

Abnormally Sustained Aldosterone Secretion during Salt Loading in Patients with Various Forms of Benign Hypertension; Relation to Plasma Renin Activity

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ABSTRACT Among 25 patients with benign, essential hypertension, and an equal number with other benign forms of hypertension, without serious cardiac, renal, or cerebrovascular impairment, 41 cases failed to reduce aldosterone excretion rates into the normal range (less than 5 $\mu\text{g/day}$) on a daily intake of 300 mEq of sodium. The hypertensive patients excreted slightly less than the normal fraction of labeled aldosterone as acid-hydrolyzable conjugate. Secretion rates were significantly higher in the hypertensive patients than in normotensive controls taking the high-sodium intake.

On a 10 mEq sodium intake, the increase in excretion and secretion rates of aldosterone in the hypertensive patients could be correlated with plasma renin activity (PRA). The patients with the least increase in PRA had subnormal increase in aldosterone secretion and excretion, while unusually large rises in aldosterone secretion accompanied high PRA, especially in the cases with increased plasma angiotensinogen induced by oral contraceptives.

The persistence of inappropriately high aldosterone secretion in most hypertensive patients during sodium loading could be related to a higher PRA than that found in normotensive controls under comparable conditions. In other hypertensives, whose PRA was unresponsive to sodium depletion, there was no significant correlation between PRA and aldosterone output, and no known stimulus to aldosterone production was detected. Five obvious cases of hyperaldosteronism were found among the 16 low-renin patients. The cause of the nonsuppressible aldosterone production in the other low-renin cases remains to be determined.

INTRODUCTION

Is aldosterone secretion rate normal in benign, essential hypertension? Earlier reports (1-3) suggested that aldosterone excretion rate was increased in as many as 25% of hypertensive patients, some of whom might be unrecognized cases of primary aldosteronism (4). Other observers found that hyperaldosteronism was common in malignant hypertension, but increased secretion rate was rarely found in benign, essential hypertension unless complicating cardiovascular or renal disease existed (5-9). Most of the patients in the foregoing studies received diets containing between 100 and 150 mEq sodium per day.

Aldosterone production in normal man is strongly influenced by sodium intake (10, 11). In examining the physiological range of secretion rate, it is essential to define the response to a wide range of sodium loads. We suggest that under heavy sodium loads, hypertensive patients may not show the normal degree of suppression of aldosterone secretion (12). Secretion rate may also fail to increase normally during sodium depletion in certain hypertensive patients (13).

The effect of sodium intake on aldosterone secretion is thought to be mediated principally by the renin-angiotensin system (14). Plasma renin activity (PRA) has been found to be closely correlated with aldosterone secretion and excretion in normal men (11) and in many hypertensive patients (12, 13). By comparing PRA with aldosterone secretion at different levels of dietary sodium, it is possible to detect abnormalities of aldosterone regulation. The results of these analyses have been related to the clinical data and diagnosis.

METHODS

Patients. 11 normal volunteers and 4 normotensive patients without overt disease comprise group 1.

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TABLE I
Aldosterone Excretion in 15 Normotensive Controls

Sodium intake activity	300 mEq/day		190 mEq/day, active	120 mEq/day, active	10 mEq/day						
	Resting	Active			Day...1	2	3	4	5	6	7
Men*											
No. of observations	5	12	9	2	3	3	2	3	4		
Range	2.4-5.1	2.6-7.4	7.0-13.0	10.3-12.9	7.5-15.3	11.9-22	16.9-22.8	30.3-34.9	30-55		
Mean	3.8	5.17	9.37	11.6	12.1	18.1	19.8	33.2	41.2		
SEM	±0.58	±0.43	±0.69								
Women†											
No. of observations	18	18	4	5			2	3	6	3	3
Range	1.1-4.4	1.0-4.5	4.5-8.2	7.7-14.5			16.1-53	30.5-56	20-91	63-124	64-97
Mean	2.87	2.74	6.65	10.1			34.5	43.6	49.8	85.3	80.3
SEM	±0.23	±0.21	±0.89	±1.2							
Pooled											
No. of observations	23	30	13	7			4	6	10		
Mean	3.09	3.71	8.45	10.56			27.2	38.4	46.4		
SEM	±0.23	±0.30	±0.67	±0.94			±8.7	±4.1	±6.6		

SEM = standard error of mean.

* Five normal men.

† Six normal women and four normotensive patients.

Hypertensive patients were accepted in the study only after thorough medical work-up. Pertinent information is given in the Appendix. The stated blood pressure was taken in the sitting position at mid-day in the hospital.

Patients with papilledema or other evidence of malignant hypertension were excluded. No patient with a recent history of cardiac decompensation or cerebrovascular disease was subjected to salt loading. Renal function was not seriously impaired in any case studied.

25 patients were considered to have benign, essential hypertension (Appendix A). Rapid-sequence intravenous pyelography disclosed no abnormality. Results of radioactive renogram or arteriogram, when performed, were normal. Urinary catecholamine and VMA excretion rates were normal.

