MEDICAL GRAND ROUNDS

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Primary hyperaldosteronism

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INTRODUCTION

Historical Notes:

The adrenal glands have been a source of fascination for several centuries. In the 19th century Thomas Addison identified a clinical syndrome resulting from the destruction of the adrenal glands.

In the decades ahead, many authors did extractions of animal adrenals and injected them into patients with adrenal insufficiency with varying degrees of success. As a consequence of these studies, deoxycorticosterone was extracted and later on synthesized and used initially in the treatment of Addisonian patients. In the course of the studies it was observed that administration of salt and DOCA resulted in hypertension with hypokalemia, weakness, and eventually paralysis, setting up the grounds for the description of mineralocorticoid hypertension. In the 1940's many other steroids were isolated and identified, and it was observed that in the course of extraction and crystalization that there was a fraction that refused to crystalize. As such, it was called amorphous fraction. However, it had great biological activity similar to, but more potent than, DOCA.

In 1953 Simpson and Tait (Mr. & Mrs. Tait), in collaboration with Ciba, Basle group of steroid chemists, succeeded in isolating, crystalizing, and elucidating the structure of a steroid initially called Electrocortin. This steroid was later called aldosterone (4-pregnen-11β,21-diol-3,20-dione-18-al) because of an aldehyde function.

In 1954 Conn reported in his presidential address at the Central Society a new syndrome consisting of hypertension, hypokalemia, hypernatremia, and alkalosis associated with an adrenal adenoma which produced

large amounts of aldosterone.

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Biosynthesis of Aldosterone:

Aldosterone is produced in the zona glomerulosa of the adrenal gland. The principal postulated biosynthetic pathway to aldosterone is shown in Figure 1.

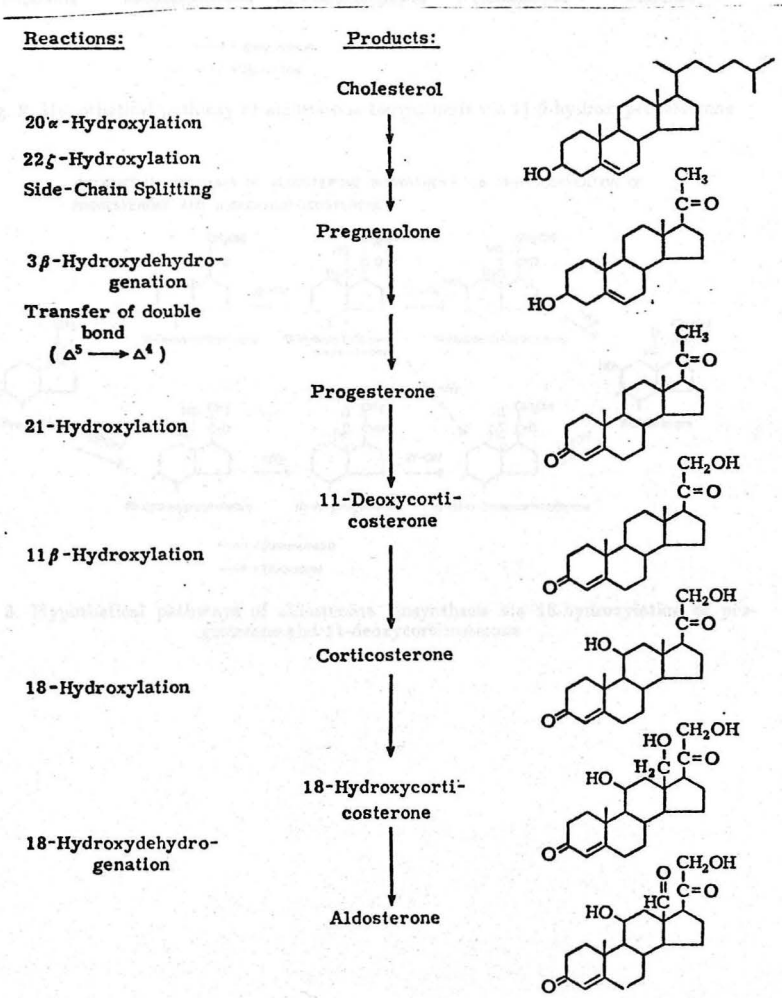

Fig. 1. Pathway of aldosterone biosynthesis

Even though the Figure 1 pathway is thought to be the most important, there are two other hypothetical pathways that have been shown to operate when the adrenal is incubated with the appropriate precursors (Figures 2 & 3).

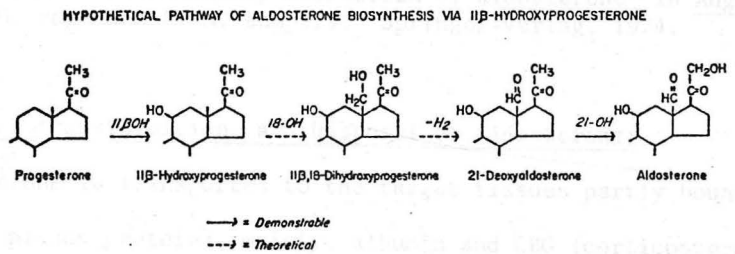

Fig. 2. Hypothetical pathway of aldosterone biosynthesis via 11 β-hydroxyprogesterone

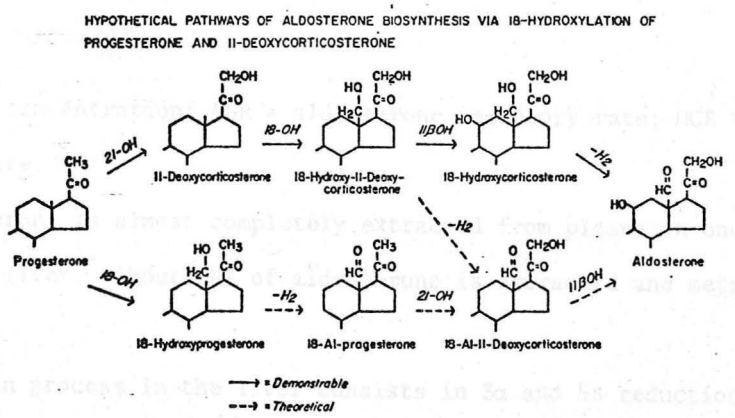

Fig. 3. Hypothetical pathways of aldosterone biosynthesis via 18-hydroxylation of progesterone and 11-deoxycorticosterone

The reason for showing these pathways is that the most widely accepted pathway suffers from the presence of some experimental facts that cannot be explained at present and which are beyond the scope of this presentation.

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Transport, Biotransformation, and Disposal of Aldosterone:

Aldosterone is transported to the target tissues partly bound with low affinity to plasma proteins--mainly, albumin and CBG (corticosteroid binding globulin). The concentration of aldosterone in plasma depends on the relation:

$$PC = \frac{ASR}{MCR}$$

PC = plasma concentration; ASR = aldosterone secretory rate; MCR = metabolic clearance rate.

Aldosterone is almost completely extracted from plasma in one passage through the liver. About 10% of aldosterone is extracted and metabolized by the kidney.

The main process in the liver consists in 3α and 5β reduction to form 3α,5β tetrahydroaldosterone which is conjugated to glucuronic acid to form a 3-glucuronide. In the kidney, a fraction of aldosterone follows a similar fate but, in addition, a distinct mode of metabolism occurs which consists in conjugation at the 18 position to form aldosterone 18-oxo-glucuronide (called 3-oxo-glucuronide or acid labile metabolite) which is excreted in the urine. The measurement of the latter is what is popularly, but improperly, called urinary aldosterone or, more properly, aldosterone excretion rate (AEC).

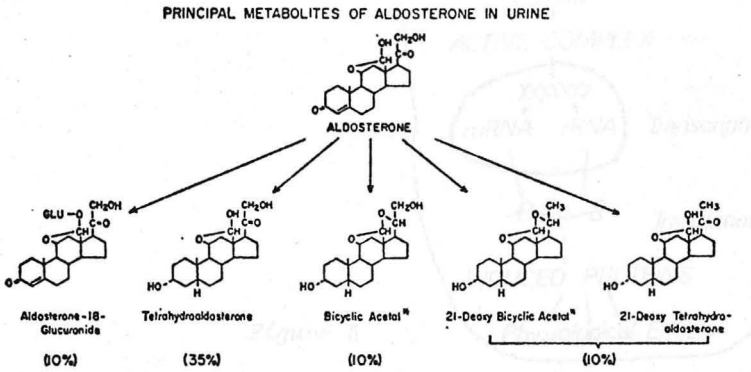

Fig. 4. Principal metabolites of aldosterone in urine
- Percentage figures in parentheses represent the portion of total radioactivity excreted in urine as the specific metabolite following intravenous injection of labeled aldosterone in man.
* Bicyclic Acetal = 3 α, 21-Dihydroxy-5 β-pregnane-11 β, 18 S: 18 S, 20 α-Diepoxide
21-Deoxybicyclic Acetal = 3 α-Hydroxy-5 β-pregnane-11 β, 18 S: 20 α-Diepoxide.

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Mechanism of Action:

The subcellular mechanism of action of aldosterone follows a general pattern which applies for all steroid hormones: (1) binding of the hormone to high affinity, stereospecific receptors in the cytoplasm of target tissue cells; (2) transfer of the steroid-receptor complex to the nucleus where it binds chromatin; (3) DNA-dependent, RNA-mediated protein synthesis; and (4) expression of the physiological effect(s) by the induced protein (Figure 5).

