Influence of Acute Stimuli on Plasma Aldosterone Concentration in Anephric Man and Kidney Allograft Recipients


ABSTRACT

The response of plasma aldosterone concentration to postural variation, adrenocorticotropic hormone (ACTH), and angiotensin II was studied in five kidney allograft recipients and compared with the response observed in the same five subjects during the anephric period. Normal subjects acted as intact controls. After 2 hours of normal ambulation, plasma aldosterone levels increased in normal subjects (6.7 ± 1.6 to 22.9 ± 2.7 ng/100 ml plasma), remained unchanged in anephric patients (4.5 ± 1.0 to 5.2 ± 1.1 ng/100 ml plasma), and increased in kidney allograft recipients (6.8 ± 1.5 to 25.6 ± 1.9 ng/100 ml plasma). After ACTH administration, plasma aldosterone levels increased in normal subjects (7.5 ± 1.8 to 24.3 ± 2.5 ng/100 ml plasma), anephric subjects studied immediately after hemodialysis (16.6 ± 1.6 to 30.0 ± 2.6 ng/100 ml plasma), and kidney allograft recipients (5.0 ± 1.6 to 22.3 ± 1.4 ng/100 ml plasma). After angiotensin II infusion, plasma aldosterone levels increased in normal subjects (7.2 ± 1.8 to 42.5 ± 3.6 ng/100 ml plasma), remained unchanged in anephric subjects (8.6 ± 2.1 to 7.4 ± 1.6 ng/100 ml plasma), and increased in kidney allograft recipients (6.3 ± 1.5 to 40.2 ± 3.1 ng/100 ml plasma). In anephric man after prolonged absence of the renal renin-angiotensin system ACTH increased the rate of aldosterone secretion but angiotensin II had little effect. An intact renal renin-angiotensin system was necessary for increased aldosterone secretion in response to postural variation.

KEY WORDS angiotensin II posture ACTH renin hemodialysis adrenal cortex radioimmunoassay potassium cortisol sodium

Nephrectomized man retains the capacity to maintain a basal level of aldosterone secretion and plasma aldosterone concentration in the absence of the renal renin-angiotensin system. Recent studies from our laboratory (1) as well as studies from other laboratories (2, 3) indicate that the plasma aldosterone concentration in the anephric human being is within normal physiological limits despite the lack of kidneys to produce renin. Aldosterone secretion can be stimulated in nephrectomized man by adrenocorticotropic hormone (ACTH) (2, 4) and increased plasma potassium concentration (3, 5). Furthermore, plasma aldosterone concentration increases in nephrectomized patients during the course of hemodialysis when plasma sodium concentration is decreased even though plasma renin activity measured at the same time is always undetectable (1). On the other hand, we have not been able to demonstrate a significant increase in plasma aldosterone concentration in response to postural variation (6) or infusion of a pressor dose of angiotensin II (7) in anephric man after prolonged absence of the renal renin-angiotensin system.

The present study was designed to quantitatively evaluate changes in plasma aldosterone concentration in response to postural variation, administration of ACTH, and infusion of angiotensin II into kidney allograft recipients and to compare this response with that observed in the same subjects during the nephrectomized period. Normal subjects acted as intact controls for this study.

Methods

Five nephrectomized human subjects maintained on chronic intermittent hemodialysis while awaiting kidney transplantation were used in this study to determine the
influence of postural variation, administration of ACTH, and infusion of angiotensin II on the plasma concentration of aldosterone and cortisol. The response observed in these patients, who had been nephrectomized for 3–36 months, was compared with the response observed in the same five patients studied 6 weeks after kidney allograft transplantation. The anephric patients and the kidney allograft recipients were on diets restricted to 34 mEq/day of sodium and 60 mEq/day of potassium. Healthy informed volunteers served as intact controls for this study. The following experimental protocol was used to determine the influence of normal ambulation on plasma aldosterone concentration in normal subjects, nephrectomized patients, and kidney allograft recipients. The subjects were required to remain standing for 2 hours after having been recumbent for 2 hours. Blood samples were drawn immediately before and after 2 hours of normal ambulation. Five of the normal subjects were placed on a high-sodium diet (ad libitum diet plus 12 g/day of NaCl added to the diet in weighed capsules), and another five normal subjects were placed on a low-sodium diet (less than 20 mEq/day for 5 days). On the fifth day blood samples were collected from the normal subjects immediately before and after 2 hours of normal ambulation to determine the effect of postural variation on plasma aldosterone concentration in normal subjects on high- and low-sodium diets.

