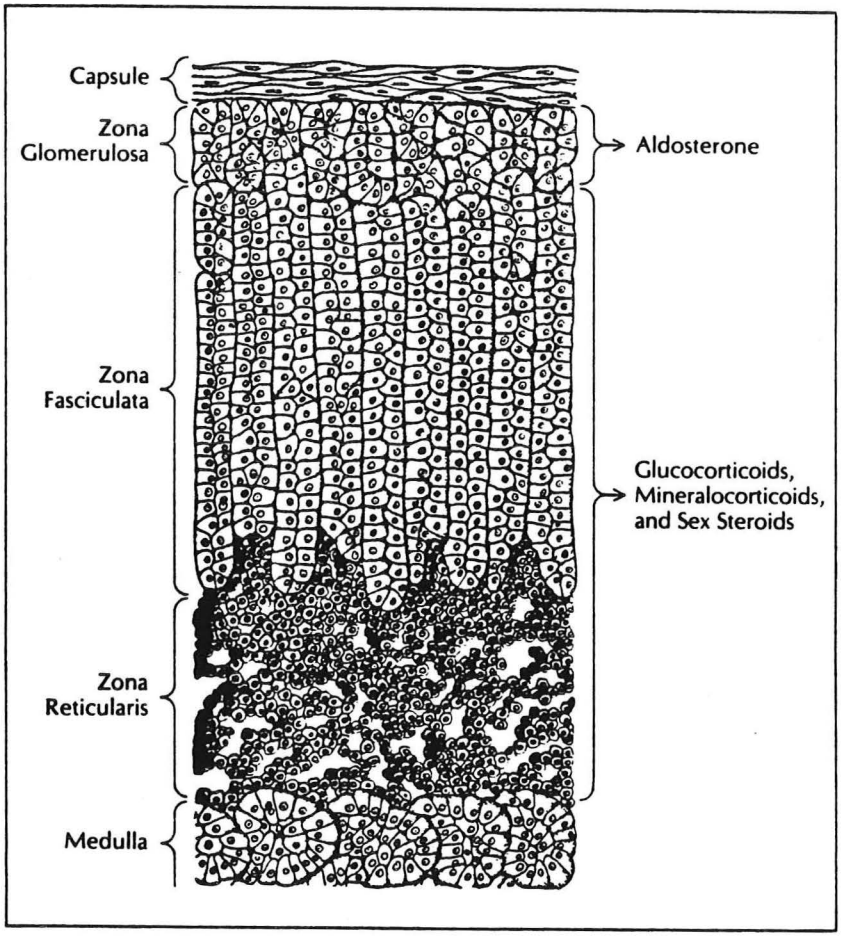
# PRIMARY

# HYPERALDOSTERONISM


## MOSHE LEVI, M.D.


INTERNAL MEDICINE GRAND ROUNDS

UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL CENTER

OCTOBER 19, 1989

## INTRODUCTION

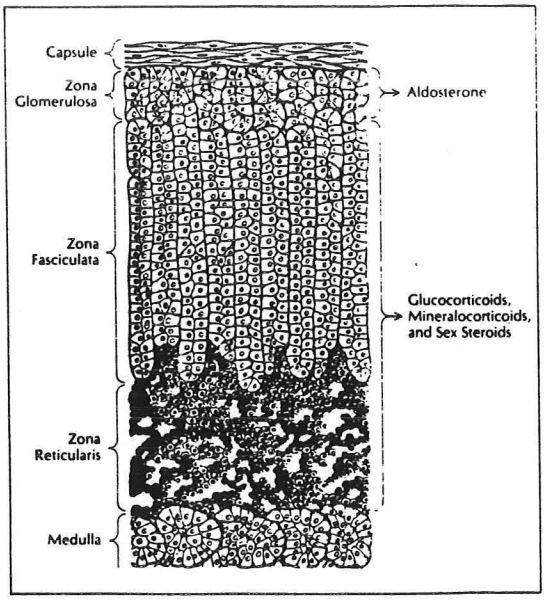
The clinical syndrome of primary aldosteronism was first described by Dr. Jerome W. Conn at the presidential address of the 27th Annual Meeting of the Central Society for Clinical Research, October 29, 1954 (1). The patient was a 34 year old female who had presented with a 7 year history of intermittent spasms, weaknes and paralysis of muscles. Her BP 170/100, $S_{Na}$ 151, $S_{K}$ 1.6, $S_{Cl}$ 102, $S_{CO2}$ 40. She had no peripheral edema. Urinary aldosterone secretion rate was markedly increased, 104 μg/day. On surgery she was found to have a right adrenal adenoma of 4cm in diameter. Post operatively her symtoms resolved, she became normotensive, BP 120/80, serum chemistries normal.

In the past 35 years major advances have been made in the recognition, diagnosis, and treatment of primary hyperaldosteronism. 35 years later however, primary hyperaldosteronism is still a challanging diagnosis because of its low incidence and variable subtypes and pathophysiology, which still remains a mystery to many health care providers.

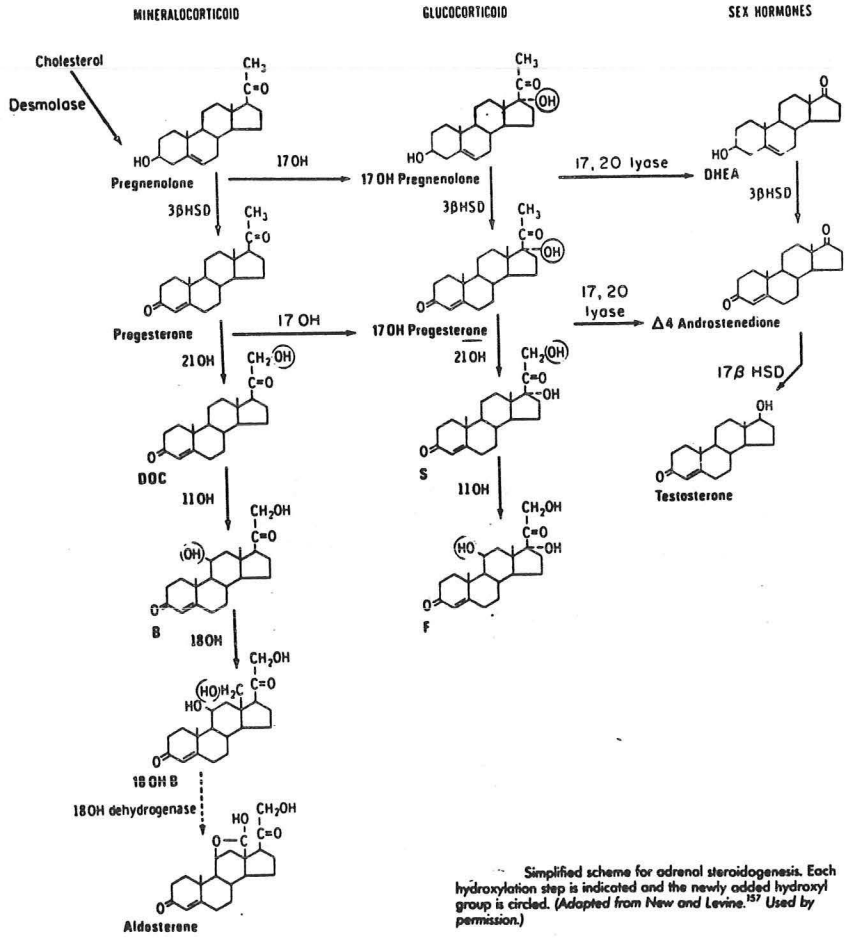
Primary hyperaldosteronism is a general term used for disorders in which chronic aldosterone excess exists independently or semi-independently of the renin angiotensin system. Estimates of the incidence of primary hyperaldosteronism in the hypertensive population in this country vary from 0.5% to 1.0%. Although it is a relatively uncommon disorder, it is an important diagnosis to make since most if not all of the patients respond extremely well to surgical and/or medical therapy (2-5).

## REGULATION OF ALDOSTERONE SECRETION

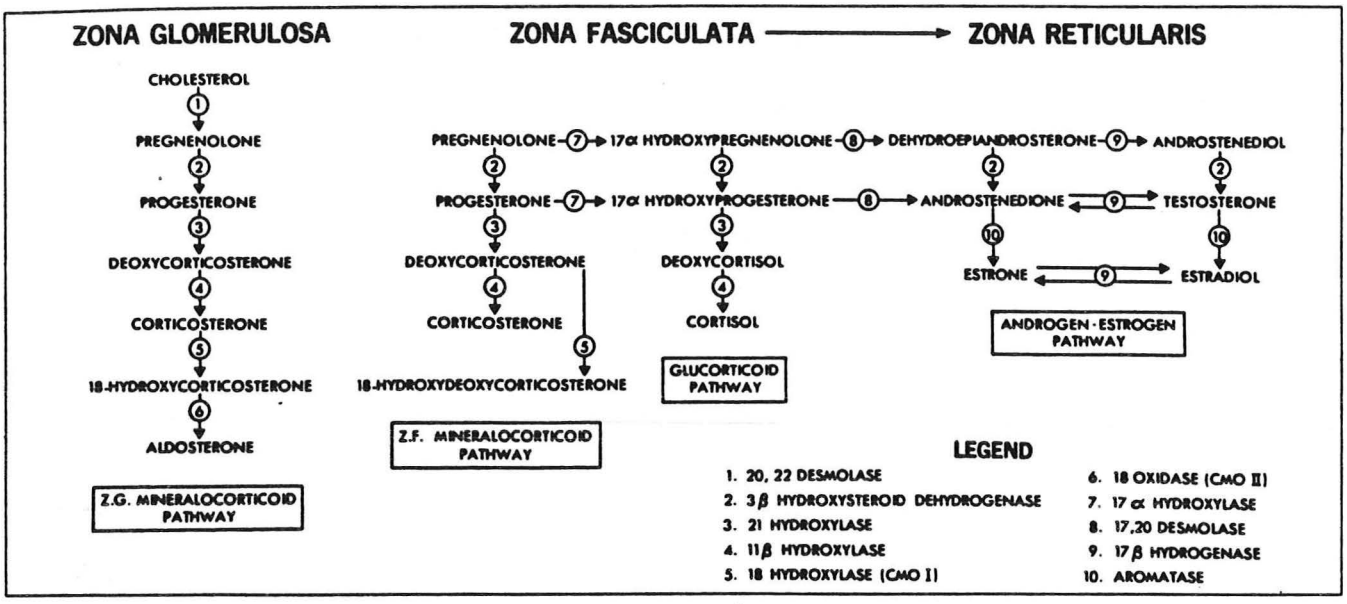
Aldosterone is the major mineralocorticoid in humans and is produced exclusively in the zona glomerulosa of the adrenal cortex. Although it does bind weakly to albumin, aldosterone circulates primarily as a free moiety. Aldosterone is metabolized rapidly by the liver and is excreted as tetrahydroaldosterone. A small portion is metabolized in the kidney and excreted in the urine as aldosterone 18-glucoronide.




**Cells of the adrenal cortex form in the subcapsular region and are apparently biochemically multipotent. Their functional capacity, however, seems to be determined by their final locus within the cortex, which is arranged in three peripheral zones, or layers. Cells in the zona glomerulosa synthesize only mineralocorticoids, principally aldosterone. Cells in the zona fasciculata and zona reticularis synthesize glucocorticoids (principally cortisol), but also mineralocorticoids (except aldosterone) and sex steroids.**

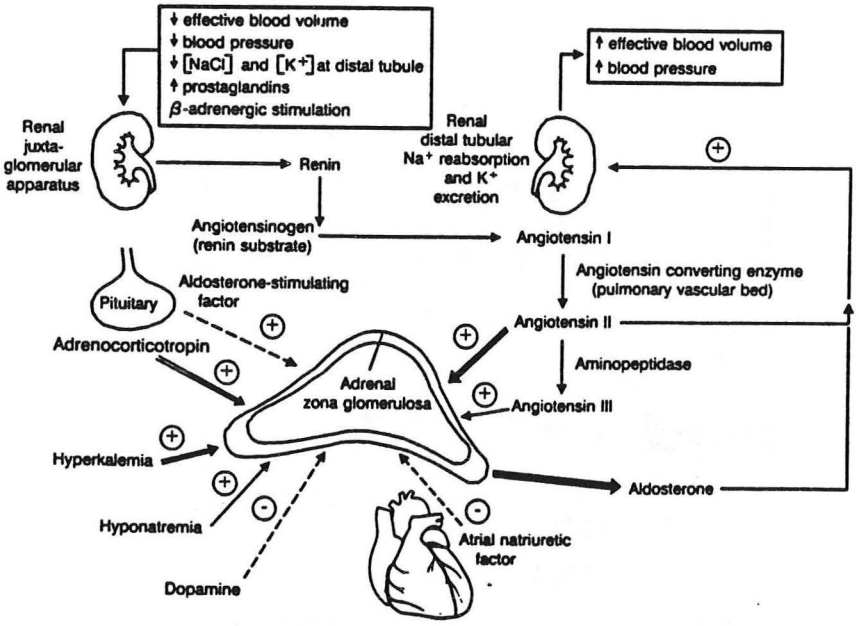



**Simplified scheme for adrenal steroidogenesis. Each hydroxylation step is indicated and the newly added hydroxyl group is circled. *(Adapted from New and Levine.[157] Used by permission.)***




**Biosynthesis pathways and sites of enzymatic action.**

**Aldosterone secretion is regulated by three well established stimulator which are a) the renin-angiotensin system, b) adrenocorticotropic hormone (ACTH), and c) potassium (K)**




Regulation of aldosterone secretion. *Plus* and *minus signs* indicate stimulation and inhibition, respectively.

In recent years several additional hormonal factors have also been identified which either stimulate or inhibit aldosterone secretion.

## STIMULATORS AND INHIBITORS OF ALDOSTERONE SECRETION

### STIMULATORS

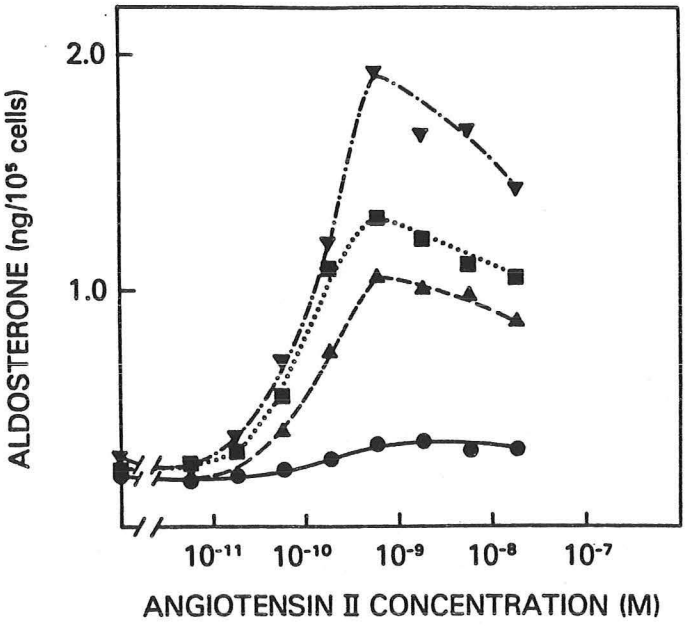
Renin-Angiotensin system
Adrenocorticotropic hormone
Potassium
Pituitary factors: POMC peptides, ASF
Endothelin
Serotonin

### INHIBITORS

Dopamine
Atrial natriuretic hormone
Somatostatin

**Renin-Angiotension System:**

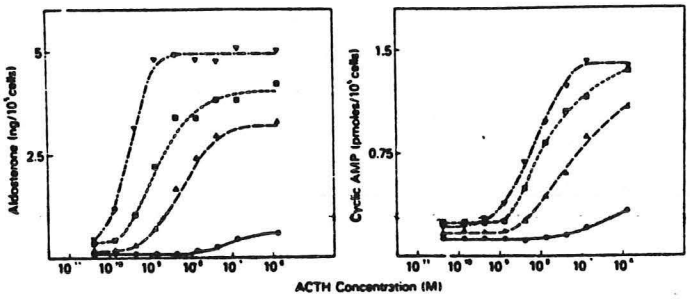
Angiotensin II is the most important stimulator of aldosterone production and secretion. There is a close correlation between plasma AII concentration and plasma aldosterone concentration. Infusion of A-II **in vivo** or incubation of adrenal cells with AII in vitro increases aldosterone production and secretion. AII stimulates both the early and late phases of aldosterone biosynthesis. The early-phase stimulation is a calcium and protein kinase C-dependent process




Angiotensin II dose-response curves for aldosterone production by rat zona glomerulosa cells at differing calcium concentrations. Cells prepared in media containing no calcium (●——●), 0.2 mM calcium (▲- -▲), 0.5 mM calcium (■· · ·■), or 1.2 mM calcium (▼- · -▼) were incubated with angiotensin II at the concentrations indicated.

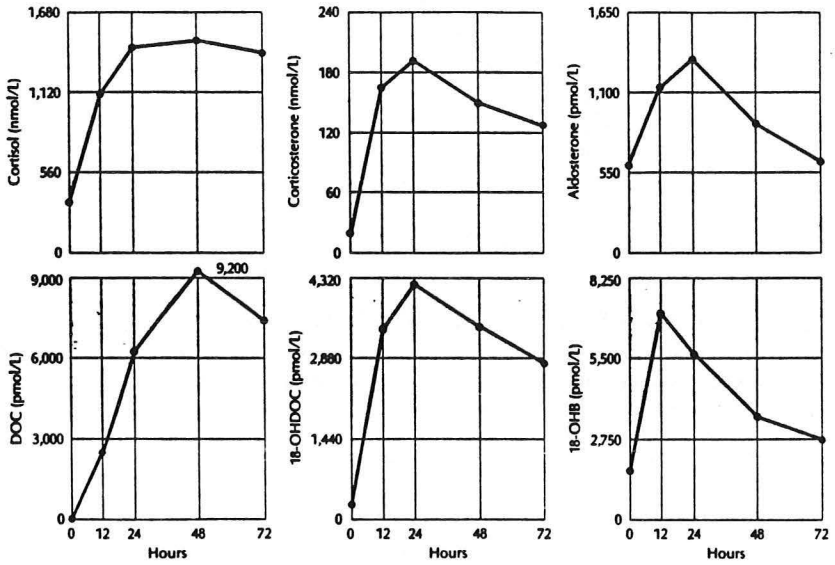
**ACTH:**

ACTH is also an important stimulator of aldosterone production. ACTH stimulates the early phases of steroidogenesis, specifically, the conversion of cholesterol to pregnenolone. Acute infusion of physiologic amounts of ACTH in humans causes pronounced and rapid stimulation of aldosterone secretion. In vitro, secretion of aldosterone from isolated adrenal cells is also vigorously stimulated by ACTH. Cyclic AMP functions as a second messenger, but calcium is also required for the optimal ACTH response. ( 6-8).




