arriza and colleagues²⁰⁵ when they expressed the cloned human MR in a cell line. These results were remarkable given that cortisol circulates at a 100-fold or higher free concentration than does aldosterone. Thus, there had to be some mechanism other than the receptor structure that allowed aldosterone selective access and denied cortisol. Stephenson and colleagues²⁰⁶ suggested that this might be extravascular cortisol-binding globulin that bound cortisol in preference to aldosterone. However, in the 10-day-old rat that is deficient in cortisol-binding globulin, the *in vivo* selectivity of the MR was still maintained.²⁰⁷

We put forward the hypothesis that the selectivity of the type I MR was due to the presence of 11 β -HSD in the kidney.²⁰⁸ In our model, the enzyme prevented cortisol from gaining access to the receptor by metabolizing active cortisol to inactive cortisone (Fig. 128-14). To prove this, we carried out studies in which labeled glucocorticoid (³H-corticosterone) was given to an adrenalectomized rat and then performed autoradiography on the kidney. An insignificant amount of the isotope was taken up by the kidney. When, however, this experiment was repeated after treatment of the rat with glycyrrhizic acid (converted to glycyrrhetic acid [GE] *in vivo*) (see "Licorice and Related Drugs"), there was now marked uptake of the label in the distal nephron. A subsequent study showed that this could be displaced by unlabeled aldosterone, indicating that it was bound to renal MR.²⁰⁸ Our explanation was that inhibition of 11 β -HSD now allowed direct access of glucocorticoid to the nonspecific MR (see Fig. 128-14).

For this mechanism to be effective, it is vital that aldosterone is not a substrate for 11 β -HSD. At first sight of the structure of aldosterone with an 11 β -hydroxyl group, it might be anticipated that this would be true (Fig. 128-15). However, further study has shown that aldosterone does not appear to exist in the 11 β -hydroxy, 11 β -aldehyde form. At physiologic pH, the predominant species would appear to be one with an 11,18-hemiacetal bridge.²⁰⁹ This allows aldosterone to "cross the moat" of the enzyme and gain selective access.

Further work has shown that this protective mechanism is an autocrine rather than a paracrine system.^{210,211} The isoform of the enzyme in the distal nephron is distinct from that in the liver, being nicotinamide adenine dinucleotide dependent rather than nicotinamide adenine dinucleotide phosphate dependent.²¹²⁻²¹⁵ The liver enzyme is now known as 11 β -HSD1, and the kidney protector of the MR as 11 β -HSD2. The former is responsible for the conversion of cortisone to cortisol and plays a key role in the control of intrahepatic glucocorticoid levels and thus gluconeogenesis. This has been clearly demonstrated in mice in which this enzyme has been knocked out by homologous recombination.²¹⁶ The kidney enzyme has also been knocked out with the consequent production of animals with all the features of the AME syndrome.²¹⁷ It would seem likely that this enzyme-mediated protection of MR is highly conserved. Experiments using the toad bladder have shown that the enzyme is present in the bladder and that carbenoxolone treatment results in marked potentiation of sodium transport in response to corticosterone.^{218,219}

As already indicated, there appear to be two types of AME. In the type 2 syndrome, cortisol metabolism is impaired, as indicated by the markedly reduced cortisol metabolic clearance rate.^{201,202,220} However, the ratio of urinary cortisol to cortisone metabolites is normal. Ulick and associates²²¹ put forward the idea that the major metabolic error in AME syndrome is defective A ring reduction of cortisol rather than a failure of 11 β -hydroxydehydrogenation. It has been found, however, that it is possible to have marked impairment of 11 β -HSD without a change in the ratio of cortisol to cortisone

metabolites (see subsequent discussion of carbenoxolone). The normal cortisol-cortisone ratio in the AME type 2 syndrome cannot be used to infer that 11β -HSD is normal, and indeed studies using labeled cortisol (see later) have demonstrated that there is indeed defective conversion of cortisol to cortisone.

