SUMMARY During the past 10 years, we have found renin-secreting renal juxtaglomerular cell tumors in three hypertensive patients (two women, one man, aged 22, 69, and 21 years, respectively). The major chemical and biological findings revealed the association of severe hypertension with hypokalemia and increased plasma renin activity and plasma aldosterone. The diagnosis of such tumors is difficult, and two of the three patients were followed up for four and five years respectively before undergoing surgery. The pharmacological blockade of the renin system by various agents (beta-blockers, angiotensin II antagonists, and captopril) and its effects on blood pressure and plasma renin activity proved to be unreliable. Renal venous catheterization for renin measurements failed to provide adequate localization of the tumor. Direct radioimmunoassay, however, showed the total plasma renin to be markedly elevated. In addition, renal arteriography showed an avascular area corresponding to the renin-secreting tumor in each of the three patients. All three patients were cured of hypertension and hypokalemia by excision of the tumor.

(Hypertension 6: 760-766, 1984)

KKY WORDS • renin-secreting tumor • hypertension • surgery

THE role of the renin-angiotensin system in the genesis and maintenance of essential hypertension is the subject of intense controversy. Juxtaglomerular cell tumors with hypersecretion of renin have provided the clearest evidence of renin-dependent hypertension, since removal of the tumor results in a reduction of blood pressure to normotensive levels and suppression of secondary hyperaldosteronism.

In this study, we report three cases of renin-secreting tumors observed in our hypertension clinic. We have reviewed our diagnostic approach to evaluating a severely hypertensive patient suspected of having a renal renin tumor. Only 20 cases have been reported in the literature to date since the first case described in 1967 (see complete review in reference 2). We believe that appropriate evaluation may increase the recognition of such tumors.

Methods

Measurement of Plasma Renin

Plasma renin was measured by its enzymatic activity (plasma renin activity, PRA) or by its immunoreactivity (direct radioimmunoassay, RIA). The PRA was measured1 by the production of angiotensin I (ANG I) from endogenous angiotensinogen during incubation at pH 5.7, at 37°C. Normal values are 0.82 ± 0.49 ng ANG I/ml/hr in the supine position and 2.37 ± 1.3 ng ANG I/ml/hr in the upright position. Total renin was detected after activation by acidification at pH 3.3, as previously described by Morris and Lumbers4 and modified by Guyenne et al.5 Normal values are 11.1 ± 5.1 ng ANG I/ml/hr and 12.7 ± 5.5 ng ANG I/ml/hr in the supine and upright positions, respectively.

The direct renin RIA measures active and inactive renin1 simultaneously with use of a human renin antibody raised in rabbit.6 The limit of sensitivity of this assay does not allow the detection of renin in "normal" renin patients. During sodium restriction, the renin value in patients with renovascular or accelerated hypertension is 0.50 ± 0.35 ng/ml in the upright position.

Measurement of Plasma Aldosterone

Plasma aldosterone was measured by RIA.7 In subjects on a 120 mEq sodium intake, normal values are 5.7 ± 2.2 ng/100 ml and 11.1 ± 5.6 ng/100 ml in the supine and upright positions, respectively.
Saralasin Infusion
Saralasin infusion was performed according to the procedure described by Streeten et al.8 Infusion was started at 1 /g/kg/min and increased to 2, 4, and 10 /g/kg/min for 10-minute periods for each dose and for 20 minutes for the highest dose. Mean arterial blood pressure, heart rate, PRA, and plasma aldosterone were determined before, during, and 1 hour after the infusion.

Case Reports

Case 1
A 22-year-old woman was hospitalized in 1971 with a recent history of high blood pressure (245/100 mm Hg). Two years earlier after her first pregnancy, a systolic blood pressure of 170 mm Hg was discovered. One year later, the systolic blood pressure was again 170 mm Hg. An intravenous pyelogram was normal.

Examination
Blood pressure in the hospital was 200/120 and 190/130 mm Hg in the supine and upright positions, respectively. Optic fundi showed Grade I hypertensive changes, and there was a moderate left ventricular hypertrophy revealed by electrocardiography (ECG). Creatinine clearance was normal (110 ml/min), although protein excretion was 2.6 g/24 hr. Marked hypokalemia (2.1 mEq/liter) and hyponatremia (133 mEq/liter) with metabolic alkalosis (bicarbonate = 30 mEq/liter) were noted. Urinary potassium excretion ranged from 50 to 100 mEq/24 hr. Supine PRA and plasma aldosterone were elevated; PRA did not increase upon upright position (Table 1). A renal arteriogram was normal.