ACTH dose-response curves for aldosterone and cAMP production by rat zona glomerulosa cells at differing extracellular calcium concentrations. Rat zona glomerulosa cells prepared in media containing no calcium (●——●), 0.1 mM calcium (▲- -▲), 0.4 mM calcium (■- -■), or 1.2 mM calcium (▼- — -▼) were incubated with ACTH at the concentrations indicated.

In contrast to acute administration of ACTH, prolonged administration of ACTH, even in low doses, has a biphasic effect. After a short period of stimulation, aldosterone secretion decreases to baseline. This phenomenon is known as the aldosterone escape from ACTH. The aldosterone response to ACTH is modulated by the activity of the renin-angiotensin system. Activation of the renin-angiotensin system however, is able to adelay, but not supress the changes induced in the zona glomerulos by prolonged ACTH stimulation (10-11).

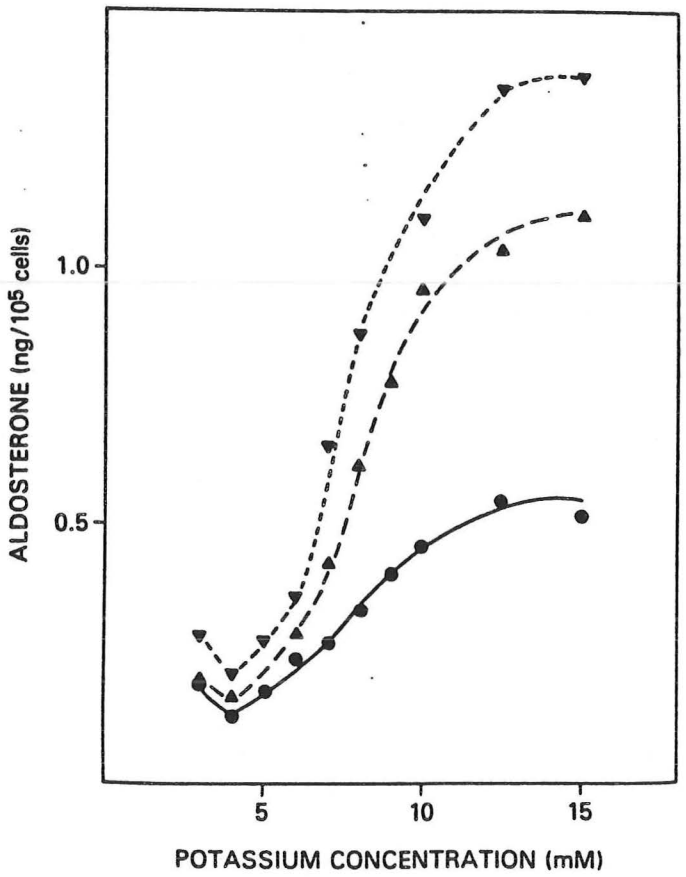



Secretory responses of cortisol and aldosterone to continuous ACTH stimulation differ significantly in duration, as reflected in mean plasma hormone levels of five normal adults before and during administration of supraphysiologic amounts of the corticotropic hormone (20 IU intramuscularly every eight hours for three consecutive days). Initially, ACTH stimulated secretion of both mineralocorticoids and cortisol, but after 24 hours, aldosterone and its immediate precursor, 18-hydroxycorticosterone (18-OHB), declined to near baseline levels. With the exception of deoxycorticosterone (DOC), other mineralocorticoids—corticosterone and 18-hydroxydeoxycorticosterone (18-OHDOC)—also declined, while cortisol remained elevated throughout the three-day period.

Further evidence that chronic regulation of aldosterone secretion does not depend on ACTH is that hypophysectomized animals and ACTH-deficient humans have normal levels of circulating aldosterone.

**POTASSIUM:**

**In vivo**, even small changes in plasma potassium (K) concentration alters aldosterone levels significantly. A high K diet increases and a low K diet decreases the responsiveness of aldosterone to AII. Also the stimulation of aldosterone secretion by K is enhanced by AII and is attenuated by previously administered converting enzyme inhibitors. Exposure of adrenal cells to increasing concentration of K **in vitro** also causes a pronounced increase in aldosterone secretion. K stimulates both the early and the late steroid metabolic pathways and the early- phase stimulation is calcium dependent (6-7).

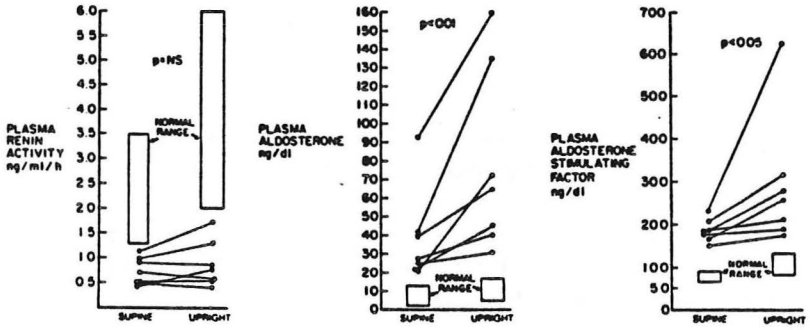



Aldosterone production by dog zona glomerulosa cells in response to potassium as a function of extracellular calcium concentration. Cells prepared in media containing 0.2 mM calcium (●——●), 0.5 mM calcium (▲— —▲), or 1.2 mM calcium (▼- -▼) were incubated with potassium chloride at the concentrations indicated.

**Pituitary Factor:**

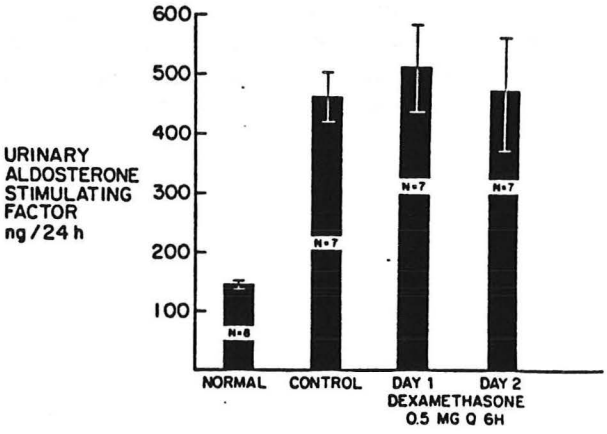
Several lines of evidence suggest that a pituitary factor other than ACTH may be also involved in aldosterone secretion. In recent years several pituitary hormones mostly derived from the large precursor molecule pro-opiomelanocortin (POMC) have been shown to stimulate aldosterone secretion. These include ß-Endorphin, ß-LPH, g-MSH, and α-MSH (13-14).

Another pituitary factor is aldosterone-stimulating factor (ASF). ASF is a glycoprotein with a molecular weight of 26,000. ASF stimulates aldosterone secretion by a non-cyclic AMP dependent mechanism, and ASF-stimulated aldosterone secretion is not blocked by specific competitive antagonists of ACTH or AII. To date, experimental evidence suggests that the source of ASF is the anterior pituitary gland and that the adrenal cortex is the target organ for its biological activity. Basal plasma and urinary ASF is elevated in patients with idiopathic hyperaldosteronism. Circulating ASF does not change with upright posture in normal subjects, but increases in parallel with aldosterone in idiopathic hyperaldosteronism. Plasma and urinary ASF do not suppress with dexamethasone in patients with idiopathic hyperaldosteronism (15-17).




Individual Concentrations of Plasma Renin Activity, Aldosterone, and Aldosterone-Stimulating Factor in Patients with Idiopathic Hyperaldosteronism (N = 7), at 8:00 a.m., after Having Been in the Supine Position Overnight, and at 12:00 Noon, after Four Hours of Upright Posture.

The ranges of values in 15 normal control subjects under the same conditions are depicted by the rectangular boxes. P values indicate differences between the supine and upright position in patients with idiopathic hyperaldosteronism.

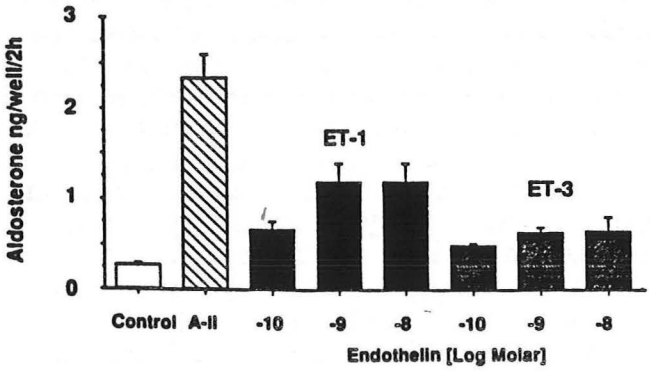



Urinary Excretion of Aldosterone-Stimulating Factor (Mean ±1 S.E.) in Normal Subjects and Patients with Idiopathic Hyperaldosteronism.

Normal values and control values in patients with idiopathic hyperaldosteronism were determined during free ambulation without medications. After control values had been measured in the patients with idiopathic hyperaldosteronism, urine collections were continued for 48 hours during dexamethasone administration.

**Endothelin:**

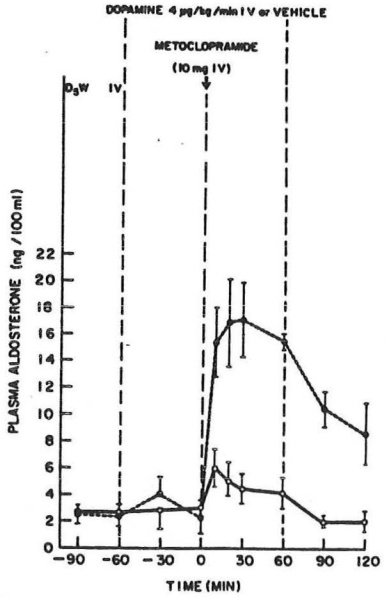
Endothelin, a recently described endothelium-dependent contracting factor, when given intravenously to anesthetized or conscious dogs has been shown to cause an increase in plasma aldosterone. A recent study in calf zona glomerulosa cells in culture has shown that endothelin, like AII, binds to the adrenal cells and stimulates aldosterone secretion (19).




Stimulation by angiotensin II, ET-1 and ET-3 of aldosterone secretion by calf zona glomerulosa cells in culture. A representative experiment is shown ($n = 3$). Each point is the mean±SEM of four wells. The increase of aldosterone secretion was significant ($P < 0.05$) with all doses.

**Dopamine:**

Several studies in humans show that metoclopramide, a competitive antagonist of dopamine in the central nervous system and the periphery, increases plasma aldosterone concentrations in normal humans without a concomitant increase in plasma renin activity or plasma cortisol concentrations. Administration of dopamine abolishes metoclopromide stimulation **in vitro** and **in vivo** (20).

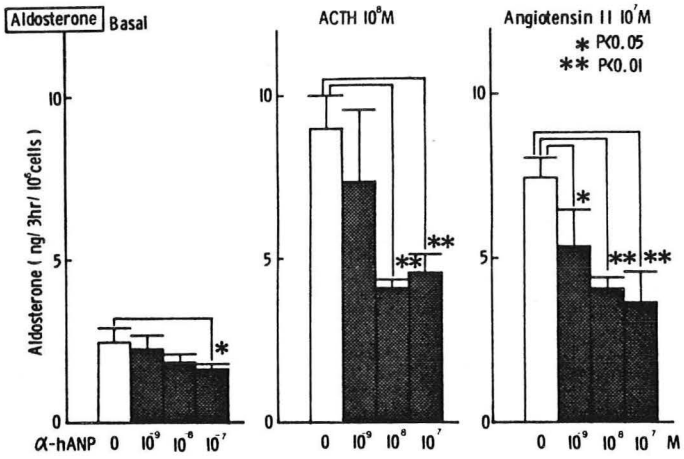



Blood pressure, aldosterone, and prolactin responses to metoclopramide 10 mg iv in five normal subjects (mean ± SE). Dashed lines and solid circles represent data for Study Day 1 (vehicle infusion). Solid lines and open circles represent data for Study 2 (dopamine 4 µg/kg/min infusion). Metoclopramide-induced increases in plasma aldosterone and serum prolactin concentrations were inhibited significantly by dopamine 4 µg/kg/min.

Dopamine modulates the response of aldosterone secretion to AII, as a function of dietary Na intake. During a low Na diet, dopamine reduces the slope of the AII-aldosterone dose response curve to that seen during a high Na diet Dopamine also inhibits basal plasma aldosterone levels in patients with primary aldosteronism, but does not blunt the subsequent increase in plasma aldosterone in response to ACTH administration (17-21).

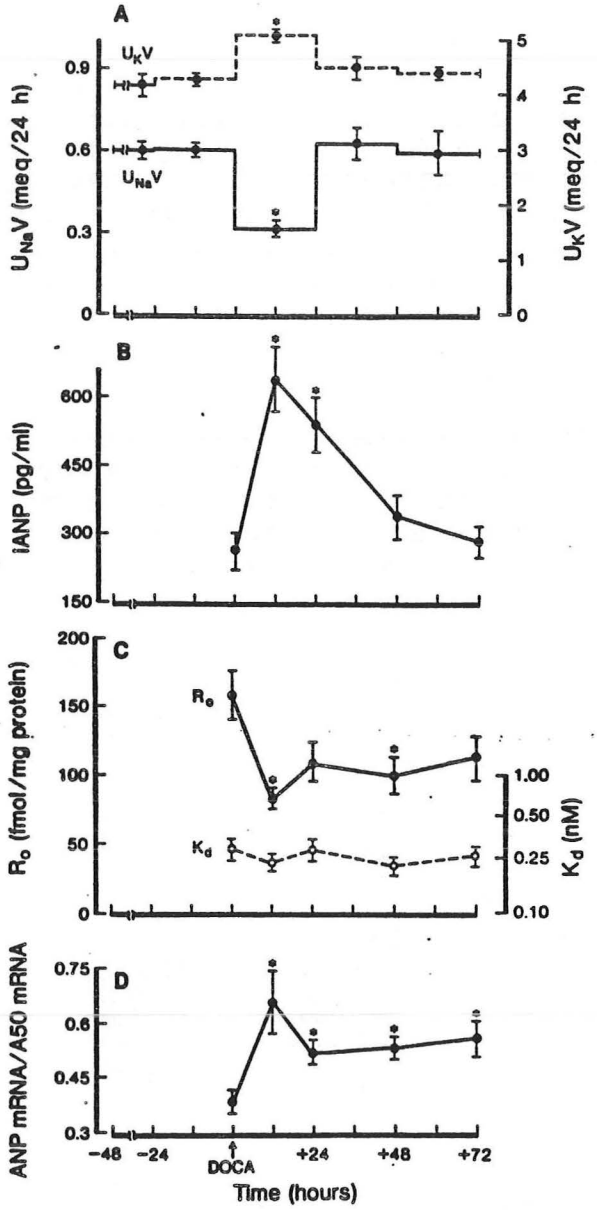
**Atrial Natriuretic Hormone:**

In addition to its potent diuretic, natriurtic, and vasorelaxant activity, ANH also has a prominent suppressive, effect on aldosterone secretion both **in vivo,** and **in vitro** in isolated glomerulose cells. Postulated intracellular mechanisms include an increase in cyclic GMP, a decrease in cyclic AMP, and an inhibition of calcium influx (22-25).

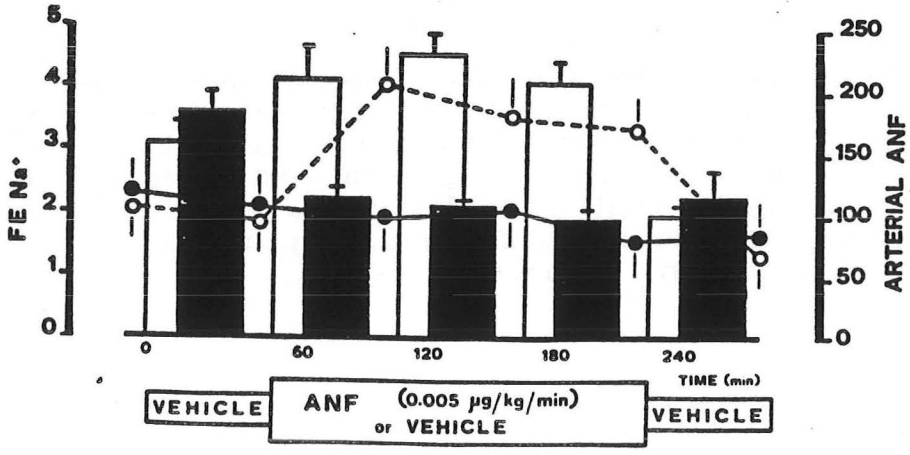



Effect of αhANP on aldosterone secretion from cultured human adrenal cells. Various amounts of αhANP were added to triplicate cell culture dishes stimulated for 3 h with $10^{-8}$ M ACTH or $10^{-7}$ M AII. Each *bar* represents the mean ± SD of triplicate dishes. $P < 0.05$, group without αhANP (*left*) *vs.* ACTH treatment group (*center*) or AII treatment group (*right*).

In patients with primary hyperaldosteronism there is a close correlation between plasma aldosterone and plasma ANH levels. In addition, following exogenous minerolocorticord administration in the rat there is a prompt increase in ANH synthesis and plasma levels, which closely parallel the renal escape from minerolocorticoid effects. A physiologic role for ANH is further supported by the fact that infusion of low doses of ANH to subjects with primary aldosteronism causes a significant natriuresis. Finally, following adrenal surgery in subjects with primary aldosteronism there is a decline in plasma ANH levels. The evidence therefore suggests that in addition to this inhibitory effect on aldosterone production, ANH may also play an important role in the aldosterone escape phenomenon (26-31).




The profile of (*A*) 24-h urinary sodium ($U_{Na}V$) and potassium excretion ($U_KV$), (*B*) plasma iANP, (*C*) renal glomerular ANP receptor density ($R_0$) and equilibrium $K_d$, and (*D*) relative atrial pre-pro-ANP mRNA (the ratio of pre-pro-ANP mRNA/A50 mRNA), as a function of time after a single depot injection of DOCA, 10 mg. All data points reflect mean values for 10 measurements at each time point, except in *D*, where the 12-h time point represents the mean of eight measurements (*$P < 0.05$).