The following experimental protocol was used for the ACTH study. Each subject was required to remain recumbent for 2 hours in the Artificial Kidney Unit before the start of the study. After a 2-hour period of quiet resting, control blood samples were collected and 250 μg of ACTH (Cortrosyn, Organon) was administered intravenously. The subjects were required to remain recumbent for the period of study. Blood samples were collected at 15-minute intervals for 1 hour after the injection. The anephric subjects were studied on two separate occasions: first while they were in the sodium-replete, volume-replete state immediately before hemodialysis and second 4 days later immediately after hemodialysis while they were in the sodium-deplete, volume-deplete state.

The following experimental protocol for the angiotensin II study was used. Each subject was required to remain recumbent in the Artificial Kidney Unit for 2 hours before the start of the study. During this time butterfly catheters were inserted into the brachial veins in both the right and left arms. The catheter in the left brachial vein was connected to a syringe filled with a solution of angiotensin II; the syringe was placed into a Harvard infusion pump to control the rate of infusion of angiotensin II. Blood pressure was measured in the subjects each minute until there was no fluctuation in the diastolic pressure for 5 minutes. A control blood sample was then collected from the butterfly catheter in the right brachial vein. Infusion of angiotensin II was then started at a rate of 2 ng/kg min⁻¹. The blood pressure was measured and recorded each minute for the next 5 minutes. At the end of 5 minutes, the rate of infusion of angiotensin II was increased by 2 ng to 4 ng/kg min⁻¹. This procedure was continued until there was a 20-mm Hg increase in diastolic pressure.
renin activity increased from 0.42 ng/ml hour$^{-1}$ to 1.5 ng/ml hour$^{-1}$ ($P < 0.01$) in response to upright posture. Figure 2 illustrates the change in plasma aldosterone concentration in response to poostural variation in five kidney allograft recipients and compares the response with that observed in the same five patients during the anephric state. Plasma aldosterone concentration averaged 4.5 ± 1.0 ng/100 ml plasma in five anephric subjects on the second day after hemodialysis in the recumbent position and did not change significantly in these anephric subjects in response to upright posture (3.2 ± 1.1 ng/100 ml plasma, $P > 0.20$). Plasma renin activity was undetectable in the nephrectomized patients.

In five kidney allograft recipients, plasma aldosterone concentration increased from 6.8 ± 1.5 ng/100 ml plasma to 25.6 ± 1.9 ng/100 ml plasma ($P < 0.01$) in response to upright posture. Plasma renin activity in the allograft recipients increased from 2.50 to 5.89 ng/ml hour$^{-1}$ ($P < 0.05$) with upright posture. As shown in Figure 2, 2 hours of normal ambulation had no effect on the plasma cortisol concentration, serum sodium concentration, or serum potassium concentration in either the anephric or the transplanted patients.

