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Regulation of plasma aldosterone concentration in anephric man and renal transplant recipients

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Regulation of plasma aldosterone concentration in anephric man and renal transplant recipients. Regulatory factors controlling plasma aldosterone in the anephric state were further examined in bilaterally nephrectomized patients and renal transplant recipients. The effect of supine and upright posture on the concentration of plasma aldosterone, and the possible role of potassium in these responses in the anephric patients, was studied on the first and either the third or fourth day post-dialysis (anephric patients) and during periods of high and low sodium intake (renal transplant recipients). As previously reported, a significant correlation between plasma aldosterone and serum potassium concentration ($r=0.871$, $P<0.001$) could be demonstrated in anephric patients. In addition, the present studies demonstrate that in a single anephric individual, changes in serum potassium concentration are associated with concordant alterations in plasma aldosterone concentration (r value for Δ plasma aldosterone concentration in anephric patients on the third or fourth day post-dialysis was 0.911, $P<0.005$). Changes in posture from supine to upright produced no change in the concentration of plasma aldosterone in the anephric patients that could not be attributed to variations in the serum potassium concentration. In contrast, the plasma aldosterone concentration in renal transplant recipients increased significantly after two hours of ambulation during both high and low sodium intake, and was correlated with plasma renin activity (PRA). These studies demonstrate that plasma aldosterone, in the absence of the kidneys, is unresponsive to postural variation under conditions in which significant changes in plasma aldosterone concentrations are observed in renal transplant recipients. Thus, additional evidence indicating that changes in potassium rather than volume-related stimuli are the primary regulator of plasma aldosterone in anephric patients is provided.

Régulation de la concentration plasmatique d'aldostérone au cours de l'anéphrie et après la transplantation rénale. Les facteurs régulateurs contrôlant la secrétion d'aldostérone au cours de l'anéphrie ont été étudiés chez des malades ayant subi une néphrectomie bilatérale et chez des transplantés. L'effet de la position couchée ou debout sur la concentration plasmatique d'aldostérone et le rôle possible du potassium dans ces réponses chez le malade anéphrique ont été étudiés le premier et le troisième ou quatrième jour après dialyse (malades anéphriques) et durant des périodes de régime riche puis pauvre en sodium (receveurs de reins transplantés). Ainsi que nous l'avons antérieurement rapporté il existe une corrélation significative entre les concentrations plasmatiques d'aldostérone et de potassium ($r=0{,}871$; $P<0{,}001$) chez le malade anéphrique. De surcroît, l'étude actuelle démontre que chez un même sujet anéphrique les modifications de la concentration du potassium sont associées à des modifications concordantes de la concentration plasmatique d'aldostérone (le r de la corrélation Δ du potassium plasmatique avec Δ d'aldostérone plasmatique chez le sujet anéphrique le troisième ou le quatrième jour post dialyse est égal à 0,911; $P<0{,}005$). Le passage de la position couchée à la position debout ne produit pas de modification de l'aldostérone plasmatique, chez les sujets anéphriques, qui ne pourraient être attribués aux modifications du potassium plasmatique. Al'opposé, l'aldostérone plasmatique chez les transplantés augmente significativement après 2 heures d'ambulation, que le régime soit riche ou pauvre en sel, et elle est correlée avec l'activité rénine plasmatique. Ces résultats démontrent que la secrétion d'aldostérone, en l'absence de reins, ne répond pas auxh modifications posturales dans des conditions où des modifications significatives de la concentration plasmatique d'aldostérone sont observées chez les sujets transplantés. Ainsi des arguments supplémentaires indiquent que les modifications de potassium, plus que des stimuli volémiques, sont le facteur primaire de la régulation de la secrétion d'aldostérone chez l'anéphrique.