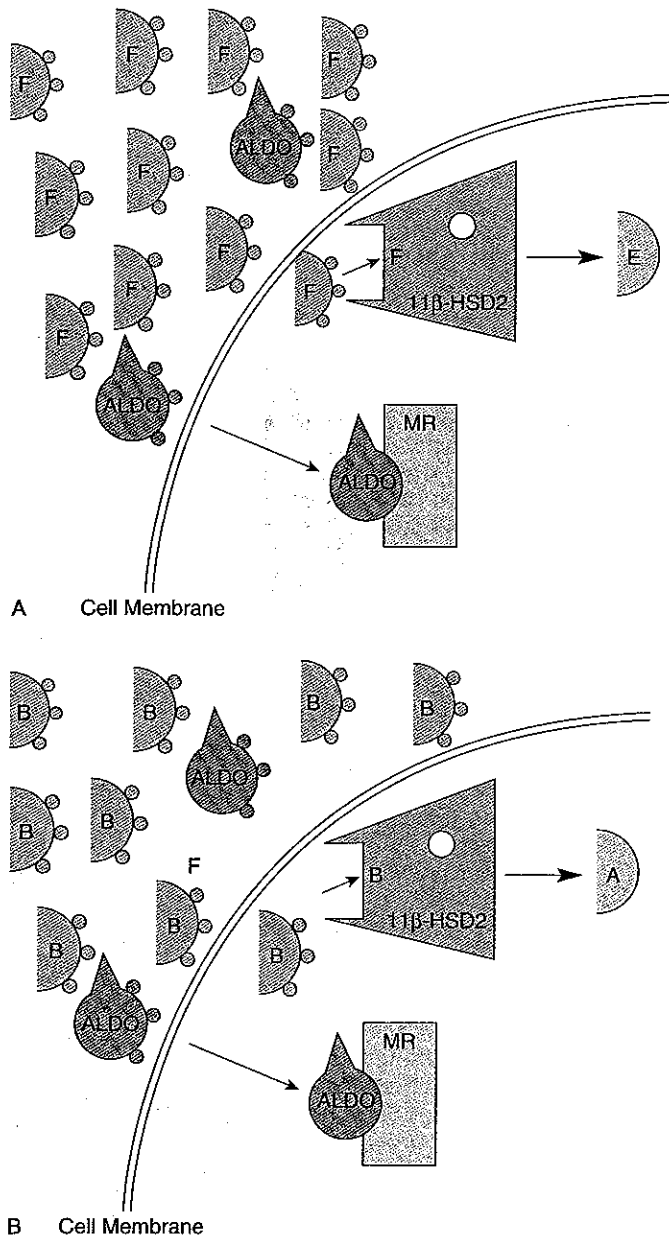


Figure 128-14. **A,** Model of the mechanism responsible for conferring specificity on the human type I mineralocorticoid receptor (MR). In aldosterone-selective tissues such as the kidney, colon, and parotid, the receptor is protected from cortisol exposure by the 11β -hydroxysteroid dehydrogenase type 2 enzyme (11β -HSD2), which metabolizes cortisol (F) to inactive cortisone (E). The fact that aldosterone (ALDO) is not a substrate for 11β -HSD2 allows it to gain direct access to the receptor. In the syndrome of apparent mineralocorticoid excess, there is a failure of cortisol inactivation by 11β -HSD2 that allows cortisol direct access to the MR. Even though aldosterone can bind to MR, in practice, the vast excess of cortisol results in sodium retention and suppression of the renin-angiotensin-aldosterone axis. **B,** In the rat, the enzyme converts corticosterone (B) to the inactive 11-dehydrocorticosterone (A). Inhibition of the enzyme with glycyrrhetic acid allows corticosterone to get direct access to the MR (for details, see text).

Pathology and Clinical Spectrum

AME syndrome produces the expected pathologic consequences of hypertension and hypokalemia but also those that have been observed but poorly explained in other causes of mineralocorticoid excess: nephrocalcinosis and renal cysts. As indicated previously, it is now known that the cellular pathology of AME syndrome is due to loss-of-function mutations in the 11β -HSD2 gene (Fig. 128-16). There is a correlation between the severity of the syndrome and the genetic defect.^{222-228,235} To date, nearly all cases described have been in children.²⁰⁴ Most patients have had a life-long history of polydipsia and polyuria (secondary to nephrogenic diabetes insipidus related to long-standing hypokalemia) associated with marked impairment of growth. The clinical and biochemical features of the syndrome are summarized in Table 128-5. The condition is most frequently sporadic but can be familial. All three siblings in one family had AME syndrome²²⁹ and another two patients were sisters.²³⁰

Diagnosis

AME syndrome should be suspected in a patient (especially a child) with hypertension, hypokalemia, low PRA, and low plasma aldosterone (see Table 128-5). The key to diagnosis has been the measurement of the ratio of urinary cortisol (tetrahydrocortisol [THF] + allo-THF) to tetrahydrocortisone (THE) metabolites (Fig. 128-17). In normal subjects, the ratio is approximately unity, but in AME syndrome type 1, it is greater than 7.5. An alternative method is to give [11α - 3 H]cortisol, which in normal subjects is converted to cortisone + 3 H- H_2O . In AME syndrome, there is virtually no conversion, with a consequent prolongation of the half-life of the labeled steroid.^{203,231} With improvement of steroid assay methodology, many laboratories can now measure urinary free cortisol (uFF) and cortisone (uFE) and their ratio is a useful diagnostic test.²³² These authors suggested that the presence of an altered UFF-UFE ratio in both type 1 and 2 AME syndrome, although with different degrees of severity, calls for reevaluation and the classification of AME syndrome as a single disorder.

In patients with type 1 AME syndrome, urinary free cortisol is usually increased despite normal plasma cortisol levels and a normal circadian rhythm of plasma cortisol. In contrast, in the type 2 variant urinary cortisol is in the lower part of the normal range. The urinary excretion of total metabolites of cortisol is decreased in both forms of AME syndrome, but the ratio of THF + allo-THF to THE is normal in the type 2 syndrome. In addition, in type 1, the ratio of urinary 5α - to 5β -cortisol metabolites is increased (e.g., allo-THF/THF) but not in type 2.

Differential Diagnosis

It is important to distinguish AME syndrome from other mineralocorticoid excess syndromes in which aldosterone secretion is low. In children, the two hypertensive forms of congenital adrenal hyperplasia (17α -hydroxylase deficiency and 11β -hydroxylase deficiency) and Liddle's syndrome may be confused but can be readily separated by the pattern of urinary steroid metabolites. In adults, licorice or carbenoxolone ingestion should be excluded, both substances being inhibitors of 11β -HSD2 and producing AME syndrome (see later). Exogenous mineralocorticoid administration also needs to be excluded. Thus, several patients have developed severe hypertension and hypokalemia with suppression of the renin-angiotensin-aldosterone system after the continued use of a nasal spray for chronic rhinitis containing 9α -fluoroprednisolone.²³³ A 2-month-old breastfed infant was also found to be severely hypertensive and hypokalemic after the mother's use of this steroid in an ointment on her nipples.