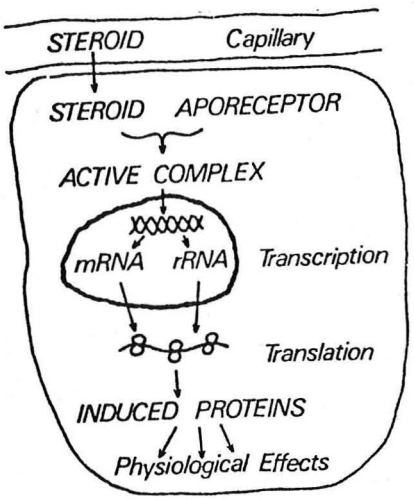

Figure 5

The target tissues include:
1. Kidney
2. Salivary glands
3. Gut
4. Sweat Glands
5. Muscle
6. Bone
7. Hypothalamus (salt appetite)

The kidney is probably the most important target tissue quantitatively. Aldosterone increases sodium reabsorption and potassium excretion. Aldosterone action is felt to be exerted in the distal end of the distal convoluted tubule and cortical segment of the collecting duct as shown by Dr. Jim Gross from the renal group of our institution. At that level, reabsorption of sodium and exchange for potassium and hydrogen ions occur.

Recently, David Morris has popularized the view that the sodium retention and potassium excretion are separable phenomena. His main data comes from his demonstration of the dissociation of sodium retention and potassium excretion.

These observations are contradictory to the standard ideas of the exchange between sodium and potassium. I have great reservations about the former observations and, in somewhat similar studies to those of Morris, we found very significant variations between animals and could not demonstrate a dissociation.

When aldosterone or other mineralocorticoids are administered continuously in the presence of an adequate sodium diet, they produce an initial sodium retention followed by sodium escape after a period of 4-5 days. This latter phenomenon is probably accompanied by activation of the renal kallikrein system (Holland, Gomez-Sanchez, unpublished results).

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Regulation of Aldosterone Secretion:

Aldosterone secretion is regulated by:
(1) Renin-angiotensin system
(2) ACTH
(3) Increase in plasma potassium
(4) Sodium depletion

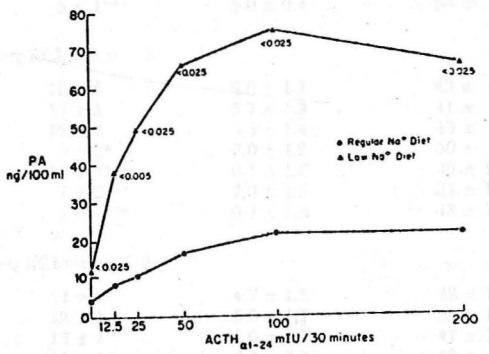
There are miscellaneous other stimuli, which most likely have no physiological importance.

In 1960 it was discovered that the kidney is the source of a potent aldosterone-stimulating agent. A multiplicity of agents were infused. It was finally found that synthetic angiotensin II stimulated aldosterone excretion and aldosterone secretion in man. Thereafter, a large body of evidence has accumulated supporting a role for angiotensin as the most important stimulus of aldosterone secretion.

Recently it has been suggested that angiotensin II is converted to angiotensin III, which has equal or greater ability to stimulate aldosterone secretion, but only about 10-20% hypertensive effect.

ACTH:

The administration of ACTH produces a brisk increase in aldosterone production as shown in Figure 6.



The median plasma aldosterone (PA) response to ACTH infusion while on a normal diet is compared to the response after 3 days of a 13 mEq sodium diet. The p values indicate the significance of differences between comparable infusion rates during the different dietary periods.

Potassium:

Increases in plasma K as little as 0.4 mEq/L produce an increase in aldosterone production as shown in Figure 7. Increase in potassium administration even without detectable changes in plasma K produce an increase in aldosterone production. However, the exact mechanism is unclear. It is thought to be a direct action on the adrenal gland.

Conversely, a decrease in plasma K produces an inhibition of the secretion of aldosterone (Figure 8).

POTASSIUM-ALDOSTERONE-RENIN INTERRELATIONSHIPS

Response of plasma renin activity, angiotensin II, aldosterone, cortisol and potassium to graded constant potassium chloride infusions over 2 h

Time min	Potassium meq/liter	Aldosterone ng/100 ml	Cortisol μg/100 ml	Renin activity ng/ml/h	Angiotensin II pg/ml
			0.17 meq KCl/min n = 8		
0	4.0 ± 0.1	28 ± 7	11 ± 1	5.9 ± 1.0	45 ± 7
10	4.0 ± 0.1	28 ± 7	12 ± 2	5.4 ± 0.9	48 ± 5
20	4.0 ± 0.1	28 ± 6	10 ± 1	5.4 ± 0.8	46 ± 5
30	4.0 ± 0.1	33 ± 5	8 ± 1	5.4 ± 0.8	42 ± 7
60	4.1 ± 0.1	38 ± 7***	6 ± 1**	6.8 ± 1.3	47 ± 8
90	4.2 ± 0.1	41 ± 6***	7 ± 1**	6.3 ± 1.0	47 ± 7
120	4.2 ± 0.1*	35 ± 6**	5 ± 1***	5.0 ± 0.4	54 ± 8
			0.33 meq KCl/min n = 5		
0	4.3 ± 0.2	27 ± 4	12 ± 2	5.6 ± 1.1	43 ± 9
10	4.3 ± 0.2	32 ± 4	13 ± 1	5.7 ± 1.3	41 ± 8
20	4.4 ± 0.2	34 ± 6	12 ± 2	5.3 ± 1.4	43 ± 7
30	4.7 ± 0.3*	48 ± 7***	9 ± 2*	6.0 ± 1.2	50 ± 9
60	4.9 ± 0.3**	50 ± 6***	10 ± 1*	6.1 ± 1.6	46 ± 11
90	5.0 ± 0.2***	48 ± 8***	7 ± 2***	7.0 ± 1.6	55 ± 13
120	5.0 ± 0.4***	49 ± 9***	6 ± 1***	6.7 ± 1.8	48 ± 12
			0.5 meq KCl/min n = 5		
0	4.2 ± 0.1	16 ± 4	14 ± 2	4.7 ± 1.5	42 ± 14
10	4.4 ± 0.1*	18 ± 3	12 ± 1	5.3 ± 1.7	55 ± 17
20	4.5 ± 0.1**	21 ± 2	13 ± 2	5.0 ± 1.3	47 ± 17
30	4.6 ± 0.1***	23 ± 1*	11 ± 2	6.3 ± 2.2	48 ± 9
60	4.7 ± 0.2***	31 ± 4***	9 ± 1**	6.2 ± 1.5	48 ± 14
90	4.9 ± 0.1***	33 ± 4***	7 ± 2***	5.0 ± 0.9	45 ± 11
120	5.1 ± 0.2***	33 ± 6***	8 ± 2***	6.0 ± 2.0	57 ± 13

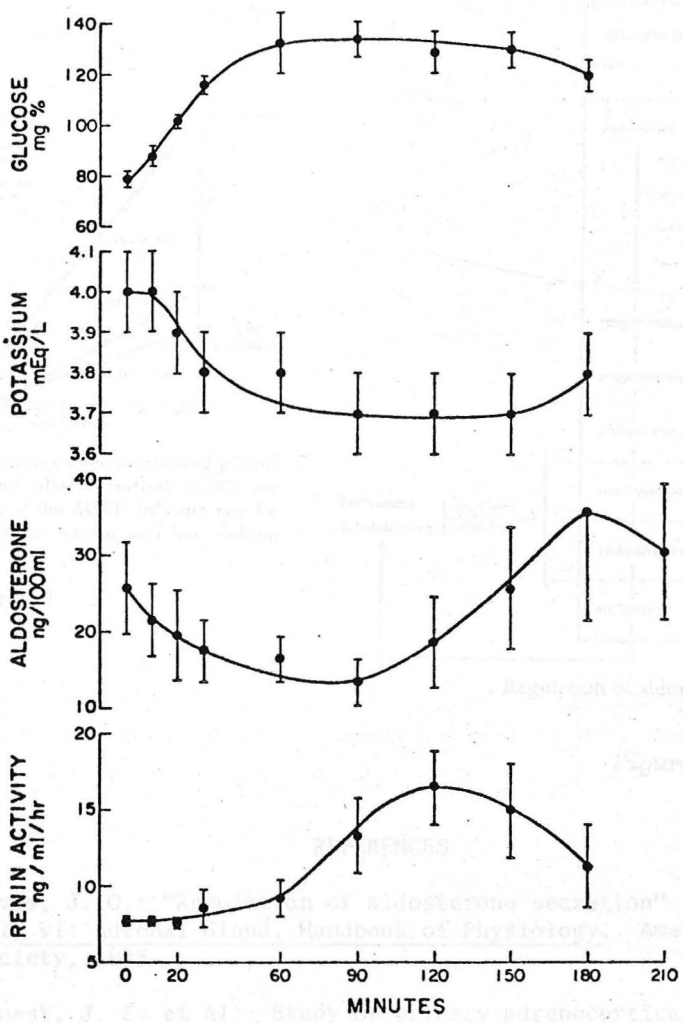
Mean ± SEM of normal subjects on a 10 meq Na+/100 meq K+ diet.
* $P < 0.05$ significantly different from control.
** $P < 0.02$ significantly different from control.
*** $P < 0.01$ significantly different from control.