In previous studies on bilaterally nephrectomized patients, we observed a significant correlation between the concentration of plasma aldosterone and the serum potassium concentration but we could not demonstrate consistent changes in the concentration of plasma aldosterone in response to changes in posture and sodium balance [1]. Recently, Mitra et al [2] reported an increase in the concentration of plasma aldosterone in anephric patients after two hours of quiet standing associated with a significant reduction of mean arterial blood pressure. In a preliminary communication, McCaa et al [3] also reported an increase in the concentration of plasma aldosterone in

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anephric patients following acute sodium and volume depletion produced by hemodialysis. However, gradual volume depletion produced by hypertonic peritoneal dialysis was not associated with an increase in the concentration of plasma aldosterone in the studies of Mitra et al [2].

In the present studies, we have extended our observations on bilaterally nephrectomized patients and have examined the role of potassium in any changes in the concentration of plasma aldosterone noted in relation to postural variation. In addition, since studies on renal transplant recipients have shown that renin is released by the transplanted kidney [4–6] and that renin responses to changes in posture and sodium intake resemble those of normal individuals [7–9], we have studied the effects of upright posture and ambulation on the concentration of plasma aldosterone in a group of transplant recipients and have compared the responses noted to those of the anephric patients who have no detectable PRA, or, at least, in whom the renin-angiotensin system appears to be functionally absent.

Methods

Studies on anephric patients. Studies were performed on 12 anephric patients, five females and seven males, ranging in age from 15 to 52 years. All patients, with one exception (T.G.), were studied both on the first day postdialysis and the third or fourth day postdialysis. The patients were studied on both occasions while in the supine position, before arising in the morning, and after two hours of normal ambulation. Dietary sodium and potassium intake in the interval between the studies (first day to third or fourth day postdialysis) was only moderately restricted; change in body weight and serum sodium concentration served as indices of sodium intake. In the two-hour interval between the supine and postambulatory studies, the patients remained fasting. The techniques employed in the collection of blood samples and separation of plasma for determinations of PRA and plasma aldosterone concentration have been described previously [1]. Blood samples were also obtained for determination of serum potassium concentration (supine and postambulatory).

Studies on renal transplant recipients. Eleven renal transplant recipients, five females and six males, were studied; the age range was 16 to 53 years. The post-transplant interval prior to the studies was 3 to 17 months. Seven patients received kidneys from cadaveric donors and four received kidneys from a sibling. The prednisone dosages were 15 or 20 mg/day for all recipents of cadaveric kidneys and 10 mg/day for one recipient of a sibling kidney. The other recipients of sibling kidneys were treated with azathioprine only. All patients were studied while on a high sodium intake (regular diet plus 6 g of sodium chloride per day for five days) and on the fifth day of a period of restricted sodium intake (less than 17 mEq of sodium per day). The estimated potassium intake in both periods was 60 to 80 mEq per day. Blood samples were obtained at the end of both study periods for determination of PRA and plasma aldosterone concentration in the supine position and after two hours of normal ambulation. Additional blood samples were collected for determinations of serum sodium, potassium and creatinine concentrations.

Analytical methods. Analytical methods and sensitivities have been described previously [1, 10]. PRA in six plasma samples from three anephric patients (A.D., D.J. and D.W.) was determined by bioassay. All the other plasma samples were analyzed for PRA by radioimmunoassay. For statistical purposes, detectable PRA lower than 0.2 ng angiotensin I generated/ml plasma/hr and plasma aldosterone lower than 0.5 ng/100 ml plasma are arbitrarily reported as 0.2 ng and 0.5 ng respectively.

Results

Studies on anephric patients. Data on PRA, plasma aldosterone concentration and serum potassium concentration are shown in Tables 1 (first day postdialysis) and 2 (third or fourth day postdialysis).[1] PRA could be detected in only one patient, H.S., on the first day postdialysis and in two patients, D.J. and B.G., on the third or fourth day postdialysis. No effect of upright posture (two hours of ambulation) on the concentration of plasma aldosterone (supine vs. upright) could be demonstrated on either the