Therapy

In both type 1 and 2 AME syndrome, it is clear that cortisol acts as a potent mineralocorticoid.^{203,231,234} Treatment with

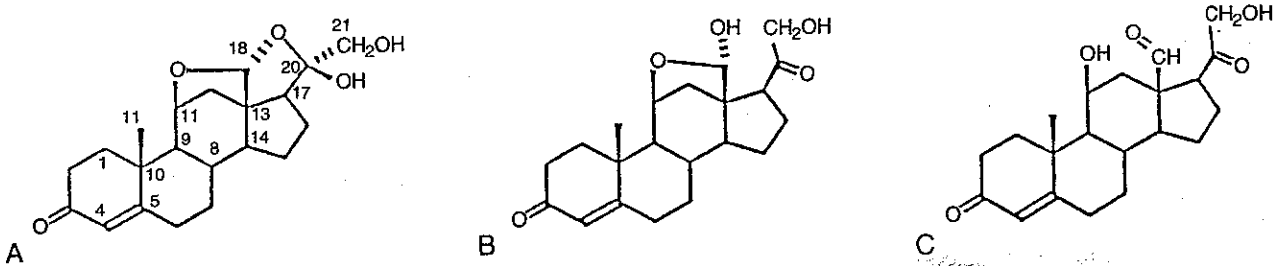


Figure 128-15 Three proposed structures for aldosterone: **A**, 11,18-epoxy-18,20-hemiacetal; **B**, 20-oxo-11,18-hemiacetal; **C**, 11 β -hydroxy, 18-aldehyde.

dexamethasone, which has a much higher affinity for the glucocorticoid than for the mineralocorticoid receptor, by suppressing cortisol production may have marked benefit. Our adult patient has had normal serum potassium, PRA, and aldosterone on this therapy for 20 years.²³¹ However, despite improvement in blood pressure on dexamethasone, it has not been satisfactorily controlled with this alone. With the addition of an ACE inhibitor and a loop diuretic, blood pressure has been normal in this patient for years. Not surprisingly, given the apparent mineralocorticoid excess, most patients have been treated with the aldosterone receptor antagonist spironolactone. This has produced some benefit in terms of elevation of plasma potassium but has not been effective in controlling blood pressure. In AME syndrome, cortisol has direct access to MRs. Despite the decrease in cortisol secretion rate in AME syndrome, the MRs are likely to be exposed to milligram amounts of cortisol.

An alternative approach has been to use inhibitors of renal tubular ionic transport such as amiloride and triamterene. Neither has been very effective in AME syndrome, unlike in Liddle's syndrome.

ACQUIRED APPARENT MINERALOCORTICOID EXCESS SYNDROMES

Licorice and Related Drugs

The sweet root of *Glycyrrhiza glabra* has been used in medicine for more than 5000 years.²³⁶ Its major constituents are glycyrrhizic acid and its hydrolytic product glycyrrhetic acid. In 1948, Reeves²³⁷ reported that patients with peptic ulcers treated with licorice could develop breathlessness and ankle

edema. It subsequently became clear that doses as low as 700 mg/d of glycyrrhizic acid cause sodium retention, hypertension, and hypokalemia with suppression of the renin-angiotensin-aldosterone axis.²³⁸⁻²⁴⁰ These features can be reversed by the MR antagonist spironolactone,^{62,197} suggesting that there was direct activation of type I MRs by the active component of licorice, GE. Similar adverse effects have been reported for carbenoxolone, the hemisuccinate derivative of GE, again suggesting that this drug was also a mineralocorticoid (for review, see Stewart et al.²⁴¹).

Evidence favoring a direct mineralocorticoid action of licorice came from in vitro studies on the binding of GE to MR.^{242,243} GE was shown to bind to MR, but its affinity was only 10⁻⁴ that of aldosterone. Evidence against a direct mineralocorticoid action came from studies of the effects of licorice on sodium retention in humans and rats. It became clear that GE did not produce sodium retention unless either the adrenal glands were present or glucocorticoid replacement therapy was given.²⁴⁴ In rats that had been adrenalectomized²⁴⁵ or patients with Addison's disease on no therapy,^{246,247} licorice was ineffective in retaining sodium. However, when patients with Addison's disease were given either hydrocortisone or cortisone acetate, licorice produced a mineralocorticoid effect.^{246,247}

A further observation was that administration of licorice increased urinary free cortisol but had no effect on plasma cortisol levels.²⁴⁸ These authors also reported on the urinary cortisol metabolites during licorice ingestion. The increase in the ratio of THF to THE was not appreciated, but in retrospect it was suggestive of inhibition of 11 β -HSD2. Another interesting but at the time poorly understood experiment was the discovery that dexamethasone at a dose of 2 mg/d produced natriuresis in subjects taking GE.²⁴⁹ It thus occurred to us that there were remarkable parallels between congenital AME syndrome and the syndrome that results from excessive ingestion of licorice²⁵⁰ (Table 128-5). This

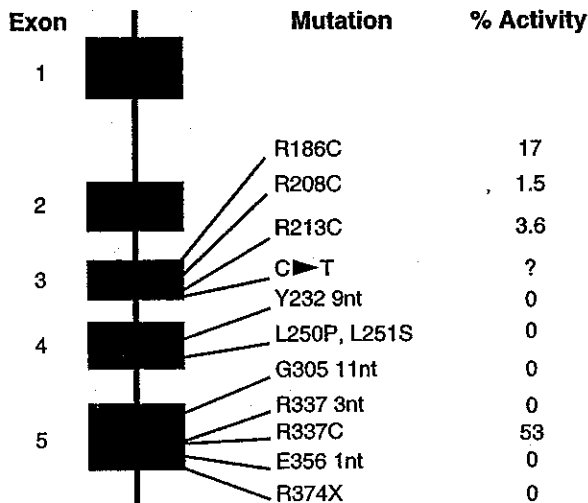


Figure 128-16 Some of the mutations associated with the syndrome of apparent mineralocorticoid excess. (Adapted from Mune T, White PC: Apparent mineralocorticoid excess: Genotype is correlated with biochemical phenotype. Hypertension 27:1193-1199, 1996.)