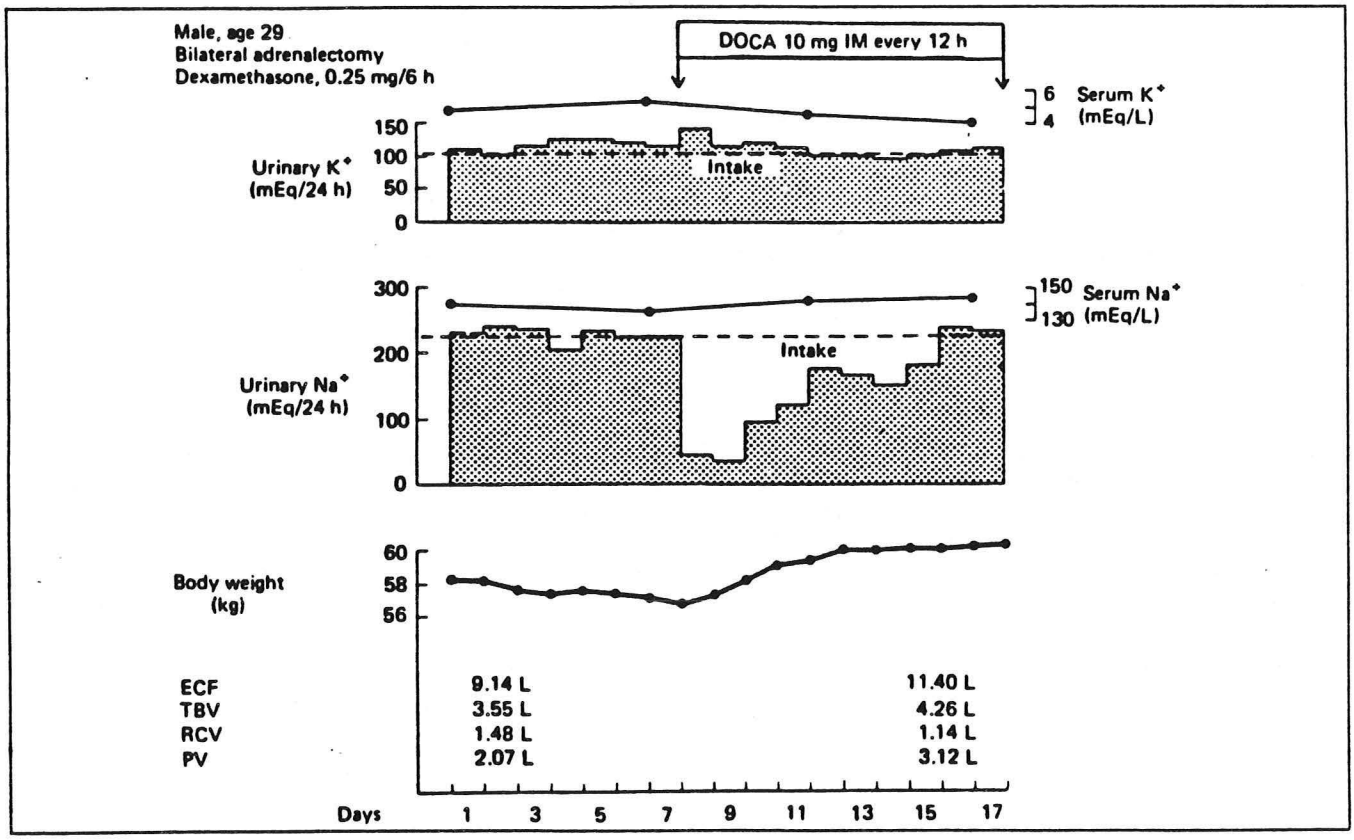



*Arterial atrial natriuretic factor (ANF) (pg/ml) values during vehicle (●—●) or exogenous ANF (○—○) infusion as contrasted with the behavior of fractional urinary sodium excretion (FE $Na^+$) (%) during the corresponding phases of the trial (full bars, vehicle; empty bars, ANF). Mean±SEM. FE $Na^+$, F=5.7, p<0.001 (analysis of variance, interaction time * phases).*

**THE EFFECTS OF ALDOSTERONE ON RENAL TUBULAR SODIUM, POTASSIUM, AND HYDROGEN ION TRANSPORT.**

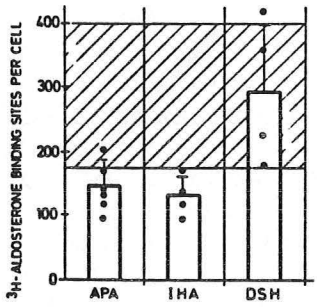
The effects of aldosterone on renal tubular ion transport has recently been discussed in detail in the Southwestern Medical Grand Rounds by Dr. Robert J. Alpern (April 13, 1989) and Dr. Steven R. Hays (August 4, 1989). The net effect of aldosterone is to enhance $Na^+$ reabsorption and $K^+$ and $H^+$ secretion, which results in the extracellular fluid volume expansion, hypokalemia and metabolic alkalosis in patients with primary aldosteronism. In addition to the well established effects of aldosterone on the cortical and medullary collecting tubule, (32-33) recent studies have shown that aldosterone also modulates $Na^+$ reabsorption in the medullary thick ascending limb of Henle, probably by stimulating luminal $Na^+$ transport and basolateral membrane Na, K-ATPase activity (43-37).

Although aldosterone mediated increase in renal tubular $Na^+$ transport results in ECFV expansion, edema is not a common feature in patients with primary aldosteronism. When normal individuals are given mineralocorticoids, Na retention ensues with demonstrable weight gain. However, when mineralocorticoid administration is continued over several days, Na balance is restored, no further weight gain occurs, and the amount of urinary Na excreted approaches intake. The phenomenon has been termed MINERALOCORTICOID ESCAPE, because the kidney escapes from the Na-retaining effect of the hormone. During mineralocorticoid escape excessive urinary $K^+$ and $H^+$ excretion however continue.




**Sodium escape from sodium-retaining steroids (deoxycorticosterone).**

The mechanism by which mineralocorticoid escape occurs remains unresolved and controversial. The signal for escape appears to be ECFV expansion. However, the mechanism by which the expansion is translated into altered renal sodium handling is still controversial. The proposed mechanisms include **a)** hemodynamic and physical factors, **b)** suppression of angiotensin II production, **c)** decreased sympathetic nervous system activity, **d)** increased prostaglandin activity, **e)** increased atrial natriuretic hormone activity, and **f)** increased dopamine activity. An additional mechanism which has been proposed is that mineralocorticoid excess produces down-regulation of mineralocorticoid receptors, which, in turn, may contribute to the genesis of the ALDO ESCAPE phenomenon. In fact, the number of aldo-binding sites in the mononuclear leukocytes of subjects with primary aldosteronism has been found to be significantly reduced (38).



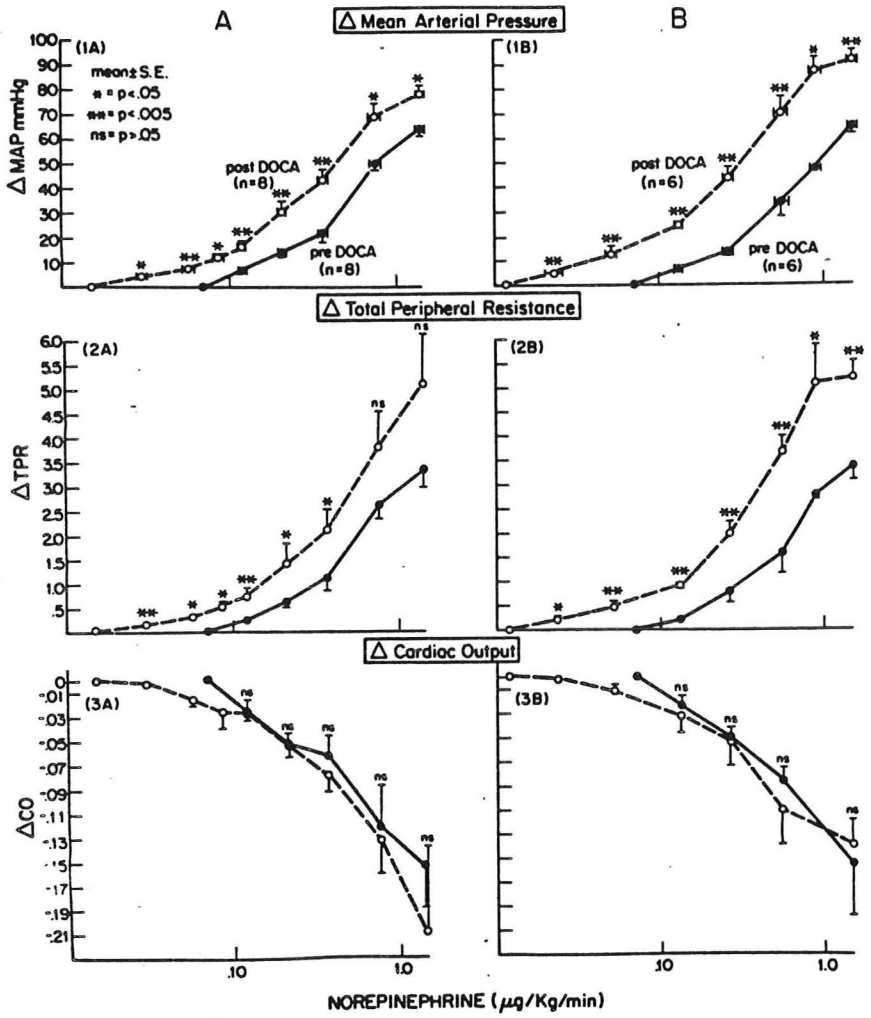

The number of aldo-binding sites in HML of patients with various forms of primary hyperaldosteronism. The *shaded area* indicates the normal range (mean ± SD), and the *vertical brackets on top of each bar* indicate the SD in that group.

**THE PATHOGENESIS OF MINERALOCORTICOID HYPERTENSION.**

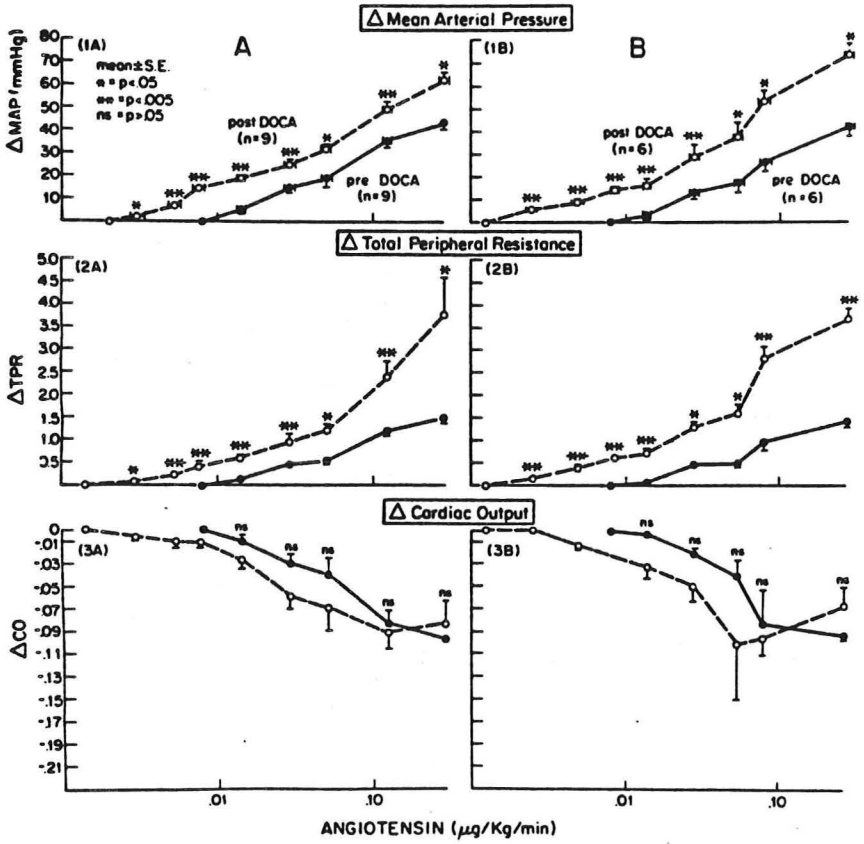
In spite of extensive research efforts the pathogenesis of mineralocorticoid hypertension, like that of mineralocorticoid escape, remains unresolved (39-41). The hypertension initially results from a series of hemodynamic alterations including early expansion of intravascular blood volume and increased cardiac output. The total peripheral vascular resistance increses and plasma volume and cardiac output fall to near normal levels.

In the deoxycorticosterone acetate (DOCA)-salt hypertensive rat, an experimental model of mineralocorticoid hypertension, the increases in arterial blood pressure and peripheral vascular resistance are caused by enhanced vasoconstrictive and impaired vasodilator response to vasoactive hormone and substances.

In the DOCA-salt hypertensive pig, relativeneorepinephrine and/or norepinephrine and angiotensin II sensitivity, defined as amount of neorepinephrine and/or norepinephrine and angiotensin II required to increased mean arterial pressure by 20mmHg, is markedly increased which indicates enhanced vasoconstrictive response to norephinephrine and AII (42).

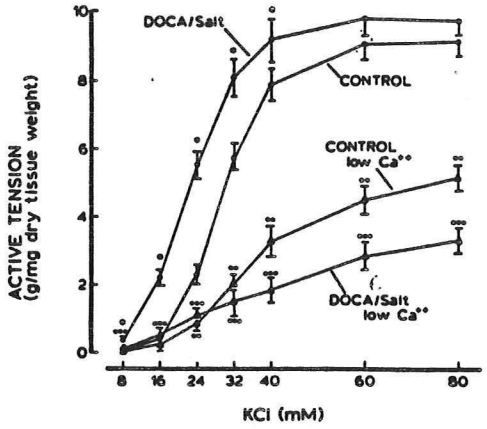



*Systemic reactivity in DOCA hypertension; comparison between pre-DOCA norepinephrine response curves and curves obtained at two intervals after DOCA implantation. A = 1 week post-DOCA (n = 8); B = 1 month post-DOCA (n = 6). Data are expressed as mean change ± SE. 1A and 1B Δ MAP; 2A and 2B = Δ TPR; 3A and 3B Δ CO. Paired t-analysis was carried out to determine the significances of the differences between pre- and post-DOCA results. CO and TPR are expressed in arbitrary units (mm pen deflection/kg and mm Hg/mm pen deflection per kg × $10^2$, respectively).*

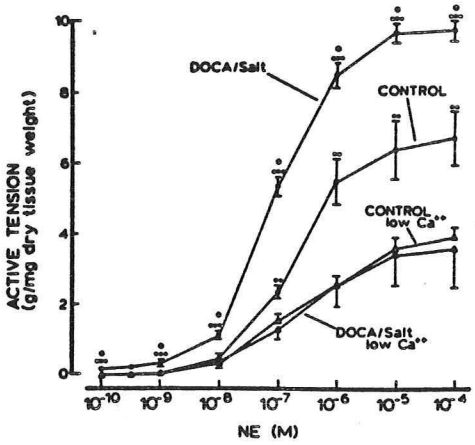



*Systemic reactivity in DOCA hypertension; comparison between pre-DOCA angiotensin response curves and curves obtained at two intervals after DOCA implantation. A = 1 week post-DOCA (n = 9); B = 1 month post-DOCA (n = 6). Data are expressed as mean change ± SE. 1A and 1B = Δ MAP; 2A and 2B = Δ TPR; 3A and 3B = Δ CO. Paired t-analysis was carried out to determine the significances of the differences between pre- and post-DOCA results. CO and TPR are expressed in arbitrary units (mm pen deflection/kg and mm Hg/mm pen deflection per kg × $10^2$, respectively).*

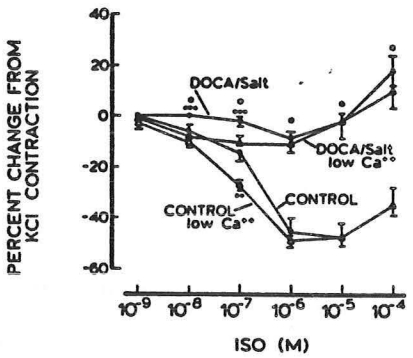
In femoral artery strips isolated from control and DOCA-salt hypertensive rats, the **in vitro** active tension development in response to KCL and Norepinephrine is markedly enhanced, whereas the relaxation in response to isoproterenol and sodium nitrate following KCL contraction is markedly impaired (43-45).



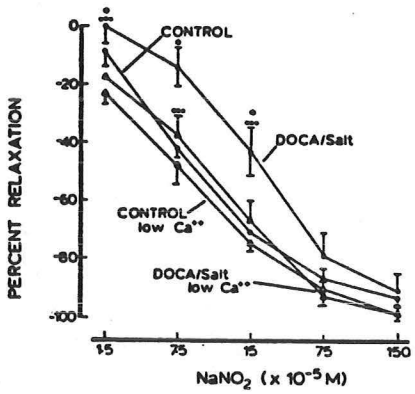

*Dose-response relationship between concentration of KCl and development of active tension by rings of femoral artery from control and DOCA-salt hypertensive rats in either normal (2.5 mM) or low (0.25 mM) calcium Krebs physiological solution. Each point represents the mean ± SE of 12 rings. Single asterisks indicate DOCA-salt significantly different from control ($p<0.05$). Double asterisks indicate control response in low calcium significantly different from control response in normal calcium ($p<0.05$). Triple asterisks indicate DOCA-salt response in low calcium significantly different from DOCA-salt response in normal calcium ($p<0.05$).*




*Dose-response relationship between concentration of norepinephrine (NE) and development of active tension by rings of femoral artery from control and DOCA-salt hypertensive rats in either normal (2.5 mM) or low (0.25 mM) calcium Krebs physiological solution. Each point represents the mean ± SE of 12 rings. Symbols for statistical significance are the same as those in Figure 2.*

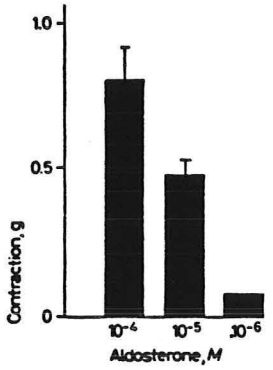



*Dose-response relationship between concentration of isoproterenol (ISO) and percent change from KCl contraction of rings of femoral artery from control and DOCA-salt hypertensive rats in either normal (2.5 mM) or low (0.25 mM) calcium Krebs physiological solution. Each point represents the mean ± SE of 12 rings. Symbols for statistical significance are the same as those in Figure 2.*

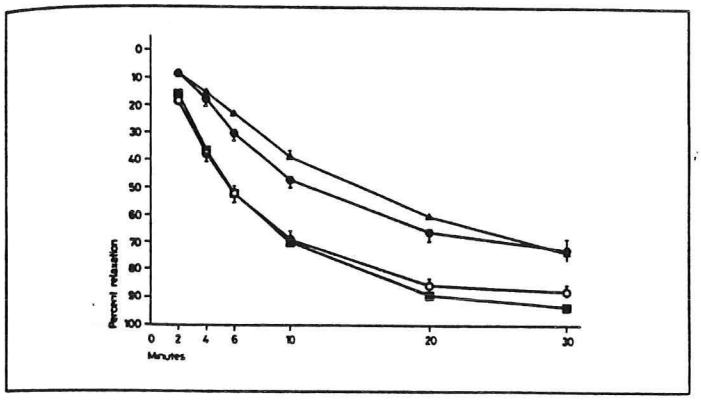



*Dose-response relationship between concentration of $NaNO_2$ and percent relaxation of rings of femoral artery from control and DOCA-salt hypertensive rats following KCl contraction in either normal (2.5 mM) or low (0.25 mM) calcium Krebs physiological solution. Each point represents the mean ± SE of 12 rings. Symbols for statistical significance are the same as those in Figure 2.*

It is not clear whether the mineralocorticoid or the positive sodium balance per se or both modiate the increase in vascular-activity to vasoconstrictive hormones. In isolated rings of rabbit thoracic aorta the presence of aldosterone has been shown to both increase vascular contraction and also to impair the relaxation of norepinephrine-contracted blood vessels (46).