In 13 cases, an abnormality of one or both kidneys was noted (Appendix B to D). Five patients had significant obstruction of a renal artery, demonstrated by arteriography and by differences in size or function of the kidneys. Glomerulo or pyelonephritis was present in three cases. Five patients had abnormal structure of kidney or pelvis.

Eight patients developed hypertension while taking oral contraceptive (Appendix E and Table IV). As previously reported (15, 16), blood pressure fell gradually when oral contraceptive was withheld. Eight patients were studied after medication was discontinued (Appendix E and Table V).

In five cases, the laboratory findings were considered diagnostic of primary aldosteronism (4). Two have been explored surgically. Excision of an adenoma in case 20 resulted in cure. Improvement in hypertension and metabolic abnormalities in case 69 followed removal of both adrenal glands, which were enlarged and contained numerous

small nodules. Three other patients are under observation on aldosterone-blocking agents.

Plan of study. Normal volunteers and hypertensive patients were asked to take liberal salt intake and to discontinue all medications (except as stated) before admission to the hospital. After entering the General Clinical Research Center, all patients received a diet containing at least 300 mEq of sodium per day for 3 days or until the sodium excretion exceeded 300 mEq/day. Sodium intake was then reduced to less than 10 mEq/day for a period of 5 days or until the urinary sodium fell below the intake. Aldosterone secretion rate was measured by isotope dilution on the 2nd day of the high-sodium intake and on the 3rd and 5th days of the low-sodium regimen. Aldosterone excretion rate was determined by the double-isotope derivative assay on other representative days of the high-sodium and low-sodium periods.¹ Plasma renin activity (PRA) was measured by the method of Boucher and Genest (18) at the end of each dietary period. Blood was drawn for PRA at 8 a.m. after 8 hr in the recumbent state and at noon after 4 hr of quiet ambulation. Plasma angiotensinogen was estimated after adding excess renin (16). Plasma and urinary electrolytes were measured by flame photometry. Completeness of urine collection was checked by daily measurements of urinary creatinine.

Standard statistical methods have been used to analyze the data. Logarithms of PRA and aldosterone have been used to calculate correlation and regression in order to

¹ Aldosterone excretion rate means daily excretion of acid-hydrolyzable conjugate, extracted from urine after 24 hr at pH 1 and room temperature. Aldosterone released at pH 1 was also used for measurement of secretion rate (17).

TABLE II
Aldosterone Excretion in 25 Cases of Benign, Essential Hypertension

Sodium intake...		300 mEq/day			10 mEq/day						
Case No.	PRA	Day...1	2	3	1	2	3	4	5	6	7
1	Normal	9.8		8.1		32.4		56.2		54.5	
2	Normal	6.4		4.9		12.8		14.8		12.8	
3	Normal	9.9	8.6	8.9	10.1	15.0	21.0	27.0	25.6	28.7	
4	Normal			14.0	12.5		22.0	21.6	27.5		
5	Normal	11.2	9.0	8.1		19.8	35.0	31.7	46.8	50.8	
45	Normal	7.5	8.9	7.2				26.5	17.8	21.7	
49	Normal		9.6	12.2				38.2	47.6	37.9	
50	Normal		12.1	6.0			19.1	28.4	22.0		
71	Normal		6.1	4.4				24.6	25.9		
77	Normal		10.5	12.5					29.0	28.2	35.2
78	Normal		10.0	15.5				57.0	66.8		
87	Normal	18.5		12.7				20.2		24.3	27.2
94	Normal	6.8	5.9	6.4				30.1	29.3	28.3	
Mean	(Normal)	10.0	9.0	9.3		20.0	24.3	31.4	33.8	31.9	
6	High	3.5	3.4	4.2		23.3	44.0	65.7	75.0		
12	High		38.0	21.0	56.0		65.0		124	98.0	
13	High		6.7	12.0					24.7		
37	High		8.1	13.0			14.1	29.5	25.6		
43	High		24.4	19.6			43.9	60.3	68.0		
47	High	4.0	3.6	2.6					14.2		
Mean	(High)		14.0	12.1			41.8	51.8	55.3		
14	Low	9.2	10.0	8.4		10.1	11.2				12.0
15	Low		3.0	3.4					9.9	10.3	
16	Low		8.1	6.4		9.0		21.1		14.0	
17	Low	9.1	11.5	11.1		14.0	14.4	16.4	16.6		
36	Low		15.0	16.2			23.6				22.6
64	Low		5.8	5.9			7.8			11.1	11.6
Mean	(Low)		8.9	8.6		11.0	14.3	18.8	13.3	11.8	15.4
Mean	(all cases)		10.4	9.8				33.5	38.7	32.3	

achieve a more uniform variance over a wide range of values. Measurements of PRA in blood drawn at noon in the upright posture have been used for the calculations of correlation with aldosterone.