Table 1. Data from anephric patients studied on the first day postdialysis

Patient	PRA *ng/ml/hr*		Plasma aldosterone *ng/100 ml*		Serum K *mEq/liter*	
	Supine	Upright	Supine	Upright	Supine	Upright
A.D.	ND	ND[a]	0.5	0.5	4.6	5.0
D.J.	ND[a]	ND[a]	0.6	0.6	3.8	—
E.S.	ND	ND	1.0	1.3	4.8	4.8
H.S.	ND	0.2	0.8	0.5	—	4.4
D.W.	ND[a]	ND[a]	2.8	2.7	5.1	4.8
P.C.	ND	ND	1.8	1.2	4.7	4.9
R.A.	ND	ND	0.5	3.4	4.6	3.1
B.G.	ND	ND	2.3	3.5	4.4	5.3
T.G.	ND	ND	3.7	5.2	3.5	3.4
J.W.	ND	ND	1.6	0.9	4.1	3.9
Mean			1.6	2.0	4.4	4.4
SD			±0.9	±1.6	±0.6	±0.9

ND = PRA not detectable by the assay procedures.
[a] PRA determined by bioassay (ng angiotensin II formed/ml plasma/hr).

[1] Data from the studies on A.D., D.J., E.S., H.S., D.W., H.G. and J.Ba. were previously reported [1]. Only the studies (first day or third or fourth day postdialysis) in which both supine and postambulatory values were obtained are included in the present report.

Table 2. Data from anephric patients studied on the third or fourth day postdialysis

Patient	PRA *ng/ml/hr*		Plasma aldosterone *ng/100 ml*		Serum K *mEq/liter*	
	Supine	Upright	Supine	Upright	Supine	Upright
H.G.	ND	ND	0.5	1.0	4.9	—
D.J.	3.0[a]	ND	6.6	10.9	6.0	5.9
E.S.	ND	ND	3.9	3.9	5.0	4.5
J.Ba.	ND	ND	41.4	60.2	6.9	7.7
D.W.	ND	ND	10.4	8.3	6.3	—
P.C.	ND	ND	15.3	2.3	6.0	4.8
R.A.	ND	ND	17.0	12.5	6.4	5.1
B.G.	ND	0.5	15.6	9.5	5.5	5.0
J.W.	ND	ND	1.4	4.6	5.1	5.2
Mean			12.5	12.6	5.8	5.5
SD			±12.6	±18.3	±0.6	±1.1

ND = PRA not detectable by the assay procedures.
[a] PRA determined by bioassay (ng angiotensin II formed/ml plasma/hr).

first day postdialysis ($P>0.2$) or the third or fourth day postdialysis ($P>0.6$). However, the concentrations detected on the third or fourth day postdialysis, compared to those in the same patients on the first day postdialysis, were significantly increased (supine, $P<0.02$; upright, $P<0.01$).

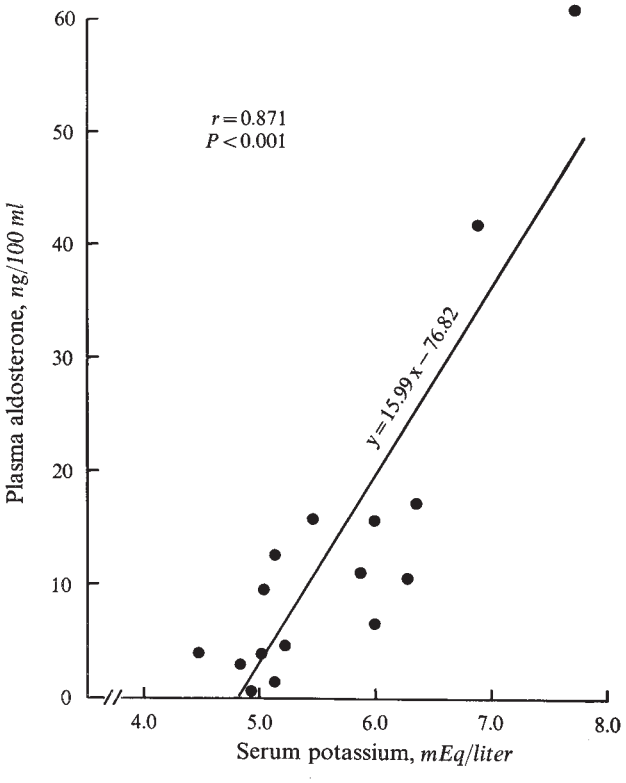

Fig. 1. *Correlation of plasma aldosterone concentration with serum potasssium concentration, supine and postambulatory values, on the third or fourth day postdialysis.*

