Hyporeninemic Hypoaldosteronism in Diabetes Mellitus

Studies of the Autonomic Nervous System's Control of Renin Release

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SUMMARY

The proposal that neurogenic mechanisms may contribute to suppressed plasma renin activity in diabetic patients with hyporeninemic hypoaldosteronism was examined. Five hyperkalemic, diabetic patients with mild to moderate renal insufficiency and evidence of autonomic or peripheral neuropathy were studied. Mean plasma renin (1.1 ± 0.2 ng/ml/h) and aldosterone (2.8 ± 0.8 ng/dl) values were low and showed minimal increase after a low-sodium diet. Sequential renin responses during 4 h upright posture were significantly diminished in all patients compared with control subjects. The normal increment in plasma norepinephrine after upright posture and exercise was also blunted in the patients. Infusion of the beta-adrenergic agonist isoproterenol at a dose to augment pulse rate by 20% of baseline produced a rapid twofold increase in renin in control subjects. The patients had no renin response to isoproterenol infusion at doses that elicited similar cardiovascular responses in both groups. These findings suggest that in hyporeninemic hypoaldosteronism associated with diabetes mellitus and neuropathy, an alteration in sympathetic nervous system activity may contribute to the decreased plasma renin levels. The diminished catecholamine response to upright posture could lead to a blunting of renin response during orthostasis and other maneuvers. Secondly, loss of renin response to isoproterenol infusion in the face of normal cardiovascular responses is consistent with a localized intrarenal defect at the beta-adrenergic receptor level or at more distal sites in patients with hyporeninemic hypoaldosteronism. DIABETES 28:237–241, March 1979.

Patients with diabetes mellitus complicated by diabetic nephropathy and neuropathy may develop hyperkalemia disproportionate to their degree of renal failure. Low levels of plasma renin activity and concomitant reductions in aldosterone have been reported in most of these patients.[1–11] This syndrome has been termed hyporeninemic hypoaldosteronism and has been noted in diabetic and other forms of renal failure. Several abnormalities in the renin-angiotensin system have been proposed in these patients, but no consistent pathophysiologic mechanism has been established.

The present study was initiated to examine whether abnormalities in the sympathetic nervous system accompanying diabetic neuropathy could contribute to defective renin release in these patients. Both upright posture and infusion of catecholamines stimulate renin release through sympathetic nervous system-mediated mechanisms. Therefore, plasma renin activity and norepinephrine response to upright posture and exercise and plasma renin activity response to isoproterenol infusion were examined in control subjects and patients with diabetes mellitus and hyporeninemic hypoaldosteronism.

MATERIALS AND METHODS

Five male patients with diabetes mellitus and hyporeninemic hypoaldosteronism and six normal control subjects were studied on the metabolic ward of the Sepulveda VA Hospital. Informed consent was obtained and the studies were approved by the Human Subjects Committee. Two patients had juvenile-onset diabetes mellitus of greater than 15-yr duration and three had adult-onset diabetes mellitus of 4–18-yr duration. Renal insufficiency was present in every patient. Two patients had biopsy-proven diabetic nephropathy and the others had presumed, but not proven, diabetic nephropathy. One patient was overtly nephrotic. Orthostatic hypotension and other findings suggestive of diabetic autonomic neuropathy were noted in two patients and painful peripheral neuropathy in another. The remaining two patients had decreased achilles tendon reflexes and loss of vibratory sensation in the feet. Diabetic reinopathy was evident in four of the five patients. Other causes of hyper-

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TABLE 1
Summary of admission clinical and biochemical data in five patients with diabetes mellitus and hyporeninemic hypoaldosteronism

Patient	Age (yr)	Duration of diabetes (yr)	Blood pressure (mm Hg)	Creatinine clearance (ml/min)	Urine protein (mg/24 h)	Fasting blood sugar (mg/100 ml)	Serum potassium (meq/L)	Serum bicarbonate (meq/L)
1	45	23	142/96	18	3900	236	6.2	20.6
2	64	7	160/104	36	800	167	5.4	24.0
3	53	4	116/72	22	2220	360	7.2	18.2
4	72	18	153/92	57	1320	134	6.4	21.8
5	40	17	132/84	31	630	288	5.8	23.2

kalemia, such as potassium load, severe acidosis, acute adrenal insufficiency, and acute renal failure were excluded.