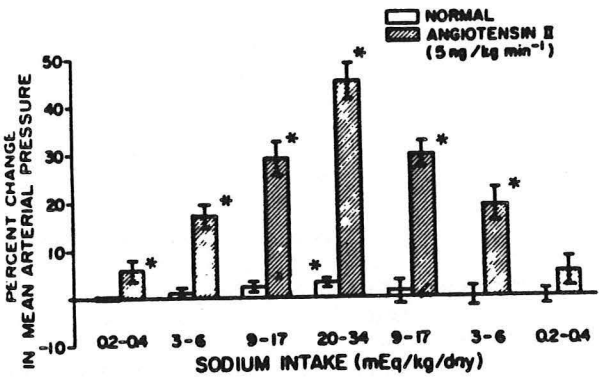


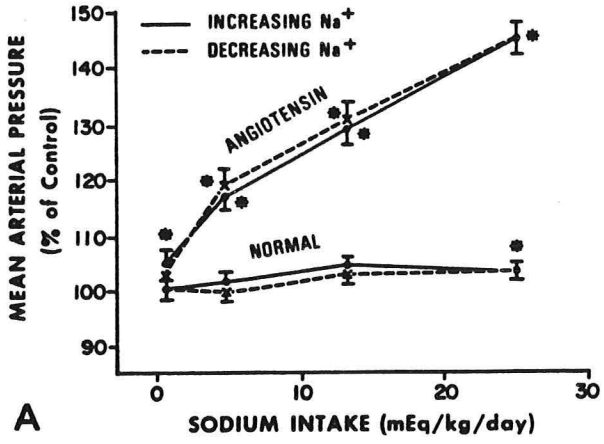

Contractions caused by aldosterone in vessels previously contracted to a steady-state of 1.5–3.5 g with NE. Data are expressed as mean ± SEM.




Relaxation of NE-contracted vessels after immersion in oil, in the presence of ethanol diluent (o), 10 μM (■), 30 μM (●) and 100 μM (▲) aldosterone. Data are expressed as mean ± SEM percent relaxation (n = 7–10).

On the other hand, long-term sodium chloride infusion in the dog, which in itself does not alter blood pressure, also increases the blood pressure response to otherwise subpressor amounts of angiotensin. The pressor response to angiotensin II occurs as a function of the sodium chloride infusion rate, indicating that the positive sodium balance perse is also an important regulator of vascular reactivity (47).



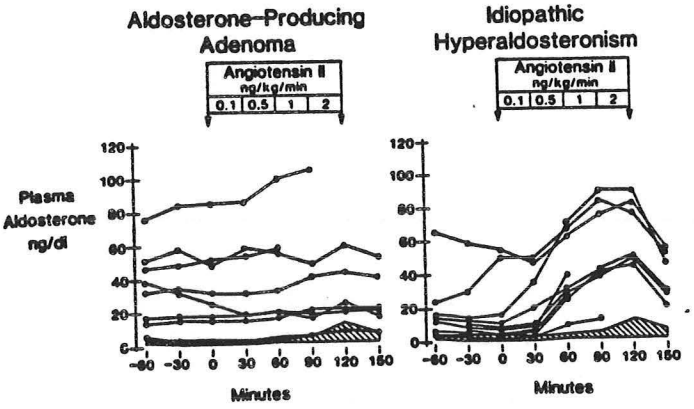




In addition to the roles of mineralocorticoid and sodium balance, other additional factors such as the negative potassium, calcium, and magnesium balance, and the increase in circulating factor with ou-bain-like immunoreactivity may also play a role in the pathogenesis of mineralocorticoid hypertension (49).

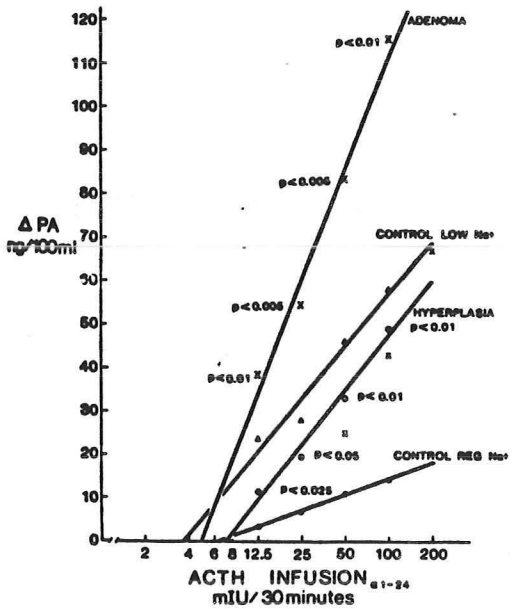
## SUBTYPES OF PRIMARY HYPERALDOSTERONISM

### ALDOSTERONE-PRODUCING ADENOMA (APA)

Unilateral APA are the most frequently diagnosed cause of primary aldosteronism in adults. Production of aldosterone in APA is only partly autonomous. Aldosterone no longer responds to angiotensin II, but aldosterone still responds to changes in ACTH levels, and plasma aldosterone concentration in APA still exhibits a circadian rhythm parallel to that of ACTH levels (50-52).




Effect of angiotensin II on plasma aldosterone concentrations in 8 patients with aldosterone-producing adenoma and 9 patients with idiopathic hyperaldosteronism. Range of aldosterone concentrations in 13 normal subjects is shown by the *hatched area.*

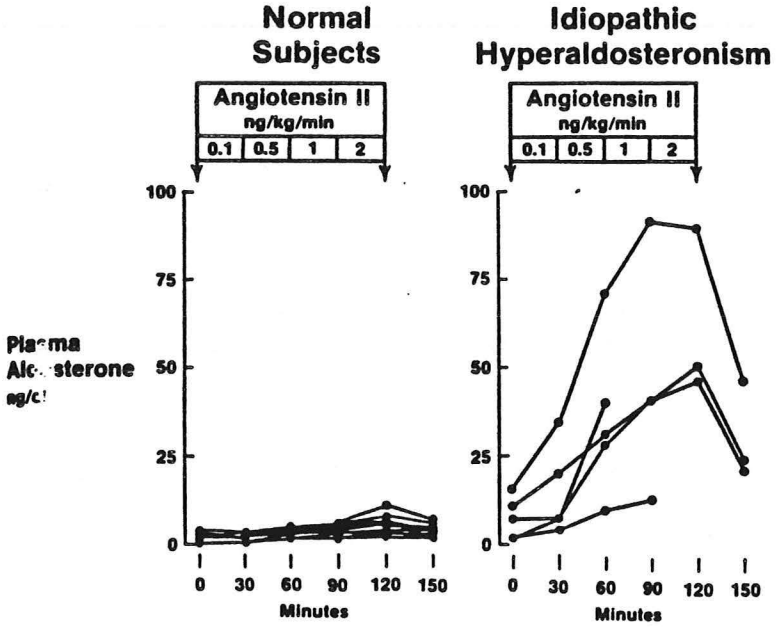



The median increase over base line of plasma aldosterone (ΔPA) is plotted against the log of the ACTH infusion rate. The data from the 4 patients with an adenoma who did not have 12.5 and 25 mIU infusions are presented separately with a small x. The *P* values indicate the significant difference in the response of the patients with 1° aldosteronism from the control subjects on a similar diet.

Cells found in the adenoma resemble cells from all three cortical layers. There are also hybrid cells that exhibit features of both glomerulosa and fasciculate cells. The adenoma is usually single, less than 3cm in size. The mean diameter of the adenoma in 143 surgically treated patients with APA at the Mayo Clinic was 1.8cm, and 19 percent were smaller than 1cm in diameter (4).

## IDIOPATHIC HYPERALDOSTERONISM (IHA)

Bilateral IHA is the second most commonly diagnosed form of primary aldosteronism in adults and the most common form in children. Hyperplasia of the zona glomerulosa is found with or without microscopic and macroscopic nodules. In contrast to patients with APA, in patients with IHA the plasma aldosterone concentration does not parallel the circadian rhythm of the ACTH concentration. Intravenous infusion of angiotensin II however produces exaggerated aldosterone secretion in patients with IHA compared with normal subjects and patients with APA (51,53).




Effect of angiotensin II on plasma aldosterone in 5 patients with idiopathic hyperaldosteronism and 13 normal subjects. Angiotensin II was infused after 2 days of supplemental sodium and dexamethasone and 2 h of supine posture.

The hyperplasia associated with bilateral IHA is most likely due to an extra-adrenal stimulatus or an amplifier of angiotensin II effect. Several substances have been proposed as adrenal stimulators or amplifiers of angiotensin II. Levels of several POMC peptide, including g-MSH and ß-endorphin may be elevated in IHA -ASF is also found to be elevated. The serotonin antagonist cyproheptadine suppresses aldosterone in IHA, suggesting possible involvement of a serotonin-mediated aldosterone stimulator in this condition. One patient with IHA had hyperplasia of the intermediate lobe of the pituitary, further strengthening the argument that an unidentified pituitary hormone is an etiologic factor in IHA.

**PRIMARY ADRENAL HYPERPLASIA (PAH)**

PAH is a disorder associated with bilateral adrenal hyperplasia, but in terms of hormonal studies it resembles APA (55). In a recent series of 150 patients with primary aldosteronism at San Francisco General Hospital Medical center 5 subjects were diagnosed with PAH (68). As will be discussed in more detail later, these patients respond very well to unilateral or bilateral subtotal adrenalectomy.

**ALDOSTERONE PRODUCING - RENIN RESPONSIVE ADENOMA (AP-RRA)**

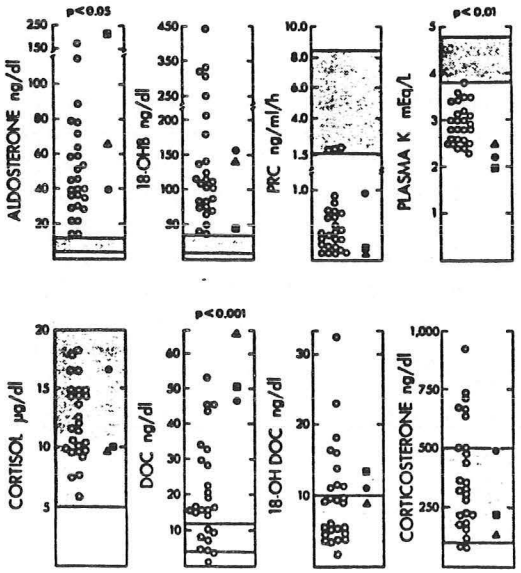
AP-RRA mimics APA morphologically, but in terms of hormonal studies it resembles IHA (68). In a recent series of 150 patients with primary aldosteronism at San Francisco General Hospital Medical Center 4 subjects were diagnosed with AP-RRA (68). As will be discussed in more detail later, these patients response very well to unilateral adrenalectomy.

**ALDOSTERONE PRODUCING ADRENOCORTICAL CARCINOMA**

Aldosterone producing adrenocortical carcinoma is a very rare cause of primary aldosteronism. Although these malignancies may secret only aldosterone, more often they are associated with concomitant aldosterone precursor, glucocorticoid, or sex steroid excess. The biochemical abnormalities in these patients are usually severe and patients may present with severe hypertension and hypokalemia. Aldosterone levels are very high and visually do not respond to ACTH (57-58).

The best single diagnostic criterion is the size of the tumor. Most aldosterone- secreting adrenal carcinomas are very large, greater than 3cmm, and there may also be presence of metastases.

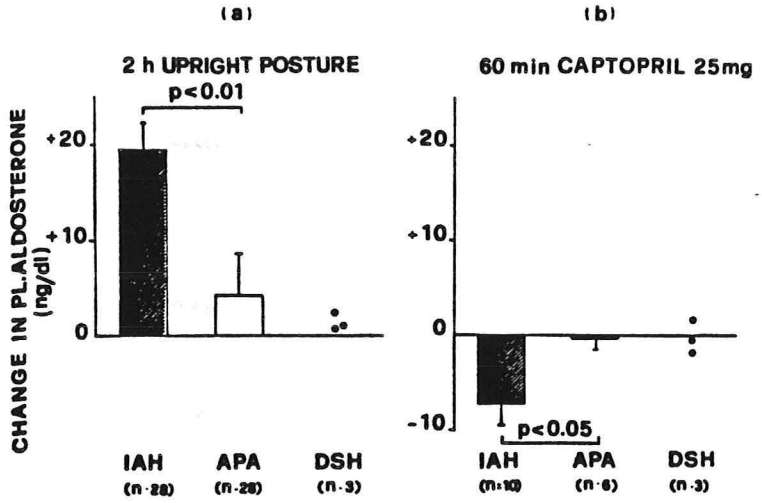
In addition to adrenocortical tumors, some ovarian tumors have also been reported to secret aldosterone.



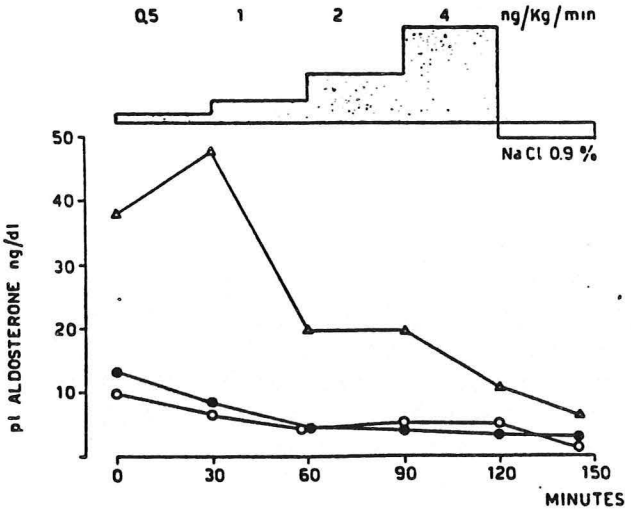

0800-hour plasma steroid, potassium, and renin concentrations after overnight recumbency in 26 patients with an aldosterone-producing adenoma (open circle) and in three patients with adrenal carcinoma (triangle, square, closed circle). Stippled areas represent normal ranges. A Student's unpaired *t*-test was done to compare both groups. DOC = deoxycorticosterone; 18-OHB = 18-hydroxycorticosterone; 18-OH DOC = 18-hydroxydeoxycorticosterone; PRC = plasma renin concentration.

## GLUCOCORTICOID-SUPPRESSIBLE HYPERALDOSTERONISM (GSHA)

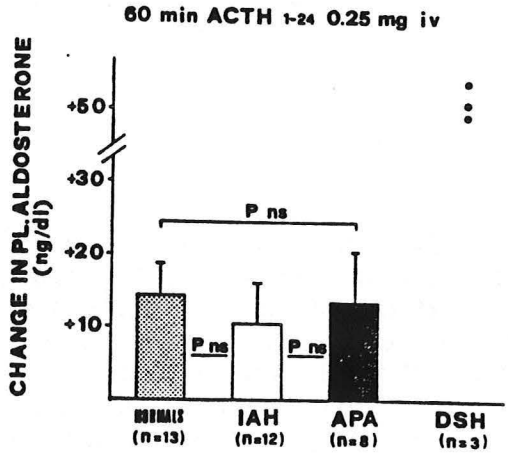
GSHA was first described in 1964 by Sutherland et al in a father and son with hypertension, increased aldosterone secretion and low plasma renin activity, which all responded to dexamethasone treatment (59). Since then more than 60 cases has been described. Genetic studies show no HLA linkage and suggest to an autosomal dominant mode of inheritance. Biochemically GSHA can be differentiated from IAH since aldosterone does not respond to upright posture, to angiotensin II infusion, and to angiotensin converting enzyme inhibitor. In contrast, morphologically GSHA is similar to IAH, since the adrenal glands from patients who have undergone operation revealed macronodular and micronodular hyperplasia. GSHA however is differentiated from IAH and APA by hyperresponsiveness of aldosterone secretion to acute ACTH administration as well as by the failure of aldosterone secretion to escape from prolonged ACTH stimulation(60-61).




Plasma aldosterone change from basal values after 2 h of upright posture (a) and 60 min after the administration of 25 mg captopril (b) in patients with IAH, APA and DSH. For the captopril test the patients were evaluated at 10:00 AM maintaining a comfortably sitting position 2 h before and for all the duration of the study [46]. Data for IAH and APA are expressed was mean ± SEM; comparison between values was made using the unpaired *t*-test

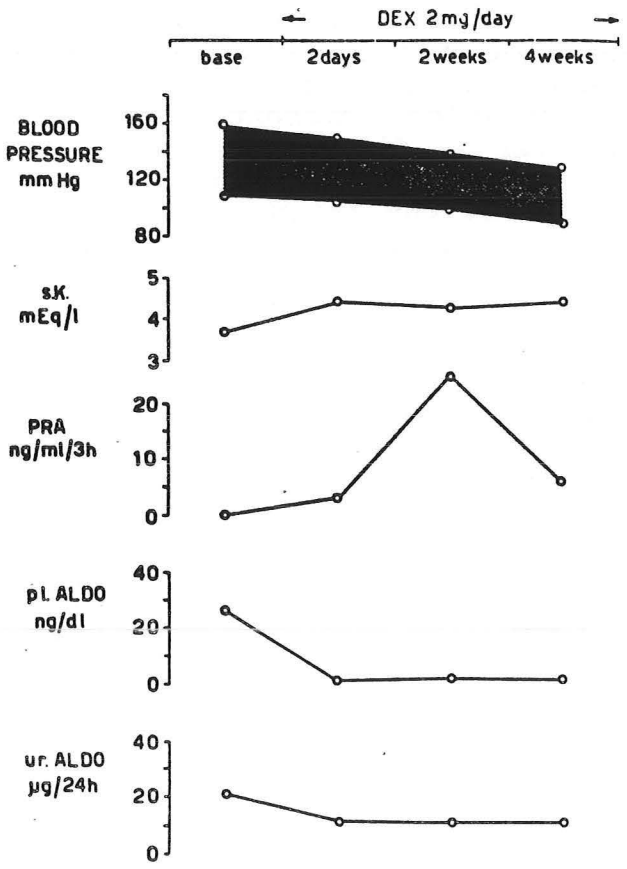



Plasma aldosterone response to angiotensin II infusion in three siblings with DSH. [Asp$^1$–Val$^5$] angiotensin (Hypertensin, Ciba-Geigy) was infused at the rate of 0.5, 1.0, 2.0, 4.0 ng/kg/min in four consecutive 30-min periods, followed by another period of saline [8]




Plasma aldosterone change from basal values 60 min after the administration of ACTH 1–24 (Synacthen, Ciba-Geigy) 0.25 mg as a bolus i.v. in normal subjects and in patients with IAH, APA, and DSH. Injection was performed at 9:00 AM after the subjects has been comfortably seated for 30 min [8]. For statistical analysis see the legend of Fig. 1

The final diagnosis of GSHA rests upon prompt reversal of the features of mineralocorticoid excess by glucocorticoid therapy.