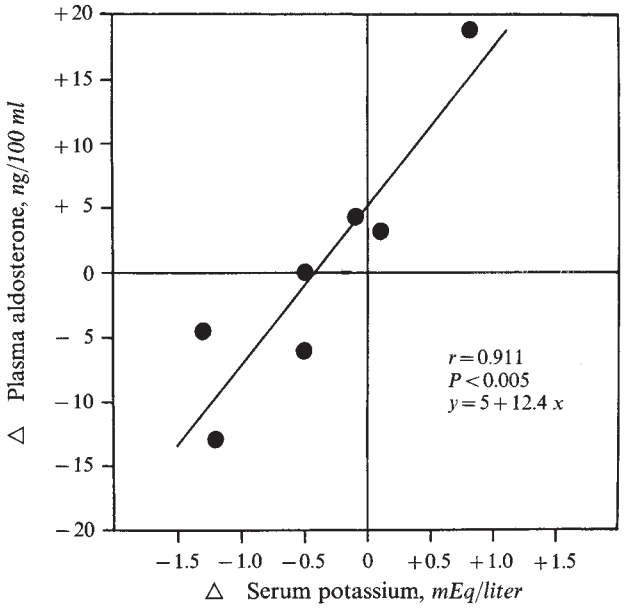

Fig. 2. *Differences between supine and postambulatory plasma aldosterone concentrations on the third or fourth day postdialysis correlated with the differences between the supine and postambulatory serum potassium concentrations.*

This increase in the concentration of plasma aldosterone occurred despite an increase in body weight (0.9, SEM ± 0.2 kg in the patients with paired data shown in both Table 1 and Table 2).

The serum potassium concentration in the supine position increased significantly between the first day postdialysis and the third or fourth day postdialysis ($P<0.005$). After two hours of ambulation, the serum potassium concentration was not significantly altered (first day, $P>0.7$; third or fourth day, $P>0.2$), although individual variations in the concentration between supine and postambulatory patients were greater on the third or fourth day postdialysis than on the first day postdialysis. As shown in Fig. 1, there was a highly significant correlation ($r=0.871$, $P<0.001$) between the serum potassium concentrations (supine and upright) and the plasma aldosterone concentrations (supine and upright) on the third or fourth day postdialysis. More convincing evidence that serum potassium concentration is a major factor in the regulation of plasma aldosterone concentration is obtained by comparing changes in serum potassium concentration in the individual anephric patient with corresponding changes in plasma aldosterone concentration. The correlation between the changes in serum potassium concentration and the corresponding changes in plasma aldosterone concentration in each anephric patient for whom complete data are available in Table 2 (Fig. 2) is highly significant ($r=0.911$, $P<0.005$), indicating that, in the anephric individual, both increases and decreases in serum potassium concentration are associated with concordant changes in plasma aldosterone concentration. These correlations were not demon-

Table 3. Data from renal transplant recipients studied while on a high sodium intake