Table 1 summarizes the individual clinical findings and pertinent biochemical data in the five patients. Mean age was 55 yr with a range of 40–72 yr. The known duration of diabetes mellitus was from 4–23 yr. On admission, the mean serum potassium was 6.2 ± 0.6 meq/L, with a range of 5.4–7.2 meq/L; mean serum sodium, 136 ± 2; chloride, 110 ± 6; and CO_2, 21 ± 3 meq/L. Admission fasting blood sugar was elevated in all patients. During the study periods, fasting blood sugar levels ranged from 142–240 mg/100 ml with diet and insulin therapy. Mean creatinine clearance was 32 ± 4 ml/min, with a range of 18–57 ml/min. All patients exhibited a 24-h urinary protein excretion above normal, ranging from 630–3900 mg/24 h.

Patients and controls were maintained on either a constant 120 meq sodium/100 meq potassium or a 10 meq sodium/100 meq potassium diet during the study period. Urinary electrolytes were monitored daily to determine sodium and potassium balance. Each patient was studied off all medications except insulin under the following protocols. After 5 days on a constant 120 meq sodium diet, blood samples were obtained for upright plasma renin activity, aldosterone, cortisol, sodium, and potassium. A 24-h urine for creatinine, sodium, potassium, and aldosterone excretion rate was collected. Patients were restudied under an identical protocol after 5 days of a constant 10 meq sodium diet.

The posture study was performed in the five patients and five control subjects studied in balance on a 120 meq sodium and 100 meq potassium intake. Subjects remained supine for 12 h before the study. An antecubital scalp vein needle was inserted 30 min before the first sample was obtained and used for subsequent blood sampling. At 0900 h, supine samples for plasma renin and norepinephrine were obtained. Subjects then assumed upright posture and constant exercise consisting of continuous walking for 240 min. Samples for plasma renin were obtained every 30 min and plasma norepinephrine at 60 and 120 min. Radial pulse, determined by palpation, and blood pressure, determined by auscultation, were measured at 0, 5, 10, 30, 60, 90, 120, and 240 min during the study. Additionally, in three patients and four controls, samples for plasma norepinephrine were taken after 5 min of upright posture. In these patients, isometric hand grip exercise using a partially-inflated sphygmomanometer cuff was carried out for an additional 5 min, at which time a sample for plasma norepinephrine was obtained.

The isoproterenol infusion was performed in five patients and five controls studied recumbent on a 120 meq sodium intake. Isoproterenol (Isuprel) was diluted in 250 ml dextrose and water and infused for 45 min by means of a constant-infusion pump. The infusion rate was adjusted to maintain pulse rate at 20% over baseline. In most cases, this resulted in an infusion rate of 1.5–3.0 μg/min. Heart rate and electrocardiogram were constantly monitored during the infusion. Additionally, blood pressure was continuously monitored (Arteriosonde, Roche Laboratories). Samples for plasma renin activity were obtained at 0, 5, 10, and 45 min.

All blood samples were immediately processed in a refrigerated centrifuge and plasma separated and frozen until time for assay. Samples for renin were collected on ice, using EDTA as an anticoagulant. Aldosterone and cortisol were collected in heparinized tubes. Sodium and potassium in urine and blood were measured by flame photometry, using lithium as an internal standard. Plasma renin activity was measured by radioimmunoassay of generated angiotensin I.[12,13] Plasma aldosterone and cortisol were measured by displacement analysis techniques as described by Underwood and Williams.[14] Aldosterone excretion rate was measured by the method of Williams and Underwood.[15]

Plasma norepinephrine was determined by the single isotope method of Passon and Peuler.[16] In this procedure, [^{3}H]S-adenosylmethionine is used as the methyl donor in the conversion of norepinephrine to epinephrine by the enzyme phenylethanolamine-N-methyltransferase. When a 0.25 ml plasma sample is used, this assay method has a sensitivity of 20–30 pg of norepinephrine. In ten assays using pooled plasma, the interassay coefficient of variation was 8% for norepinephrine. Plasma samples were collected in iced tubes containing EGTA and glutathione.