Effect of dexamethasone (*Dex*) treatment on blood pressure, serum K, PRA, plasma and urinary aldosterone (*ALDO*) in a typical case of DSH [8]

The studies on the pathophysiology of GSHA have suggested this interesting disorder to be caused by abnormalities of **a)** pituitary (ACTH and/or other aldosterone stimulating pituitary factors) and/or **b)** adrenal gland (new steroid production, including 18-hydroxycortisol and 18-oxocortisol, by transitional cells having either fasciculata-or glomerulosa-like characteristics and capable of synthesizing aldosterone, cortisol and the two new steroids which result from metabolism of cortisol through the 18-methyloxidase system).

## CLINICAL PRESENTATION OF PRIMARY HYPERALDOSTERONISM

The most important findings in patients with primary aldosteronism are hypertension and hypokalemia. In addition, mild metabolic alkalosis and mild hypernatremia are also present. Although several symptoms may be reported, usually a consequence of chronic hypokalemia and metabolic alkalosis, they are nonspecific and do not aid with the diagnosis (64-65).

SYMPTOMS IN 103 PATIENTS WITH PRIMARY ALDOSTERONISM

| Symptom | Female Patients (Number and Per cent) | Male Patients (Number and Per cent) | Combined |
|---|---|---|---|
| Muscle weakness | 54 (71) | 21 (78) | 75 (73) |
| Polyuria (nocturia) | 53 (70) | 21 (78) | 74 (72) |
| Headache | 41 (54) | 12 (44) | 53 (51) |
| Polydipsia | 34 (45) | 13 (48) | 47 (46) |
| Paresthesias | 23 (30) | 2 ( 7) | 25 (24) |
| Visual disturbance | 16 (21) | 6 (22) | 22 (21) |
| Intermittent paralysis | 18 (24) | 3 (11) | 21 (21) |
| Tetany | 20 (26) | 1 ( 4) | 21 (21) |
| Fatigue | 17 (22) | 3 (11) | 20 (19) |
| Muscle discomfort | 13 (13) | 3 (11) | 16 (16) |
| No symptoms | 4 ( 5) | 2 ( 7) | 6 ( 6) |
| Total | 76 (74) | 29 (26) | 103 |

## DIAGNOSIS OF PRIMARY HYPERALDOSTERONISM

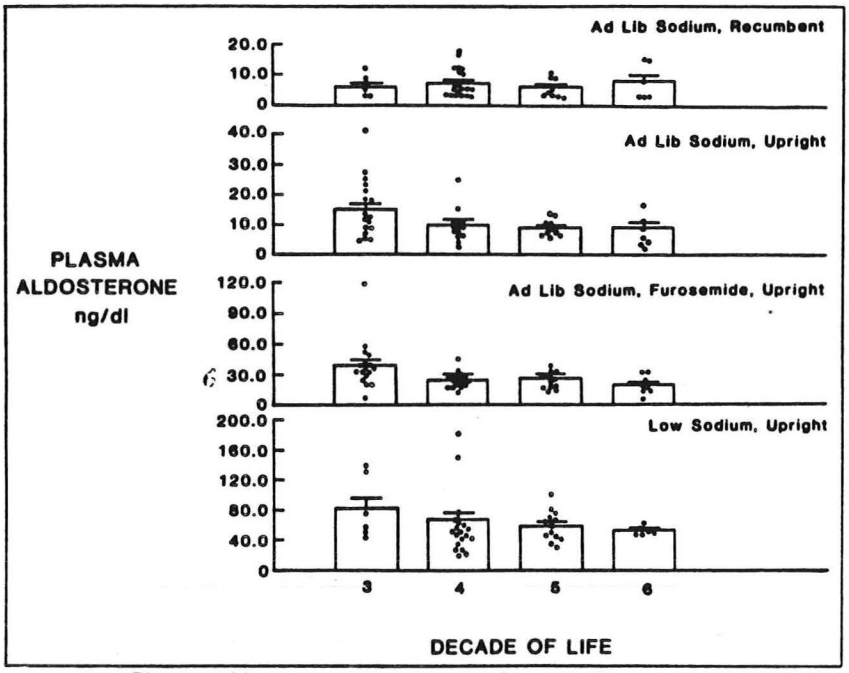
The differential diagnosis of hypertension and hypokalemia is rather extensive. The wider availability of reliable commercial assays for renin and aldosterone has made it possible for accurate hormonal confirmation of primary hyperaldosteronism by the demonstration of **a)** nonsupressible urine or plasma aldosterone levels, **b)** low plasma renin activity, and **c)** normal glucocorticoid excretion.

*Differential Diagnosis of Hypertension and Hypokalemia*

| |
|---|
| Primary hyperaldosteronism |
| Hyperdeoxycorticosteronism |
| DOC-producing adrenal tumors |
| Congenital adrenal hyperplasia |
| 11-hydroxylase deficiency |
| 17-hydroxylase deficiency |
| Secondary hyperaldosteronism |
| Antihypertensive therapy |
| Ethanol abuse and withdrawal |
| Coexistent sodium chloride deficiency or loss or hypovolemia |
| Renovascular hypertension |
| Malignant hypertension |
| Pheochromocytoma |
| Cushing's syndrome |
| Primary hyper-reninism |
| Ectopic |
| Renin-secreting renal tumor |
| Exogenous mineralocorticoid |
| High dose cortisol |
| Fludrocortisone |
| 9-alpha-fluoroprednisolone |
| Carbenoxolone |
| Licorice |
| Chewing tobacco |
| Other endogenous mineralocorticoids |
| 18-OH-DOC |
| 19-Nor-DOC |
| Abnormal steroid metabolites[67] |
| Liddle's syndrome |

Prior to performing the hormonal studies it is important to **a)** discontinue medications which are known to interfere with the renin-angiotensin-aldosterone axis: spironolactone and estrogens for 6 weeks; diuretics, prostaglandin synthetase inhibitors and converting enzyme inhibitors for 2 weeks, calcium channel antagonists for 1 week; **b)** correct the hypokalemia which is known to inhibit aldosterone secretion; **c)** control for the sodium and volume status, since a low sodium diet may further stimulate renin activity and aldosterone secretion.

Another important criteria which needs to be considered is the age-related decrease in plasma aldosterone concentration and urinary aldosterone secretion rate (66). The age of the patient needs therefore to be taken account to avoid false-negative hormonal studies.




*Plasma aldosterone concentration in normal recumbent and upright subjects while on an ad lib sodium diet, and after sodium depletion with furosemide or a 20 meq sodium diet. The brackets represent the SEM.*

The diagnostic investigation of primary aldosteronism is divided into two distinct series of studies. The first series involves the studies necessary to confirm the diagnosis of primary aldosteronism. The second series involves studies performed to diagnose the subtype of primary aldosteronism, especially to distinguish between APA and IHA.

**SALINE INFUSION TEST**

The saline infusion test is most helpful in demonstrating that the increase in plasma aldosterone concentration and/or urinary aldosterone excretion rate is nonsuppressible, i.e. the increase in aldosterone is PRIMARY and not secondary due to renin stimulation.

The most optimal way to perform the test is: **a)** patients should be on a 120meq sodium diet for at least 3 days, **b)** patient should be recumbent overnight, **c)** baseline plasma renin, aldosterone, 18-hydroxycorticosterone, and cortisol are drawn at 8 a.m. **d)** 1250 ml of isotonic saline is infused intravenously between 8 a.m. and 10 a.m., **e)** plasma renin, aldosterone, 18-hydroxycorticosterone, and cortisol are drawn again at the end of the saline infusion, **f)** if there are any cardiovascular contraindications, saline may be infused at a slower rate and over a longer period of time.

In addition to demonstrating the nonsuppressibility of aldosterone secretion, the saline infusion test is also helpful in distinguishing between APA and IHA (67).

In patients with APA: **a)** plasma renin activity is low and there is

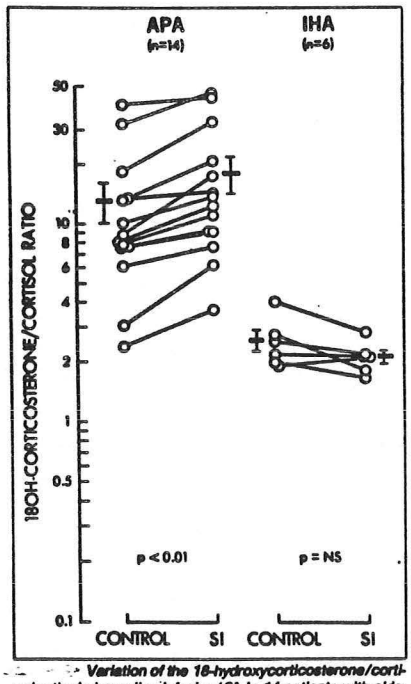
no further reduction after saline, **b)** there are significant reductions in plasma cortisol (49%), aldosterone (24%), and 18-hydroxycorticosterone (31%) due to the circadian decrease in ACTH at 10 a.m. compared to 8 a.m.

In patients with IHA: **a)** plasma renin activity is also low, but there is a further reduction after saline, **b)** there are significant reductions in plasma cortisol (40%), aldosterone (44%), and 18-hydroxycorticosterone (51%). The relatively greater reductions in aldosterone and 18-hydroxycorticosterone are due to the combined effects of the circadian decrease in ACTH and further suppression of plasma renin activity.

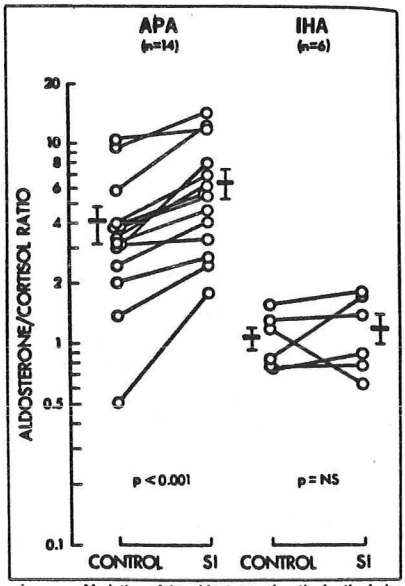
**RESULTS OF SALINE INFUSION**

| | RENIN | | CORTISOL | | ALDOSTERONE | | 18-OHB | |
|---|---|---|---|---|---|---|---|---|
| | PRE | POST | PRE | POST | PRE | POST | PRE | POST |
| APA | 0.92 | 0.80 | 12.9 | 6.6* | 52.3 | 39.5* | 168.1 | 116.2* |
| IHA | 1.67 | 1.38* | 11.4 | 6.9* | 12.4 | 7.0* | 29.4 | 14.5* |

On the basis of the greater reductions in 18 OH-corticosterone and aldosterone in IHA, the 18 OH-corticosterone/cortisol and aldosterone/cortisol ratios can be useful in differentiating APA from IHA. The 18 OH-corticosterone/cortisol ratio is a better discriminating test as a ratio less than 3.0 after saline infusion is diagnostic of IHA, whereas a ratio greater than 3.0 after saline infusion is compatible with the diagnosis of APA.

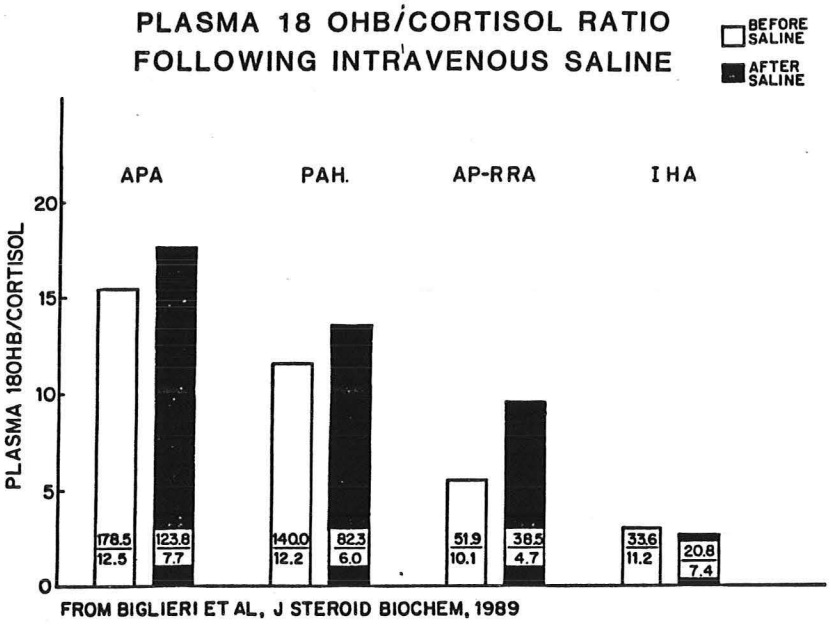



*Variation of the 18-hydroxycorticosterone/cortisol ratio during saline infusion (SI) in 14 patients with aldosterone-producing adenoma (APA) and six with idiopathic hyperaldosteronism (IHA). The ratios were calculated by dividing the actual values of 18-hydroxycorticosterone (ng/dl) by those of cortisol (μg/dl). Statistical analysis was performed by the paired Student t test comparing the values before (control) and after saline infusion in each group.*




*Variation of the aldosterone/cortisol ratio during saline infusion (SI) in 14 patients with aldosterone-producing adenoma (APA) and six with idiopathic hyperaldosteronism (IHA). The ratios were calculated by dividing the actual values of aldosterone (ng/dl) by those of cortisol (μg/dl). Statistical analysis was performed by the paired Student t test comparing the values before (control) and after saline infusion in each group.*

The 18 OH-corticosterone/cortisol ratio is also helpful in investigating patients with PAH, which resemble APA, and AP-RRA, which resemble IHA in regulation of aldosterone secretion (68).

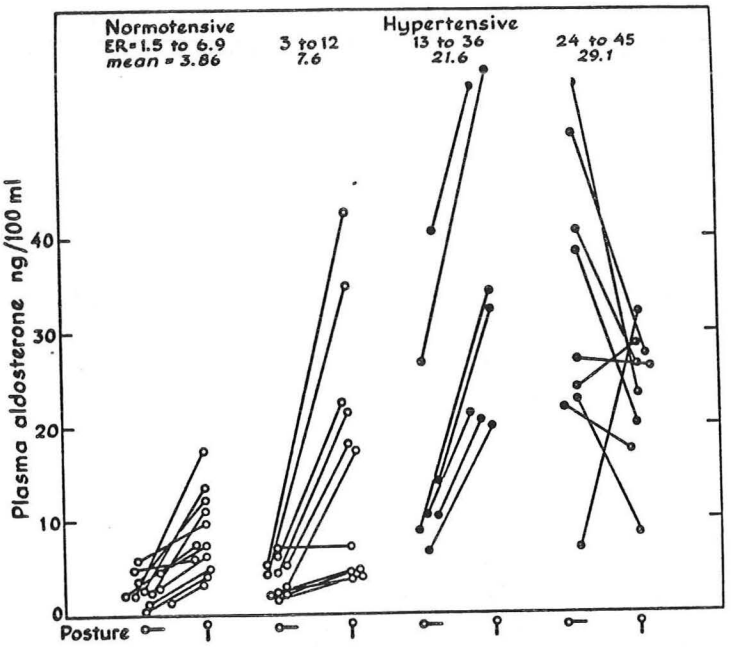



**POSTURAL STUDIES**

Postural studies are most helpful in distinguishing APA from IHA. It takes advantage of the fact that in APA aldosterone secretion is sensitive to changes in ACTH, and IHA aldosterone secretion is sensitive to angiotensin II.

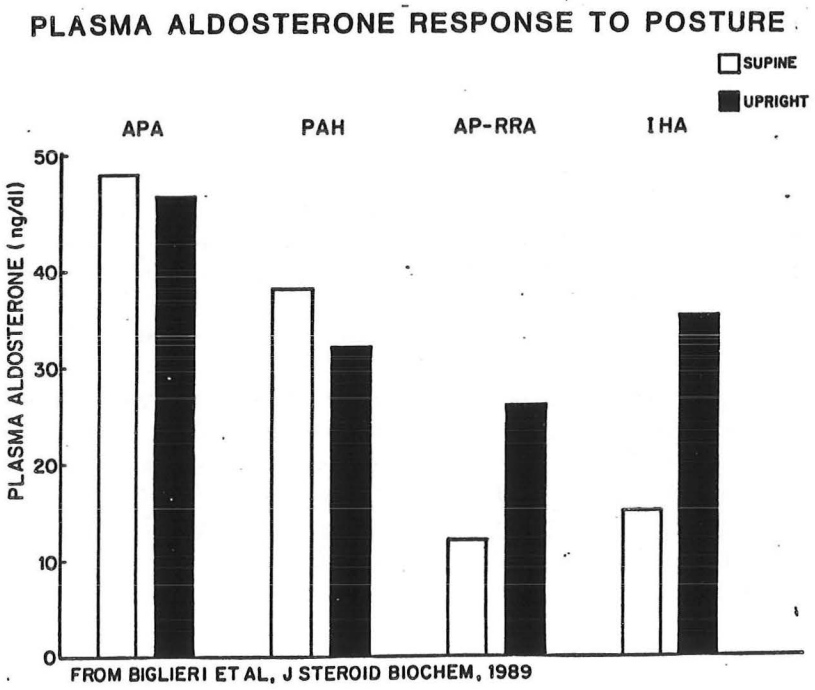
The most optimal way to perform the test is: **a)** patient should be on a 120meq sodium diet for at least 3 days, **b)** patient should be recumbent overnight, **c)** baseline plasma renin, aldosterone, and cortisol are drawn at 8 a.m., **d)** patient is asked to ambulate for 4 hours and/or 80mg furosemide is administered orally, **e)** at 12 noon plasma renin, aldosterone, and cortisol are drawn again.

In patients with primary aldosteronism the postural test has been very helpful in distinguishing most cases of IHA from APA. In IHA, compared to 8 a.m., the 12 noon aldosterone levels are higher due to a further stimulation by AII whereas in APA, compared to 8a.m., the 12 noon plasma aldosterone levels are lower due to the circadian decrease in ACTH level (69-70).




Effects of 4 hours' standing on plasma aldosterone concentration in normal controls (left), in essential hypertension (left center), and in hyperaldosteronism due to bilateral hyperplasia (right center) or adenoma (right). Circles show plasma aldosterone in recumbent posture o- and after standing ♀ . Lines connect observations in individual patients. Numbers at top give range and mean of aldosterone excretion rate (ER) for each group.