Figure 7

Sodium Depletion:

Multiple mechanisms seem to work together in this situation. (a) Sodium depletion produces stimulation of the renin-angiotensin system. This mechanism is accepted by most people as the most important one. Our group and others have very serious reservations about this point. (b) (Figure 9) Increased sensitivity of the adrenal to ACTH and angiotensin. (c) Increased intracellular concentration of potassium. More sophisticated

techniques have been unable to prove it. (d) Secretion of a hormone as yet unidentified. There is ample indirect evidence of this possibility, but it remains unproven.

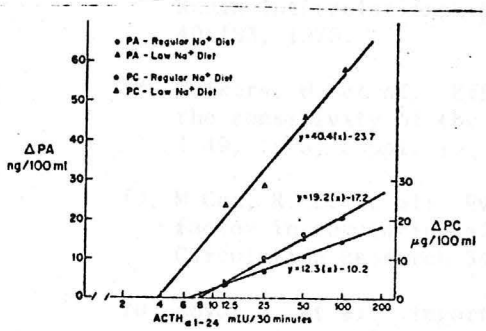


Responses of plasma potassium, renin activity, cortisol and aldosterone following glucose ingestion (0.25 g/kg/15 min from 0–120 min). (Mean ± SEM; n = 6).

Figure 8

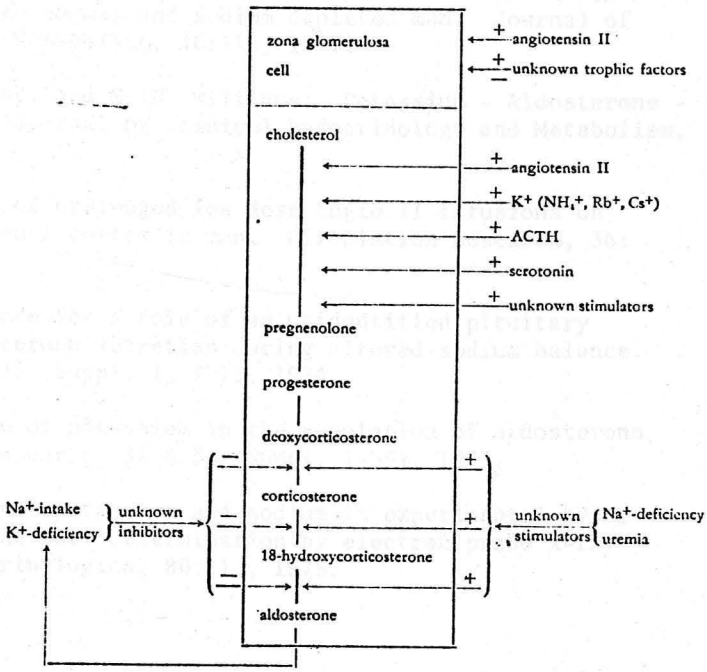
There are two step limiting reactions where the regulation of aldosterone secretion is exerted. They are summarized in Figure10. At any time or in any situation, the regulation of aldosterone secretion usually

involves multifactorial mechanisms.



The median increase over baseline of plasma aldosterone (ΔPA) and plasma cortisol (ΔPC) are plotted against the log of the ACTH infusion rate for the subjects while on the normal and low sodium diets.

Figure 9



Regulation of aldosterone biosynthesis in the rat

Figure 10

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Primary Hyperaldosteronism:

Primary hyperaldosteronism is a syndrome resulting from excessive secretion of aldosterone and not due to increased secretion of the known stimuli. As such, any increased secretion of the known stimuli with resultant hypersecretion of aldosterone will be called secondary hyperaldosteronism.

Incidence:

As many as 7% of patients referred to the University of Michigan Medical Center have primary aldosteronism. However, in most centers this frequency is on the order of 1%.

Pathophysiology:

Hypersecretion of aldosterone results in an increased reabsorption of sodium with increased total body sodium as well as extracellular sodium content. After a period of positive sodium balance, the individuals go into the so-called sodium escape--producing a new steady state remaining with an increased total body exchangeable sodium. The mechanism of hypertension is related to sodium retention, but the exact mechanism is unclear. Plasma volumes in general are not different from normals.

It is probable that the increased body sodium is associated with alterations in arteriolar sodium content and altered responsiveness to sympathetic stimuli.

Effect on Electrolytes:

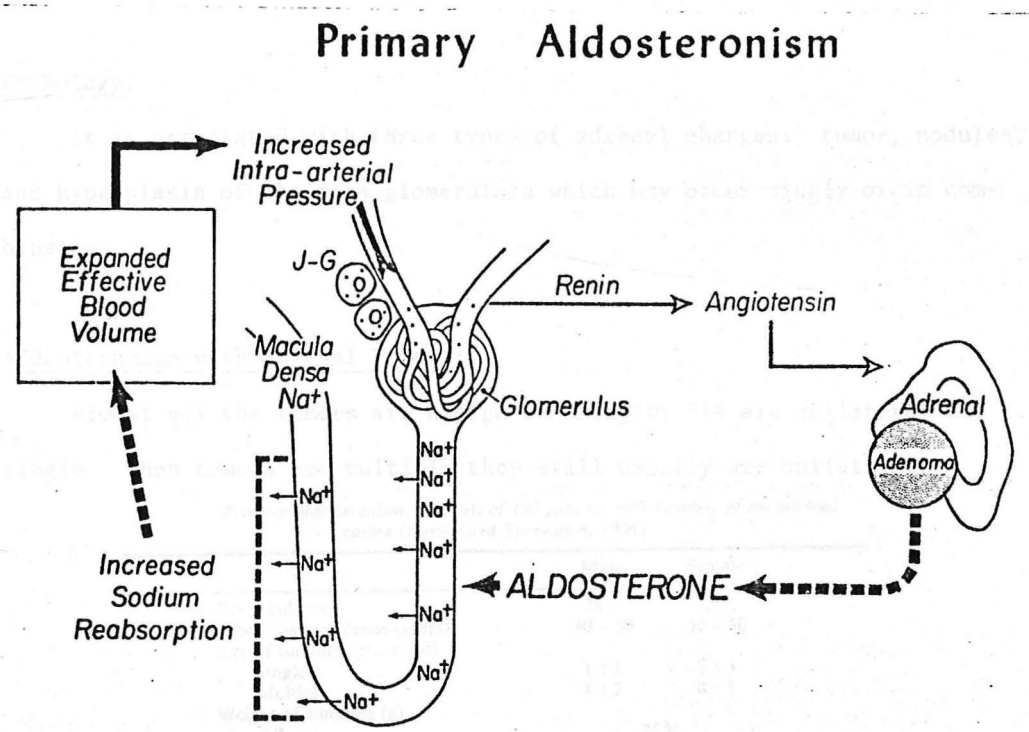
In contrast to the escape from the sodium-retaining effect once a new steady state has been reached with increased extracellular volume and exchangeable sodium, the effect on potassium excretion continues producing a negative potassium balance with decreased total exchangeable potassium and eventually hypokalemia. Apart from the kidney, the other excretory target organs do not show escape mechanism.

In primary aldosteronism there is a negative magnesium balance and low plasma magnesium concentrations, resulting eventually in reduced excretion of magnesium.

The effects on calcium are variable. Many of the neuromuscular and renal responses in primary aldosteronism are related to potassium depletion. Aldosterone also increases the excretion of hydrogen ions especially in the form of the ammonium ion. A systemic alkalosis is found and this

correlates best with the potassium depletion per se. Potassium depletion often causes a nephrogenic type diabetes insipidus which is usually reversed by potassium repletion.

As a consequence of increased extracellular fluid volume, plasma renin activity is suppressed (Figure 11).



Mechanism for suppressed PRA in patients with primary aldosteronism. The increased sodium reabsorption induced by the excess aldosterone expands blood volume and increases pressure at the juxtaglomerular cells.

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Pathology:

It is associated with three types of adrenal changes: tumor, nodules, and hyperplasia of the zona glomerulosa which may occur singly or in combination.

Aldosteronism with Adrenal Tumors:

Almost all the tumors are benign and single; 91% are unilateral and single. When tumors are multiple they still usually are unilateral.

Primary aldosteronism. Analysis of 199 patients with tumours of the adrenal cortex (Neville and Symington, 1966)

	Male	Female
Sex incidence	28%	72%
Modal age incidence (years)	30 – 50	30 – 50
Site of tumours (left:right)		
Single	1 : 1	7 : 3
Multiple	1 : 2	8 : 1
Weight of tumours (g)		
<2	25%	
<4	47%	

Table I

Hyperaldosteronism without tumors:

This condition tends to be present in older individuals and affects each sex equally. The different patterns are shown in Table II.

Uncertain Pathology:

In some cases it is microscopically impossible to differentiate between a macronodule or an adenoma (Table II).