Statistical evaluation was done using either the paired or the Student's *t* test. All results are expressed as mean ± SEM and significance is $P < 0.05$ unless otherwise indicated.

RESULTS

Dietary sodium study. Table 2 summarizes the results of the dietary sodium studies in the controls and patients with hyporeninemic hypoaldosteronism. Mean, upright plasma renin activity (1.1 ± 0.2 ng/ml/h) and aldosterone (2.8 ± 0.8 ng/100 ml) levels on 120 meq sodium intake were significantly below control levels. Likewise, there was minimal increase in plasma renin activity and aldosterone during the 10 meq sodium intake, whereas the normal subjects exhibited two–threefold increments over the levels on 120 meq sodium intake. The mean urinary aldosterone excretion rate was significantly ($P < 0.01$) below control levels on both normal and low sodium intake. Urinary sodium excretion measured on day 5 of the 120 meq sodium diet was similar to controls, but on the 10 meq sodium diet, it was significantly ($P < 0.05$) higher than in control subjects. Mean

TABLE 2
Electrolyte balance and renin-aldosterone levels in response to 120 meq and 10 meq dietary sodium intakes and 4 h upright posture in five patients with hyporeninemic hypoaldosteronism and six controls

Dietary study	PRA (ng/ml/h)	PA (ng/dl)	Plasma cortisol (μg/dl)	Aldosterone excretion rate (μg/24°)	U_{na} (meq/24°)	U_k (meq/24°)	S_{na} (meq/L)	S_k (meq/L)
120 meq Na/100 meq K								
Patient	1.1* ± 0.2	2.8* ± 0.8	8.6 ± 0.7	3.0* ± 0.9	108 ± 8	43* ± 6	138 ± 2	5.3* ± 0.2
Control	2.4 ± 0.4	7.6 ± 1.2	9.4 ± 1.0	8.2 ± 1.6	114 ± 10	52 ± 8	141 ± 1	4.1 ± 0.5
10 meq Na/100 meq K								
Patient	1.6* ± 0.5	3.7* ± 1.0	9.2 ± 1.1	4.4* ± 1.1	48* ± 5	27* ± 4	136 ± 2	5.7* ± 1
Control	7.2 ± 1.6	18.3 ± 1.6	10.1 ± 0.9	24 ± 2.2	13 ± 3	46 ± 10	140 ± 1	4.0 ± 0.3

Mean ± SEM.
* $P < 0.05$ as compared with controls.

urinary potassium excretion in the patients was significantly ($P < 0.025$) below that for normal controls on a 100 meq potassium intake on either sodium diet. Mean serum potassium levels were significantly ($P < 0.05$) greater in patients than in controls during the 120 and 10 meq sodium intakes. Plasma cortisol levels in the patients were indistinguishable from controls on both diets.

Posture study. The patients had minimal response in plasma renin activity to 4 h upright posture, whereas controls demonstrated up to threefold increments over supine values (Figure 1). The supine levels of plasma renin activity in controls (3.1 ± 0.6 ng/ml/h) were also significantly greater than supine levels in the study patients (0.6 ± 0.1 ng/ml/h). In the two patients with orthostatic hypotension, there was a decrease of at least 26 mm Hg in mean blood pressure after 5 min standing, accompanied by an increase in pulse rate (16 beats/min). The three other patients also showed a very mild orthostatic fall in blood pressure that was not significantly different from the posture response in normal controls. The controls demonstrated minimal to no fall in arterial pressure after upright posture with an increase in pulse rate (12 beats/min).