Course
The patient was hospitalized on several occasions between 1972 and 1976 because of severe and resistant hypertension, despite the use of two to four different antihypertensive agents. A saralasin infusion induced a marked blood pressure decrease at the lowest dose used (1 /g/kg/min); this decrease was from 169/135 to 114/90 mm Hg. PRA did not increase during the saralasin infusion (76 and 56 ng ANG I/ml/hr before and after the infusion, respectively; Table 1).

Three renal arteriograms were performed during the 1971-1976 observation period. All were considered normal. Later, after discovery of the tumor at surgery, a second a posteriori reading of the arteriogram revealed a tumor at the inferior pole of the left kidney. Separate venous renal samplings performed on three different occasions did not localize the tumor (Table 2). On one occasion, the renin ratio was elevated on the right side, the unaffected kidney, probably because of dilution of the left renal vein blood by the uterine-ovarian vein.

Operation
The patient was operated on in 1976 without preoperative localization of the tumor because of the high

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PRA (ng ANG I/ml/hr)</th>
<th>PA (ng/100 ml)</th>
<th>BP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supine</td>
<td>76</td>
<td>250</td>
<td>200/120</td>
</tr>
<tr>
<td>Upright</td>
<td>68</td>
<td>392</td>
<td>190/130</td>
</tr>
<tr>
<td>SAR Ala ANG II infusion:*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>76</td>
<td>202</td>
<td>169/136</td>
</tr>
<tr>
<td>During</td>
<td>56</td>
<td>160</td>
<td>114/90</td>
</tr>
<tr>
<td>None (80 mEq Na):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>18</td>
<td>184</td>
<td>142/184</td>
</tr>
<tr>
<td>Upright</td>
<td>18</td>
<td>184</td>
<td>142/184</td>
</tr>
<tr>
<td>SAR Thr ANG II infusion:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>9.7</td>
<td>28</td>
<td>142/103</td>
</tr>
<tr>
<td>During</td>
<td>11.6</td>
<td>15</td>
<td>126/94</td>
</tr>
<tr>
<td>ACEBUTOL (1 g/day x 2):%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before, upright</td>
<td>15</td>
<td>188</td>
<td>128</td>
</tr>
<tr>
<td>After, upright</td>
<td>8.9</td>
<td>178</td>
<td>125</td>
</tr>
<tr>
<td>Captopril (150 mg/day x 5):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before, supine</td>
<td>10</td>
<td>188</td>
<td>130</td>
</tr>
<tr>
<td>After, supine</td>
<td>22</td>
<td>158</td>
<td>102</td>
</tr>
</tbody>
</table>

PRA = plasma renin activity; PA = plasma aldosterone; BP = blood pressure; ANG II = angiotensin II.

*Sar, Ala ANG II infusion. The protocol used is that described in reference 8.

†Sar, Thr ANG II infusion according to the protocol in reference 8.

%Short-term administration of acebutolol (total dose of 2 g in 48 hours). The protocol used has been described in detail in reference 9.

$Captopril was given as a single dose of 65 mg. The BP and PRA were measured as described in reference 10.
TABLE 2. Plasma Renin Activity in the Renal Veins of Three Patients with Juxtaglomerular Cell Renin Tumors

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Right renal vein</th>
<th>Left renal vein</th>
<th>Inferior vena cava</th>
<th>Tumor side/unaffected side</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium depletion + beta-blockers</td>
<td>56.5</td>
<td>46</td>
<td>48</td>
<td>0.8</td>
</tr>
<tr>
<td>Case 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium depletion</td>
<td>26.5</td>
<td>19.5</td>
<td>26</td>
<td>1.4</td>
</tr>
<tr>
<td>Sodium depletion</td>
<td>18.5</td>
<td>15.2</td>
<td>16</td>
<td>1.2</td>
</tr>
<tr>
<td>Captopril</td>
<td>80</td>
<td>14</td>
<td>39</td>
<td>5.7</td>
</tr>
<tr>
<td>Case 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal sodium intake</td>
<td>17.2</td>
<td>12.4</td>
<td>18.15</td>
<td>0.7</td>
</tr>
<tr>
<td>Captopril</td>
<td>8.8</td>
<td>Selective sampling:</td>
<td>8.5</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Main renal</td>
<td>12.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mesorenal</td>
<td>10.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inferior polar</td>
<td>6.7</td>
<td></td>
</tr>
</tbody>
</table>