Classification of adrenal changes in hyperaldosteronism with low plasma renin[a]

Group	Histological subdivisions	Incidence No.	Incidence %
1. Adrenocortical tumour	Adrenal adenoma with hyperplasia of zona glomerulosa	23	72
	Adrenal adenoma with hyperplasia of zona glomerulosa and with micronodules	32	
	Adrenal carcinoma[b]	2	
2. No adrenocortical tumour	Hyperplasia of zona glomerulosa	3	19
	Hyperplasia of zona glomerulosa with micronodules	8	
	Hyperplasia of zona glomerulosa with micronodules and macronodules	3	
	Normal zona glomerulosa with micronodules	2	
3. Uncertain pathology	Either an adrenal adenoma *or* an adrenal macronodule; hyperplasia of zona glomerulosa with micronodules also present	7	9

[a]Based upon a series of 80 patients, most previously reported by Neville and Symington (1966) and Ferris et al (1970)
[b]Attached and/or contralateral gland was not available for study in the examples personally studied

Table II

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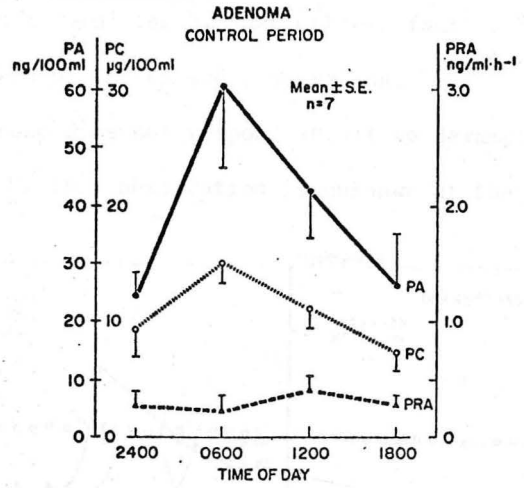
Regulation of Aldosterone Secretion in Primary Aldosteronism:

It was assumed that patients with primary aldosteronism secrete aldosterone autonomously with no relation to the known stimuli and, as such, most tests use this principle for the diagnosis. But, in fact, aldosterone secretion seems to continue being regulated by changes in the known stimuli and, as such, is not entirely autonomous.

Aldosterone secretion follows a circadian variation both in the normal population and in patients with primary aldosteronism. Peak values are seen in the early morning, with lowest values in the late afternoon (Figure 12).



Mean plasma aldosterone (PA), cortisol (PC), and renin activity (PRA), during the control period are plotted for seven recumbent patients with primary aldosteronism and adenoma on a regular sodium diet.

Figure 12

The secretion occurs in bursts of intermittent activity with moments of apparently no activity. ACTH appears to be a major determinant of the circadian rhythm of plasma aldosterone in patients with aldosteronism caused by an adenoma. Administration of dexamethasone causes a suppression of the episodic secretion acutely. After a few days, at least total production returns to previous levels even though episodic secretory bursts are suppressed. In hyperplasia there are at least three responses which might help classify these cases as suggested by David Kem. One group, as seen in the patient initially described by Sutherland, has glucocorticoid suppressible aldosteronism and the administration of dexamethasone diminishes considerably aldosterone production with complete remission of the clinical syndrome. This group is by far the most rare.

A second group of patients is partially suppressed with complete blunting of the episodic secretion even after 2 weeks of dexamethasone, but excretion rates did not significantly change. This suggests that

basal secretion is mediated by some unknown factor, but ACTH intervenes in the regulation of the episodic secretion.

A third group does not respond at all to dexamethasone suppression. The importance of this observation is unknown at the present time.

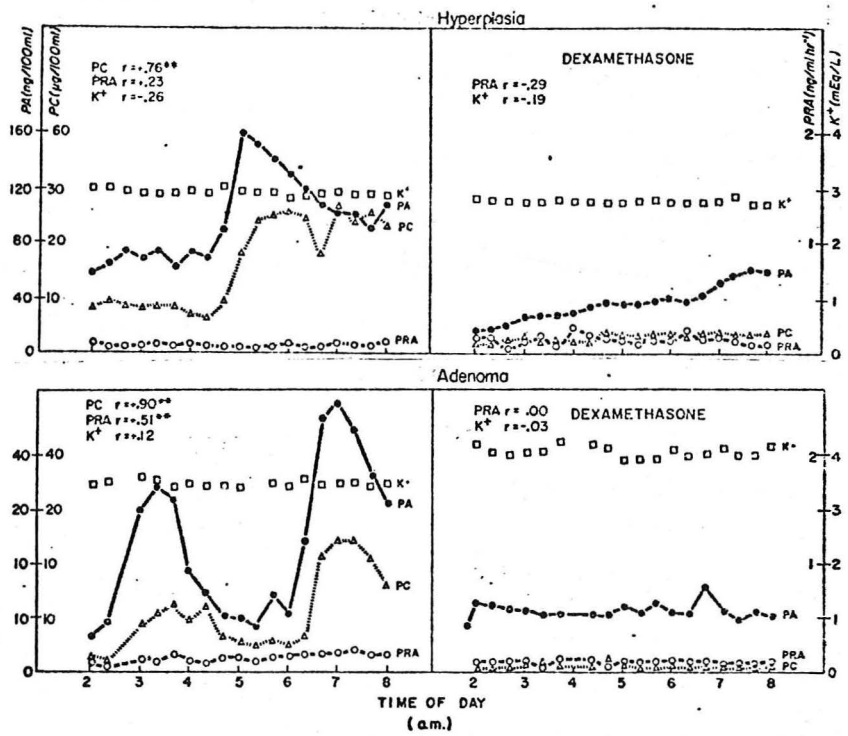


Figure 13

Sodium depletion increases aldosterone secretion, but the increases are less pronounced than that of normal subjects. Angiotensin infusions also increase aldosterone secretion. This group of patients is very sensitive to the hypertensive effect of angiotensin, and this limits the amount that can be administered so that an adequate dose response curve cannot be obtained.

Volume expansion produces a marked suppression of plasma aldosterone concentration and aldosterone secretion in normal individuals but has no

effect on patients with primary aldosteronism. Infusions of saline are rapidly eliminated concomitant, with a marked increase in potassium excretion.

Other maneuvers of producing volume expansion, like administration of DOCA or 9α-fluorocortisol, have similar effects on normal individuals but do not affect aldosterone secretion in patients with primary aldosteronism. We will discuss this aspect more when talking about diagnostic maneuvers.

But, probably the most exciting new development in aldosteronism is the tentative demonstration of a trophic factor present in plasma from a patient with aldosteronism with bilateral adrenal hyperplasia. Nicholls et al injected plasma from a patient with hyperplasia into the arterial side of a cervical adrenal transplant and collected the venous effluent. Plasma from this patient produced a consistent increase in aldosterone production. As a control experiment, plasma from a patient with adenoma was tested and did not produce any increase.

These experiments support the hypothesis of the secretion of an unidentified hormone causing aldosteronism with adrenal hyperplasia (Figure 14).

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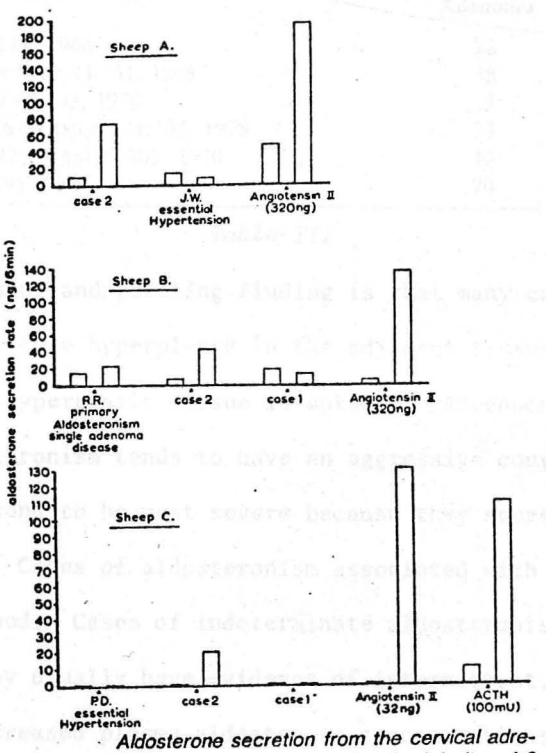


Aldosterone secretion from the cervical adrenal transplant in sheep before and after the infusion of 2 ml of plasma from the patients (Cases 1 and 2), and comparison with response to plasma from two subjects with essential hypertension and one patient with primary aldosteronism due to a single adenoma. Also shown is the aldosterone secretion after standard injections of angiotensin II and ACTH.

Figure 14

Classification:

1. Aldosterone-producing adenoma
2. Aldosteronism with adrenal hyperplasia
3. Aldosterone-producing adrenal carcinoma
4. Glucocorticoid remediable aldosteronism
5. Indeterminate aldosteronism
6. Aldosteronism due to nonadrenal cancer

Benign adrenal adenomas were the most frequent cause of aldosteronism in the early series. The incidence of adrenal hyperplasia has increased considerably and in our own experience is more common than adrenal adenomas.