Table 128-5 Similarities between Congenital 11 β -hydroxysteroid Dehydrogenase Type 2 Enzyme Deficiency (Apparent Mineralocorticoid Excess Syndrome) and Licorice Excess

	11 β -HSD2 Deficiency	Licorice Excess
Sodium retention	+	+
Hypokalemia	+	+
↓ Plasma renin activity	+	+
↓ Plasma aldosterone	+	+
Response to spironolactone	+/-	+
↑ Urinary free cortisol	+	+
Natriuresis with dexamethasone	+	+
↑ Tetrahydrocortisol:tetrahydrocortisone ratio	+	+

11 β -HSD2, 11 β -hydroxysteroid dehydrogenase; ↓, decrease; ↑, increase.

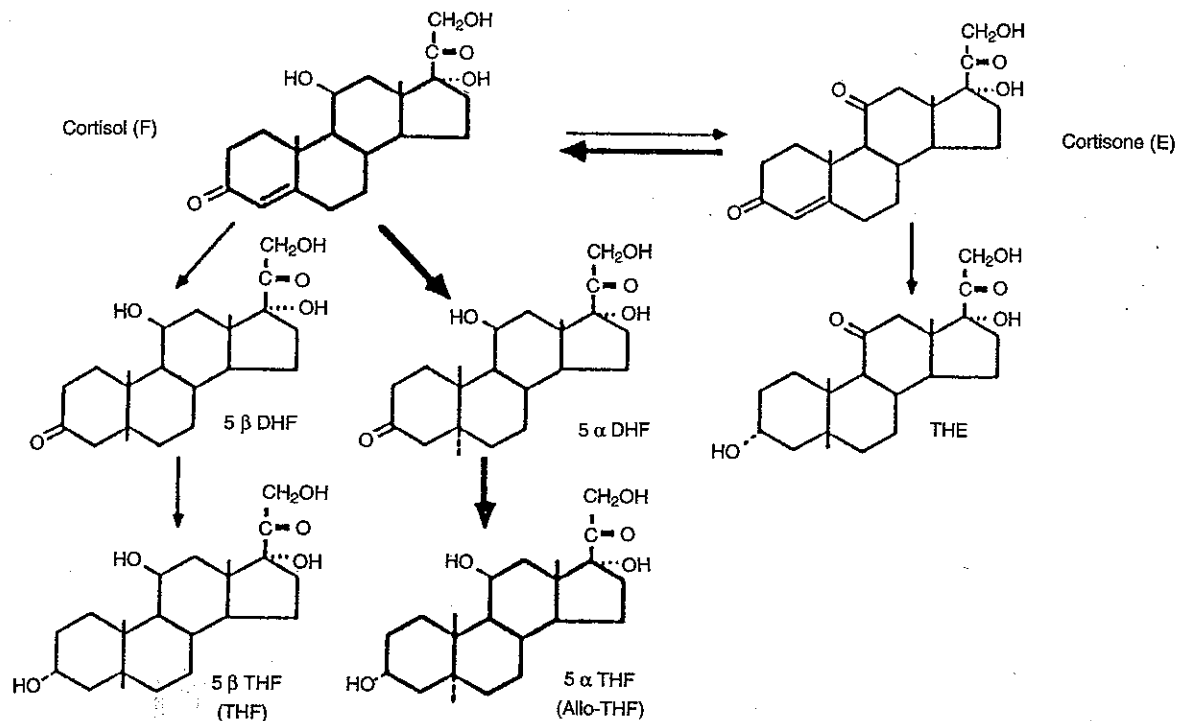


Figure 128-17 The abnormalities of cortisol metabolism in type 1 apparent mineralocorticoid excess syndrome with impaired conversion of cortisol to cortisone but normal or enhanced conversion of cortisone to cortisol. Also, the preferential metabolism of cortisol via the 5α as compared with the 5β pathway. DHF, dihydrocortisol; THE, tetrahydrocortisone; THF, tetrahydrocortisol.

raised the obvious question: Does licorice act by an indirect means by inhibition of 11β -HSD?

Effects of Licorice and Carbenoxolone on 11β -Hydroxysteroid Dehydrogenase

Licorice

To determine whether licorice affected cortisol metabolism, we studied this in seven normal volunteers given licorice 200 g/d (containing 580 mg glycyrrhizic acid). Cortisol metabolism was investigated by two different methods. In the first, $[11\alpha\text{-}^3\text{H}]\text{cortisol}$ was given intravenously before and after 7 days on licorice. In normal subjects, this is metabolized by 11β -HSD2 to cortisone + $^3\text{H}\text{-H}_2\text{O}$. With inhibition of 11β -HSD2, there is decreased production of $^3\text{H}\text{-H}_2\text{O}$ and a prolongation of the half-life of $[11\alpha\text{-}^3\text{H}]\text{cortisol}$. The second method was to measure the urinary metabolites of cortisol and calculate the ratio of THF + allo-THF to THE. As with the congenital syndrome of AME, an increase in the ratio is indicative of inhibition of 11β -HSD2.