The ratio of the tumor side/unaffected side (> 1.5) was accurate in only one occasion, in a single patient.

suspicion of a renin tumor. Successive clamping of the two renal pedicles during surgery was performed to try to localize the tumor. Each clamping lasted 15 minutes. Clamping of the right pedicle lowered the mean arterial blood pressure (MAP) from 164 to 153 mm Hg, and clamping of the left kidney decreased the MAP from 157 to 152 mm Hg. The PRA decreased from 120 ng ANG I/ml/hr to 73 and 86 ng ANG I/ml/hr during clamping of the right and left kidneys, respectively. Surgical exploration of the posterior surface of the left kidney revealed a 5 x 3 cm tumor located at the inferior pole. The tumor was excised, and the kidney was left intact. Blood pressure normalized within a few hours (120/80 mm Hg), and PRA dropped to 2.86 ng ANG I/ml/hr.

Postoperative Course

The blood pressure has remained below 140/90 mm Hg. However, a diastolic blood pressure of 96 mm Hg was noted during the third trimester of a second pregnancy (1980) with moderate proteinuria (< 2 g/24 hr), which required transitory antihypertensive treatment.

Case 2

A blood pressure of 240/145 mm Hg was discovered in a 21-year-old man in 1978. No history of high blood pressure was previously recorded, although a slight proteinuria (not quantified) was noticed one month before.

Examination

During hospitalization, the blood pressure was 178/112 and 176/125 mm Hg with a heart rate of 96 and 100 bpm in the supine and upright positions, respectively. Physical examination was completely normal. The ECG showed U waves in leads V2 to V6. Plasma electrolytes showed profound abnormalities: Na = 131 mEq/liter, K = 2.9 mEq/liter, CO₂ = 32 mEq/liter. Urinary potassium excretion was 58 mEq/24 hr. Creatinine clearance was 80 ml/min, and slight proteinuria (0.5 g/24 hr) was again noted. The intravenous pyelogram was normal. The PRA was 18 ng ANG I/ml/hr with the patient in the upright position and on a 120 mEq sodium intake; it was not increased when he was on a 20 mEq sodium diet in the supine position (16 ng ANG I/ml/hr) or even upright (18 ng ANG I/ml/hr). Plasma aldosterone was 24 and 80 ng/100 ml in the supine and upright positions, respectively.

Blockade of the renin-angiotensin system gave conflicting results. Infusion of Sâ^-Thrg-angiotensin II (ANG II) slightly lowered the blood pressure from 142/103 to 126/94 mm Hg and increased the PRA from 9.7 to 11.6 ng ANG I/ml/hr (Table 1). Administration of a total dose of 2 g of acebutolol over 48 hours did not affect the blood pressure (188/128 before, 178/125 mm Hg after, acebutolol), although PRA was decreased by 40%, from 15 to 8.9 ng ANG I/ml/hr. Despite antihypertensive therapy with a low sodium diet, 100 mg spironolactone, 320 mg oxprenolol, and 600/xg clonidine, the blood pressure still remained abnormally elevated (143/97 mm Hg).

Course

During a subsequent hospitalization, captopril at a maximum dose of 300 mg/24 hr associated with 50 mg
of hydrochlorothiazide normalized the blood pressure. The MAP dropped from 169 to 72 mm Hg. After 15 days of treatment, captopril increased PRA from 10 to 46 ng ANG I/ml/hr, but its beneficial effects did not persist. After 21 months of captopril treatment (150 mg X 2 per day), the blood pressure rose again and hypokalemia recurred, which suggested inadequate blockade by captopril. To document this possibility, the blood pressure, PRA, and plasma aldosterone were measured 12 hours after a 150 mg dose of captopril was given and then 3 hours after the second daily dose of 150 mg. The blood pressure fell from 196/122 to 144/195 mm Hg, PRA increased from 28.2 to 44.6 ng ANG I/ml/hr, and plasma aldosterone fell from 44.6 to 4.8 ng/100 ml. It is therefore likely that captopril, after 41 months of tumor evolution, did not adequately block the renin system during the 24 hours of treatment and observation.