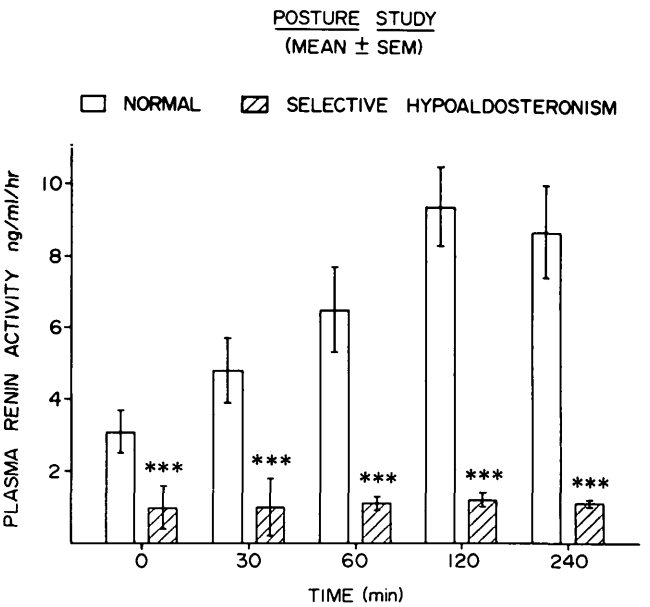
The mean plasma norepinephrine response to upright posture was also blunted in the patients showing a 1.4-fold nonsignificant increment from baseline at 60 and 120 min (Figure 2). Control subjects showed a 2.4-fold increase in mean plasma norepinephrine during upright posture, a response significantly different from the patients (Figure 2). However, it should be noted that there was no significant difference between the two groups in recumbent plasma norepinephrine levels. The two patients with orthostatic hypotension did have less plasma norepinephrine response to posture than the other patients. Three patients were also studied after 5 min standing to delineate their acute catecholamine responses. They also showed no significant increase in mean upright plasma norepinephrine levels (280 ± 34 pg/ml) over recumbent levels (306 ± 40 pg/ml). Conversely, normal subjects had a twofold increase in plasma norepinephrine after 5 min of upright posture. Normal subjects further augmented plasma norepinephrine levels during isometric hand gripping, whereas three patients showed no plasma norepinephrine response to this procedure.

Isoproterenol infusion. Infusion of isoproterenol in control subjects resulted in a brisk twofold increase in plasma renin activity at 5 min, with further increments at 10 and 45 min (Figure 3). Similar infusions in the patients failed to produce a response in plasma renin activity to this beta-adrenergic agonist (Figure 3). Differences in renin levels in normals and patients were significant at all study points. In both groups, pulse rate increments were similar, as were the mean infusion rates required to maintain pulse rate. There were no significant reductions in blood pressure during isoproterenol administration in either group.

DISCUSSION

Our patients with hyporeninemic hypoaldosteronism and diabetes mellitus demonstrated subnormal responses of

FIGURE 1. The response of plasma renin activity to 240 min of upright posture and constant activity in five controls and five patients with selective hypoaldosteronism. Patients were studied on 120 meq sodium/100 meq potassium intake and were recumbent (zero time) for 12 h before study. Statistical analysis (mean ± SEM) compares controls and patients at each time interval. ***, $P < 0.001$.