In the seven normal volunteers, licorice produced the characteristic sodium retention, potassium loss, and suppression of the renin-angiotensin-aldosterone axis. Urinary free cortisol increased significantly, with no change in plasma cortisol, as previously found by Epstein and colleagues.²⁴⁸ (This is presumably due to the failure of the intrarenal conversion of cortisol to cortisone resulting in enhanced renal clearance of cortisol and does not reflect increased filtration of unbound cortisol). The studies of cortisol metabolism showed inhibition of 11β -HSD2. There was a significant increase in the THF + allo-THF:THE ratio ($P < 0.05$ on day 4 and $P < 0.01$ on day 10 of licorice ingestion) and a prolongation of the half-life of $[11\alpha\text{-}^3\text{H}]\text{cortisol}$ from 40.7 to 84.3 minutes with a decrease in the percentage of total tritium excreted in the urine as $^3\text{H}\text{-H}_2\text{O}$ from 27.7% to 12.3% after 1 week of licorice ingestion.

These effects of the active component of licorice, GE, on cortisol metabolism were confirmed by MacKenzie and coworkers.²⁵¹ They gave normal subjects 500 mg/d of GE and measured plasma and urinary cortisol and cortisone. As

expected, plasma cortisol levels did not change significantly, but urinary cortisol increased with GE administration. Plasma and urinary cortisone levels fell during GE administration, indicating a rapid inhibition of the conversion of cortisol to cortisone.

In vitro studies have confirmed that GE is a potent inhibitor of 11β -HSD2.²⁵² Dispersed renal tubular preparations, homogenates of kidney and microsomes, rapidly convert corticosterone to 11-dehydrocorticosterone (i.e., have 11β -HSD2 activity). The addition of GE to these preparations inhibited the conversion in a dose-dependent manner. The K_i depended on the preparation used. With the homogenates and microsomes, the K_i was approximately 10^{-9} to 10^{-8} mol/L, but with intact tubules, it was 10^{-5} to 10^{-6} mol/L. In vitro, the reductase component of 11β -HSD (11β -HSD1, the enzyme responsible for the conversion of cortisone to cortisol) was not affected by GE.

The human and animal studies discussed have been acute experiments. Farese and associates²⁴⁰ studied cortisol metabolism in a 70-year-old man with hypertension and hypokalemia responsive to spironolactone therapy who was chronically addicted to licorice. During the study, the patient was taking approximately 100 g/d of licorice. The licorice was discontinued after 1 week. During licorice ingestion, urinary cortisol excretion was elevated and the ratio of THF + allo-THF to THE was elevated, indicating inhibition of 11β -HSD2. After licorice was stopped, the ratio gradually returned to normal by day 27. Of interest was the ratio of 5α - to 5β -cortisol metabolites. In the congenital type of AME syndrome, this ratio is increased. This is also the case in acute licorice administration. However, in this patient, the ratio was decreased during licorice ingestion and increased on stopping.

Carbenoxolone

It might be anticipated that carbenoxolone, the hemisuccinate derivative of GE, might have the same effects as GE on cortisol metabolism. In our studies it is clear that carbenoxolone is an inhibitor of 11β -HSD, but there are interesting differences

between it and GE. In a study similar to our original one with licorice, normal volunteers were given carbenoxolone 300 mg/d for 14 days.²⁴¹ This produced the expected sodium retention with suppression of the renin-angiotensin-aldosterone system. However, as previously observed, unlike licorice, carbenoxolone produces hypokalemia without an associated kaliuresis. Cortisol metabolism was affected as judged by a marked prolongation of the half-life of [11α - ^3H]cortisol (from 39 to 123 minutes). However, there was no effect on the ratio of urinary cortisol to cortisone metabolites, and, unlike licorice, carbenoxolone produced no reduction of plasma cortisone levels. The reason for the differences between the effects of licorice and carbenoxolone is not clear. One possibility is that carbenoxolone inhibits both the dehydrogenase (11β -HSD2) and the reductase (11β -HSD1) isoforms of 11β -HSD. Evidence in support of this comes from a study in normal volunteers given cortisone acetate with or without carbenoxolone.²⁴¹ On treatment, the resultant plasma cortisol levels were lower than in the control experiment, suggesting an effect of the drug on the 11β -HSD1 enzyme. Animal experiments have confirmed that carbenoxolone potentiates the mineralocorticoid effects of glucocorticoids. In rats given either corticosterone or cortisol, the steroids alone were found not to have any intrinsic sodium-retaining activity.²⁵³ However, both steroids showed very significant sodium retention and kaliuretic properties after the animals had been pretreated with carbenoxolone. This drug alone was not antinatriuretic or kaliuretic. Further studies have shown that the mineralocorticoid-like actions of glucocorticoids, when they are given with carbenoxolone, are blocked by the specific MR antagonist RU28318.²⁵⁴

In vitro experiments have demonstrated that carbenoxolone, in addition to its effect on 11β -HSD, has, as has been reported for licorice derivatives, a wide variety of other effects. These include inhibition of 5β -reductase and 3β -HSD,²⁵⁵ inhibition of prostaglandin synthesis,²⁵⁶ with inhibition of cyclooxygenase and also effects on 5- and 12-lipoxygenase,²⁵⁷ and, at high concentration, inhibition of Na^+/K^+ -ATPase.²⁵⁸ It is unclear to what extent these effects contribute to the mineralocorticoid actions of corticosterone or licorice. Certainly, many of them have been shown only at high concentration. It is also important to remember that GE and carbenoxolone are strongly protein bound so that the free concentrations are very low (possibly less than 0.05% of the total). If, however, inhibition of 11β -HSD was the sole explanation, one would imagine that the mineralocorticoid effects would be manifest only when the drugs were given with glucocorticoids (i.e., with steroids such as cortisol containing an 11β -hydroxyl group). This does not seem to be the case. Morris and Souness²⁵⁹ have shown that in adrenalectomized rats, carbenoxolone can amplify the sodium-retaining properties of 11-DOC (which has no 11β -hydroxyl group) and aldosterone (which has an 11 to 18 bridge that protects the steroid from metabolism by 11β -HSD). As with corticosterone and cortisol, these amplified effects could be blocked by the type 1 receptor antagonist RU28318.²⁵⁴