During a 4-year follow-up, renal venous sampling and renal arteriograms were each repeated three times. On only one occasion did the renal venous sampling correctly localize the tumor (Table 2). The first two arteriograms failed to reveal a lesion of the main renal arteries and of their branches. In January 1982, a third renal arteriogram was performed with oblique views to detect the putative renin tumor. As shown in Figure 1, a poorly vascularized cortical tumor (diameter, 3 cm) was visualized at the lower pole of the right kidney. This tumor had not been detected in the previous arteriograms probably because of its small size and its peripheral localization on the postero-inferior part of the kidney.

**Operation**

Tumorectomy was performed in April 1982. Within 4 hours the blood pressure decreased to 130/85 mm Hg. The PRA also decreased as soon as the first postoperative day to 1.2 ng ANG I/ml/hr in the supine position and 1.9 ng ANG I/ml/hr in the upright position. Follow-up at 6 months after surgery showed that the blood pressure was normal, although a slight tachycardia persisted.

**Case 3**

In 1966, a 53-year-old woman was discovered to have hypertension and was treated with clonidine. In 1973, she had symptoms of tetany. An intravenous pyelogram was normal and antihypertensive treatment with clonidine and furosemide was instituted. In 1975, a decrease in serum potassium (2.2 mEq/liter) was noted. The PRA was reported to be normal, and the hypokalemia was attributed to the thiazide diuretic. In 1976, the blood pressure was 220/140 mm Hg, serum K+ was 2.8 mEq/liter, and PRA was 10.3 ng ANG I/ml/hr. A renal arteriogram and a separate renal venous sampling were normal.

**Examination**

In 1982 at age 69, the patient was hospitalized for the first time in our hypertension clinic. The blood pressure was 225/130 mm Hg supine and 230/120 mm Hg upright, with corresponding heart rates of 66 and 72 bpm. The systolic blood pressure fluctuated between 100 and 180 mm Hg, and the diastolic blood pressure fluctuated between 74 and 110 mm Hg. Optic fundi were Grade II. There was a slight increase in the cardiothoracic ratio on chest x-ray (0.53). The ECG was normal. Serum K was 3.2 mEq/liter, Na was 142 mEq/liter, and creatinine clearance was 83 ml/min. No proteinuria was noted. With the patient on a 120 mEq sodium daily intake, supine and upright PRA were 5.9 and 9.3 ng ANG I/ml/hr, respectively, with corresponding plasma aldosterone concentrations of 42.5 and 80 ng/100 ml. With the patient on a 10 mEq sodium diet, PRA increased to 15 and 18.2 ng ANG I/ml/hr in the supine and upright positions, respectively. Pharmacological blockade of the renin system was explored with the patient on a 10 mEq Na+ diet. Administration of a total dose of 2 g of acebutolol over 48 hours decreased both blood pressure and PRA. Administration of an acute oral dose of captopril (1 mg/kg) decreased the blood pressure but paradoxically did not increase PRA (28.2 ng ANG I/ml/hr before and 21.9 ng ANG/ml/hr 3 hours after, captopril; Table 1).

The tumor was easily located by intravenous pyelography with tomography, by renal echography, by renal arteriography that showed a round avascular tumor at the surface of the inferior pole of the left kidney, and by computer tomography scanning that confirmed the location of the mass (Figure 2). Results of separate renal venous sampling were conflicting (Table 2). Selective sampling showed that the PRA of the left mesorenal vein was higher (10.35 ng ANG I/ml/hr) than that in the inferior polar vein (6.65 ng ANG I/ml/hr).

![FIGURE 1. Case 2. Arteriogram of an avascular tumor at the lower and internal pole of the right kidney. A peritumoral arteriole can be seen (arrow).](http://hyper.ahajournals.org/).
Operation

Tumorectomy was performed in 1982. The tumor weighed 10 g. Blood pressure initially decreased from 230/130 to 130/90 mm Hg during the first postoperative hours but subsequently rose transiently. On the 5th postoperative day, the blood pressure was normal (140/80 mm Hg) without treatment. Postoperative renin measurements were also normal: 1 and 4.2 ng ANG 1/ml/hr in supine and upright positions, respectively.