**Response to ACTH**

Figure 3 illustrates the change in plasma aldosterone concentration and plasma cortisol concentration following a single injection of ACTH into normal subjects and kidney allograft recipients. Plasma cortisol concentration increased from control levels of 13.8 ± 1.5 µg/100 ml plasma to 27.3 ± 2.1 µg/100 ml plasma ($P < 0.05$) within 15 minutes after ACTH injection in the normal subjects and reached a plateau level of 33.0 ± 3.2 µg/100 ml plasma by 1 hour. Plasma cortisol concentration did not increase in the kidney allograft recipients in response to ACTH; however, these patients were being treated with 50 mg/day of prednisone. Plasma aldosterone concentration increased from control levels of 7.5 ± 1.8 ng/100 ml plasma to 24.3 ± 2.5 ng/100 ml plasma ($P < 0.01$) within 15 minutes in the normal subjects in response to ACTH and remained elevated for 1 hour after ACTH administration. Plasma aldosterone concentration increased in the kidney allograft recipients from control levels of 5.0 ± 1.6 ng/100 ml plasma to 20.0 ± 2.7 ng/100 ml plasma ($P < 0.01$) within 15 minutes after ACTH injection. Additionally, plasma aldosterone concentration did not change in the anephric patients during the anephric state.
plasma to 22.3 ± 1.4 ng/100 ml plasma (P < 0.01) within 15 minutes and remained elevated for 1 hour. Apparently ACTH can stimulate aldosterone secretion in kidney allograft recipients without causing a concomitant increase in plasma cortisol concentration.

Figure 4 compares the effect of ACTH injection into anephric subjects during the sodium-replete, volume-replete state immediately before hemodialysis with the response exhibited 1 week later by the same subjects during the sodium-deplete, volume-deplete state immediately following hemodialysis. On both occasions, the plasma cortisol response was essentially the same. In patients studied before hemodialysis plasma aldosterone concentration was 6.5 ± 1.6 ng/100 ml plasma, and the level did not significantly increase during the first 30 minutes after injection of ACTH. At the 45-minute collection time, plasma aldosterone concentration was slightly increased to 10.2 ± 2.1 ng/100 ml plasma (P > 0.10).

Plasma aldosterone concentration was increased above predialysis levels in patients studied immediately after hemodialysis. Hemodialysis and ultrafiltration caused significant decreases in plasma sodium concentration (138.5 mEq/liter to 130.5 mEq/liter) and fluid volume (~1.5 kg), which may explain the increased plasma aldosterone concentration observed postdialysis. Administration of ACTH to these sodium-deplete, volume-deplete anephric subjects resulted in an increase in plasma aldosterone concentration from 16.6 ± 1.6 ng/100 ml plasma to 30.0 ± 2.6 ng/100 ml plasma (P < 0.05) within 15 minutes, and plasma aldosterone concentration remained elevated above control levels for the next hour.

**RESPONSE TO ANGIOTENSIN II INFUSION**

The pressor response to angiotensin II and the effect of angiotensin II infusion on plasma aldosterone concentration in normal subjects, anephric patients in various states of fluid and sodium balance, and renal allograft recipients are shown in Table 1. Normal subjects and kidney allograft recipients...
TABLE 1

Effect of Angiotensin II Infusion on Plasma Aldosterone Concentration in Normal Subjects, Nephrectomized Patients, and Kidney Allograft Recipients

<table>
<thead>
<tr>
<th>Subject</th>
<th>Average pressor dose of angiotensin II (ng/kg min⁻¹)</th>
<th>Time for pressor dose (min)</th>
<th>Control (ng/100 ml plasma)</th>
<th>After angiotensin II (ng/100 ml plasma)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>8 ± 1</td>
<td>18.5 ± 2.5</td>
<td>7.2 ± 1.8</td>
<td>42.5 ± 3.8*</td>
</tr>
<tr>
<td>Renal allograft recipients</td>
<td>9 ± 2</td>
<td>21.0 ± 3.0</td>
<td>6.3 ± 1.5</td>
<td>40.2 ± 3.1*</td>
</tr>
<tr>
<td>Anephric subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediately before hemodialysis</td>
<td>4 ± 1</td>
<td>6.0 ± 2.0</td>
<td>8.6 ± 2.1</td>
<td>7.4 ± 1.6</td>
</tr>
<tr>
<td>During hemodialysis</td>
<td>12 ± 2</td>
<td>28.0 ± 3.0</td>
<td>12.3 ± 2.5</td>
<td>12.5 ± 3.1</td>
</tr>
<tr>
<td>Immediately after hemodialysis</td>
<td>8 ± 3</td>
<td>26.0 ± 2.0</td>
<td>16.4 ± 3.1</td>
<td>13.3 ± 3.2</td>
</tr>
</tbody>
</table>

*Difference between control and experimental values is statistically significant (P < 0.05).