Pathology of Primary Aldosteronism

Reference	Adenoma	Hyperplasia
Conn: *JAMA* 195:111, 1966	22	0
Priestly: *Mayo Clin Proc* 43:761, 1968	48	2
George: *Am J Med* 48:343, 1970	13	6
Biglieri: *Circ Res* 26-27 (suppl 1):195, 1970	35	12
Baer: *Circ Res* 26-27 (suppl 1):203, 1970	12	11
Ferriss: *Lancet* 2:995, 1970	20	9

Table III

The surprising and puzzling finding is that many cases of adenomas have focal or diffuse hyperplasia in the adjacent tissue. The exact significance of this hyperplasic tissue is unknown. Adrenocortical cancer which produces aldosteronism tends to have an aggressive course--the metabolic manifestations tend to be most severe because they secrete enormous amounts of aldosterone. Cases of aldosteronism associated with an arrhenoblastoma has been described. Cases of indeterminate aldosteronism, in our experience, are common. They usually have evidence of intermittent, unprovoked hypokalemia with increased plasma aldosterone concentrations, increased excretion rates, and suppressed plasma renin activity. Their peculiarity is that they exhibit normal suppression to a saline infusion and sometimes to Florinef administration.

The differentiation between cases of adenomas and hyperplasia is of importance. The latter respond very poorly to total adrenalectomy and, as such, surgery should be avoided.

Clinical Features:

Hypertension - usually mild to moderate, but there are cases with accelerated or malignant hypertension. There is not a good correlation between aldosterone production and degree of hypertension.

Hypokalemia - uniform in the initial cases. Technological improvements have made it possible to detect cases with aldosteronism and intermittent hypokalemia or even normokalemic aldosteronism.

These patients tend to be very sensitive to hypokalemia produced by thiazides. But, conversely, the large majority of thiazide-induced hypokalemia patients do not have hyperaldosteronism. The majority of manifestations of primary aldosteronism are in relation to hypokalemia.

CHARACTERISTIC SYMPTOMS OF CONN'S SYNDROME AND THEIR FREQUENCY
(after Conn, 1961, 1963, 1965)

Most common symptoms	Frequency %
Hypertension	100
Hypokalaemia	100
Hypochloraemic alkalosis	100
Increased aldosterone	100
Low renin	100
Proteinuria	85
Pitressin-resistant hyposthenuria	80
Impairment in urinary acidification	80
ECG changes	80
Increased urinary potassium	75
Muscle weakness	73
Nocturnal polyuria	72
Hypernatraemia	65
Glucose tolerance test decreased	60
Headache	51
Retinopathy	50
Polydipsia	46
Paraesthesia	24
Periodic paralysis	21
Tetany	21
Fatigue	19
Muscular pain	16
Asymptomatic	6
Oedema	3

Table IV

One important aspect of hypokalemia is that there is an inhibition of aldosterone synthesis which may mask evidence of hyperproduction.

Urinary Aldosterone Excretion in Patients with Primary Aldosteronism When Hypokalemic and Normokalemic

	Hypokalemic		Normokalemic	
Patient	Serum K+ (mEq/liter)	Urinary aldosterone (μg/day)	Serum K+ (mEq/liter)	Urinary aldosterone (μg/day)
A.M.	3.1	12.8	3.7	25.1
M.J.	2.8	14.9	3.5	23.2
E.H.	2.9	18.7	3.6	30.8
N.C.	3.1	19.4	3.5	26.1
O.S.	2.5	23.1	3.5	34.0

Normal urinary aldosterone = 5 to 20 μg/day.

Table V

Diagnosis:

The evaluation of the diagnostic criteria up to 1967, according to Conn, is shown in Table VI. Even though normokalemic aldosteronism exists, it is rare. Routine evaluation for primary aldosteronism in normokalemic hypertensive patients is not recommended at the present time. The yield of patients is probably on the order of 1% or less and would be too costly an undertaking. Patients with unprovoked hypokalemia or intermittent hypokalemia deserve a work-up. In these cases urinary potassium before starting potassium replacement is helpful. If the excretion is above 30 mEq/day, further work-up is indicated. The urinary sodium must be greater than 100 mEq/day for this criterion to be valid.

Evolution of diagnostic criteria for primary aldosteronism

1954—1964	I	Hypokalemia — below 3.0 mEq/L
	II	Overproduction of aldosterone
	III	Normal 17 OHCS and 17 KS
To help rule out renal hypertension	IV	Absence of hyponatremia
	V	Absence of papilledema
	VI	Normal renal arteriograms
1964—1965	VII	Suppression of renin activity (low Na — ↑)
	I	Hypokalemia — below 3.8 mEq/L
	II	Overproduction of aldosterone
	III	Normal 17 OHCS and 17 KS
1965—1967	VII	Suppression of renin activity (low Na — ↑)
	II	Overproduction of aldosterone
	III	Normal 17 OHCS and 17 KS

Table VI

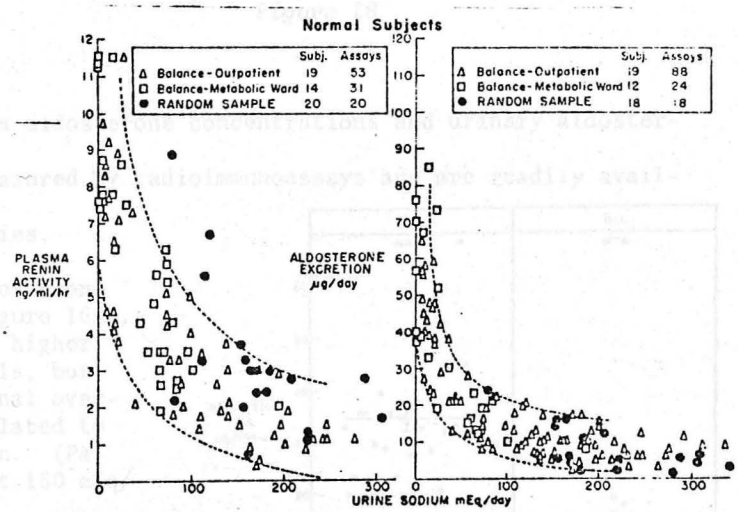
As a consequence of volume expansion, plasma renin activity (PRA) is suppressed. Following the dictum of endocrinology that in hyposecretion one stimulates, a series of maneuvers have been advocated in order to stimulate PRA.

A word of caution about PRA's: The current methods employ a radioimmunoassay of angiotensin I which is generated after incubation of the plasma in the presence of inhibitors against converting enzyme and angiotensinases. Conditions such as type of inhibitors, pH, dilution, time of incubation, antibody, and tracer employed for the RIA affect significantly the results. Each laboratory has to establish normal values and these can vary tremendously between laboratories. A very low value is certainly helpful regardless of the method, but the limits between low and normal can only be determined with the established values of the particular assay.

Stimulation Maneuvers for PRA:

A. Sodium depletion for 3-4 days and 2 hr upright position.

B. Moderate sodium depletion and upright posture for 4 hr and values related to sodium excretion of the 24-hr urine of the same day (Laraghgram) (Figure 15).



Relation of both renin activity in plasma samples obtained at noon and of the corresponding twenty-four hour urinary excretion of aldosterone to the concurrent daily rate of sodium excretion. For these normal subjects, the data describe a similar dynamic hyperbolic relationship between each hormone and sodium excretion. Of note is the fact that subjects studied on random diets outside the hospital exhibited similar relationships, a finding which validates the use of this nomogram in studying outpatients or subjects not receiving constant diets.

C. Pharmacologic stimulation--intravenous Lasix test. PRA is measured 30 minutes after the IV injection of 40 mg of furosemide followed by upright posture. This test has the advantage that it is less dependent on sodium intake provided that it is between 50-150 mEq/day and is a safe outpatient test. Since the Parkland lab is now utilizing our assay method for PRA determinations, the values shown in figure 16 can be utilized. The patients should be off antihypertensive medications for 2-4 weeks (3 months for estrogens) before testing.

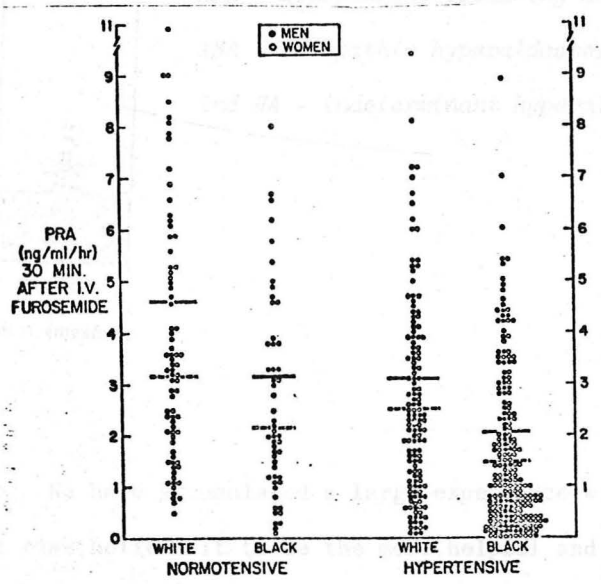
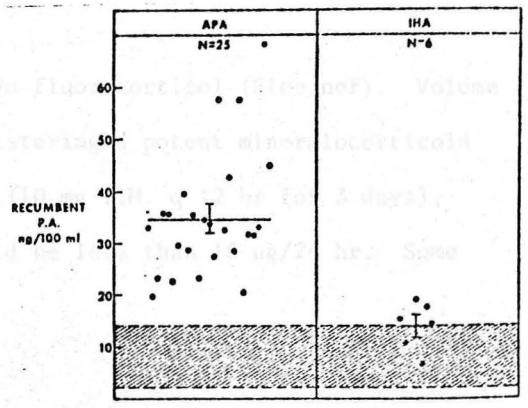


Figure 16

Aldosterone Measurements:

Currently, both plasma aldosterone concentrations and urinary aldosterone excretion rates are measured by radioimmunoassays and are readily available in referral laboratories.