Renin Measurements and Histological Examinations
(Cases 1, 2, and 3)

As shown in Table 3, in the two renin tumors where total renin was determined after plasma acidification, inactive renin represented as much as 88% to 91% of the total circulating renin. These results can be compared to those obtained in normal volunteers and in 17 high-renin hypertensive patients already described.5

Table 3 also shows the very high values of renin measured by direct RIA compared to those observed in high-renin patients. Renin measurement performed in the three renin-secreting tumors as well as immunofluorescent and electron microscopy studies confirmed the existence of a renin-rich tumor developed from the afferent arteriole myocytes. Figure 3 illustrates the findings from immunofluorescent and electron microscopy in the second renin tumor (Case 2).

Discussion

These three cases illustrate the difficulty of diagnosing juxtaglomerular cell tumors. The failure to recognize such tumors might account for the apparent low prevalence of this disease. In these cases as in most cases reported in the literature,2 the diagnosis was evoked by the following features: hyperreninemia and secondary hyperaldosteronism without evidence of renovascular, malignant, or accelerating hypertension. These findings were not specific, but they were suggestive. Most often, hypertension was severe, but the third patient had a long history of mildly elevated blood pressure.

Before the diagnosis of renin tumor could be established, investigation of these patients included pharmacological blockade of the renin-angiotensin system, which is the procedure in our clinic with any case of hypertension with severe hyperaldosteronism. In retrospect, this maneuver failed to facilitate the diagnosis because of the variability of the results obtained. This variability is not surprising because it is already clear from the previous literature2 that renin secretion by juxtaglomerular cell tumors is affected in different ways by sympathetic drive, posture, sodium balance, and ANG II negative feedback.

Beta-adrenergic blockade of the beta receptors of the afferent arteriole decreases renin secretion.12 We were therefore tempted to speculate that this regulation is altered in cases of renin tumor. Mimran et al.12 have reported that 2 g of acebutolol slightly lowered the diastolic blood pressure from 160 to 140 mm Hg in a

### Table 3. Plasma Renin Measurements in Normotensive Subjects, High-Renin Hypertensive Patients, and Renin-Tumor Hypertensive Patients

<table>
<thead>
<tr>
<th></th>
<th>PRA (ng ANG 1/ml/hr)</th>
<th>Total renin (ng ANG 1/ml/hr)</th>
<th>Inactive/total renin (%)</th>
<th>Direct renin RIA (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal subjects (n = 12)</td>
<td>0.8 ± 0.5</td>
<td>11.0 ± 5.1</td>
<td>90.6 ± 0.5</td>
<td>undetectable</td>
</tr>
<tr>
<td>High-renin hypertensive patients (n = 17)</td>
<td>27.2 ± 5.5</td>
<td>68.1 ± 12.8</td>
<td>45 ± 15</td>
<td>0.6 ± 0.05</td>
</tr>
<tr>
<td>Renin-tumor hypertensive patients (n = 3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 1: 76</td>
<td>—</td>
<td></td>
<td>—</td>
<td>57.8</td>
</tr>
<tr>
<td>Case 2: 18</td>
<td>801</td>
<td></td>
<td>91</td>
<td>4</td>
</tr>
<tr>
<td>Case 3: 8.6</td>
<td>73</td>
<td>88</td>
<td>1.7</td>
<td></td>
</tr>
</tbody>
</table>

Data are from Guyenne et al. (see reference 5). PRA = plasma renin activity; ANG I = angiotensin I; RIA = radioimmunoassay.
FIGURE 3. Case 2. Microscopic findings in a juxtaglomerular cell tumor. A. Indirect immunofluorescence performed with a polyclonal human renin antiserum. Cytoplasmic positivities can be seen in numerous cells (x 230). B. Electron microscopic study showing a portion of two cells including a losangic protogranule (arrow), homogeneous mature granules (dense and spherical granules), and the Golgi apparatus. Also shown are intracytoplasmic myofilaments (star) with attachment bodies (x 213).