When considering the hypertension induced by licorice and carbenoxolone, it is important to remember that these substances have many sites of action other than the distal nephron, as 11β -HSD2 is expressed in a wide variety of sites. In some of these, the effect may be to enhance mineralocorticoid activity (e.g., the kidney); in others, the enzyme appears to modulate access to glucocorticoid receptors.²⁶⁰ Thus, important effects on blood pressure could result from inhibition of 11β -HSD found in vascular smooth muscle²⁶¹ or from effects on the enzyme in the central nervous system.²⁶²

disease.²⁶³⁻²⁶⁵ It has been suggested that this might be due to excess secretion of DOC (see Walker et al.²⁶⁵ for review) or to the higher cortisol secretion in the ectopic syndrome.²⁶³ Given the low apparent mineralocorticoid activity of cortisol, the latter explanation might appear to be surprising. However, recent information suggests that the ectopic ACTH syndrome may result in a situation akin to the AME syndrome, with cortisol acting as a mineralocorticoid. Ulick and colleagues²⁶⁴ studied two patients with the ectopic ACTH syndrome with hypertension and hypokalemia. In both, urinary metabolites of aldosterone were low and those of DOC were high. Of particular interest was the ratio of cortisol to cortisone metabolites (THF + allo-THF-THE). This was approximately twice normal, suggesting relative 11β -HSD2 deficiency. Ulick and colleagues also derived an A-ring reduction constant that was very abnormal, with values similar to the type 2 variant of AME syndrome. They suggested that in the ectopic ACTH syndrome, there was cortisol inactivation overload.

Our own studies on nine patients with the ectopic ACTH syndrome, 15 with pituitary-dependent Cushing's disease, and 2 with adrenal adenomas causing the syndrome led to slightly different conclusions.²⁶⁵ In normal subjects, cortisol infusions produced an elevation of plasma cortisone, but graded ACTH infusion resulting in the same range of plasma cortisol did not elevate plasma cortisone. Similarly, elevation of endogenous cortisol with insulin-induced hypoglycemia did not increase plasma cortisone. The plasma cortisol-cortisone ratio (an index of 11β -HSD2 activity) was higher in patients with the ectopic ACTH syndrome than in those with other forms of Cushing's syndrome. This suggested that either ACTH or an ACTH-related steroid inhibits 11β -HSD2, thus allowing cortisol direct access to renal MRs. However, the cortisol-cortisone ratio was no better a predictor of hypokalemia than were the levels of DOC or corticosterone. This suggests that the mineralocorticoid excess found in this syndrome can be accounted for by a combination of increased secretion of cortisol, corticosterone, and DOC and decreased inactivation of cortisol, and probably also corticosterone, by 11β -HSD2.

GLUCOCORTICOID RESISTANCE

It might be anticipated that glucocorticoid resistance would be associated with hypotension rather than hypertension. However, the patients described with this syndrome have frequently been hypertensive and have presented with manifestations of either androgen or mineralocorticoid excess or both.²⁶⁶⁻²⁶⁸

The key features of the syndrome are the association of increased cortisol secretion with none of the stigmata of Cushing's syndrome and a failure to suppress cortisol secretion with low-dose dexamethasone. Both total and free plasma cortisol levels are elevated, as are urinary free cortisol levels. ACTH levels are increased and result in enhanced adrenal androgen, corticosterone, and DOC secretion.

Studies of the first reported kindred showed that the glucocorticoid resistance appeared to be due to a point mutation in the glucocorticoid receptor steroid-binding domain²⁶⁹ (Val641 mutant). This resulted in a two- to threefold reduction in glucocorticoid binding in the propositus, who was homozygous for the mutation, and a less marked effect on glucocorticoid binding in the mildly affected son and nephew, who were heterozygotes. Expression studies with either the wild-type or Val641 mutant receptors showed that the binding affinity of the mutant receptor was threefold lower than that of the wild type. The mechanism of hypertension in those patients with mineralocorticoid excess is not entirely clear. One possibility is that it results from excess secretion of DOC and corticosterone and is thus analogous to the hypertension in patients with 17α -hydroxylase deficiency. An alternative or additional mechanism relates to the

ECTOPIC ADRENOCORTICOTROPIC HORMONE SYNDROME

Hypokalemic alkalosis and hypertension are frequently found in patients with the ectopic ACTH syndrome and are less prominent in patients with pituitary-dependent Cushing's

effect of elevated cortisol levels acting via MRs. As already discussed, these are normally protected from cortisol occupancy by 11β -HSD2. One possibility is that the capacity of this inactivating mechanism is exceeded, as proposed by Ulick and colleagues,²⁶⁴ in the ectopic ACTH syndrome. However, it is more likely that there is partial 11β -HSD2 deficiency induced by ACTH excess. Thus, as we have found in the ectopic ACTH syndrome, the hypertension and mineralocorticoid excess can best be explained by a combination of cortisol excess, partial inhibition of 11β -HSD2 allowing cortisol access to MRs, and elevated DOC and corticosterone levels.²⁶⁵