Recipients exhibited a similar pressor response to angiotensin II. A pressor response was obtained in the normal subjects after 18.5 ± 2.5 minutes when the rate of angiotensin II infusion was 8 ± 1 ng/kg min⁻¹. A pressor response was obtained in the renal allograft recipients after 21.0 ± 3.0 minutes when the rate of angiotensin II infusion was 9 ± 2 ng/kg min⁻¹.

The pressor response to angiotensin II by the nephrectomized subjects was variable. Immediately before hemodialysis, when the subjects were in an overhydrated, sodium-replete state, there was an increased sensitivity to angiotensin II with a pressor response being obtained after 6.0 ± 2.0 minutes when the rate of angiotensin II infusion was 4 ± 1 ng/kg min⁻¹. In contrast, immediately after hemodialysis and ultrafiltration with removal of fluid and electrolytes, the pressor response was normal and was obtained after 20.0 ± 2.0 minutes when the rate of infusion was 8 ± 3 ng/kg min⁻¹. When the anephric subjects were undergoing hemodialysis, a pressor response was obtained after 29.0 ± 3.0 minutes when the rate of infusion was 12 ± 2 ng/kg min⁻¹.

Infusion of a pressor dose of angiotensin II into normal subjects resulted in a significant increase in plasma aldosterone concentration (P < 0.05). Yet, no significant increase in plasma aldosterone concentration was observed in the anephric patients in response to angiotensin II infusion immediately before, during, or immediately after hemodialysis. Within 6 weeks after kidney transplantation, these same subjects exhibited a normal aldosterone response to angiotensin II infusion (P < 0.05).

The time course of the effects of angiotensin II infusion on plasma aldosterone and cortisol concentration in normal subjects, anephric patients immediately before hemodialysis, and renal allograft recipients is illustrated in Figure 5. Plasma cortisol concentration did not change significantly in any of the subjects in response to a pressor dose of angiotensin II. Plasma aldosterone concentration increased significantly in both the normal subjects and the renal allograft recipients (P < 0.05), but plasma aldosterone concentration did not increase in the anephric patients in response to a pressor dose of angiotensin II. Infusion of angiotensin II was stopped immediately after a pressor response was obtained. Within 25 minutes after stopping the infusion of angiotensin II in normal subjects and kidney allograft recipients, plasma aldosterone concentration was significantly diminished from...
peak values and had almost returned to control levels.

Discussion

Recent studies by several investigators (1–3, 11) have demonstrated that plasma aldosterone concentration is within normal physiological limits in the nephrectomized human being despite the lack of kidneys to produce renin. Balkian et al. (12) found a high normal plasma concentration and blood production rate of aldosterone in an anephric patient; however, aldosterone secretion and plasma aldosterone concentration did not increase in response to postural variation in this anephric patient. Subsequent studies by Bayard et al. (3) and McCaa et al. (6) confirmed this observation. In contrast, Mitra et al. (2) reported a significant increase in plasma aldosterone concentration in anephric patients in response to upright posture. However, it is important to note the differences in the experimental procedure of the present study and that of Mitra et al. (2). Mitra et al. (2) observed an increase in plasma aldosterone concentration in anephric patients after 2 hours of quiet standing (mean increment = 11.4 ng/100 ml plasma). Most of their patients required support to remain standing for 2 hours. Also, they observed a significant reduction in arterial blood pressure and a marginally significant increase in plasma cortisol concentration following 2 hours of quiet standing.