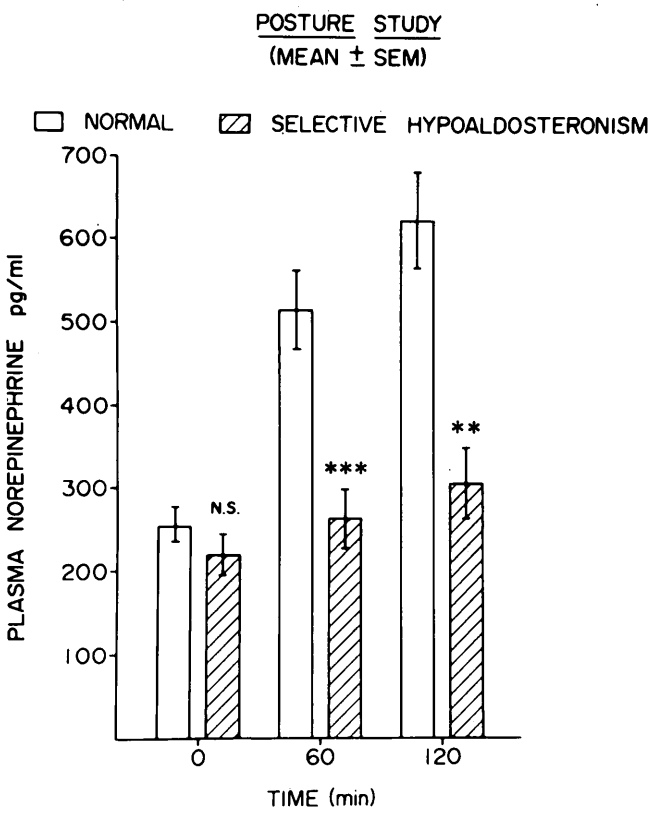


FIGURE 2. The response of plasma norepinephrine to 120 min of upright posture and constant activity in five controls and five patients with selective hypoaldosteronism. Statistical analysis (mean ± SEM) compares controls and patients at each time interval. **, $P < 0.01$; ***, $P < 0.001$.

plasma renin activity and norepinephrine to upright posture and exercise. Since all patients had evidence of peripheral nervous system complications of diabetes mellitus, this raises the possibility that peripheral and autonomic dysfunction may contribute to the impaired renin release in this disorder. The syndrome of hyporeninemic hypoaldosteronism has been noted with high frequency in diabetes with chronic renal failure and in several patients who also had evidence of peripheral and autonomic neuropathy.[5,6,7,9,10,11] All patients in the present study demonstrated these abnormalities, including peripheral neuropathy in three and autonomic neuropathy in two patients.

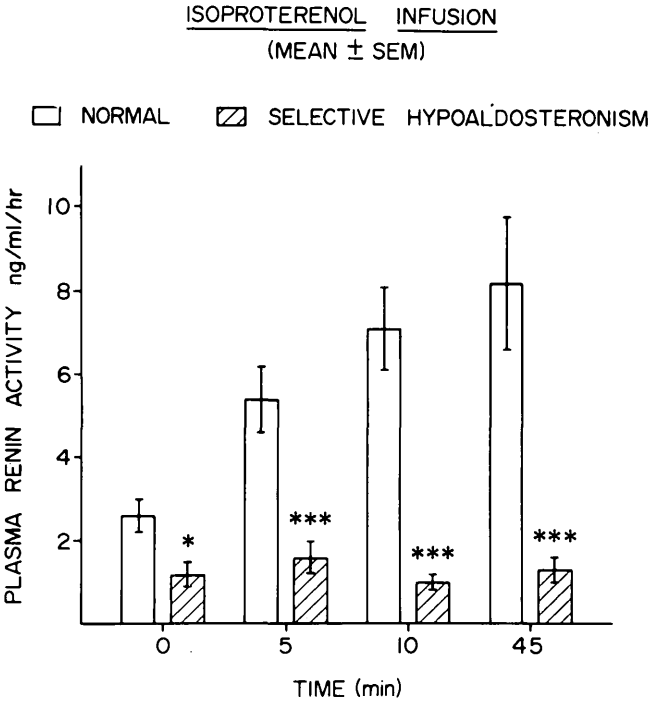
Previous studies described decreased circulatory levels of catecholamines in patients with diabetes mellitus and peripheral neuropathy.[17,18,19] Others have shown that diabetic patients exhibit enhanced pressor sensitivity to exogenous catecholamines, suggesting decreased circulating levels of this hormone.[20] Likewise, Christlieb et al. described a decreased response of plasma renin activity to orthostasis in diabetic patients with orthostatic hypotension.[21,22] Matched diabetic controls without orthostatic hypotension had normal plasma renin activity responses. Signs of diabetic neuropathy and nephropathy were more frequent in patients with orthostatic hypotension. As suggested by Christlieb et al., a deficiency of catecholamines could lead to diminished renin release in these patients.[22]