RESULTS

Aldosterone excretion in relation to clinical diagnosis

Normotensive controls. Aldosterone excretion decreased as sodium intake was increased to 300 mEq/day (Table I). The 14 normotensive controls, while resting and taking more than 300 mEq sodium per day, excreted between 1.1 and 5.1 μg (mean 3.09) of aldosterone per day. When sodium intake was decreased to 10 mEq/day in 10 normotensive controls, aldosterone excretion increased, as anticipated (Table I).

Benign, essential hypertension (Table II). In 20 of 25 patients, urinary aldosterone did not decrease to a normal extent on a sodium intake of 300 mEq. The mean for the group was more than three times as high as the average of the normal control group. The difference between means was significant at the level of $P = 0.001$. The response to sodium deprivation was highly variable.

Renal artery stenosis and various renal disorders (Table III). A small group of patients of each type were studied. Three-fourths of the patients had abnormally high aldosterone excretion on a 300 mEq intake of sodium.

Patients receiving oral contraceptives (Table IV). Five of eight patients had aldosterone excretion rates greater than normal on the high-sodium intake. During sodium deprivation, three of eight patients had unusually

TABLE III
Aldosterone Excretion in 12 Patients with Renovascular Hypertension Parenchymatous Renal Disease, or Anomaly of Kidney or Renal Pelvis

Sodium intake...		>300 mEq/day			<10 mEq/day						
Case No.	PRA	Day...1	2	3	1	2	3	4	5	6	7
B. Renal artery stenosis											
25	Normal		14.7	9.8			47.0		56.0	55.0	74.0
26	Normal	9.6	4.4	1.8				38.2	46.3		
23	High		9.1		13.2	13.4		34.1			
24	High		6.8	4.3		16.4			40.2	34.5	
39	High		7.3	6.8			12.0			17.3	
C. Parenchymatous renal disease											
67	Normal		7.2	6.0					14.5	15.4	
79	Normal	19.0	11.4	6.1			41.2	58.5	70.0		
D. Anomaly of kidney or pelvis											
51	High	10.5	8.6	10.5			22.4	30.6	29.2	26.2	
72	High			9.6			27.1				
18	Low		10.6	13.0			18.7	15.1	19.8		
38	Low		8.1	11.3			15.0	11.5	12.3		
73	Low		4.2	5.5				6.7	7.1		

large rises in urinary aldosterone. When moderate hypertension persisted after stopping medication, a lesser degree of hyperaldosteronism was noted (Table V).

Hyperaldosteronism due to adrenal adenoma or idiopathic adrenal hyperplasia (Table VI). Aldosterone excretion above 20 μ g/day, not suppressed by high-sodium intake, distinguishes these cases from other "low-renin" hypertensives. Abnormally high aldosterone output ap-

peared in two patients (cases 19 and 81) on a second study. In both cases, a previous study had shown a degree of suppressibility of aldosterone excretion similar to that observed in many other hypertensive patients.

Plasma renin activity

Normotensive controls (Table VII, group 1). PRA was inversely related to sodium intake, and was higher

TABLE IV
Aldosterone Excretion in Eight Cases of Hypertension with High Plasma Renin Activity and Increased Renin Substrate Induced by Oral Contraceptive

Sodium intake...		>300 mEq/day			10 mEq/day					
Case No. (Entry)	Day...1	2	3	1	2	3	4	5	6	
7(1)			18.5			25.0				
9(1)	22.0		4.7	17.5	15.9		31.4			31.0
48(2)		16.5	17.2				131			156
65(1)		14.1	16.0					34.3		44.8
68(1)		4.5	5.5				135	154		
10(3)	31.8	26.5	25.2							
76(1)		3.7	4.2			104	122	160		
80(1)			39.0					62.0		
Mean	26.9	13.1	16.3			64.5	104.8	102.6		77.3
SEM		4.5	3.3				24.6	32.0		

TABLE V
Aldosterone Excretion in Eight Cases of Hypertension Persisting after Discontinuing Oral Contraceptive

Case No. (Entry)	Sodium intake... PRA	> 300 mEq/day			10 mEq/day						
		Day...1	2	3	1	2	3	4	5	6	7
8(1)	Normal	9.1	10.2	9.1	6.9	12.0	12.0	15.0	18.5	32.3	
11(1)	Normal		4.6	6.1		13.0			46.0	53.0	
48(6)	Normal		6.6	11.3				81.0	62.0		
53(4)	Normal		4.8	2.9					17.9	20.3	
68(6)	Normal		5.2	4.9			22.0	38.9	42.0		
7(2)	High		4.6	4.8			39.0	32.0	37.8		
10(2)	Normal	24.8	25.7	9.4	23.0		15.4	23.2			
10(6)	Low	6.1	5.1	10.6			13.9	17.2	28.8		
65(4)	Low		18.3	12.2					20.0	20.0	
Mean			9.46	7.92			20.46	34.55	34.12	31.4	
SEM			2.52	1.10			4.93	9.99	5.56	7.75	

after standing than in the recumbent state, as previously reported (19). There was a strong correlation between the recumbent and the standing value for each individual patient.