Patient	PRA *ng/ml/hr*		Plasma aldosterone *ng/100 ml*		Serum K *mEq/liter*	Serum creatinine *mg/100 ml*	Body weight *kg*
	Supine	Upright	Supine	Upright			
J.Br.	0.2	3.8	1.6	8.0	3.9	1.3	60.9
D.W.	0.2	1.4	0.6	0.5	4.0	1.5	40.0
S.M.	ND	ND	4.2	2.8	4.2	1.0	63.2
F.A.	0.5	2.3	8.7	7.7	4.0	1.3	96.0
A.S.	ND	2.9	—	37.5	3.3	1.1	76.9
D.M.	0.3	1.4	2.3	17.6	2.8	1.0	63.8
R.A.	0.5	2.4	1.3	21.0	3.9	1.0	79.4
P.K.[a]	ND	0.6	4.0	34.0	4.5	1.0	44.0
M.C.[a]	0.2	0.2	2.4	0.5	4.6	1.4	54.3
P.C.[a]	0.2	1.3	2.6	26.2	4.3	0.9	68.9
H.G.[a]	—	0.2	3.4	33.8	5.1	1.0	44.2
Mean	0.2	1.5	3.1	17.2	4.1	1.1	62.9
SD	±0.16	±1.3	±2.2	±14.3	±0.7	±0.3	±16.9

ND = PRA not detectable.
[a] Recipients of sibling kidneys.

Table 4. Data from renal transplant recipients studied while on a low sodium intake

Patient	PRA *ng/ml/hr*		Plasma aldosterone *ng/100 ml*		Serum K *mEq/liter*	Serum creatinine *mg/100 ml*	Body weight *kg*
	Supine	Upright	Supine	Upright			
J.Br.	3.5	18.9	4.0	50.0	4.3	1.2	59.7
D.W.	1.3	4.5	2.0	7.0	3.5	1.5	39.7
S.M.	1.7	2.2	4.1	48.0	4.1	1.0	61.3
F.A.	1.2	2.7	8.6	9.4	4.4	1.4	90.1
A.S.	1.2	2.6	30.9	53.0	4.0	0.9	74.3
D.M.	1.6	2.2	20.1	37.5	2.9	1.0	61.6
R.A.	0.8	3.0	2.3	48.5	4.1	1.1	78.4
P.K.[a]	2.4	2.2	22.0	70.7	4.4	1.1	42.6
M.C[a]	0.9	1.6	14.5	31.0	4.4	1.6	52.2
P.C.[a]	1.3	3.2	39.5	34.2	3.9	1.0	66.3
H.G.[a]	0.6	0.7	32.1	65.3	4.7	1.0	43.7
Mean	1.5	4.0	16.4	41.3	4.1	1.2	60.9
SD	±0.7	±5.0	±13.6	±20.2	±0.7	±0.3	±15.9

[a] Recipients of sibling kidneys.

strable in the presence of lower serum potassium and plasma aldosterone concentrations on the first day post-dialysis.

Studies on renal transplant recipients. Data from the studies on the renal transplant recipients are shown in Tables 3 and 4. The increase in PRA and plasma aldosterone concentration induced by upright activity was significant in both the period of high sodium intake (PRA, $P<0.005$; plasma aldosterone, $P<0.01$) and the period of low sodium intake (PRA, $P<0.05$; plasma aldosterone, $P<0.005$). In addition, the mean PRA and plasma aldosterone concentration in the period of low sodium intake was significantly higher in both the supine position (PRA, $P<0.001$; plasma aldosterone, $P<0.025$) and after two hours of ambulation (PRA, $P<0.05$; plasma aldosterone, $P<0.001$) than in the period of high sodium intake. The relationship between mean PRA and plasma aldosterone, supine and upright on high and low sodium intake, is shown in Fig. 3. Further examination of the relationship between PRA and plasma aldosterone using the ungrouped data ($N=42$) in both periods of high and low sodium intake shows a significant linear correlation ($r=0.329$, $P<0.05$). Spearman's rank correlation coefficient for the same ungrouped data was 0.482, $P<0.005$.