It is well established that the sympathetic nervous system has a major influence in modulating renin release.[23] Anatomic studies reveal direct sympathetic innervation of juxtaglomerular cells in the kidney.[24] Studies in the nonfiltering kidney model in dogs have shown a direct action of the renal nerves on the juxtaglomerular cells.[23,25] Furthermore, catecholamines such as epinephrine, norepinephrine, and isoproterenol can stimulate renin release by a direct action on juxtaglomerular cells.[23,26,27,28] Most evidence points to an intrarenal beta-adrenergic receptor on the juxtaglomerular cells as the mediator of this response.[23]

In the present study, the renin response to upright posture and exercise was utilized as an indicator of sympathetic nervous system influence on renin release. Upright posture is closely correlated with rapid sequential increases in renin, angiotensin II, and aldosterone levels, their incremental change beginning after 20–30 min of upright posture.[29] A second and earlier response to upright posture is a sympathetic neural discharge associated with rapid 2–5 min increments in plasma norepinephrine levels.[30,31] Evidence for an interaction of catecholamines in activation of the renin postural response is the inhibition of the early rise in plasma renin activity with upright posture after beta-adrenergic blockade.[32] The combined subnormal norepinephrine and renin responses to upright posture in our patients would imply that sympathetic nervous system dysfunction may contribute to the hyporeninemia in this disorder. However, the finding of suppressed renin levels despite normal levels of plasma norepinephrine during recumbency indicates that additional factors may explain chronic renin suppression in these patients.

A second finding in our diabetic patients with hyporeninemic hypoaldosteronism was a failure of the beta-adrenergic agonist isoproterenol to stimulate plasma renin activity levels. This response clearly differed from our control subjects, where isoproterenol infusion yielded several-

FIGURE 3. The response of plasma renin activity to isoproterenol infusion in five controls and five patients with selective hypoaldosteronism. Patients were studied recumbent in balance on a 120 meq sodium/100 meq potassium intake. Statistical analysis (mean ± SEM) compares controls and patients at each time interval. *, $P < 0.05$; ***, $P < 0.001$.



fold increments in plasma renin activity. Yet, as monitored by pulse rate and blood pressure, there were no differences in cardiovascular responses between the two groups. Weidmann et al. also described two patients with hyporeninemic hypoaldosteronism and diabetes mellitus who had no renin response to an infusion of a 10:1 norepinephrine and epinephrine mixture.[9] A single diabetic patient with orthostatic hypotension was noted by Christlieb et al. to have no renin response to both upright posture and norepinephrine infusion.[22] In our patients with diabetic neuropathy and blunted catecholamine responses, one might have expected an exaggerated cardiovascular and renin response to beta-adrenergic stimulation, as would be seen in typical cases of autonomic denervation. Since this was not the case, it is necessary to consider an additional defect in renin release in these patients localized at the level of the intrarenal beta-adrenergic receptor. Numerous studies have documented the important role of renal adrenergic receptors in modulating renal renin release under many physiologic conditions.[23–28] Very little data exist on the consequence of isolated defects in the intrarenal adrenergic receptors on the control of renin release in man. On the other hand, the lack of response to isoproterenol may be consequent to a generalized decrease in renin synthesis, with sympathetic nervous system activity providing mainly a tonic stimulus for renin formation. If this were the case, then it is entirely possible that juxtaglomerular cell responsiveness could be restored after several days priming with isoproterenol infusion. Certain precedents for this possibility arise from studies demonstrating that more prolonged volume depletion with sodium restriction and diuretics can partially restore renin release in these patients.[33,34]

One could propose a chronic hypoadrenergic condition developing in some diabetic patients with renal and neurologic complications leading to suppression of plasma renin activity and subsequent reductions in aldosterone secretion. The present study would point to both the sympathetic neurons and the intrarenal beta-adrenergic receptor as possible sites for neurogenic defects contributing to renin suppression in this disorder. Confirmation of this proposed sequence of events must await a prospective study with serial measurements of adrenergic nervous system activity and the renin-angiotensin-aldosterone axis in diabetic patients who develop renal and neurologic complications. Finally, our findings cannot exclude additional intrarenal defects distal to the adrenergic receptors for renin release.