Hypertensive patients showed a wider than normal range of PRA. In a majority of patients with benign essential hypertension, PRA was within normal limits (group 2, Table II). In other cases and other conditions, unusually high and low values of PRA are found. We have assigned these cases to groups 3-5, according to the level of PRA found and to the etiology, if known.

The mean and standard error of PRA for each group is given in Table VII.

"High PRA" was most readily observed during salt loading, when PRA in the normotensive controls was at a minimum (Table VII). High PRA in hypertensive patients was often attributed to increased renin concentration or cofactors, with normal substrate levels (group 3a). Hypertensive patients receiving oral contraceptives have been considered separately (group 3b), since plasma angiotensinogen was consistently increased 3-5 times above normal (16). The associated increase

TABLE VI
Aldosterone Excretion in Five Cases of Hypertension with Hyperaldosteronism and Low Plasma Renin Activity (Primary Aldosteronism or Idiopathic Adrenal Hyperplasia)

Case No. (Entry)	Sodium intake...	> 300 mEq/day			10 mEq/day						
		Day...1	2	3	1	2	3	4	5	6	7
19(1)		14.0		9.5		18.0			22.0	25.0	
19(2)*			27.0	30.1		33.3	42.2	29.9	27.0		
20†		76.0	82.0	77.5		90.5	141.0			103.0	129.0
69§			21.4	26.0				28.0	29.0		
81(1)				9.9				21.0	22.4	20.5	
81(2)		23.6	27.1	35.4							
82			47.2	49.1				48.0	54.8	60.1	

* Refused surgery. Later normotensive on spironolactone.

† Primary aldosteronism, due to adenoma.

§ Idiopathic, nodular adrenal hyperplasia.

|| Recently discovered cases, untreated.

TABLE VII
Plasma Renin Activity in Normotensive Controls and in Groups of Hypertensive Patients

Group	Blood pressure	PRA level	N	Plasma renin activity (ng/liter per min)							
				Sodium intake > 300 mEq/day				Sodium intake < 10 mEq/day			
				Recumbent		Standing		Recumbent		Standing	
				Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
1	Normal	Normal	15	4.63	±0.38	8.96	±1.11	35.92	±1.80	59.27	±9.48
2	High	Normal	23	7.72	±0.65	13.07	±1.08	30.33	±2.71	68.83	±6.21
3a	High	High	12	19.81	±4.57	40.73	±5.22	43.19	±5.23	81.75	±6.88
3b*	High	High	8	23.88	±5.98	41.2	±11.16	71.38	±10.65	119.48	±17.04
4	High	Low	14	4.44	±0.56	5.98	±1.11	7.77	±1.31	14.71	±1.95
5†	High	Low	5	2.86	±0.62	3.41	±0.68	3.4	±0.84	7.28	±2.02

* Patients taking oral contraceptives.

† Primary aldosteronism or idiopathic adrenal hyperplasia.

in angiotensin generation (PRA) does not necessarily involve increased renin concentration, according to published findings (15, 16, 20).

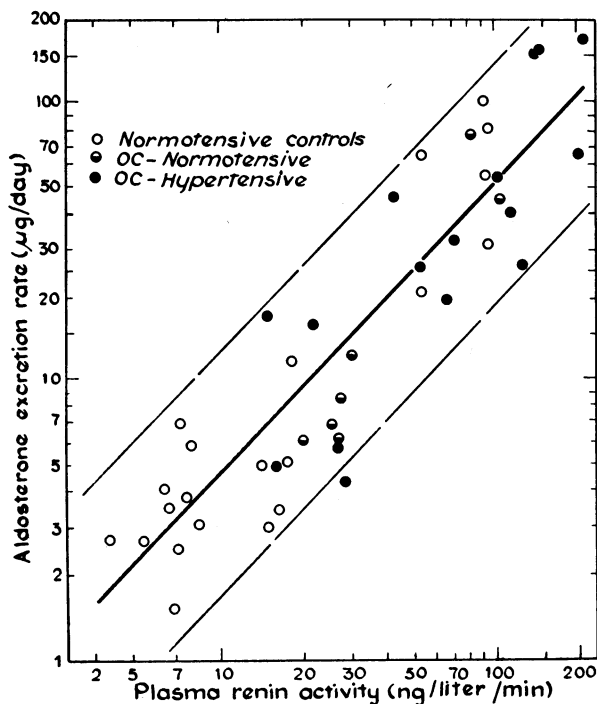


FIGURE 1 Relation between PRA and aldosterone excretion in normotensive controls (group 1) and patients receiving estrogen-gestagen (group 3b). ○ = normotensive control; ● = normotensive receiving oral contraceptive; ● = hypertensive receiving oral contraceptive. For all cases, the correlation coefficient $r = 0.89$, slope = 1.037. For the normotensive controls, $r = 0.86$, slope = 1.034. Broken, light lines are 95% confidence limits for observations on normotensive controls. The heavy line is regression computed for each group.