There was no significant difference between the serum potassium concentrations in the periods of high and low sodium intake. All patients exhibited excellent allograft function, as shown by the serum creatinine concentration

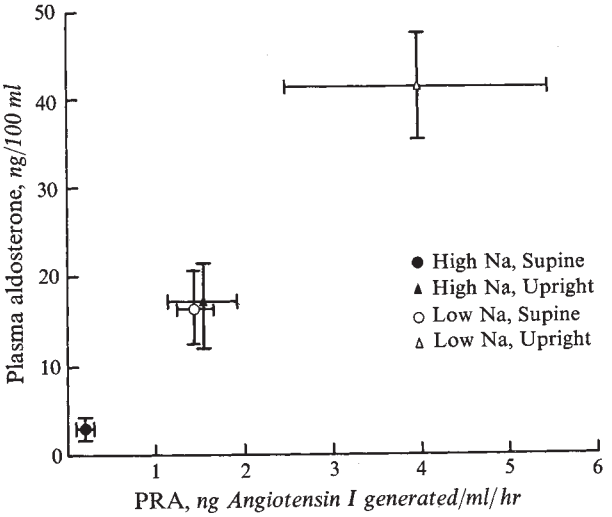

Fig. 3 *Relationship of plasma aldosterone concentration to PRA in renal transplant recipients.* Data shown are means ± SEM.

of 1.1± SD 0.3 mg/100 ml in the period of high sodium intake and 1.2± SD 0.3 mg/100 ml in the period of low sodium intake. There was no demonstrable difference between cadaveric and sibling allograft recipients or between patients receiving low doses of prednisone and those treated with azathioprine alone.

Discussion

In our earlier studies on anephric patients, including seven of the 12 subjects whose data are presented in this report, we identified three patients who exhibited an increase in the concentration of plasma aldosterone after two hours of ambulation, although, for the group, differences between the supine and postambulatory concentrations were not significant [1]. The additional data provided by the larger group of patients included in the present studies corroborate these findings; mean concentrations of plasma aldosterone, supine and postambulatory on the third or fourth day postdialysis, were identical (supine, 12.5 ng/100 ml; upright, 12.6 ng/100 ml). Moreover, the highly significant correlation between the change in plasma aldosterone concentration and the change in serum potassium concentration in individual patients on the third or fourth day postdialysis (Fig. 2) suggests that any change in the concentration of plasma aldosterone occurring in the present group of patients during periods of altered posture and activity may be attributed to individual variations in the serum potassium concentration.

A 0.5 mEq/liter or greater change (increase or decrease) in the serum potassium concentration after two hours of ambulation was noted in five of the patients studied on the third or fourth day postdialysis. Since there was no change in potassium balance, these changes in serum potassium concentration must have reflected a net movement of potassium either into or out of cells. Two factors that might have contributed to an increase in the serum potassium concentration during ambulation are the increase in skeletal muscle activity and the glycogenolytic effect of epinephrine. The latter, however, could also produce an increase in the plasma glucose concentration, which, by stimulating an insulin response, would lower the serum potassium concentration by shifting potassium into cells.

Regardless of the actual mechanism, the cells most likely to be involved in this postulated shifting of potassium are those of the liver and skeletal muscles. Whether intracellular potassium in the zona glomerulosa may have changed reciprocally or directly with the serum potassium concentration in these studies is not known. However, studies by Baumber et al [11] have suggested that aldosterone biosynthesis and adrenal cortical tissue potassium content are directly related. Thus, it seems likely in our studies that intracellular zona glomerulosa potassium concentration may have followed the serum potassium concentration and that changes in plasma aldosterone concentration during two hours of ambulation may have been related to changes in adrenal cortical tissue potassium content. Obviously, additional studies are needed to further elucidate this mechanism.

Studies by Cannon, Ames and Laragh have demonstrated that aldosterone secretion is stimulated by incremental changes in potassium intake, and that the magnitude of aldosterone responsiveness to potassium administration can be directly related to the prior rate of aldosterone production [12]. Thus, heightened sensitivity of the aldosterone secretory mechanism to changes in potassium might be expected in our studies on the third or fourth day postdialysis when the serum potassium and plasma aldosterone concentrations were both significantly increased. The lack of significant correlation between serum potassium and plasma aldosterone concentrations on the first day postdialysis may also be related to the fact that plasma aldosterone concentrations were frequently at or near the lower level of sensitivity of the assay.