REFERENCES

[1] Michelis, M. F., and Murdaugh, H. V.: Selective hypoaldosteronism. Am. J. Med. *59*:1–5, 1975.

[2] McGiff, J. C., Muzzarelli, R. E., Duffy, P. A., Gonzalez, Y., Pierce, C. E., and Frawley, T. F.: Interrelationships of renin and aldosterone in a patient with hypoaldosteronism. Am. J. Med. *48*:247–53, 1970.

[3] Gerstein, A. R., Kleeman, C. R., Gold, E. M., Franklin, S. S., Maxwell, M. H., Gonick, H. C., Feffer, M. L., and Steinman, T. I.: Aldosterone deficiency in chronic renal failure. Nephron *5*:90–105, 1968.

[4] Vagnucci, A. H.: Selective aldosterone deficiency. J. Clin. Endocrinol. Metab. *29*:279–89, 1969.

[5] Schambelan, M., Stockigt, J. R., and Biglieri, E. G.: Isolated hypoaldosteronism in adults—a renin deficiency syndrome. N. Engl. J. Med. *287*: 573–78, 1972.

[6] DeLeiva, A., Christlieb, A. R., Melby, J. C., Graham, C. A., Day, R. P., Luetscher, J. A., and Zager, P. G.: Big renin and biosynthetic defect of aldosterone in diabetes mellitus. N. Engl. J. Med. *295*:639–43, 1976.

[7] Perez, G., Siegel, L., and Schreiner, G. E.: Selective hypoaldosteronism with hyperkalemia. Ann. Intern. Med. *76*:757–63, 1972.

[8] Brown, J. J., Chin, R. H., Fraser, R., Lever, A. F., Morton, J. J., Robertson, J. I. S., Tree, M., Waite, M. A., and Park, D. M.: Recurrent hyperkalemia due to selective aldosterone deficiency: correction by angiotensin infusion. Br. Med. J. *1*:650–54, 1973.

[9] Weidmann, P., Reinhart, R., Maxwell, M. H., Rowe, P., Coburn, J. W., and Massry, S. G.: Syndrome of hyporeninemic hypoaldosteronism and hyperkalemia in renal disease. J. Clin. Endocrinol. Metab. *36*:965–77, 1973.

[10] Tuck, M. L., Barrett, J. D., and Eggena, P.: Mineralocorticoid biosynthesis and neural control of renin release in selective hypoaldosteronism. Clin. Res. *25*:140, 1977.

[11] Sparagana, M.: Hyporeninemic hypoaldosteronism with diabetic glomerulosclerosis. Biochem. Med. *14*:93–103, 1975.

[12] Haber, E., Koerner, T., Page, L. B., Kliman, B., and Purnode, A.: Application of a radioimmunoassay for angiotensin I to the physiologic measurements of plasma renin activity in normal human subjects. J. Clin. Endocrinol. Metab. *29*:1349–55, 1969.

[13] Eggena, P., Barrett, J. D., and Sambhi, M. P.: The validity of comparing the measurements of angiotensin I generated in human plasma by radioimmunoassay and bioassay. J. Clin. Endocrinol. Metab. *39*:865–72, 1974.

[14] Underwood, R. H., and Williams, G. H.: The simultaneous measurement of aldosterone, cortisol and corticosterone in human peripheral plasma by displacement analysis. J. Lab. Clin. Med. *79*:848–62, 1972.

[15] Williams, G. H., and Underwood, R. H.: Mineralocorticoids: aldosterone and deoxycorticosterone. *In*: Methods of Hormone Radioimmunoassay. Jaffe, B., and Behrman, H., Eds. New York, Academic Press, 1974, pp. 371–92.