Pharmacological blockade of the renin system by ANG II antagonists and converting enzyme inhibitors also failed to reliably establish the diagnosis of renin tumor. Blood pressure was inconsistently affected by ANG II antagonists, since in our Case 1 the blood pressure dropped, but in Case 2 it decreased only slightly. In this Case 2, captopril was first found to be efficient, but then was found ineffective after 2 years of treatment. It was also uncertain whether renin secretion by the tumor would be insensitive to ANG II negative feedback. Indeed, in Case 1, renin did not increase during saralasin infusion despite the marked fall in blood pressure. However, in Case 2 and in the case reported by Mimran et al., PRA increased during ANG II antagonist infusion. Similarly, captopril increased PRA in Case 2 and did not affect it in Case 3. From this experience it appears that these pharmacological studies are not worth doing if the diagnosis of renin tumor has already been made. But if the diagnosis has not been made, these maneuvers may be of help in detecting atypical responses of the renin secretion.

In our cases, the tumor was not consistently localized by separate renal venous sampling. As shown in Table 2, we performed renal vein catheterization on several occasions and used different stimuli for renin secretion in the same patient, but we failed to correctly
locate the tumors. Several explanations may account for this failure. First, in locating a renin tumor, it might be more advantageous to suppress the renin system than to stimulate it. Yet the use of a salt-loading procedure is not without danger in these severely hypertensive patients. Second, it is likely that most of the venous blood in these peripheral tumors is collected by the pericapsular veins and is not drained into the main renal vein. Such a hypothesis would also explain why clamping of the renal pedicles failed to decrease the blood pressure in Case 1. Finally, in Case 1 there was hemodilution of the left renal vein by the utero-ovarian vein.

Renal arteriography correctly localized the tumor prior to surgery in Cases 2 and 3 and, a posteriori, in Case 1. Angiography also eliminated the possibility of a renovascular lesion of the main renal artery or of its branches. The difficulty lies in the fact that these tumors are usually small, poorly vascularized, and located at the surface of the kidney. One should obtain several oblique views and should repeat renal arteriograms on different occasions if there is a strong suspicion of a renin tumor, as we did in our three cases. This apparent poor vascularization of the tumor in Cases 2 and 3 is in contrast to the presence of hemorrhagic areas and numerous vessels inside the tumor visualized by light microscopy in Case 1. It is possible that renin liberated within the tumor provokes a local vasoconstriction, which would account for the apparent poor vascularization of the tumor.

The renin measurements were also helpful in establishing the diagnosis in our cases. The inactive renin levels were elevated. In addition, about 90% of the circulating renin was an inactive form, whereas in high-renin hypertensive patients inactive renin usually represents only 45% of total renin. Such a finding has already been made by Day and Luetscher in a case of Wilms’ tumor and by Ruddy et al. in the case of a renin-secreting pancreatic adenocarcinoma. From these data, it appears that a very high level of inactive renin in the presence of high-renin-dependent hypertension of unknown origin should evoke the diagnosis of a renin-secreting tumor from either a renal or an ectopic source. In addition, we found that renin measured by direct RIA was extremely elevated. In no high-renin hypertensive patients could we find values higher than 1.2 ng/ml. The direct renin measurements can be compared to those of total renin measured after acid activation. A significant correlation is found in renovascular and accelerated hypertension. However, the immunoreactive renin values in the renin tumors are relatively higher than those expected from such a correlation. This is particularly true for the patient in Case 3 whose immunoreactive renin was much higher than the total renin. Taken altogether, these data suggest that the renin tumors to a large extent secrete inactive forms of renin, which can be activated and which may represent the inactive renin precursor. These tumors may also release immunoreactive forms of renin that cannot be activated probably because of unterminated synthesis or abnormal processing.

In summary, the diagnosis of renin tumor is difficult but should be systematically pursued in patients with severe or even moderate hypertension with an apparently unexplained secondary hyperaldosteronism. Among the hormonal measurements in our cases, the high inactive-renin levels and especially the extremely elevated immunoreactive-renin levels were suggestive of the diagnosis. The effects of pharmacological blockade of the renin system on blood pressure and PRA were variable. However, an atypical response of PRA to such a maneuver in a high-renin hypertensive patient might help in the diagnosis of renin tumor. Renal venous sampling proved to be unreliable. Renal arteriogram was extremely useful when it was performed selectively and on various incidences.

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