"Low PRA" was defined as being clearly below the normal range of PRA in all observations made during the low-sodium diet. As there was considerable overlap with the normal series on a high-sodium intake, this group could also be characterized as "unresponsive" to sodium depletion. Our criteria for "low PRA" agree with those of Cohen, Conn, and Rovner (19).

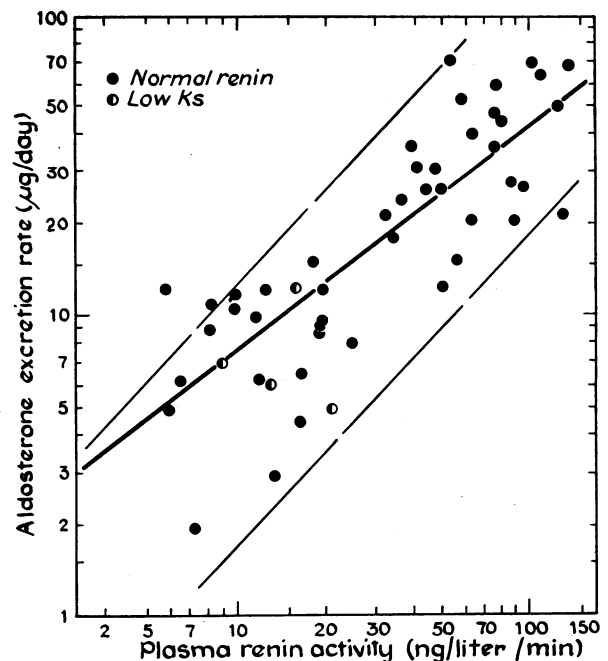


FIGURE 2 Relation between PRA and aldosterone excretion in hypertensive patients with normal PRA (group 2). ● = hypertensive; half-filled circle = hypertensive and hypokalemic. Correlation coefficient $r = 0.82$, slope = 0.785. Broken, light lines are 95% confidence limits for observations on normotensive controls. The heavy line is regression computed for each group.

TABLE VIII
Comparison of Aldosterone Excretion Rates of Normotensive Controls and Hypertensive Patients during Sodium Loading and Sodium Deprivation

Daily sodium intake	Group	Blood pressure	PRA	Medication	N	Mean aldosterone excretion	Significance level (P) of difference between stated mean and mean of group			
							1	2	3a	3b
						<i>µg/day</i>				
>300 mEq (Day 2)	1	Normal	Normal	No	23	3.09				
	2	High	Normal	No	19	9.24	0.001			
	3a	High	High	No	11	10.96	0.001	NS		
	3b	High	High	OC	5	13.10	0.001	NS	NS	
	4	High	Low	No	11	9.07	0.001	NS	NS	NS
>300 mEq (Day 3)	1	Normal	Normal	No	23	3.09				
	2	High	Normal	No	23	8.19	0.001			
	3a	High	High	No	11	9.85	0.001	NS		
	3b	High	High	OC	8	16.29	0.001	0.001	0.05	
	4	High	Low	No	13	9.49	0.001	NS	NS	0.02
<10 mEq (Day 4)	1	Normal	Normal	No	6	38.38				
	2	High	Normal	No	18	35.08	NS			
	3a	High	High	No	6	39.23	NS	NS		
	3b	High	High	OC	5	104.85	0.0125	0.001	0.005	
	4	High	Low	No	7	15.72	0.001	0.005	0.001	0.001
<10 mEq (Day 5)	1	Normal	Normal	No	10	46.40				
	2	High	Normal	No	19	37.41	NS			
	3a	High	High	No	9	48.74	NS	NS		
	3b	High	High	OC	4	102.57	0.01	0.001	0.05	
	4	High	Low	No	9	17.66	0.001	0.001	0.01	0.001

PRA = plasma renin activity; N = number of observations; OC = oral contraceptive; NS = not significant.

TABLE IX
Comparison of Aldosterone Secretion Rates of Normotensive Controls and Hypertensive Patients during Sodium Loading and Sodium Deprivation

Daily sodium intake	Group*	N	Aldosterone secretion rate		Significance level (<i>P</i>) of difference between stated mean and mean of group			
			Mean	±SEM	1	2	3a	3b
			µg/day					
>300 mEq (Day 2)	1	14	32.7	±2.9				
	2	6	98.4	±12.5	0.001			
	3a	4	175.8	±86.1	0.002	NS		
	3b	4	181.3	±81.5	0.002	NS	NS	
	4	7	106.3	±14.5	0.001	NS	NS	NS
10 mEq (Day 3)	1	1	512.0					
	2	10	399.4	±77.0				
	3a	8	370.4	±48.9		NS		
	3b	5	533.0	±152.5		NS	NS	
	4	10	208.5	±26.6		0.02	0.005	0.005
10 mEq (Day 5)	1	6	673.4	±133.7				
	2	10	333.6	±43.1	0.005			
	3a	9	455.3	±84.2	NS	NS		
	3b	3	406.0	±79.2	NS	NS	NS	
	4	5	191.4	±28.1	0.005	0.025	0.0125	0.0125

* See Table VIII for definition of groups and abbreviations.