[16] Passon, P. G., and Peuler, J. D.: A simplified radiometric assay for plasma norepinephrine and epinephrine. Anal. Biochem. *51*:618–31, 1973.

[17] Christensen, N. J.: Plasma catecholamines in long-term diabetes with and without neuropathy and in hypophysectomized subjects. J. Clin. Invest. *51*:779–87, 1972.

[18] Neubauer, B., and Christensen, N. J.: Norepinephrine, epinephrine, and dopamine contents of the cardiovascular system of long-term diabetics. Diabetes *25*:6–10, 1976.

[19] Fernandez-Cruz, A., Lassman, M. N., Noth, R. H., Hollis, J., Braddom, R., and Mulrow, P. J.: Low plasma renin activity (PRA) in normotensive patients with diabetes mellitus and neuropathy. Diabetes *24*:(Suppl. 2):414, 1975.

[20] Christlieb, A. R., Janka, H. U., Kraus, B., Solano, A., and Aiello, L. M.: Vascular reactivity to angiotensin II and to norepinephrine in diabetic subjects. Diabetes *25*:268–74, 1974.

[21] Christlieb, A. R.: Diabetes and hypertensive vascular disease: mechanism and treatment. Am. J. Cardiol. *32*:592–606, 1973.

[22] Christlieb, A. R., Munichoodappa, C., and Braaten, J. T.: Decreased response of plasma renin activity to orthostasis in diabetic patients with orthostatic hypotension. Diabetes *23*:835–40, 1974.

[23] Davis, J. O., and Freeman, R. H.: Mechanisms regulating renin release. Physiol. Rev. *56*:1–56, 1976.

[24] Wagermark, J., Ungersted, U., and Ljungquist, A.: Sympathetic innervation of the juxtaglomerular cells of the kidney. Circ. Res. *22*:149–53, 1968.

[25] Johnson, J. A., Davis, J. O., and Witty, R. T.: Effects of catecholamines and renal nerve stimulation on renin release in the nonfiltering kidney. Circ. Res. *29*:646–53, 1971.

[26] Assaykeen, T. A., Clayton, P. L., Goldfine, A., and Ganong, W. F.: Effect of alpha and beta adrenergic blocking agents on the renin response to hypoglycemia and epinephrine in dogs. Endocrinology *87*:1318–22, 1970.

[27] Assaykeen, T. A., Tanigawa, H., and Allison, D. J.: Effect of adrenoceptorblocking agents on the renin response to isoproterenol in dogs. Eur. J. Pharmacol. *26*:285–97, 1974.

[28] Reid, I. A., Schrier, R. W., and Earley, L. E.: An effect of extrarenal beta adrenergic stimulation on the release of renin. J. Clin. Invest. *51*:1861–69, 1972.

[29] Tuck, M. L., Dluhy, R. G., and Williams, G. H.: Sequential responses of the renin-angiotensin-aldosterone axis to acute postural change: effect of dietary sodium. J. Lab. Clin. Med. *86*:754–63, 1975.

[30] Cryer, P. E., Santiago, J. V., and Shah, S. D.: Measurement of norepinephrine and epinephrine in small volumes of human plasma by a single isotope derivative method: response to the upright posture. J. Clin. Endocrinol. Metab. *39*:1025–29, 1974.

[31] Kopin, I. J., Lake, R. C., and Ziegler, M.: Plasma levels of norepinephrine. Ann. Intern. Med. *88*:671–80, 1978.

[32] Salvetti, A., Arzilli, F., and Russo, R.: Postural changes of plasma renin activity. J. Nucl. Biol. Med. *15*:140–46, 1971.

[33] Oh, M. S., Carroll, H. J., and Clemmons, J. E.: A mechanism for hyporeninemic hypoaldosteronism in chronic renal disease. Metabolism *23*: 1157–66, 1974.

[34] Perez, G. O., Lespier, L. E., Oster, J. R., and Vaamonde: Effect of alterations of sodium intake in patients with hyporeninemic hypoaldosteronism. Nephron *18*:259–65, 1977.