In our study of anephric subjects we did not observe a significant change in plasma concentration of sodium, potassium, cortisol, or aldosterone after 2 hours of normal ambulation. The response of plasma aldosterone concentration to postural variation was studied on three separate occasions: immediately following hemodialysis and on the first and the third day after hemodialysis. A significant decrease in plasma aldosterone concentration was observed in response to upright posture immediately after hemodialysis. However, a similar decline in plasma aldosterone concentration was observed in anephric patients remaining supine for 2 hours after hemodialysis (5). This observation suggested that the rate of aldosterone secretion stimulated by hemodialysis (1) was falling to a lower rate of secretion during the period immediately following hemodialysis. We also failed to demonstrate a significant increase in plasma aldosterone concentration in response to upright posture in anephric patients studied on the first and third days after hemodialysis. A slight rise in plasma aldosterone concentration (3 ng/100 ml plasma) was observed in 3 of 16 anephric patients. However, a 20% reduction in the metabolic clearance rate of aldosterone which may occur in changing from the supine to the upright position could account for the slight increase in plasma aldosterone concentration (12).

An increase in plasma aldosterone concentration of the magnitude reported by Mitra et al. (2) cannot be explained by a reduction in metabolic clearance rate of aldosterone alone. Perhaps the response was due to a combination of reduced metabolic clearance rate of aldosterone and increased pituitary secretion of ACTH which occurred under the stress of quiet standing.

Within 6 weeks after renal transplantation, a significant increase in plasma aldosterone concentration was observed in five kidney allograft recipients in response to postural variation. Also, plasma renin activity increased significantly in these patients after 2 hours of normal ambulation (Fig. 2). Greene et al. (13) have shown that kidney allograft recipients respond to upright posture with an increase in plasma renin activity and to sodium depletion with an increase in both plasma renin activity and urinary excretion of aldosterone. The results of the present study indicate that a functional renal renin-angiotensin system is present within 6 weeks after renal transplantation and that the renal renin-angiotensin system is necessary for a normal increase in plasma aldosterone concentration in response to postural variation.

Acute administration of ACTH has been shown to stimulate aldosterone secretion (14) and to increase urinary aldosterone excretion (15) and plasma aldosterone concentration (16). Although we observed only a slight increase in plasma aldosterone concentration in response to ACTH by the anephric patients during the sodium-replete, volume-replete state immediately before hemodialysis, there was an increased response after sodium and volume depletion by hemodialysis. Canong et al. (17) reported that sodium depletion of dogs for 5 days increased the sensitivity of the zona glomerulosa to ACTH and in a later study (18) suggested that this increased sensitivity was due to increased renin and angiotensin II production during sodium depletion since daily injections of renin also increased the sensitivity to ACTH. Palmore et al. (19) suggested that the increased sensitivity to ACTH with sodium depletion was due to hypertrophy of the zona glomerulosa during sodium depletion. The present study indicated that sodium depletion in the absence of a renal
renin-angiotensin system could render the zona glomerulosa more sensitive to ACTH. It is unlikely that hypertrophy of the zona glomerulosa could account for the increased sensitivity in the present study, since the sodium depletion was accomplished in only 12 hours. A more credible possibility is that the increased adrenocortical sensitivity to ACTH following sodium and volume depletion by hemodialysis is due to alterations in adrenal intracellular electrolyte concentration (20). Recent studies indicate that ACTH stimulation of aldosterone secretion in sodium-deplete normal man can occur at levels of ACTH insufficient to produce maximal cortisol secretion (21). In the present study increased plasma aldosterone concentration in response to ACTH in renal allograft recipients was normal, but the plasma cortisol response was greatly blunted. The kidney allograft recipients had received massive daily doses of prednisone (50 mg/day). Patients with pituitary insufficiency receiving maintenance prednisone therapy exhibit a similar response to ACTH infusion (22).