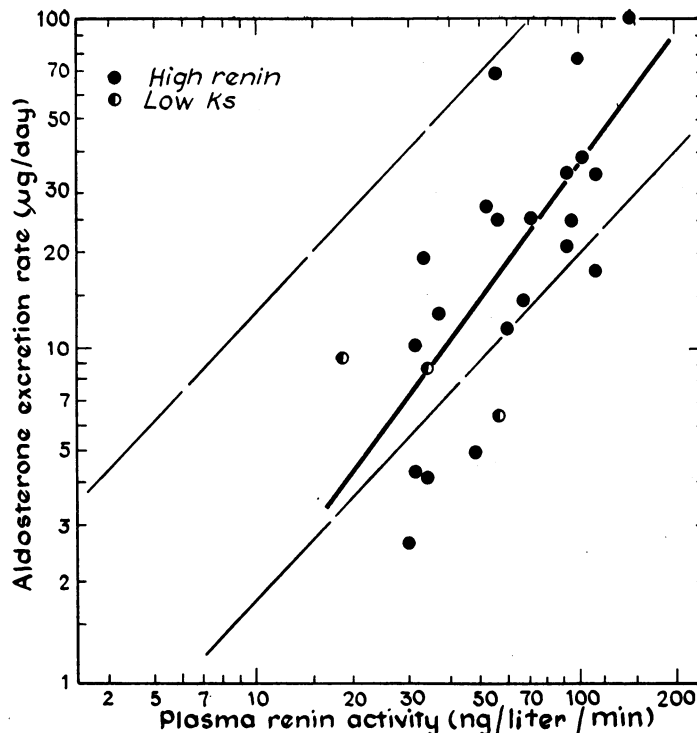


FIGURE 3 Relation between PRA and aldosterone excretion in high-renin, hypertensive patients (group 3b). ● = hypertensive; half-filled circle = hypertensive and hypokalemic. Correlation coefficient $r = 0.67$, slope = 1.322. Broken, light lines are 95% confidence limits for observations on normotensive controls. The heavy line is regression computed for each group.

Relation between aldosterone excretion and PRA

Normotensive controls (group 1). Aldosterone excretion rate showed a strong, positive correlation ($r = 0.89$) with PRA in the normotensive controls. Values of PRA in blood drawn from standing subjects are shown in Fig. 1 and have been used in calculating correlations with aldosterone.

Hypertension with normal PRA (group 2) or high PRA (group 3a). As shown in Table VIII, mean aldosterone excretion in these hypertensive patients was significantly higher than in normotensive controls during sodium loading. When dietary sodium was reduced below 10 mEq/day, aldosterone excretion increased to a normal level. Aldosterone excretion and PRA showed a significant, positive correlation (Figs. 2 and 3). The slopes of the regression lines did not differ significantly from normal, and almost all individual data points fell within the 95% confidence limits of the observations on normotensive controls.

Hypertension with high angiotensinogen and high PRA (group 3b). Patients taking combinations of estro-

gen and gestagen had the highest average PRA and aldosterone levels of any group, both during salt loading and after sodium deprivation (Table VIII). The relationship between PRA and aldosterone excretion was similar to that in the normotensive controls (Fig. 1). Individual observations were consistently within the 95% confidence limits of the normotensive series, and the regression lines were virtually identical.

Hypertension with low PRA (group 4). Aldosterone excretion was above normal in 11 of the 13 patients on high-sodium intake. On the 10 mEq sodium diet, aldosterone excretion rose only slightly, reaching a level far below the averages observed in the other normotensive and hypertensive patients (Table VIII). The correlation between aldosterone and PRA was weak ($r = 0.189$), and the slope of the regression was significantly below that for normal and hypertensive groups 1–3. Hypokalemia occurred frequently in patients with inappropriately high aldosterone excretion rates (Fig. 4).

Primary aldosteronism and idiopathic adrenal hyperplasia (group 5). This group was characterized by very low PRA, aldosterone excretion rates consistently