Until recently, it was thought that glucocorticoid resistance was a very rare syndrome in humans in contrast to New World primates, which show marked glucocorticoid resistance without apparent pathologic consequences.²⁷⁰ However, a retrospective survey of 420 patients who had had dexamethasone suppression tests revealed 7 patients (1.7%) with apparent glucocorticoid resistance.²⁷¹ Some of these had thermolability of the glucocorticoid receptor, some had a decreased number, and others had abnormal ligand binding. The group with the thermolabile receptors had increased glucocorticoid receptor mRNA levels suggesting a compensatory mechanism. Interestingly, only three patients had increased urinary free cortisol levels. These results suggest that there may be a subtle spectrum of glucocorticoid resistance that can easily be overlooked. A quick test for glucocorticoid responsiveness is the skin-blanching assay. This has been shown to correlate with glucocorticoid resistance in patients with asthma but has not been used systematically in patients with glucocorticoid resistance.²⁷²

Glucocorticoid resistance can be confirmed by the response to high-dose as compared with that to low-dose dexamethasone.²⁷⁰ This results in suppression of ACTH and normalization of plasma potassium and blood pressure. Adrenal androgen levels also fall. Not surprisingly, therapy involves a dose of dexamethasone sufficient to suppress ACTH (usually approximately 3 mg/d).

ESSENTIAL HYPERTENSION

The role of mineralocorticoids in essential hypertension has been extensively reviewed elsewhere.²⁷³ Not surprisingly, the observation that 20% to 30% of patients with apparent essential hypertension have low PRA was thought to be evidence in support of excessive mineralocorticoid activity.^{273,274} However, there are few findings to support this, as judged by the plasma electrolytes and exchangeable sodium or plasma volume.²⁷⁵ However, this does not exclude mineralocorticoid excess. As discussed, patients with glucocorticoid-suppressible aldosteronism may be normokalemic and have normal exchangeable sodium with clear evidence of mineralocorticoid excess.

Plasma aldosterone levels, although not elevated in essential hypertension, show a number of abnormalities. These include the observation that they are less readily suppressed by salt loading, and those with apparently normal renin levels show a higher than normal aldosterone-to-renin or aldosterone-to-angiotensin ratio.²⁷⁶ It has since been demonstrated that many individuals with primary aldosteronism have plasma aldosterone levels that lie within the wide normal range. This, coupled with the more recent demonstration that normokalemia is not uncommon in that condition, has led to the suggestion that many patients previously labeled as having low-renin essential hypertension may in fact have normokalemic primary aldosteronism.

There has been a long search for cryptic mineralocorticoids in essential hypertension. Suggested steroids have been 18-OH-DOC , 19-nor-DOC , and $17\alpha,20\text{-dihydroxyprogesterone}$. There is little or no evidence to support a role for these steroids as important mineralocorticoids. However, they may possibly affect blood pressure by other mechanisms.

Another possibility is that a subtle abnormality of cortisol inactivation exists in essential hypertension. We have studied this using [$11\alpha\text{-}^3\text{H}$]cortisol. In approximately one third of patients with essential hypertension, the half-life of the isotope was prolonged, suggesting partial deficiency of 11β -HSD2. However, this subgroup had no evidence of mineralocorticoid excess, as judged by testing of plasma electrolytes, PRA, and plasma aldosterone.²⁷⁷

EXOGENOUS MINERALOCORTICOIDS

Administration of large doses of hydrocortisone or of aldosterone, DOC, 9α -fludrocortisol, or 9α -fluoroprednisolone produces initial sodium retention, hypokalemia, and suppression of the renin-angiotensin-aldosterone axis. After a few days, mineralocorticoid escape occurs, in which sodium excretion increases and potassium loss diminishes. The production of hypertension depends on a high-sodium intake. The mineralocorticoid action of hydrocortisone is probably due to overload of the cortisol-cortisone shuttle mechanism protecting the MR. Aldosterone, DOC, 9α -fludrocortisol, and 9α -fluoroprednisolone are not substrates for 11β -HSD2 and can thus gain direct access to the nonspecific MR.

With the exception of patients with Addison's disease or those who have undergone bilateral adrenalectomy and have been given excessive mineralocorticoid replacement therapy, it is rare to see exogenous mineralocorticoid excess. However, this has been well described in children and adults exposed to 9α -fluoroprednisolone.²³³ This steroid has been used as a spray for chronic rhinitis and for the treatment of eczema.

ACTIVATING MUTATIONS OF THE MINERALOCORTICOID RECEPTOR

Geller and associates²⁷⁸ have recently described a very interesting form of hypertension in which a mutation in the mineralocorticoid receptor causes early-onset hypertension, which is exacerbated in pregnancy. The mutation produces constitutive activation of the MR but also alters the receptor specificity so that it is activated by steroids, such as progesterone, which lack a 21-hydroxyl group. These steroids are normally mineralocorticoid antagonists, and hence the reports of amelioration of Conn's syndrome in pregnancy (see "Special Clinical Presentation" and Drucker et al.⁷⁶). The specific mutation is S810L. Geller and associates suggest that this results in a gain of van der Waal's interaction between helix 3, which substitutes for the normal 21-hydroxyl interaction with helix 3 in the wild-type receptor. The hypertension is also exacerbated by spironolactone.