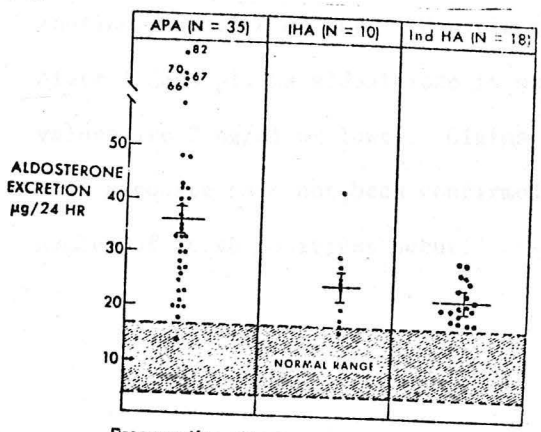
1. Supine plasma aldosterone concentration (Figure 16a). Most patients had higher values than normals, but there are occasional overlaps--probably related to episodic secretion. (Patients on at least 150 mEq/day sodium diet.)



Plasma aldosterone (P.A.) concentration after overnight recumbency in patients with surgically proven aldosterone-producing adenoma (APA) and idiopathic hyperaldosteronism (IHA).

2. Upright plasma aldosterone concentration. Overlap is large enough for this measurement to be of less value.

3. Urinary aldosterone excretion rate. Sodium in the urine should be above 150 mEq/24 hr. Normal values are 5-18 µg/24 hr (Figure 17).



Preoperative aldosterone excretion in patients with the syndrome of primary aldosteronism (mean ± standard error).

Figure 17

APA - aldosterone producing adenoma

IHA - idiopathic hyperaldosteronism

Ind HA - indeterminant hyperaldosteronism

4. Suppression tests:

(a) Saline infusion. We have accumulated a large experience with this test and at the present time believe it to be the most helpful and simple. Plasma aldosterone is measured after 2 hr in the upright posture and after a 4 hr infusion of saline at a rate of 500 ml/hr. Normal responses equal suppression of plasma aldosterone to less than 5 ng/100 ml or 25% of baseline (2 hr upright). We have not had any problems with this test even in severe hypertension (Figure 18).

(b) Administration of DOCA or 9α-fluorocortisol (Florinef). Volume expansion can also be produced by administering a potent mineralocorticoid and a high salt diet. With DOCA in oil (10 mg I.M. q 12 hr for 3 days), urinary aldosterone on the 3rd day should be less than 18 µg/24 hr. Some

patients with renovascular hypertension show less suppression, but it is usually less than 50% of baseline and below 18 µg/hr (Figure 19). Florinef has been administered for the same reason, except that it has the advantage of being administered orally. Dosage is 0.6-1.2 mg/day (0.2-0.4 tid). We routinely use 1.0 mg/day, and patients are placed on a 200 mEq sodium diet. After 3 days plasma aldosterone is measured in the supine posture. Normal values are 7 ng/dl or lower. Claims that ambulatory plasma aldosterone is also adequate have not been confirmed in our laboratory. A significant number of false positives occur.

Plasma aldosterone (PA) after eight hours recumbency (→), after two hours upright (↑), and after four hours recumbency and infusion (→ after infusion). The dotted line indicates the highest value after infusion in groups 1, 2a, and 2b.

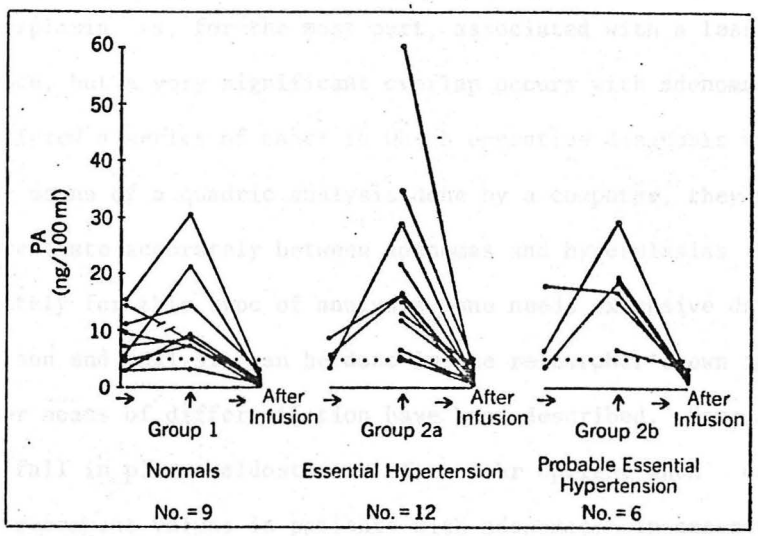
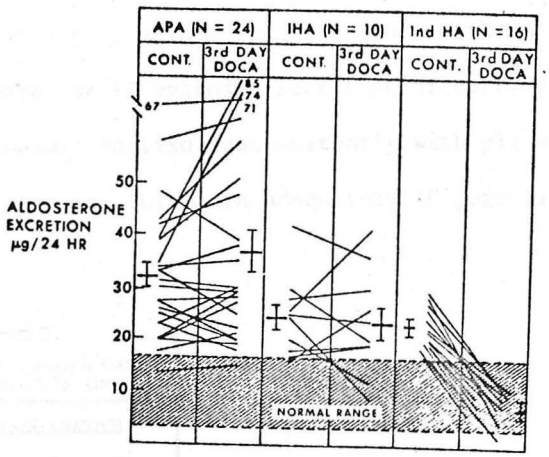


Figure 18



Preoperative effect of deoxycorticosterone acetate (DOCA) on aldosterone excretion before (Cont.) and on third day of treatment in patients with the syndrome of primary aldosteronism (mean ± standard error).

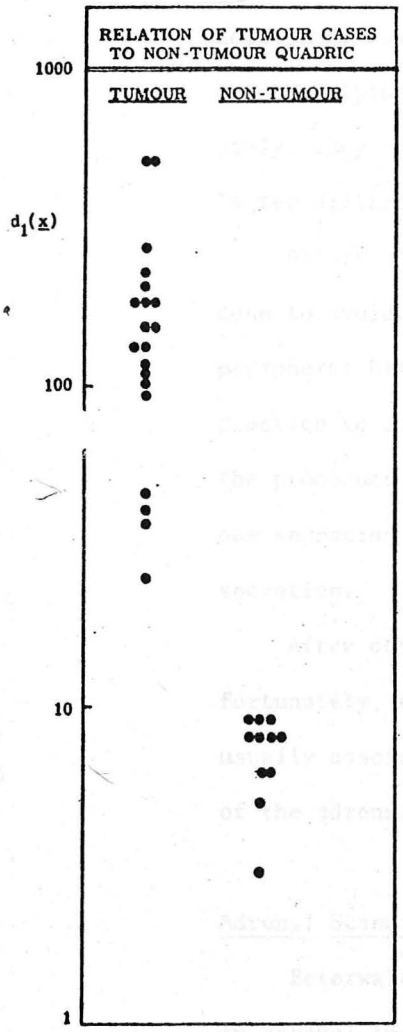
Figure 19

Differentiation between Adenoma and Hyperplasia:

Hyperplasia is, for the most part, associated with a less severe disturbance, but a very significant overlap occurs with adenomas. Ferris et al analyzed a series of cases in which operative diagnosis was available. By means of a quadric analysis done by a computer, they were able to differentiate accurately between adenomas and hyperplasias (Figure 20). Unfortunately for this type of analysis, one needs extensive data so that a comparison and analysis can be done in the researcher's own institution.

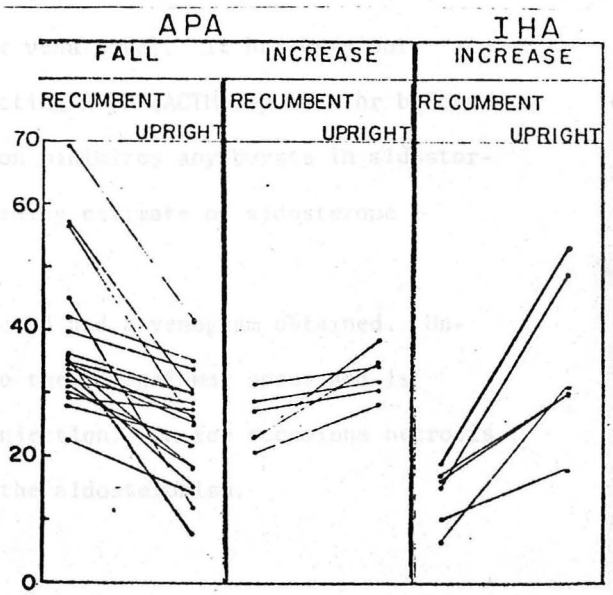
Other means of differentiation have been described. Ganguly described a fall in plasma aldosterone after 4 hr upright when compared to baseline recumbent values in patients with adenomas. In cases with hyperplasia, plasma aldosterone increased after the 4 hr of the upright position. Few cases of adenomas seem to behave aberrantly in that plasma aldosterone increased. When plasma cortisol was measured, these patients

had higher values than baseline, which indicated that the aberrant values were due to episodic secretion of cortisol. Thus, it is of importance to measure cortisol concomitantly with plasma aldosterone to be able to interpret this data adequately (Figure 21).