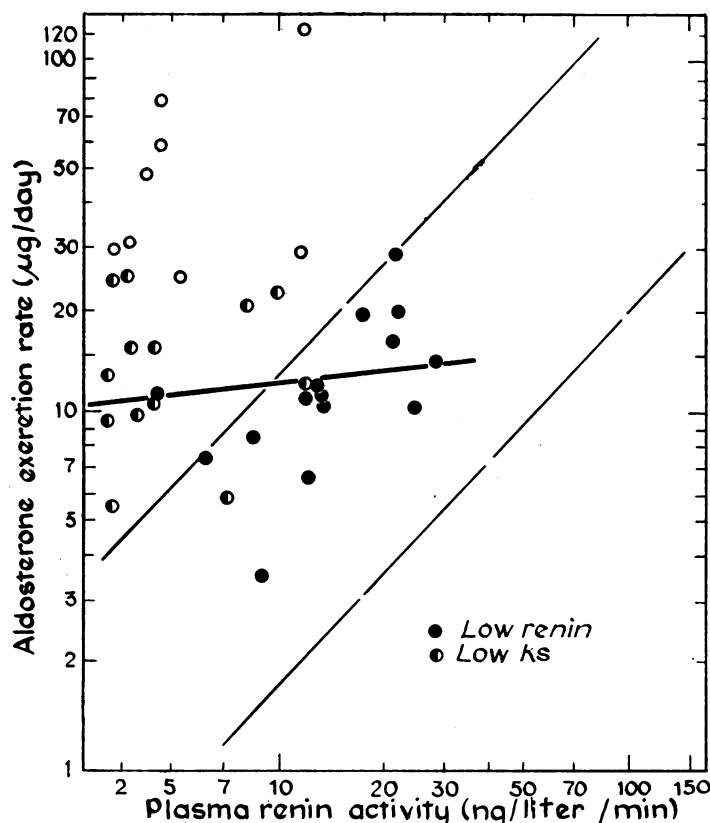


FIGURE 4 Relation between PRA and aldosterone excretion in low-renin, hypertensive patients. ● = hypertensive; half-filled circle = hypertensive and hypokalemic (group 4); ○ = primary aldosteronism or idiopathic adrenal hyperplasia (group 5). Correlation coefficient (group 4) $r=0.19$, slope = 0.099. Broken light lines are 95% confidence limits for observations on normotensive controls. The heavy line is regression computed for each group.

above 20 $\mu\text{g/day}$ (Tables VI and VII), and a low serum potassium concentration after sodium loading (Appendix F). The normal correlation between PRA and aldosterone excretion was lacking (Fig. 4).

Aldosterone secretion rate

Aldosterone secretion rates in the normotensive control group varied inversely with sodium intake. The mean secretion rate in normotensive controls taking between 100 and 150 mEq sodium per day was 102 μg , whereas in those taking between 150 and 230 mEq it was 82.8. In the normotensive controls taking 300 mEq sodium or more per day, there was no difference between the active and inactive groups, the means being respectively 32.0 and 32.1 $\mu\text{g/day}$. On a 10 mEq sodium diet, secretion rate increased to a mean of 673 $\mu\text{g/day}$.

In the hypertensive patients on a high sodium intake, aldosterone secretion rates were significantly higher than in the normotensive controls (Table IX). During sodium deprivation, the low-renin hypertensive patients (group 4) had distinctly lower aldosterone secretion than either normal controls or any other hypertensive group. By the 5th day of the low-sodium diet, the average hypertensive patient with normal plasma renin activity secreted less aldosterone than the normotensive control average.

The fraction of labeled aldosterone excreted as the acid-hydrolyzable conjugate was $10.1 \pm 0.56\%$ in 19 normotensive controls. The 48 hypertensive patients excreted 8.8% of labeled aldosterone as this conjugate. Groups 3a and 4 excreted the least (8.4% and 8.36%) and group 3b excreted the highest fraction (10.2%) of the acid-hydrolyzable conjugate.

DISCUSSION

Previous reports have described the relationship between clinically recognizable forms of hypertension and the level of aldosterone excretion or secretion (1-9, 21). Higher than normal secretion rates have been observed in primary aldosteronism, in malignant hypertension, and in some cases of renovascular hypertension. In benign, essential hypertension, aldosterone secretion has been considered to be normal or increased. In the present report, we have measured aldosterone secretion and plasma renin activity in normotensive controls and in patients with benign hypertension, both on a high and a low intake of sodium. Our aim is to define the circumstances in which aldosterone secretion may be abnormal and to suggest the nature of the disordered regulation.

When normal men ingest above 300 mEq of sodium chloride per day, aldosterone secretion rate falls to very low levels (mean 32.7 $\mu\text{g/day}$), and excretion rates decline to 5 μg or less per day. Under similar conditions, between 70 and 80% of patients with benign, essential hypertension continue to excrete more than 5 $\mu\text{g/day}$. The average secretion rates in essential and other forms of benign hypertension are 3-6 times the normal rate on the high-sodium intake.

When sodium intake was restricted to 10 mEq/day, aldosterone secretion increased as expected in the normotensive controls. Patients with hypertension had a much greater range than the normal group. In the patients with low plasma renin activity, aldosterone secretion was much below the normal range on the low-sodium diet. Patients with high plasma renin activity, especially those taking oral contraceptives, had unusually large increases in aldosterone secretion during sodium depletion. It seems likely that much of the variation in aldosterone secretion and excretion among patients on the low-sodium intake can be related to variation in the plasma renin activity.

Patients with normal or increased PRA have a normal relationship between PRA and aldosterone secretion. In these hypertensive patients, high PRA could account for the increase in basal aldosterone production. In the low-renin hypertensives, however, the smaller changes in plasma renin activity were not accompanied by corresponding changes in aldosterone production. Another factor must be assumed to explain abnormal secretion rate in these circumstances, unless a completely different relationship between angiotensin release and aldosterone production exists (22). The other factor is not ACTH, as judged from the normal levels of plasma cortisol and urinary 17-hydroxycorticoids found in the low-renin patients.