The effect of ACTH administration on plasma cortisol concentration in patients receiving prednisone is controversial. Bennett (23) reported that therapy with glucocorticoids produces atrophy of the adrenal cortices. Glucocorticoid therapy also alters pituitary histology (23, 24) and may diminish the pituitary content and secretion of endogenous ACTH (25, 26). Such treatment usually decreases endogenous cortisol secretion. Patients receiving glucocorticoids may have variable responses to exogenous ACTH depending on the particular steroid and dose administered, the duration of treatment, and the manner of administration (daily vs. alternate-day therapy) (27, 28). Our allograft recipients received 50 mg/day of prednisone at the time of testing and had been on this regimen since transplantation, for 6–8 weeks. Binder et al. (29) reported that prior administration of 15–60 mg/day of prednisone for 5–30 days significantly decreased the adrenocortical response to intravenously administered ACTH. In light of these data, our allograft recipients had been on steroid therapy long enough to demonstrate a decreased plasma cortisol response to exogenous ACTH.

The plasma cortisol concentrations were determined using the protein-binding displacement technique described by Murphy (9). Fuller's earth, which removes interfering steroids better than other agents used for separating the free and bound cortisol fractions (9), was used in this study. Our experience indicates that this method is insensitive to cortisol concentrations of less than 2 μg/100 ml plasma. Normal individuals treated with dexamethasone, 0.5 mg every 6 hours, have cortisol values of less than 2 μg/100 ml plasma, as do patients with hypoadrenalism. As shown by Figures 2–4, kidney allograft recipients had something in their plasma which gave a high blank value but was unresponsive to ACTH. Since these patients were treated with prednisone daily, 10 μg of prednisone was added to 100 ml of pooled plasma and the estimated cortisol values were not changed. However, when 10 μg of prednisolone was added to 100 ml of pooled plasma, the measured cortisol concentration increased by 93.6 ± 1.6%. This increase is comparable to that produced when 10 μg of cortisol was added to 100 ml of pooled plasma. Prednisone is rendered biologically active by conversion to prednisolone (30). Araki et al. (31) have reported that prednisolone is bound to plasma transcortin. Since the protein-binding method measures prednisolone as effectively as it does cortisol, then one can readily explain the concentration of estimated "cortisol" present in the kidney allograft recipients treated with prednisone.

Angiotensin II infusion had little or no effect on plasma aldosterone concentration in nephrectomized patients, but it acted as a potent stimulus to increase plasma aldosterone concentration in both normal subjects and kidney allograft recipients. Apparently the lack of response to angiotensin II by the anephric patients was not related to volume balance, electrolyte balance, or both, since infusion of angiotensin II before, during, or immediately after hemodialysis produced no significant change in plasma aldosterone concentration.

It is difficult to understand why angiotensin II, considered by many investigators to be the primary factor regulating aldosterone secretion under normal conditions, has little effect on aldosterone secretion in anephric man. The adrenocortical receptors or enzymes which respond to angiotensin II may become less responsive in the prolonged absence of the renal renin-angiotensin system. In the anephric patients used in our study, the renal renin-angiotensin system was absent for 3–36 months and plasma renin activity was undetectable. Other investigators, using more sensitive techniques for the determination of plasma renin activity, have demonstrated assayable renin activity in the plasma of nephrectomized men and women. Mayor et al. (32) reported that plasma renin activity in a group of anephric subjects was one-tenth of the lowest normal value and found that plasma renin activity

Circulation Research, Vol. XXXIII, September 1975
in these subjects failed to increase in response to postural variation, hemodialysis, or sodium depletion. Therefore, although plasma renin activity may not be totally absent after bilateral nephrectomy of human subjects, it appears to be decisively depressed and unresponsive to stimuli known to increase renal renin secretion.

It is of interest that in primary aldosteronism, another condition in which plasma renin activity is exceptionally low, plasma aldosterone concentration fails to increase in response to angiotensin II infusion but does increase in response to ACTH infusion (33). Following surgical removal of an aldosterone-secreting tumor, aldosterone deficiency may ensue for weeks or months (34, 35). Plasma renin activity appears after removal of the tumor, but aldosterone biosynthesis remains relatively unresponsive to the generated angiotensin II. Eventually plasma renin activity becomes supranormal and responsiveness of the aldosterone biosynthetic pathway begins to return. It is conceivable that prolonged infusion of suppressor amounts of angiotensin II into anephric patients would eventually stimulate the aldosterone biosynthetic pathway.