Differentiation of patients with 'primary' hyperaldosteronism with and without adrenocortical tumours on the basis of blood pressure and plasma renin, aldosterone and electrolyte concentrations using the technique of circumscribing quadric analysis.

Figure 20



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

Figure 21

Bilateral adrenal vein catheterization for venograms and collection of effluents. The left adrenal vein is relatively easy to localize since it drains into the left renal vein. The right adrenal drains directly into the vena cava and is difficult to catheterize. Some skilled angiographers are able to catheterize the right adrenal almost 100% of the time, but a more general success rate is about 40%. When the right adrenal vein cannot be localized, comparison of the values between the peripheral and left adrenal can be helpful in localizing the site of the adenoma (Figure 22). Unfortunately, they are worthless in differentiating adenomas from hyperplasia. This latter differentiation can only be done if both veins are catheterized.

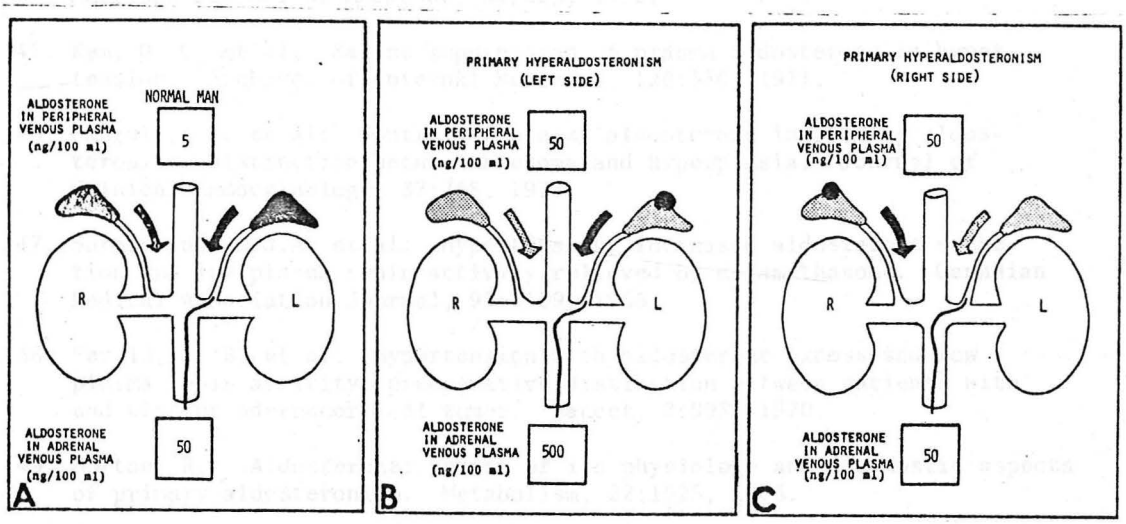
Before any dye is injected careful, slow withdrawal of blood should be done to avoid mixing blood from the IVC or left renal. At the same time, peripheral blood should be taken (inferior vena cava). It has been our practice to administer 40 units of long-acting ACTH (ACTH depot) 1 hr before the procedure. This continuous stimulation minimizes any bursts in aldosterone secretion which might provide a misleading estimate of aldosterone secretion.

After obtaining samples, dye is injected and a venogram obtained. Unfortunately, extravasation of the dye into the adrenal may occur and is usually assoicated with pain during the injection. On few occasions necrosis of the adrenal has happened with cure of the aldosteronism.

Adrenal Scanning:

Beierwaltes' group described the use of ^{131}I-19-iodocholesterol as an adrenal imaging agent. In 7 patients with an aldosterone-producing

adenoma, the label was concentrated in the side of the tumor. In adrenal hyperplasia, there is bilateral uptake. This procedure may turn out to be very good in differentiating adenomas from hyperplasia, but not enough experience is available.



Diagrammatic outline of the logic of the lateralisation techniques. A. Normal subject with adrenal venous aldosterone concentration of 50 ng/100 ml and an inferior vena caval level of 5 ng/100 ml. B. Primary aldosteronism with left-sided adenoma; both adrenal venous and vena caval levels are elevated. C. Primary aldosteronism with right-sided adenoma; vena caval concentration of aldosterone is raised, but production from left adrenal is suppressed.

Figure 22

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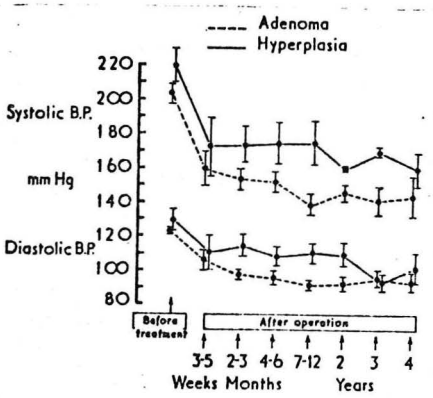
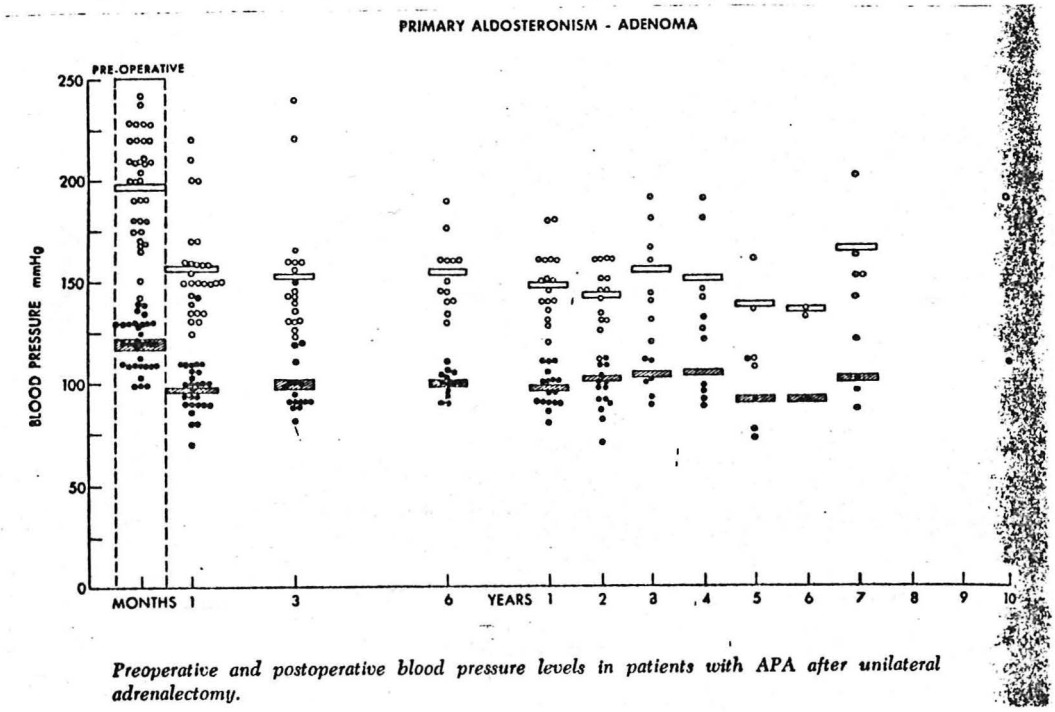
Treatment:

Removal of an aldosterone-producing adenoma usually results in improvement of the hypertension and metabolic abnormalities. Total or subtotal adrenalectomy in patients with hyperplasia usually has little or no hypotensive effect, even though the metabolic abnormality can be corrected. Figure 23 shows the results of surgery on a total of 50 patients (38 adenoma, 12 hyperplasia).



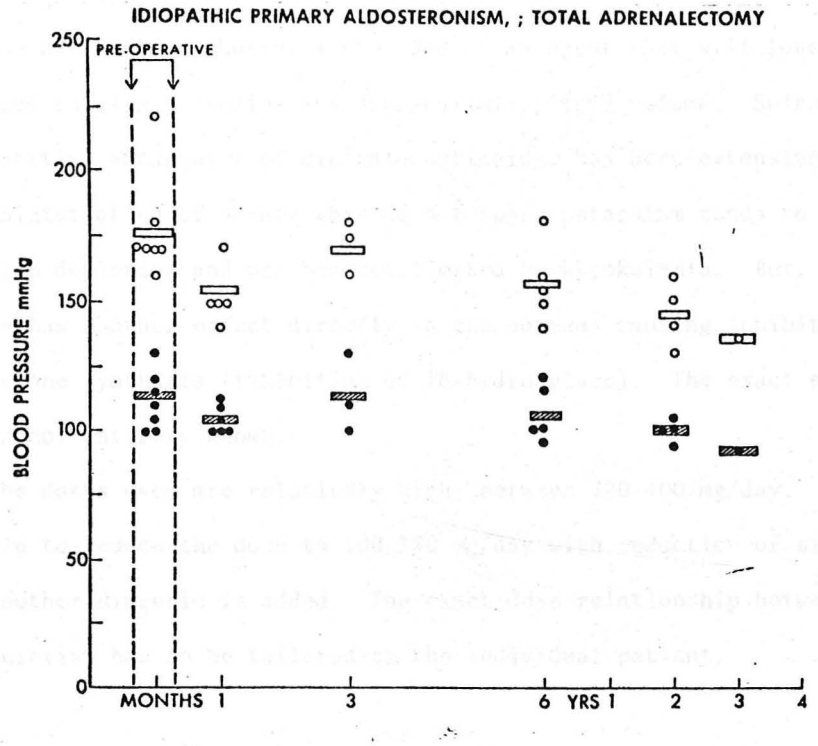
—Blood pressure (mean ± I.S.E.) before and after operation. Reading from left to right, number of patients included in reviews in adenoma group, and non-adenoma group, respectively, were 28 and 10, 8 and 7, 20 and 9, 15 and 7, 12 and 5, 11 and 4, 7 and 3, and 4 and 2.