ABNORMAL RENAL TUBULAR IONIC TRANSPORT (OR DISORDERS OF THE RENAL TUBULAR EPITHELIUM THAT MIMIC PRIMARY MINERALOCORTICOID EXCESS) (PSEUDOALDOSTERONISM)

LIDDLE'S SYNDROME

In 1963, Liddle and coworkers²⁷⁹ described a familial renal disorder simulating primary aldosteronism but with negligible aldosterone secretion. The index case was a 16-year-old girl with hypertension and hypokalemia. Her younger brother was subsequently found to have a similar clinical and biochemical condition. In both patients, aldosterone secretion was negligible. There was also evidence against excess secretion of mineralocorticoids other than aldosterone in that spironolactone therapy was ineffective. In addition, the urinary metabolites of DOC, corticosterone, and cortisol were normal. On a low-sodium diet, there was an impaired ability to conserve sodium. However, this was not due to a primary

renal defect because exogenous aldosterone produced maximal sodium retention. It was presumably the result of impaired aldosterone secretion consequent to long-term suppression of the renin-angiotensin-aldosterone axis. Liddle and coworkers suggested that the disorder was due to an abnormal facility of the renal tubules to transport ions with the result that it simulated mineralocorticoid excess. Proof in support of this hypothesis came from administration of triamterene, an inhibitor of renal tubular ionic transport. The drug produced an increase in sodium excretion and a decrease in potassium excretion in the index patient, with normalization of the blood pressure when triamterene was given with a low-sodium diet. On long-term therapy with triamterene 100 mg/d, the patient remained normal. Further investigation of the family showed that four of nine siblings had the disorder, suggesting a dominant mode of inheritance. Some members had hypokalemia without hypertension. The index patient's mother and grandmother had died of hypertensive vascular disease in their 40s; there were two maternal uncles with hypokalemic alkalosis, one of whom was hypertensive. The paternal side of the family appeared to be normal.

Gardner and colleagues²⁸⁰ studied sodium transport in red blood cells from two further patients with Liddle's syndrome. Sodium influx and fractional sodium outflux, but not sodium concentration, were significantly increased in Liddle's syndrome. These changes were not due to the changes in the circulating levels of aldosterone, renin, angiotensin II, or potassium. The increased fractional sodium outflux was reduced but not abolished by ouabain; similar results were found with sodium influx. However, approximately 40% of the increased sodium transport was not inhibited by ouabain. These results suggested that the abnormal ion transport was not confined to the kidney and that at least a part of the red blood cell transport abnormality was due to a sodium transport mechanism that does not occur in normal human erythrocytes.

It is clear that the clinical and biochemical features of Liddle's syndrome can be readily confused with those of 11 β -HSD2 deficiency. Both conditions produce hypertension with hypokalemia and suppression of the renin-angiotensin-aldosterone axis, and both may involve a positive family history. However, they can be readily distinguished by the abnormal ratio of urinary THF + allo-THF to THE found in 11 β -HSD2 deficiency and the response to triamterene but not to spironolactone in Liddle's syndrome. 11 β -HSD2-deficient patients will usually show an improvement in plasma electrolytes on high-dose spironolactone but rarely become normotensive.

The molecular basis of Liddle's syndrome is now known. The amiloride-sensitive epithelial sodium channel (ENaC) consists of three subunits: α , β , and γ . In Liddle's syndrome, there is enhanced activity of ENaC resulting from missense mutations or truncations of the C-terminal region of either the β or γ subunits. The part of the C terminus involved is a proline-rich region, the so-called PY motif (proline, tyrosine). This normally binds to the ubiquitin protein ligase Nedd4 via

its WW domains (tryptophan, tryptophan).²⁸¹ It is suggested that Nedd4 regulates sodium channel degradation and acts as a suppressor of ENaC. The PY motif in β ENaC is PPPNY, and in γ ENaC, it is PPPRY. Nedd4 mediates the ubiquitin-dependent downregulation of ENaC activity in response to increased intracellular sodium. In Liddle's syndrome, there is a loss of the normal regulatory feedback system because Nedd4 can no longer bind to the mutated or truncated C terminus of the abnormal β or γ subunits.²⁸² Overexpression of wild-type Nedd4 together with ENaC in *Xenopus* oocytes inhibits channel activity.^{282,283} Enhanced activity of the channel occurred when mutant PY motifs were expressed. This enhanced activity was due to an increase in the number of sodium channels in the membrane.

Studies in different kindreds of patients with Liddle's syndrome have shown considerable variation in the severity of hypertension and of hypokalemia.²⁸⁴ The most common mutation identified in patients with Liddle's syndrome is the T594M. Baker and colleagues²⁸⁵ screened a black population in London for this. Seventeen of 206 hypertensive patients (8.3%) as compared with 3 of 142 normotensive patients (2.1%) had the mutation (odds ratio 4:2). PRA was significantly lower in 13 hypertensive subjects with the mutation than in 39 untreated hypertensive individuals without it ($P < 0.009$). This raises the possibility that the T594M mutation could be the most common cause of secondary hypertension in black people so far identified. In this context, it is worth commenting that there is marked phenotypic variability in both the presence and severity of hypertension and hypokalemia in other conditions such as GRA and the syndrome of mineralocorticoid excess²⁸⁶ in addition to Liddle's syndrome, suggesting that these sorts of mutations may account for a greater proportion of so-called essential hypertension than has been previously thought.

CONCLUSIONS

Primary mineralocorticoid excess syndromes have been thought to be rare causes of hypertension. However, recent studies have suggested that, in unselected patients with hypertension, the prevalence of primary aldosteronism may be as high as 10%. The syndromes are important in that in some patients, the definitive diagnosis may lead to specific therapy such as unilateral adrenalectomy with associated cure. In others, increased understanding of the mechanisms involved has produced much more effective drug therapy. The molecular pathogenesis of some of the syndromes is now known (e.g., GRA and AME syndrome). This has led to the introduction of new genetic tests with apparently 100% specificity and sensitivity. It is likely that rapid advances in this area will greatly facilitate diagnosis and result in a wide recognition of conditions that are frequently underdiagnosed. It is also exciting that unraveling these experiments of nature is giving new insights into previously unrecognized aspects of normal physiology.

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