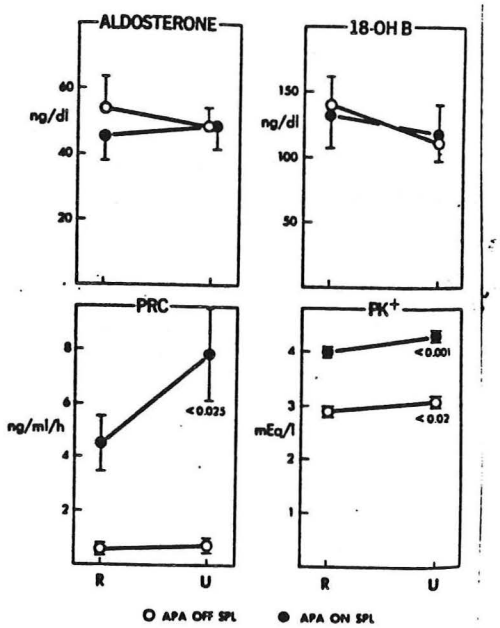
In a more recent series of 150 patients with primary aldosteronism the postural study has also been useful in investigating patients with PAH, which resemble APA, and AP-RRA, which resemble IHA in regulation of aldosterone secretion (68).



## ALDOSTERONE RESPONSE TO SPIRONOLACTONE

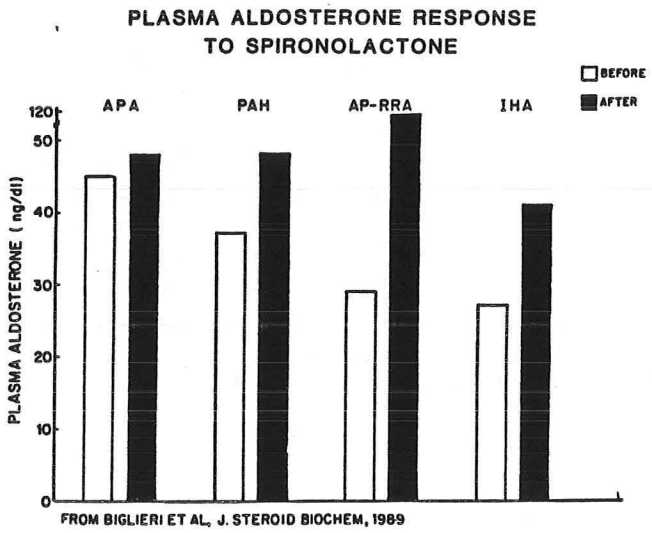
Spironolactone (Aldactone) is a competitive antagonist of the mineralocorticoid hormone receptor at the target cell, especially in the kidney. In vitro studies show that spironolactone or some of its metabolites may also inhibit aldosterone biosynthesis in isolated adrenal cells. Spironolactone has been successfully used for the medical management of primary and secondary aldosteronism. spironolactone corrects the hypertension and hypokalemia in most patients with primary aldosteronism.

In a study in 24 patients with primary aldosteronism (15 with APA and 9 with IHA) it was found that following spironolactone therapy blood pressure decreased, serum potassium and plasma renin activity normalized in both APA and IHA patients. In IHA patients there were significant increases in plasma aldosterone and 18-hydroxycorticosterone levels. In APA patients, however, both supine and upright plasma aldosterone and 18-hydroxycorticosterone levels remained unchanged. This may be due to effect of spironolactone to block renin and/or potassium-induced stimulation of aldosterone production in APA, since in an APA patients treated with amiloride there was an appropiate increase in plasma aldosterone concentration (71).



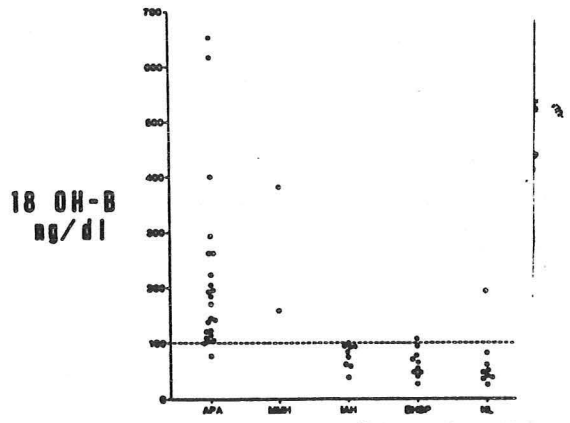

*Response of plasma aldosterone, 18-hydroxycorticosterone (18-OHB), plasma renin concentration (PRC), and plasma potassium ion ($PK^+$) to upright posture in patients with an aldosterone-producing adenoma before (○) and during (●) treatment with spironolactone. R = recumbent; U = upright.*

This unique response of plasma aldosterone response to spironolactone in patients with APA has also been useful in differentiating patients with IHA, who have an increase in plasma aldosterone, from APA, who have no increase in plasma aldosterone (68). Similarly patients with AP-RRA have an increase in plasma aldosterone,and patients with PAH have no significant change in plasma aldosterone following treatment with spironolactone (68).




**SERUM 18-HYDROXYCORTICOSTERONE LEVELS**

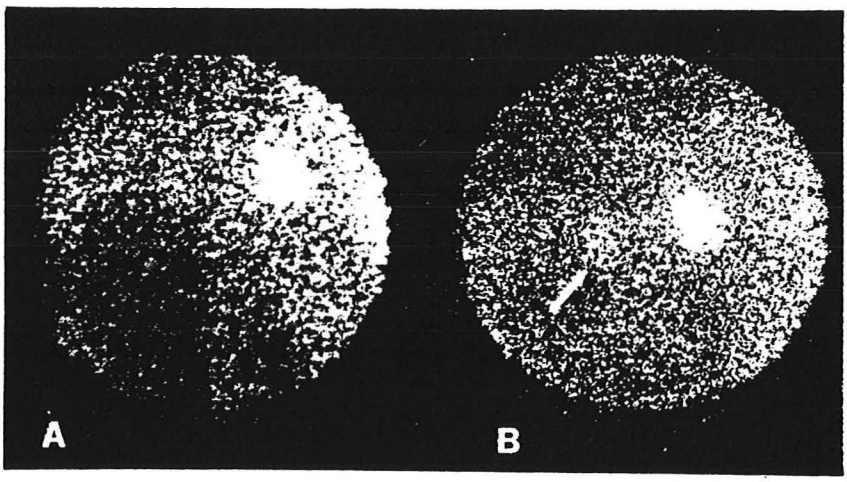
In addition to aldosterone, several precursors of aldosterone including deoxycorticosterone (DOC) and 18-hydroxycorticosterone (18OHB) have also been found to be elevated in some patients with primary aldosteronism. A recent study found that 22 of 23 patients with APA had 18OHB levels greater than 100ng/dl and 9 of 9 patients with IHA had plasma levels less than 100ng/dl ( *72* ). Thus, measurement of serum 18OHB is also a useful predictor of the etiology of primary aldosteronism.



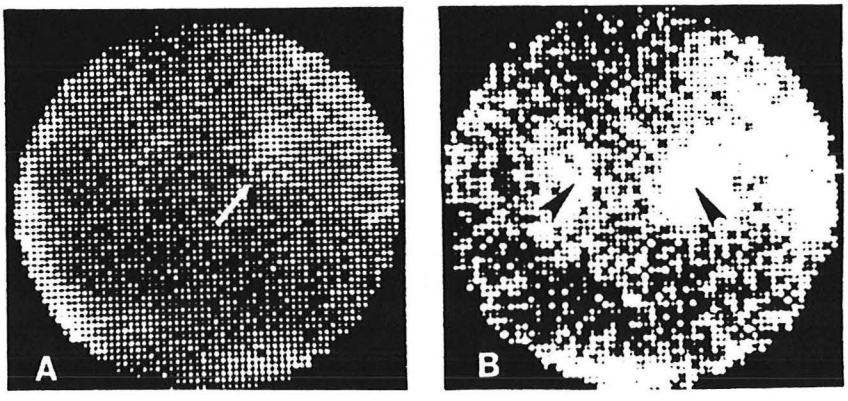

Plasma 18OHB levels (nanograms per dl) in 34 patients with primary aldosteronism, 9 patients with essential hypertension (EHBP), and 10 normal subjects (NL).

**ADRENAL SCINTIGRAPHY**

[6β-$^{131}$I] iodomethyl-19-norcholesterol (NP-59) scan provides correlation of functional and anatomic abnormalities and in experienced centers has been very useful in differentiating APA from IHA (4,73-75). Dexamethasone (1mg, po, q.i.d.) is started 7 days before administration of NP-59 and is continued for 5 days after the injection. In addition, Lugol's solution (3 drops b.i.d.) is given starting 2 days before the injection of NP-59 and is continued for 2 weeks to block tracer uptake by the thyroid gland. During dexamethasone suppression (to suppress NP-59 uptake by the normal gland) the NP-59 scan shows **a)** an asymmetric pattern in 48-72 hours in patients with APA whereas **b)** mild bilateral adrenal uptake at 72-10 hours in patients with IHA. As the normal adrenal cortex has been shown to image 120 hours or later after NP-59 injection, bilateral uptake seen after this interval is considered nondiagnostic. In a recent study the NP-59 scan correctly identified 48 of 50 subjects with APA and 35 of 37 subjects with IHA (74).




*Sequential posterior dexamethasone suppression adrenal scintiscans in a patient with primary aldosteronism due to an adrenal adenoma. **A**, right-sided adenoma, Day 3 after NP-59. **B**, right-sided adenoma, Day 5 after NP-59. Note the breakthrough of the normal contralateral adrenal (**arrow**) at this time interval.*




*Sequential posterior dexamethasone suppression adrenal scintiscans in a patient with primary aldosteronism due to bilateral adrenal hyperplasia. **A**, bilateral adrenal hyperplasia, Day 3 after NP-59. Definite right (**arrow**) activity is seen. **B**, bilateral adrenal hyperplasia (same patient), Day 4 after NP-59. Both adrenals are visualized (**arrows**).*

**Results of Dexamethasone Suppression NP-59 Scintigraphy in Primary Aldosteronism**

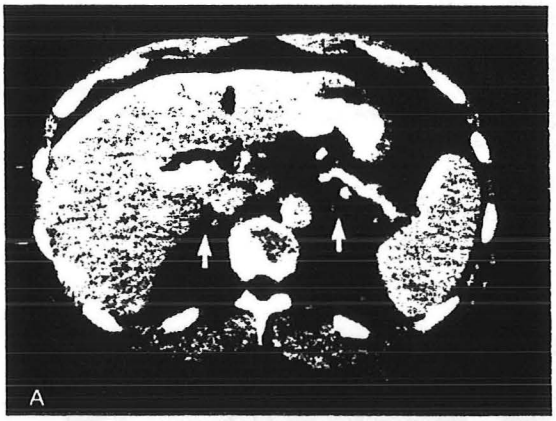
| Adenoma (50 patients) | Bilateral Adrenal Hyperplasia (37 patients) |
|---|---|
| Lateralizing scanning (true positive) (48) | Bilateral visualization (true negative) (35) (one bilateral nonvisualization) |
| Nonlateralizing scanning (false negative) (2) | Lateralizing scanning (false positive) (2) |

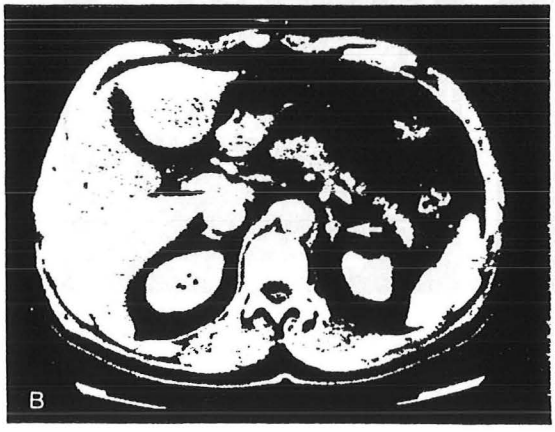
Sensitivity of lateralizing scanning (true positive/true positive + false negative) = 48 of 50 or 96 percent for adenoma detection.
Specificity of bilateral visualization (true negative/true negative + false positive) = 35 of 37 or 95 percent for bilateral hyperplasia detection.
Accuracy (overall) (true positive + true negative/true positive + true negative + false positive + false negative) = 82 of 87 or 94 percent for distinction of adenoma from bilateral adrenal hyperplasia.

The overall diagnostic accuracy of NP-59 scan in other centers is approximately 72%. Since NP-59 requires investigational new drug permission, and since the imaging takes 3-5 days, most centers do not utilize this diagnostic test.

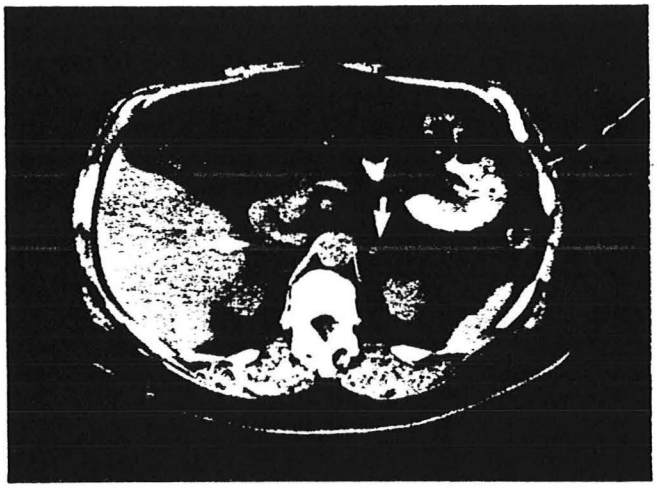
**ADRENAL CT SCANNING**

This imaging technique is very effective in locating APA. With the latest generation of CT scanners, microadenomas larger than 0.7cm can be accurately localized (4,78,79). The patient with an adrenal was greater than 3cm in diameter should be suspected of having an aldosterone-producing adrenocortical carcinoma. Patients with IHA have either normal appearing adrenal glands or changes consistent with bilateral modular hyperplasia.




Adrenal CT scanning. *A*, Normal appearance of adrenal glands. The borders of both glands normally are either concave or straight; they never are convex. The right adrenal gland *(arrow)* typically appears linear or V shaped; it is above the upper pole of the right kidney, medial to the liver, lateral to the crus of the diaphragm, and posterior to the inferior vena cava. The left adrenal gland *(arrow)* usually appears triangular or Y shaped; it is anterior and medial to the upper pole of the left kidney and lateral to the abdominal aorta. *B*, Scan from 64-year-old man who had hypertension for 13 years. Primary aldosteronism was confirmed, and preoperative evaluation with adrenal CT and a posture study suggested a left APA. The adenoma was 0.8 cm in diameter, and the entire gland weighed 7.1 g. The patient has remained normokalemic, but mild persistent hypertension has required single-drug therapy.



— Appearance of nodular IHA on adrenal CT scan from 59-year-old woman who had hypertension for 19 years. Primary aldosteronism was confirmed. The diagnosis of probable IHA was based on: (1) adrenal CT showed bilateral small adrenal nodules *(arrows)*; (2) plasma aldosterone levels increased 50 per cent in the posture study (which was validated by a 36 per cent decrease in serum cortisol level between 0800 and 1200 hours); (3) recumbent 18-OHB level was 54 ng/dl; and (4) bilateral symmetric uptake was seen with dexamethasone-suppressed iodocholesterol (NP-59) scintigraphy.

A word of caution is in order about the use of CT for diagnosis of primary aldosteronism. Since 2 to 8% of the population have small benign non functioning adenomas, and approximately 0.6 to 1.0% of body CT scans detect incidental nonfunctioning adrenal adenomas, **a)** the finding of a mass on adrenal CT in a patient with primary aldosteronism is not necessarily diagnostic of APA; results from hormonal studies and if available NP-59 scan are needed to confirm the diagnosis, **b)** unless the patient is hypertensive with hypokalemic tendency, incidental adrenal adenomas do not need further diagnostic evaluation.

**ADRENAL MAGNETIC RESONANCE IMAGING (MRI)**

In this imaging technique the adrenal glands appear as relatively homogenous low-intensity structures clearly outlined by the high-intensity retroperitoneal fat. At the present time MRI provides superior tissue contrast and CT superior spatial resolution, and the diagnostic accuracy of MRI is the same as adrenal CT (78).

**ADRENAL VENOUS SAMPLING**

Although this is the most definitive of the tests currently available to distinguish APA from IHA (4,76), it is a difficult technique and requires a skilled and experienced angiographer, and is therefore performed when the hormonal studies, NP-59 scan, and CT imaging yield conflicting data.

During the test when both adrenal veins are successfully catheterized, aldosterone and cortisol concentrations are measured from both adrenal veins as well as the inferior vena cava. Administration of ACTH during the test has increased the accuracy

since ACTH **a)** minimizes stress-induced fluctuations in aldosterone secretion and **b)** further stimulates aldosterone production by an adenoma (79). Usually, the ratio for ipsilateral to contralateral aldosterone to cortisol ratio in patients with APA is grater 10.

*Selective Adrenal Vein Catheterization in a Patient With Primary Aldosteronism*

| Site | Time (AM) | Plasma Aldosterone (ng/dl) | Plasma Cortisol (μg/dl) | Plasma Aldosterone/ Plasma Cortisol |
|---|---|---|---|---|
| Inferior vena cava* | 9:08 | 26 | 7.0 | 3.7 |
| Left adrenal | 9:32 | 57 | 27.3 | 2.1 |
| Right adrenal | 10:10 | 72 | 104.0 | 0.7 |
| Cosyntropin bolus† | 10:18 | — | — | — |
| Right adrenal | 10:44 | 30,700 | 1,710.0 | 17.9 |
| Left adrenal | 10:55 | 119 | 540.0 | 0.2 |
| Inferior vena cava* | 11:10 | 125 | 22.9 | 5.5 |

* Inferior vena cava below adrenal veins.
† 250-mg IV bolus of cosyntropin.
Plasma renin activity at 9:08 AM was 0.1 ng per ml per hour; serum potassium was 3.4 mEq per liter. The catheter remained in the right adrenal vein between 10:10 and 10:44 AM.