Anephric patients in the overhydrated, sodium-replete state immediately before hemodialysis had increased pressor sensitivity to angiotensin II (Table 1). Anephric patients studied immediately before hemodialysis received a smaller dose of angiotensin II than did either normal subjects or kidney allograft recipients, and this fact may partially explain the failure to stimulate aldosterone biosynthesis. However, anephric patients after hemodialysis and ultrafiltration had a normal pressor response to angiotensin II. The enhanced pressor response to angiotensin II in the sodium-replete, overhydrated anephric patient and the diminished pressor response to angiotensin in the sodium-deplete, volume-deplete anephric subject lends support to the concept that pressor responsiveness to angiotensin II is related to sodium and fluid balance. McCaa et al. (36), in studying the circulatory changes following angiotensin II administration, observed that sodium-deplete dogs showed a decreased pressor response to angiotensin II. Therefore, even though anephric patients before hemodialysis received less angiotensin II, those after hemodialysis received as much as the normal subjects and the kidney allograft recipients, yet they failed to respond with an increased plasma aldosterone concentration. The endogenous amount of angiotensin II was presumably less in the anephric patient, since there was no detectable renin activity, so the amount of angiotensin II appearing at the zona glomerulosa may have been less in the anephric subjects.

Failure of the normal response by the adrenal glands of the anephric patients to angiotensin II infusion could possibly be related to the infusion of heparin during hemodialysis. Clinical and experimental data obtained from heparin treatment in hypertensive vascular disease and other conditions accompanied by edema demonstrate that heparin has antialdosterone activity (37-39). Conn et al. (40) and Abbott et al. (41) have observed that heparin is capable of blocking adrenal aldosterone synthesis even in the absence of the renal renin-angiotensin system. It seems unlikely that heparin administration during hemodialysis can explain the failure of our anephric patients to increase their plasma aldosterone concentration after angiotensin II infusion. The patients were not heparinized between periods of hemodialysis. They received 5000 USP units of heparin initially and then 1000-2000 USP units/hour by constant infusion during the 12 hours of hemodialysis (this dose represented a total of 170-290 mg heparin/hemodialysis period). Patients who had hypoaldosteronism related to hepatic therapy had received 200-300 mg of heparin daily for prolonged periods (41, 42). In contrast to the anephric patients in this study, the patients receiving daily prolonged heparin treatment did not increase their aldosterone excretion after sodium depletion or ACTH administration. As shown by Figure 4, plasma aldosterone concentration increased in the anephric patients in our study in response to ACTH. We have previously shown that the plasma aldosterone concentration may increase in response to sodium depletion by hemodialysis (1). Bayard et al. (3) found no evidence that heparin administration, in the same total dose and over the same duration of time as during hemodialysis, suppressed the level of plasma aldosterone. Furthermore, the plasma concentration of aldosterone in our anephric patients was no more depressed in the ones who had been on intermittent hemodialysis and heparin treatment for 36 months than it was in those who had been on this regimen for only 3 months.

In conclusion, this study demonstrates four facts that will be significant in finally understanding regulation of aldosterone secretion. First, a functional renal renin-angiotensin system is necessary for stimulation of aldosterone secretion in response to upright posture. Second, aldosterone secretion is...
increased in response to ACTH administration in normal subjects, anephric patients, and kidney allograft recipients. Third, angiotensin II is a potent stimulus to aldosterone secretion in normal subjects and kidney allograft recipients but fails to significantly increase aldosterone secretion in anephric subjects following prolonged absence of the renal renin-angiotensin system. And, finally, kidney allograft transplantation restores the normal aldosterone response to acute stimuli within 6 weeks after surgery.

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