The increase in the concentration of plasma aldosterone produced by two hours of quiet standing in the studies on anephric patients reported by Mitra et al [2] was apparently unrelated to the serum potassium concentration. However, a significant reduction in the mean arterial blood pressure during quiet standing was also noted in these studies, which raises the possibility that hepatic blood flow was reduced and that the increase in the concentration of plasma aldosterone was due to decreased metabolic clearance, and not to increased secretion of aldosterone [13]. Studies by Culbertson et al [14] have shown that quiet erect posture (75° upright tilting) may be associated with a 40 per cent reduction in hepatic blood flow in normal subjects, even in the absence of significant changes in mean arterial blood pressure. Bougas et al [15] reported that under similar conditions the metabolic clearance rate (MCR) of aldosterone was approximately halved. The change in posture from supine to quiet standing was also associated with a

23 per cent reduction in the MCR of aldosterone in the studies of Balikian et al [16]. Whether decreased metabolic clearance could explain the magnitude of the increase in plasma aldosterone concentration reported by Mitra et al [2] is uncertain. However, it seems reasonable to assume that at least a portion of this increase may have been attributable to this mechanism. This does not exclude the possibility that protracted quiet standing, in contrast with ambulation, induces changes in aldosterone secretion which are due to increased elaboration of ACTH. An increase in plasma cortisol concentration and a positive correlation between the increment in plasma cortisol and the increment in plasma aldosterone in these studies suggests that increased elaboration of ACTH may indeed play a role.

Increased sensitivity of the zona glomerulosa to ACTH after acute volume depletion induced by hemodialysis has been postulated by McCaa et al [3]. It is also possible that decreased metabolic clearance of aldosterone due to a reduction in hepatic blood flow may have contributed to the increase in plasma aldosterone concentration in these studies. Another contributing factor may have been the reduction in plasma sodium concentration (10 mEq/liter), although studies on dogs with isolated adrenals by Davis, Urquhart and Higgins [17] have suggested that larger reductions in plasma sodium concentration may be necessary to produce an increase in aldosterone production. Gradual volume depletion induced by hypertonic peritoneal dialysis, which was accompanied by an increase rather than a decrease in the plasma sodium concentration, was not accompanied by an increase in plasma aldosterone concentration in the studies of Mitra et al [2].

In contrast with the anephric patients in our studies, the renal transplant recipients significantly elevated the concentration of plasma aldosterone after two hours of ambulation during periods of both high and low sodium intake. Similar observations were reported in a preliminary communication by McCaa et al [18]. Moreover, the concentration of plasma aldosterone detected and the variations in concentration associated with postural changes were similar to the data reported previously from studies on normal individuals [1, 16, 19]. Seven of these patients had received kidneys from cadaveric donors and were treated with large amounts of prednisone in the early posttransplant period. The sibling transplant recipient who was receiving prednisone when these studies were performed (P.K.) had also received larger doses of prednisone previously during a minor episode of threatened rejection. Thus, eight of the patients studied had received prednisone in amounts that were sufficient to suppress the pituitary release of ACTH. Despite this, the plasma aldosterone concentrations and responses to varied posture and sodium intake in these patients could not be distinguished from those of the remaining three patients who had not received prednisone.

There was no correlation between the plasma aldosterone concentration and the serum potassium concentration in the renal transplant recipients. Instead, the correlation of plasma aldosterone with PRA suggests that restoration of the renin-angiotensin system results in re-orientation of the aldosterone secretory mechanism to volume-related stimuli. All of the patients had been nephrectomized several weeks or months prior to renal transplantation and, consequently, the only major source of renin was the transplanted kidney. However, the data from these and previous studies [5, 7, 8] suggest that renin is released from the transplanted kidney in what appears to be an essentially normal response to sodium restriction and upright posture. The normal pattern of response of aldosterone in these patients may therefore be attributed to the presence of the renin-angiotensin system, which distinguishes these patients from the anephric individuals whose aldosterone secretory mechanism appears to be primarily responsive to changes in potassium.

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