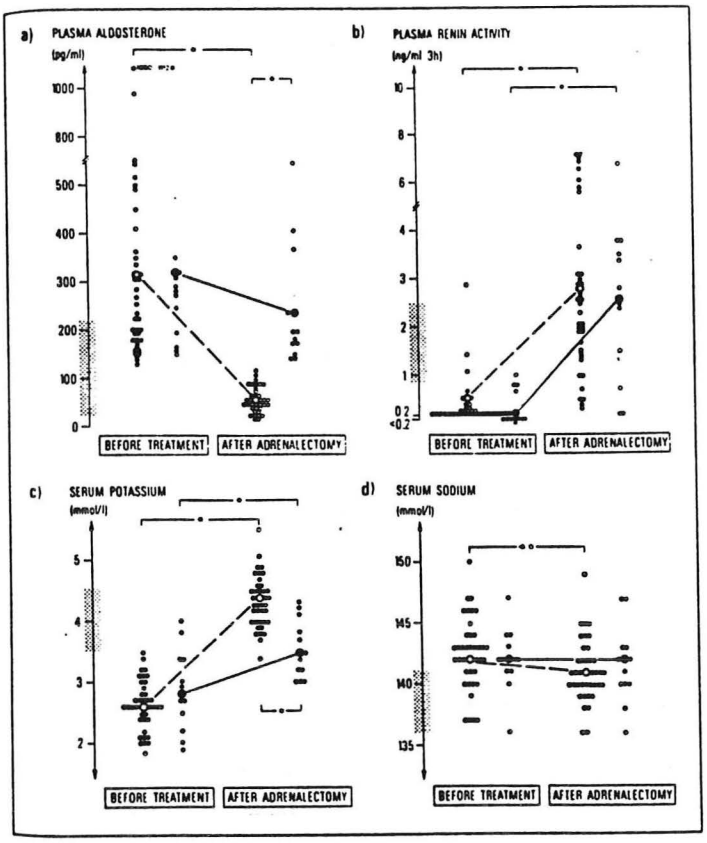
In summary, the recommended diagnostic evaluation of a patient suspected to have primary aldosteronism includes: **1)** hormonal studies, including saline infusion and postural response, **2)** adrenal CT scan and/or NP-59 scan, **3)** if above studies yield conflicting results, adrenal venous sampling. The accuracy of the non invasive tests are each better than 72%, and when the results of several tests are combined, they exceed 95%.

## MEDICAL MANAGEMENT OF PRIMARY HYPERALDOSTERONISM

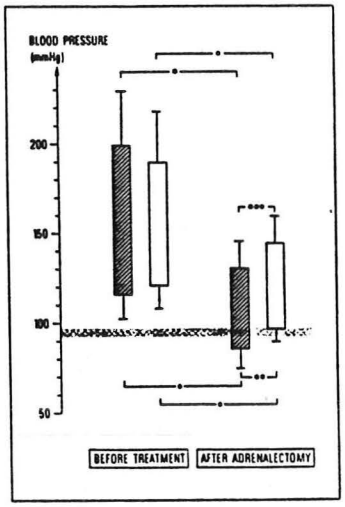
### ALDOSTERONE PRODUCING ADENOMA (APA)

The best available treatment for APA is surgical removal of the adenoma. Since the current diagnostic techniques have been very successful in providing the precise localization of the adenoma, the surgical approach used is a unilateral posterior approach which has a very low morbidity and a mortality rate close to zero.

Following removal of the adenoma approximately 2/3 of the patients become normotensive, with a decrease in plasma aldosterone, normalization of serum potassium and plasma renin activity. The rest usually require antihypertensive medications to normalize blood pressure (80,81).




Plasma aldosterone (a), plasma renin activity (b) and serum potassium (c) and serum sodium (d) in 38 patients with an aldosterone-producing adenoma (o) and 12 patients with idiopathic adrenal hyperplasia (•) before and 75 ± 12 months after unilateral adrenalectomy. Mean values are indicated by large circles. Significant differences: $^{*}p < 0.001$; $^{**}p < 0.05$.




Systolic and diastolic blood pressure in 38 patients with an aldosterone-producing adenoma (□) and 12 patients with idiopathic adrenal hyperplasia (□) before and 75 ± 12 months past unilateral adrenalectomy. Values are given as means ± SD. Significant differences: $^{*}p < 0.001$; $^{**}p < 0.005$; $^{***}p < 0.01$.

Older age, longer history of hypertension, and evidence of renal damage may predict postoperative persistence of hypertension. However, preoperative response to aldosterone is a most useful predictor. In a series of 40 patients with APA who were treated with spironolactone, 50mg, p.o. b.i.d. for 10 days, a reduction in mean blood pressure of more than 15mmHg from MAP of 137 to 114mmHg was observed in 29 of the 30 responders. The remaining one patient showed an 11mmHg reduction in mean blood pressure. On the other hand, none of the non responders revealed a reduction in mean blood pressure of more than 15mmHg (from MAP of 137 to 131mmHg) after spironolactone administration(82).

The recommended preoperative management includes repletion of potassium stores using spironolactone, 200 to 600mg per day for 2-3 weeks. In most cases, this treatment will also prevent postoperative hypoaldosteronism due to suppression of the contralateral adrenal gland.

## IDIOPATHIC HYPERALDOSTERONISM (IHA)

Medical treatment is the only effective treatment for IHA (83). Unilateral, subtotal, or total bilateral adrenalectomy results in improvement in less than 1/6 of the cases, and often with recurrence of the hypertension and hypokalemia in long term follow up (80,81). Patients with APA who decline surgery or who for other medical reasons are not candidates for surgery, are also treated medically.

## MEDICATIONS USED IN TREATMENT OF IHA AND APA

### CURRENT THERAPIES

1. ALDOSTERONE ANTAGONISTS: SPIRONOLACTONE
2. SODIUM TRANSPORT INHIBITORS: AMILORIDE, TRIAMTERENE
3. CALCIUM CHANNEL BLOCKERS: VERAPAMIL, NIFEDIPINE
4. CONVERTING ENZYME INHIBITORS: CAPTORIL, ENALAPRIL

### ALTERNATE THERAPIES

1. STEROID BIOSYNTHESIS INHIBITORS: TRILOSTANE
2. SEROTONERGIC ANTAGONISTS: CYPROHEPTADINE
3. DOPAMINE AGONISTS: BROMOCRIPTINE

### POTENTIAL THERAPIES

1. ATRIAL NATRIURETIC HORMONE AGONISTS
2. PITUITARY FACTOR INHIBITORS
3. OPIOID ANTAGONIST

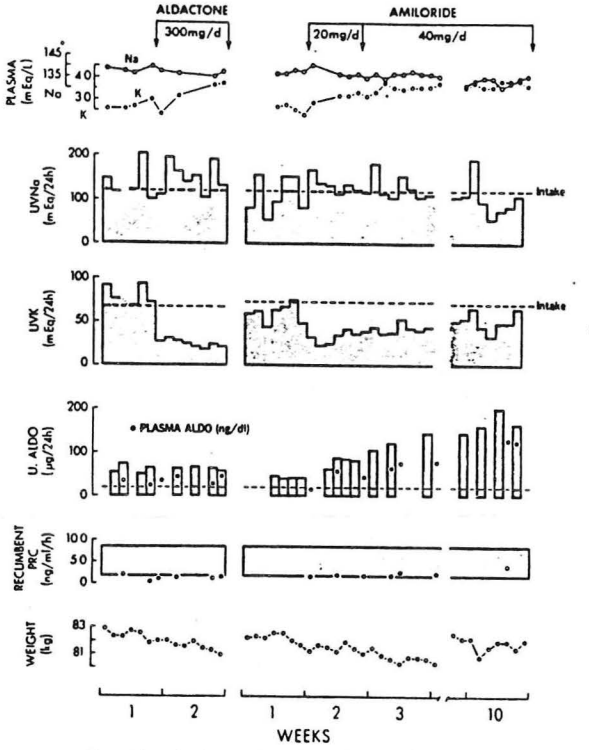
The mechanism of action of spironolactone has been discussed earlier. In addition to competitive binding to mineralocorticoid receptors, and inhibiting several enzymes of steroidogenesis, spironolactone also exhibits antiandrogenic activity which accounts for most of this side effects. In spite of its potential side effects, the medicine is well tolerated, and doses of 100 to 400mg daily has been very effective in correcting the hypertension and hypokalemia.

*The response to and side-effects of spironolactone treatment in 48 patients with primary aldosteronism*

| Features | Cases (%) |
|---|---|
| Correction of hypokalaemia | 46 (95.8) |
| Correction of hypertension when used alone | 38 (79.2) |
| Menstrual irregularity | 9 (18.8)* |
| Gynaecomastia | 8 (16.7)† |
| Abdominal pain | 2 (4.2) |
| Maculopapular rash | 2 (4.2) |
| Bleeding duodenal ulcer | 2 (4.2) |
| Anorexia | 2 (4.2) |

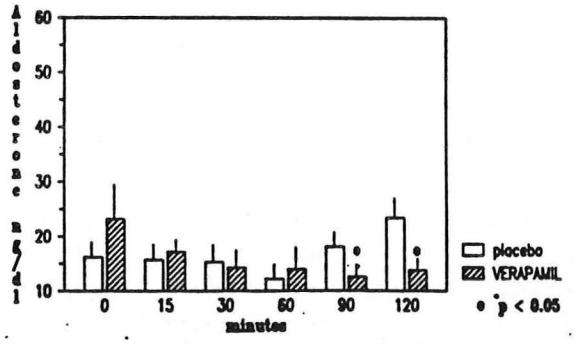
* Percentage of women only. † Percentage of men only.

Alternatively, amilride and triamterene has also been used effectively in the treatment of primary aldosteronism (71).

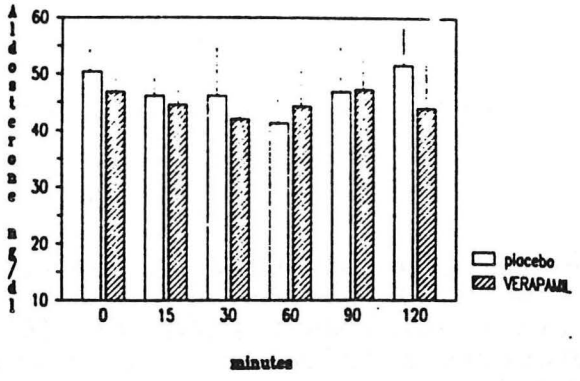



*Comparison of sodium and potassium balances and hormonal changes in a patient with an aldosterone-producing adenoma during treatment with spironolactone (Aldactone) and amiloride. Note the increase in urinary (U) and plasma aldosterone levels occurred only during amiloride treatment. Aldo = aldosterone; PRC = plasma renin concentration; V = volume.*

**The calcium channel blockers are alterative therapeutic additions since they can block aldosterone production in response to AII and potassium, and to some extent ACTH, and also block vascular response to vasoconstrictors. Intravenous administration of verapamil has been shown to a acutely decrease plasma aldosterone levels in patients with IHA but not APA (85).**

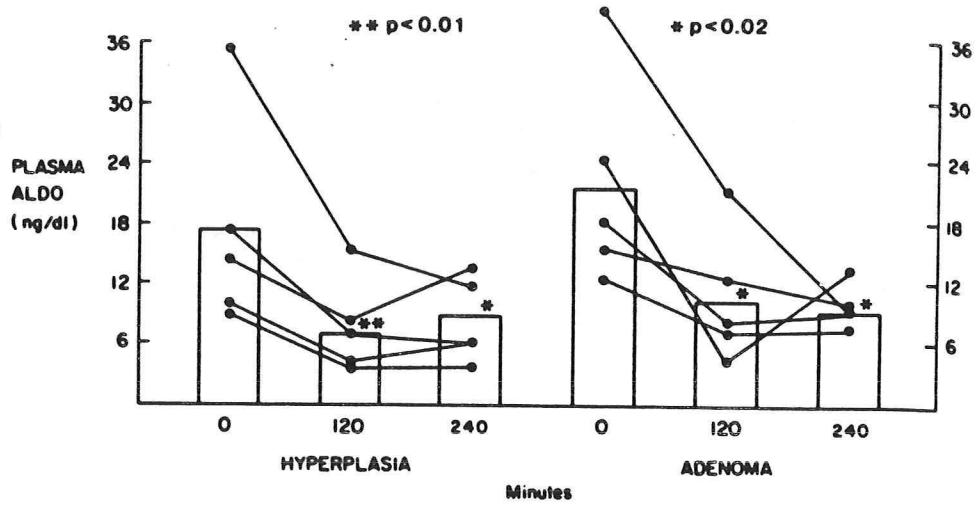



*Plasma aldosterone levels in 5 IHA patients after Verapamil 10 mg iv followed by a 0.04 mg/min infusion for two h compared with control saline infusion. A significant aldosterone decrease is observed at 90 and 120 min.*




*Plasma aldosterone levels in 6 APA patients after Verapamil 10 mg iv followed by a 0.04 mg/min for two h compared with control saline infusion. No significant variations of plasma aldosterone were observed after Verapamil infusion compared with saline.*

In two studies in this country, chronic treatment with nifedipine was shown to cause significant decreases in blood pressure (162/102 to 134/85) and plasma aldosterone (46 to 20), and a significant increase in plasma potassium (3.0 to 3.7) in patients with IHA and APA (86,87).




Supine afternoon plasma aldosterone before (0 min) and 120 and 240 min after nifedipine administration (20 mg, sublingually) in five IHA patients with five APA patients. ●, Individual patients. *Bars* represent mean plasma aldosterone levels for each group of PA patients. The decrease in plasma aldosterone (ALDO) was significant in both IHA and APA patients.

Effect of 4 weeks of nifedipine therapy on morning supine plasma aldosterone, potassium, and blood pressure in six subjects with PA

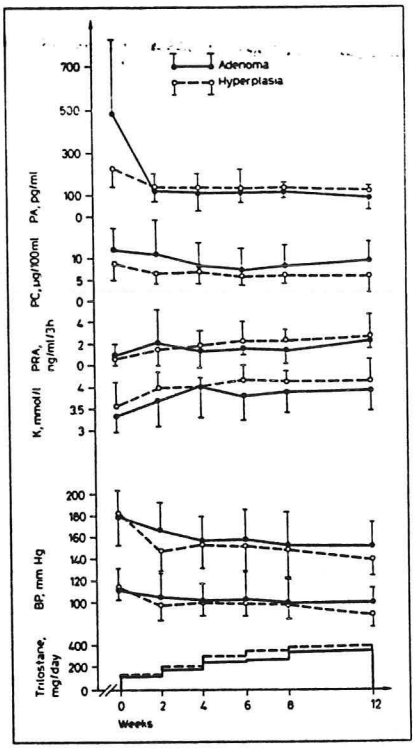
| Patient classification | Plasma aldosterone (ng/dl) | | Potassium (meq/liter) | | Blood pressure (mm Hg) | |
|---|---|---|---|---|---|---|
| | Baseline | 4 weeks[a] | Baseline | 4 weeks | Baseline | 4 weeks |
| IHA | 58 | 32 | 3.1 | 3.5 | 170/110 | 150/88 |
| IHA | 29 | 18 | 3.0 | 4.0 | 144/92 | 122/80 |
| IHA | 28 | 9 | 3.3 | 3.7 | 136/92 | 118/82 |
| IHA | 33 | 24 | 3.2 | 3.8 | 185/108 | 140/92 |
| APA | 75 | 21 | 2.6 | 3.5 | 188/112 | 142/88 |
| APA | 54 | 17 | 3.0 | 3.7 | 150/96 | 132/80 |
| Mean ± SE | 46 ± 8 | 20 ± 3 | 3.0 ± 0.1 | 3.7 ± 0.1 | 162 ± 9/102 ± 4 | 134 ± 5/85 ± 2 |
| | $P < 0.02$ | | $P < 0.01$ | | $P < 0.01$ | $P < 0.001$ |

[a] Values at 4 weeks represent the mean of pooled results from 3 and 4 week visits.

However in a study in Europe nitrendipine had no significant effects on plasma aldosterone and potassium, and only a minor effect on blood pressure (88). Nevertheless calcium channel blockers promise to be a useful adjunct therapy to spironolactone and/or amiloride.

Converting enzyme inhibitors are ideal for treatment of patients with IHA since IHA patients show enhanced sensitivity to AII. In fact in a report of 3 patients with IHA enalapril improved the hypertension, plasma aldosterone and serum potassium (89).

Trilostane, a competitive inhibitor of the 3 ß-hydroxysteroid dehydrogenase enzyme system responsible for one of the early stages of steroidogenesis, has been successfully used to treat 9 patients with APA and 9 patients with IHA, with improvement in blood pressure, serum potassium and plasma aldosterone (90).




Supine plasma aldosterone (PA) and supine plasma renin activity (PRA), plasma cortisol (PC), serum potassium ($K^+$) and blood pressure (systol./diastol.) during trilostane administration in 9 patients with unilateral adenoma (●——●) and in 9 patients with bilateral hyperplasia (○– –○). Mean Values and standard deviations are indicated.

**PRIMARY ADRENAL HYPERPLASIA (PAH)**

The recommended treatment is unilateral or subtotal adrenalectomy.

**ALDOSTERONE PRODUCING - RENIN RESPONSIVE ADENOMA**

The recommended treatment is unilateral or subtotal adrenalectomy.

**ALDOSTERONE - PRODUCING ADRENOCORTICAL CARCINOMA (APC)**

The recommended treatment is surgical resection, when possible, and when needed chemotherapy with o,p'-DDD (mitotane).

**GLUCOCORTICOID SUPPRESSIBLE HYPERALDOSTERONISM**

The recommended treatment is low dose dexamethasone (0.5 to 1.0mg per day) and also of necessary any of the medications used to treat patients with IHA.

## REFERENCES


1. Conn JW: Presidential address Part I. Painting Background Part II. Primary Aldosteronism, a new Clinical Syndrome. J. Lab. Clin. Med. 45:3-17, 1955.

2. Melby JC: Primary aldosteronism. Kidney International 26:769-778, 1984.

3. Noth RH, Biglieri, E: Primary Hyperaldosteronism. Medical Clinics of North America 72:1117-1131, 1988.

4. Young WF Jr., Klee GG: Primary Aldosteronism. Diagnostic Evaluation. Endocrinology and Metabolism Clinics of North America 17:367-395, 1988.

5. Shenker, Y: Medical Treatment of Low-Renin Aldosteronism. Endocrinology and Metabolism Clinics of North America 18:415-442, 1989.

6. Haning R, Tait SAS, and Tait JF: In vitro Effects of ACTH, Angiotensin, Serotonin and Potassium on Steroid Output and Conversion of Corticosterone to Aldosterone by Isolated Adrenal Cells. Endocrinology 87:1147-1167, 1970.

7. Fakunding JL, Chow R, and Catt KJ: The Role of Calcium in the Stimulation of Aldosterone Production by Adrenocorticotropin, Angiotensin II, and Potassium in Isolated Glomerulosa Cells. Endocrinology 105:327-333, 1979.

8. Rasmussen H, Barrett P, Takuwa Y, and Apfeldorf W: Calcium in the Regulation of Aldosterone Secretion and vascular Smooth Muscle Contraction. Hypertension 10 [Suppl I]:I-23-I26, 1987.

9. Ishizuka T, Miura K, Nagao S, and Nozawa Y: Differential Redistribution of Protein Kinase C in Human Aldosteronoma Cells and Adjacent Adrenal cells Stimulated with ACTH and Angiotensin II. Biochemical and Biophysical Research Communications 155:643-649, 1988.

10. Gaillard RC, Riondel AM, Favrod-Coune CA, Vallotton MB, and Muller AF: Aldosterone escape to chronic ACTH administration in man. Acta Endocrinologica 103:116-124, 1983.

11. Biglieri EG: ACTH Effects on Aldosterone, Cortisol, and Other Steroids. Hospital Practice 117-136, 1989.

12. Mizuno K, Ojima M, Hashimoto S, Tani M, Niimura S, Kunii N, Yabe R, Watari H, Inagami T, and Fukuchi S: Multiple forms of immunoreactive renin in human adrenocortical tumor tissue from patients with primary aldosteronism. Clinical Science 72:669-704, 1987.