Figure 23



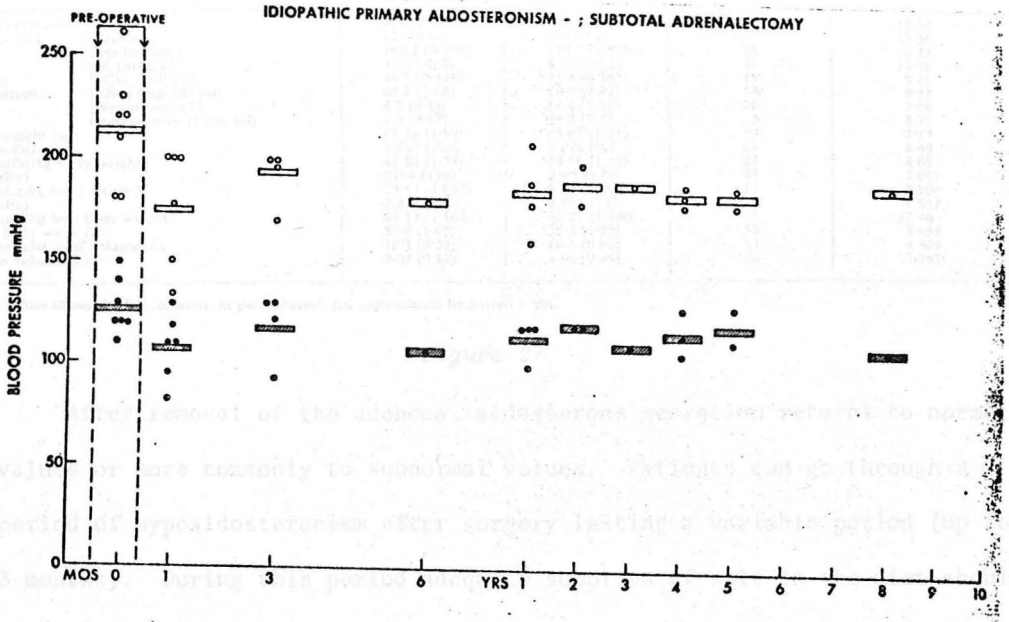
Preoperative and postoperative blood pressure levels in patients with APA after unilateral adrenalectomy.

Figure 24



Preoperative and postoperative blood pressure levels in patients with IHA after total adrenalectomy.

Figure 25



Preoperative and postoperative blood pressure levels in patients with IHA after subtotal adrenalectomy.

Figure 26

The alternative therapy is the use of an agent that will lower the increased total body sodium and extracellular fluid volume. Spironolactone, a competitive antagonist of mineralocorticoids, has been extensively used. The administration of agents that do not spare potassium tends to worsen potassium depletion and use becomes limited by hypokalemia. But, spironolactone has another effect directly in the adrenal causing inhibition of aldosterone synthesis (inhibition of 18-hydroxylase). The exact extent of this is not entirely known.

The doses used are relatively high, between 200-400 mg/day. It is possible to reduce the dose to 100-150 mg/day with reduction of side effects when another diuretic is added. The exact dose relationship between the two diuretics has to be tailored to the individual patient.

Effects of Spironolactone

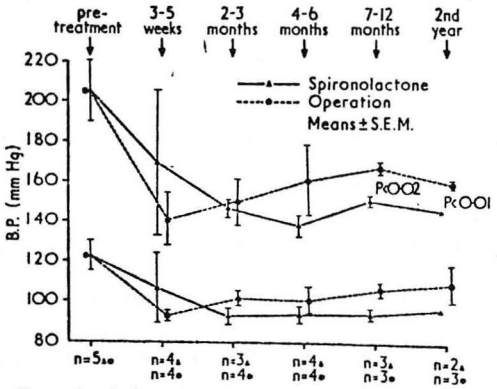
Observation		Before Treatment	During Spironolactone	No. of Pairs	*t*	P
Blood pressure (mm Hg)	Systolic	201 (2·94)	149 (3·33)	67	15·82	<0·001
	Diastolic	122 (1·48)	97 (1·84)	67	15·36	<0·001
Plasma or serum	Na (mEq/l.)	142·3 (0·356)	138·3 (0·355)	56	8·42	<0·001
	K (mEq/l.)	3·1 (0·087)	4·5 (0·052)	57	12·78	<0·001
	tCO_2 (mEq/l.)	28·5 (0·494)	23·6 (0·393)	49	9·14	<0·001
	Urea (mg/100 ml)	35·2 (1·58)	49·8 (2·77)	54	8·57	<0·001
	Renin (units/l.)	4·8 (0·34)	19·4 (1·97)	29	7·99	<0·001
	Angiotensin II (pg/ml)	5·3 (0·57)	43·2 (7·7)	3	5·27	<0·05
Body weight (kg)		65·36 (1·90)	63·82 (1·81)	33	2·23	<0·05
N_{aE} (mEq)		2,967 (110)	2,494 (99)	21	6·43	<0·001
N_{aE} (mEq/kg body weight)		45·56 (1·35)	39·61 (1·17)	21	4·85	<0.001
K_E (mEq)		2189 (136)	2386 (129)	21	2·097	<0·05
K_E (mEq/kg body weight)		33·53 (1·867)	37·27 (1·604)	21	2·508	<0 025
K_T (mEq)		2,256 (219)	2,951 (342)	3	4·637	<0·05
K_T (mEq/kg lean body weight)		49·13 (1·562)	61·27 (1·246)	3	12·46	<0·01
Total body water (l.)		37·9 (1·83)	35·3 (1·95)	15	3·654	<0·01
Extracellular fluid volume (l.)		19·3 (0·79)	16·6 (0·82)	13	4·305	<0·01
Plasma volume (l.)		3·07 (0·21)	2·80 (0·24)	10	2·267	<0·05

Mean values shown (±S.E. of mean in parentheses). All comparisons by paired *t* test.

Figure 27

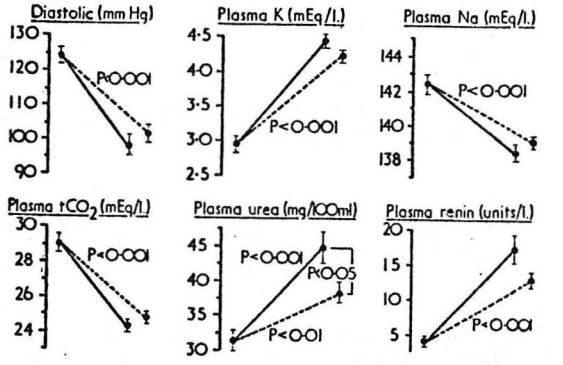
After removal of the adenoma, aldosterone secretion returns to normal values or more commonly to subnormal values. Patients can go through a period of hypoaldosteronism after surgery lasting a variable period (up to 3 months). During this period adequate supplies of salt in the diet should

be available and occasional checks of potassium levels should be done. Almost never is additional therapy required. Potassium should be checked especially if therapy is continued with spironolactone.



—Comparison in five patients eventually shown not to have an adenoma ot the effect of preoperative spironolactone on blood pressure with that of subsequent surgery. Mean systolic pressure significantly lower during spironolactone treatment at 7–12 months, and in second year. All five shown to have normal plasma aldosterone levels after surgery.

Figure 28



—Comparison in the 32 operated patients of mean preoperative changes induced by spironolactone (continuous lines) with those subsequent to surgery (broken lines) (means ± standard error of means). All readings after four weeks. Differences in mean changes were significant only for plasma urea ($P < 0.05$).

Figure 29

Spironolactone before surgery increases plasma renin activity, but aldosterone responsiveness is unchanged and patients develop hypoaldosteronism after surgery in any case. The main limitation of spironolactone therapy is the side effects.

In males, gynecomastia and impotence are very common at high doses. Spironolactone inhibits the 17,20 lyase and synthesis of androgens drop. In addition, it also is an antagonist of dihydrotestosterone binding to its receptor, decreasing its biological effect. But, main side effects are hyperkalemia--which most commonly occurs in patients with impaired renal function--and gastrointestinal side effects such as anorexia and nausea. Patients with hyperplasia should be treated medically, but if there is inability to take a potassium-sparing diuretic and supplementation cannot keep up and maintain potassium within a reasonable level (above 3 mEq), then surgery would be indicated (total adrenalectomy).

Any patient with an adenoma that is not a candidate for surgery, for any reason, can be well handled with spironolactone. Response to spironolactone is highly correlated with good surgical response.

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