The state of body potassium and serum potassium concentration must also be taken into account. Hypokalemia is uncommon in these cases, it is not associated

with unusually high aldosterone secretion. Ledingham, Bull, and Laragh (11) described low aldosterone production and high plasma renin activity in a small group of hypertensive patients, and found that a normal relationship between aldosterone and plasma renin activity was restored after giving potassium salts.

A different situation exists in patients with low plasma renin activity, in whom hypokalemia occurs most commonly at high levels of aldosterone production. Hyperaldosteronism is clearly present when secretion rate exceeds 200 $\mu\text{g/day}$. Other patients with hypokalemia have secretion rates below 200 μg , but higher than the usual hypertensive patient's nonsuppressible secretion rate of about 100 $\mu\text{g/day}$. Replacement of the potassium deficit may raise aldosterone production rate into a range compatible with the diagnosis of primary aldosteronism or idiopathic adrenal hyperplasia (23, 24).

There remains a group of patients with essential hypertension and low plasma renin activity, who are normokalemic, but whose aldosterone production, at the upper limits of normal, seems out of proportion to the low PRA. Woods, Liddle, Stant, Michelakis, and Brill (25) have described similar patients who secrete an inappropriate quantity of adrenal mineralocorticoid, who have higher extracellular fluid volume than other hypertensive patients, and who have a greater fall in blood pressure when an inhibitor of adrenal biosynthesis, glutethimide, is administered. These patients are frequently salt losers on a low-sodium regime, as they fail to increase aldosterone production or reduce sodium excretion normally during sodium deprivation (13).

These observations and hypotheses point out the need for further study of control mechanisms not well understood at present. What factors control the release of renin and the generation of angiotensin in plasma, and why do many patients with benign, essential hypertension fail to suppress PRA and aldosterone production normally after heavy sodium chloride loads? If the renin-angiotensin system is not responsible for the sustained aldosterone secretion in patients with low PRA, what underlies the nonsuppressible release of aldosterone, and possibly other corticosteroids, in the patient without an adrenal adenoma?

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APPENDIX
Other Clinical Data

PRA	Number and sex of patients	Age	Serum creatinine	Blood pressure
		yr	Mean, mg/100 ml	Mean, mm Hg
A. Benign, essential hypertension				
Normal	13 (7F + 6M)	41.4 ± 3.2*	1.02 ± 0.07	$\frac{165 \pm 6.2}{103 \pm 3.2}$
High	6 (5F + 1M)	37.3 ± 5.3	0.92 ± 0.08	$\frac{157 \pm 7.5}{102 \pm 5.4}$
Low	6 (3F + 3M)	56.0 ± 4.1	1.03 ± 0.09	$\frac{177 \pm 16.1}{106 \pm 11.4}$
B. Renal artery stenosis				
Normal	2 (1F + 1M)	42 to 44	0.80	$\frac{150}{94}$
High	3 (3F)	39 to 75	0.97	$\frac{167}{98}$
C. Parenchymatous renal disease				
Normal	2 (1F + 1M)	18 to 24	1.55	$\frac{144}{98}$
Low	1 (1F)	30	0.90	$\frac{168}{110}$
D. Anomaly of kidneys or urinary tract				
High	2 (1F + 1M)	13 to 48	1.05	$\frac{174}{115}$
Low	3 (2F + 1M)	26 to 55	0.87	$\frac{150}{97}$
E. Hypertension (In patients taking oral contraceptives)				
High	8F	31.1 ± 2.9	0.89 ± 0.09	$\frac{176 \pm 5.0}{114 \pm 3.7}$
(Renin substrate high) (In patients after discontinuing oral contraceptives)				
Normal	6F	38.0	0.88 ± 0.04	$\frac{152 \pm 4.2}{90 \pm 3.2}$
High	1F	25.0	1.0	$\frac{135}{68}$
Low	2F	30 to 35	0.90	$\frac{139}{96}$
F. Hyperaldosteronism, due to adenoma or idiopathic hyperplasia of adrenal cortex				

Group 4 or 5: low plasma renin activity

Case (Entry)	Age/Sex	Serum creatinine	Blood pressure	Serum potassium (on high Na intake)	Aldosterone suppression	Subsequent follow-up
19(1)	49/M	1.2	170/120	3.2	Yes	(BP and Ks controlled on spironolactone)
(2)		(3 months later)		3.5	No	
20(1)	45/F	0.8	190/123	2.7	No	(Adenoma removed, BP normal postop)
69(1)	44/M	1.2	172/118	3.5	No	(Nodular hyperplasia, bilateral adrenalectomy)
(2)		(3 months later)		3.2	No	(BP 130-155/90-100 postop)
81(1)	48/F	0.8	194/115	2.9	Yes	(BP and Ks controlled on spironolactone)
(2)		(5 months later)		2.8	No	
82(1)	62/M	1.6	200/100	2.5	No	(Ks controlled, BP not controlled on spironolactone)

* Mean and standard error of the mean.

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