13. Miyamori I, Yasuhara S, Matsubara T, Okamoto S, Ikeda M, Koshida H, Morise T, Takeda Y, Takeda R, and Vecsei P: Effects of Corticotropin-Releasing Factor (CFR) on Aldosterone and 18-Hydroxycorticosterone in Essential Hypertension and Primary Aldosteronism. Endocrinol Japan 34:809-819, 1987.

14. Fallo F, Boscaro M, Sonino N, and Mantero F: Effects of naloxone on adrenal cortex regulation in patients with primary aldosteronism. J. Endocrinol. Invest. 11:262-265, 1988.

15. Carey RM, Sen S, Dolan LM, Malchoff CD, and Bumpus FM: Idiopathic Hyperaldosteronism, A Possible Role for Aldosterone-Stimulating Factor. N. Engl. J. Med 311:94-100, 1984.

16. Biglieri EG: The Pituitary and Idiopathic Hyperaldosteronism. N. Engl. J. Med. 311:120-121, 1984.

17. Carey RM, and Sen S: Recent Progress in the Control of Aldosterone Secretion. Recent Progress in Hormone Research 42:251-296, 1986.

18. Merrill DC, Ebert TJ, Skelton MM, and Cowley AW Jr: Effect of Plasma Sodium on Aldosterone Secretion During Angiotensin II Stimulation in Normal Humans. Hypertension 14:64-169,1989.

19. Cozza EN, Gomez-Sanchez CE, Foecking MF, and Chiou S: Endothelin Binding to Cultured Calf Adrenal Zona Glomerulosa Cells and Stimulation of Aldosterone Secretion. The Journal of Clinical Investigation 84:1032-1035, 1989.

20. Holland OB, Thomas C, Brown H, Schindelwolf D, Hillier Y, and Gomez-Sanchez C: Aldosterone Suppression with Dopamine Infusion in Low-Renin Hypertension. The Journal of Clinical Investigation 72:754-766, 1983.

21. Drake CR Jr, Ragsdale V, Kaiser DL, and Carey RM: Dopaminergic Suppression of Angiotensin II-Induced Aldosterone Secretion in Man: Differential Responses During Sodium Loading and Depletion. Metabolism 33:68-702, 1984.

22. Atarashi K, Mulrow PJ, and Franco-Saenz R: Effect of Atrial Peptides on Aldosterone Production. J. Clin. Invest. 76:1807-1811, 1985.

23. Higuchi K, Nawata H, Kato K, Ibayashi H, Matsuo H: α-Human Atrial Natriuretic Polypeptide Inhibits Steroidogenesis in Cultured Human Adrenal cells. J. Clin. Endocrinol Metab. 62:941-944, 1986.

24. Naruse M, Obana K, Naruse K, Yamaguchi H, Demura H, Inagami T, and Shizume K: Atrial natriuretic Polypeptide Inhibits Cortisol Secretion as Well as Aldosterone Secretion in Vitro from Human Adrenal Tissue. J. Clin. Endocrinol. Metab. 64;10-16, 1987.

25. Chartier L, and Schiffrin EL: Role of calcium in effects of atrial natriuretic peptide on aldosterone production in adrenal glomerulosa cells. Am. J. Physiol. 252(Endocrinol. Metab. 15):E485-E491, 1987.

26. Ballermann BJ, Bloch KD, Seidman JG, and Brenner BM: Arterial natriuretic peptide Transcription, Secretion, and Glomerular Receptor activity during Mineralocorticoid Escape in the Rat. J. Clin. Invest. 78:840-843, 1986.

27. Kelly TM, and Nelson DH: Sodium Excretion and Atrial Natriuretic peptide levels During Mineralocorticoid Administration: A Mechanism for the Escape from Hyperaldosteronism. Endocrine Research 13(4):363-383, 1987.

28. Nakamura T, Ichikawa D, Sakamaki T, Sato k, Kogure M, Tajima Y, Kato T, and Murata K: Role of Atrial Natriuretic peptide in Mineralocorticoid Escape Phenomenon in Patients with Primary Aldosteronism. Proceedings of the Society for Experimental Biology and Medicine 185:448-454, 1987.

29. Pedrinelli R, Bruschi G, Gaziadei L, Taddei S, Panarace G, Orlandini G, Natali A, Borghetti A, and Salvetti A: Dietary Sodium Change in Primary Aldosteronism: Atrial Natriuretic Factor, Hormonal, and Vascular Responses. Hypertension 12:192-198, 1988.

30. Pedrinelli R, Panarace G, Spessot M, Taddei S, Favilla S, Graziadei L, Lucarini A, and Salvetti A: Low Dose Atrial natriuretic Factor in Primary Aldosteronism: Renal, Hemodynamic, and Vascular Effects. Hypertension 14:156-163, 1989.

31. Nakada T, Furuta H, Katayama T, Sumiya H, and Shimazaki J: The Effect of Adrenal Surgery on Plasma Atrial natriuretic Factor and Sodium Escape Phenomenon in Patients with Primary Aldosteronism. The Journal of Urology 142:13-18, 1989.

32. Horster MF, Schmolke M, and Gleich R: Expression of Sodium Pump Activity and of Transepithelial Voltage Induced by Hormones in Cultured Cortical Collecting Tubule Cells. Miner Electrolyte Metab.15:137-143, 1989.

33. Paillard M, and Bichara M: Recent Advances in the Cellular Mechanisms and Hormonal Regulation of Urine Acidification. Adv. Nephrol. 18:141-168, 1989.

34. Stanton BA: Regulation by Adrenal Corticosteroid of Sodium and Potassium Transport in Loop of Henle and Distal Tubule of Rat Kidney. J. Clin. Invest. 78:1612-1620, 1986.

35. Work J, and Jamison RL: Effect of Adrenalectomy on Transport in the Rat Medullary Thick Ascending Limb. J. Clin. Invest. 80:1160-1164, 1987.

36. Grossman EB, and Hebert SC: Modulation of Na-K-ATPase Activity in the Mouse Medullary Thick Ascending Limb of Henle: Effects of Mineralocorticoids and Sodium. J. Clin. Invest. 81:885-892, 1988 .

37. Oberleithner H, Weight M, Westphale JH, and Wang W: Aldosterone activates $Na^+/H^+$ exchange and raises cytoplasmic pH in target cells of the amphibian Kidney. Proc. Natl. Acad. Sci. USA 84:1464-1468, 1987.

38. Armanini D, Witzgall H, Wehling M, Kuhnle U, and Weber PC: Aldosterone Receptors in Different Types of Primary Hyperaldosteronism. J. Clin. Endocrinol. Metab. 65:101-104, 1987.

39. Hamlyn JM, and Blaustein MP: Sodium chloride, extracellular fluid volume, and blood pressure regulation. Am. J. Physiol. 251 (Renal Fluid Electrolyte Physiol. 20):F563-F575, 1986.

40. Robertson JIS: Salt, volume, and hypertension: Causation or correlation? Kidney International 32:590-602, 1987.

41. Luft FC: Salt and hypertension: Recent advances and perspectives. J. Lab. Clin. Med. 114:215-21, 1989.

42. Berecek KH, and Bohr DF: Whole body vascular reactivity during the development of deoxycorticosterno acetate hypertension in the pig. Circ. Res. 42:764-771, 1978.

43. Van de Voorde J, and Leusen I: Endothelium-dependent and independent relaxation of aortic rings from hypertensive rats. Am. J. Physiol. 250(Heart Cir. Physiol 19):H711-H717, 1986.

44. Soltis EE, and Field FP: Extracellular Calcium and Altered Vascular Responsiveness in the Deoxycorticosterone Acetate-Salt Rat. Hypertension 8:526-532, 1986.

45. Soltis EE, Iloeje E, and Katovich MJ: Dietary Potassium, Blood Pressure and Peripheral Adrenergic Responsiveness in the Deoxycorticosterone Acetate-Salt Rat. Clin. and Exper. Hyper.-Theory and Practice, A10:447-466, 1988.

46. Purdy RE, Weber MA: Enhancement and Prolongation of Vascular Smooth Muscle Contraction by Aldosterone. Blood Vessels 20:34-43, 1983.

47. DeClue JW, Guyton AC, Cowley AW Jr., Coleman TG, Norman RA Jr., and McCaa RE: Subpressor Angiotensin Infusion, Renal Sodium Handling, and Salt-Induced Hypertension in the Dog. Circ. Res. 43:503-512, 1978.

48. Kimura G, Saito F, Kojima S, Yoshimi H, Abe H, Kawano Y, Yoshida K, Ashida T, Kawamura M, Kuramochi M, Ito K, and Omae

T: Renal Function Curve in Patients with Secondary Forms of Hypertension. Hypertension 10:11-15, 1987.

49. Masugi F, Ogihara T, Hasegawa T, Tomii A, Nagano M, Higashimori K, Kumahara K, and Yoshitake T: Circulating Factor with Ouabain-Like Immunoreactivity In Patients With Primary Aldosteronism. Biochemical and Biophysical Research Communications 135:41-45, 1986.

50. Kem DC, Weinberger MH, Higgins JR, Kramer NJ, Gomez-Sanchez C, and Holland B: Plasma Aldosterone Response to ACTH in Primary Aldosteronism and In Patients with Low Renin Hypertension. J. clin. Endocrinol. Metab 46:552-560, 1978.

51. Wisgerhof M, Brown RD, Hogan MJ, Carpenter PC, and Edis AJ: The Plasma Aldosterone Response to Angiotensin II Infusion in Aldosterone-Producing Adenoma and Idiopathic Hyperaldosteronism. J. Clin. Endocrinol. Metab. 52:195-198, 1981.

52. Pham-Huu-Trung MT, Duclos JM, Pagny JY, Bogyo A, Leneuve P, and Girard F: In vitro studies in primary aldosteronism: Baseline steroid production and aldosterone responses to ACTH and angiotensin II. Acta Endocrinologica (Copenh) 117:135-144, 1988.

53. Wisgerhof M, Carpenter PC, and Brown RD: Increased Adrenal Sensitivity to Angiotensin II in Idiopathic Hyperaldosteronism. J. Clin. Endocrinol. Metab. 47:938-943, 1978.

54. Ganguly A, Zager PG, and Luetscher JA: Primary Aldosteronism due to Unilateral Adrenal Hyperplasia. J. Clin. Endocrinol. Metab. 51:1190-1194, 1980.

55. Banks WA, Kastin AJ, Biglieri G, and Ruiz AE: Primary Adrenal Hyperplasia: A New Subset of Primary Hyperaldosteronism. J. Clin. Endocrinol. Metab. 58:783-785, 1984.

56. Dye NV, Litton NJ, Varma M, and Isley W: Unilateral Adrenal Hyperplasia as a Cause of Primary Aldosteronism. Southern Med. J. 82:82-86, 1989.

57. Arteaga E, Biglieri EG, Kater CE, Lopez JM, and Schambelan M: Aldosterone-Producing Adrenocortical Carcinoma: preoperative Recognition and Course in Three Cases. Annals of Internal Medicine. 101:316-321, 1984.

58. Farge D, Chatellier G, Pagny JY, Jeunemaitre X, Plouin PF, Corvol P: Isolated Clinical Syndrome of Primary Aldosteronism in Four Patients with adrenocortical Carcinoma. The American Journal of Medicine 83:635-640, 1987.

59. Sutherland DJA, Ruse JL, and Laidlaw JC: Hypertension, Increased Aldosterone Secretion and Low Plasma Renin Activity Relieved by Dexamethasone. The Canadian Medical Association Journal 95:1109-1119, 1966.

60. Connell JMC, Kenyon CJ, Corrie JET, Fraser R, Watt R, and Lever AF: Dexamethasone-Suppressible Hyperaldosteronism: Adrenal Transition Cell Hyperplasia? Hypertension 8:669-676, 1986.

61. Fallo F, Sonino N, Boscaro M, Armanini d, Mantero F, Dörr HG, Knorr D, an Kuhnle U. Dexamethasone-Suppressible Hyperaldosteronism: Pathophysiology, Clinical Aspects, and New Insights into the Pathogenesis. Klin. Wochenschr 65:437-444, 1987.

62. Stockigt JR, and Scoggins BA: Long Term Evolution of Glucocorticoid-Suppressible Hyperaldosteronism. J. Clin. Endocrinol. Metab. 64:22-26, 1987.

63. Kato S, Haji M, Yanase T, Nawata H, Kato K-I, and Ibayashi H: A Case of Glucocorticoid-Suppressible Hyperaldosteronism with Aldosterone Producing Adenoma. Endocrinol. Japan 35:311-320, 1988.

64. Conn JW, Knopf RF, and Nesbit RM: Clinical Characteristics of Primary Aldosteronism from an Analysis of 145 Cases. American Journal of Surgery, 107:159-172, 1964.

65. Bravo EL, Tarazi RC, Dustan HP, Fouad FM, Textor SC, Gifford RW, and Vidt G: The Changing Clinical Spectrum of Primary Aldosteronism. The American Journal of Medicine 74:641-651, 1983.

66. Hegstad R, Brown RD, Jiang N-S, Kao P, Weinshilboum RM, Strong C, and Wisgerhof M: Aging and Aldosterone. The American Journal of Medicine 74:442-448, 1983.

67. Arteaga E, Klein R, Biglieri EG: Use of the Saline Infusion Test to Diagnose the Cause of Primary Aldosteronism. The American Journal of Medicine 79:722-728, 1985.

68. Biglieri EG, Irony I, and Kater CE: Identification and Implications of New Types of Mineralocorticoid Hypertension. J. Steroid Biochem. 32:199-204, 1989.

69. Ganguly A, Dowdy AJ, Luetscher JA, and Melada GA: Anomalous Response of Plasma Aldosterone Concentration In Patients With Aldosterone-Producing Adrenal Adenoma. J. Clin. Endocrinol Metab. 36:401-404, 1973.

70. Ganguly A, Melada GA, Luetscher JA, and Dowdy AJ: Control of Plasma Aldosterone in Primary Aldosteronism: Distinction Between Adenoma and Hyperplasia. J. Clin. Endocrinol. Metab.

37:765-775, 1973.

71. Kater CE, Biglieri EG, Schambelan M, and Arteaga E: Studies of Impaired Aldosterone Response to Spironolactone-Induced Renin and Potassium Elevations in Adenomatous but Not Hyperplastic primary Aldosteronism. Hypertension 5:V-115-V-121, 1983.

72. Kem DC, Tang K, Hanson CS, Brown RD, Painton R, Weinberger M, and Hollifield JW: The Prediction of Anatomical Morphology of Primary Aldosteronism Using Serum 18-Hydroxycorticosterone levels. J. Clin. Endocrinol. Metab. 60:67-73, 1985.

73. Sarkar SD, Beierwaltes WH, Ice RD, Basmadjian GP, Hetzel KR, Kennedy WP, and Mason MM: A New and Superior Adrenal Scanning Agent, NP-59. Journal of Nuclear Medicine 16:1038-1042, 1975.

74. Gross MD, Shapiro B, Grekin RJ, Freitas JE, Glazer G, Beierwaltes WH, and Thompson NW: Scintigraphic Localization of Adrenal Lesions in Primary Aldosteronism. The American Journal of Medicine 77:839-884, 1984.

75. Watson NE, Cowan RJ, and Chilton HM: The Utility of Adrenal Scintigraphy in Cushing's Syndrome and Hyperaldosteronism. Clinical Nuclear medicine 10:539-542, 1985.

76. Ma JTC, Wang C, Lam KSL, Yeung RTT, Chan FL, Boey J, Cheung PSY, Coghlan JP, Scoggins BA, and Stockigt JR: Fifty Cases of Primary Hyperaldosteronism in Hong Kong Chinese with a High Frequency of Periodic Paralysis. Evaluation of Techniques for Tumour Localisation. Quarterly Journal of Medicine 61:1021-1037, 1986.

77. Velchik MG, Kressel HY, Noel AW, and Alavi A: Primary Aldosteronism CT, MRI, Scintigraphic Correlation. Invest. Radiol. 20:237-241, 1985.

78. Hietakorpi S, Korhonen T, Aro A, Lampainen E, Alhava E, Karjalainen P, and Wiljasalo S: The value of scintigraphy and computed tomography for the differential diagnosis of primary hyperaldosteronism. Acta Endocrinologica 113:118-122, 1986.

79. Noth RH, Glaser SL, Palmaz JC: Cosyntropin Stimulation in Adrenal vein Testing for Aldosteronoma. The Western Journal of Medicine 142:92-94, 1985.

80. Groth H, Vetter W, Stimpel M, Greminger P, Tenschert W, Klaiber E, and Vetter H: Adrenalectomy in Primary Aldosteronism: A Long-Term Follow-up Study. Cardiology 72:(Suppl 1):107-116, 1985

81. Horky K, Widimsky J Jr., Hradec E, Gregorova I, and Hradec M: Long-Term Results of Surgical and Conservative Treatment of patients with Primary Aldosteronism. Exp. Clin. Endocrinol.

90:336-346, 1987.

82. Saruta T, Suzuki H, Takita T, Saito I, Murai M, and Tazaki H: Pre-operative evalutation of the prognosis of hypertension in primary aldosteronism owing to adenoma. Acta Endocrinologica 116:229-234, 1987.

83. Hsueh WA: New Insights into the Medical Management of primary Aldosteronism. Hypertension 8:76-82, 1986.

84. Bravo EL, Fouad-Tarazi FM, Tarazi RC, Pohl M, Gifford RW, and Vidt DG: Clinical Implications of Primary Aldosteronism with Resistant Hypertension. Hypertension 11[Suppl I]:I-207-I211, 1988.

85. Opocher G, Rocco S, Murgia A, and Mantero F: Effect of Verapamil on aldosterone secretion in primary aldosteronism. J. Endocrinol. Invest. 10:491-494, 1987.

86. Nadler, JL, Hsueh W, and Horton R: Therapeutic Effect of Calcium Channel Blckade in Primary Aldosteronism*. J. Clin. Endocrinol. Metab. 60:896-899, 1985.

87. Bravo EL, Fouad FM, and Tarazi RC: Calcium Channel Blckade with Nifedipine in Primary Aldosteronism. Hypertension 8 [Suppl I]:I-191-I-194, 1986.

88. Stimpel M, Ivens K, Volkmann H-P, Wambach G, and Kaufmann W: Therapeutic Value of Calcium Antagonists in Autonomous Hyperaldosteronism. Klin Wochenschr 67:248-252, 1989.

89. Griffing GT, Melby JC: The therapeutic Effect of a New Angiotensin-Converting Enzyme Inhibitor, Enacapril Maleate, in Idiopathic Hyperaldosteronism. J. Clin. Hypertens 1:265-268, 1985.

90. Winterbegrg B, Vetter W, Groth H, Greminger P, Vetter H: Primary Aldosteronism: Treatment with Trilostane. Cardiology 72:117-121, 1985.