RENIN AND CONTROL OF ARTERIAL BLOOD PRESSURE DURING TERMINAL RENAL FAILURE TREATED BY HAEMODIALYSIS AND BY TRANSPLANTATION

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SUMMARY

1. Plasma renin concentrations were determined in 1068 samples obtained in 113 patients in the end stage of chronic renal failure treated by repeated haemodialyses or by renal transplantation.

2. Patients with malignant nephroangiosclerosis have a very high concentration of plasma renin; this differentiates them from other disease groups, where renin concentration is sometimes normal and sometimes elevated; there is no significant difference between the glomerulonephritis and pyelonephritis groups.

3. There is a weak but significant correlation between plasma renin concentration and arterial blood pressure. In the terminal stage of chronic renal insufficiency, blood pressure appears to be controlled by other quantitatively more important factors. However, the hypertension of some cases, characterized by high concentrations of plasma renin, can be controlled only by bilateral nephrectomy.

4. There is an inverse and highly significant correlation between plasma renin and sodium concentrations. This is also the case in transplanted patients where an inverse correlation also exists between plasma renin concentration and daily urinary output of sodium.

5. The juxtaglomerular granulation index correlates positively with the plasma renin concentration.

6. In terminal renal failure the kidney retains its capacity to secrete renin as a response to acute haemorrhage or other stimuli.

7. Renin is present in the blood of anephric patients and its concentration is not correlated either with the patient’s sex or with the time elapsed after binephrectomy.

8. During rejection episodes in transplanted patients a rise of plasma renin concentration is frequently but not invariably observed. Elevation of plasma renin concentration is evident in very acute rejection crises.

Key words: renin, hypertension, haemodialysis, renal failure, blood pressure.

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Arterial hypertension is a frequent complication of the end stage of chronic renal failure. Of the 120 patients treated in our dialysis unit, ninety-eight were hypertensive as judged by an average diastolic blood pressure \( \geq 95 \text{ mmHg} \).

The factors responsible for hypertension probably vary from case to case. In most patients it may be corrected by removal of excess water and sodium (Comty, Rottke & Shaldon, 1964; Funck-Brentano, Chaumont, Perrin, Zingraff & Vantelon, 1965). However, these measures sometimes fail and control is achieved by bilateral nephrectomy (Toussaint, Cremer, Heuse, Vereerstraeten, Van Geertruyden, Cuykens & Verniory, 1966; Brown, Curtis, Lever, Robertsson, de Wardener & Wing, 1969b; Traeger, Zech, Francois, Heyendael, Moskovtchenko, Dubois, Pozet & Sassard, 1969; Stokes, Mani & Stewart, 1970). This last observation suggests that the diseased kidney is responsible for the production of an endogenous hypertensive principle and renin is an obvious candidate for this role.

The present study was done on patients suffering from end stage renal failure who were maintained on regular haemodialysis and eventually underwent kidney transplantation. Their plasma renin concentrations were determined at frequent intervals to gain insight into the role of renin in the pathogenesis of hypertension and sodium homeostasis.

Earlier analyses of values from some of these patients have been reported (Toussaint et al., 1966; Verniory, Cuykens, Lotteau & Toussaint, 1967; Toussaint, Verniory, Cremer, Vereerstraeten, Kinnaert & Van Geertruyden, 1968; Verniory, Potvliege, Van Geertruyden, Vereerstraeten, Kinnaert, Lotteau & Toussaint, 1970).

**MATERIALS AND METHODS**

Investigation was made on 113 patients, sixty-seven men and forty-six women, aged from 6 to 59 years. All were treated by haemodialyses; sixty-four underwent one or several kidney transplantations; a total of seventy-five kidneys were grafted, eighteen being given by living donors and fifty-seven coming from cadavers. In fifty patients both kidneys were removed before renal transplantation in thirty-seven cases; bilateral nephrectomy followed transplantation in five cases and it was done at the same time as transplantation in eight cases. Plasma renin concentrations were determined before the operation in thirty-one of these fifty cases who, according to the indication of the nephrectomy, were divided into two groups: (1) uncontrolled hypertension (twelve patients), and (2) renal infection (nineteen patients).

In eighty-four cases the aetiology of the renal disease was based on histological examination of kidney biopsies or autopsy specimens. In the absence of histological examination the clinical diagnosis was made on the basis of clinical and radiological data. The cases, with the number in parentheses, comprised: chronic glomerulonephritis (59); chronic pyelonephritis and interstitial nephritis (acknowledged phenacetin abuse: three cases) (33); polycystic kidney disease (6); malignant nephroangiosclerosis (3); polyarteritis nodosa (1); disseminated lupus erythematosus (1); diagnosis questionable (9); complex pathology (hydronephrosis and pyelonephritis of right kidney and nephroangiosclerosis of left kidney) (1).

In all patients the clearance of endogenous creatinine was less than 4 ml/min; they were dialysed twice weekly; their daily diet contained 1 g of protein/kg body wt. and appropriate amounts of water and salt, in accordance with their renal excretions. Before each dialysis the
blood pressure was taken and a sample of arterial blood was removed for renin, sodium, potassium and urea determinations.

Plasma renin concentration was measured by the method of Brown, Davies, Lever, Robertson & Tree (1964c) slightly modified for the calculation of results. Our normal values drawn from the study of seventeen healthy subjects ranged from 4 to 22 units/l (mean ± SD = 12.4 ± 6.1) which is close to the normal range of 4–20 units, reported by Brown, Chinn, Dusterdieck, Fraser, Gleadle, Lever, Robertson & Tree (1969a). A total of 1068 determinations were obtained, 522 in cases of terminal renal failure, 186 in anephric patients and 360 in transplanted subjects. Values from ninety of these patients were obtained by Verniory et al. (1970).

In forty-nine cases a granulation index and a size index of the juxtaglomerular apparatuses were measured by a modification of the method of Hartroft & Hartroft (1953). All index calculations were made by the same pathologist without knowledge of the results of renin determinations.

Statistical calculations of all measurements were made with a G.E. 235 computer.

RESULTS

Relationship between plasma renin concentration and aetiology of the kidney disease

The mean values of several determinations were calculated for ninety-one patients who according to the nature of their nephropathy were divided into four groups (Table 1). Since the

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of cases</th>
<th>Average (units/l)</th>
<th>No. of cases &gt;25 units/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic glomerulonephritis</td>
<td>54</td>
<td>16.8</td>
<td>10</td>
</tr>
<tr>
<td>Chronic pyelonephritis</td>
<td>28</td>
<td>12.8</td>
<td>3</td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
<td>5</td>
<td>11.7</td>
<td>1</td>
</tr>
<tr>
<td>Malignant nephroangiosclerosis (including one case of polyarteritis nodosa)</td>
<td>4</td>
<td>196.4</td>
<td>4</td>
</tr>
</tbody>
</table>

Analysis of variance of the log of reninaemia

<table>
<thead>
<tr>
<th>Source of variation</th>
<th>Degrees of freedom</th>
<th>Sum of squares</th>
<th>Mean square</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diseases</td>
<td>3</td>
<td>28.30</td>
<td>9.43</td>
<td>12.41</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Malignant nephroangiosclerosis or other renal diseases</td>
<td>1</td>
<td>26.56</td>
<td>26.56</td>
<td>34.95</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other renal diseases, nephroangiosclerosis excluded</td>
<td>2</td>
<td>1.74</td>
<td>0.87</td>
<td>1.14</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Patients</td>
<td>87</td>
<td>66.15</td>
<td>0.76</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Total</td>
<td>90</td>
<td>94.45</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
plasma renin concentration has a lognormal frequency distribution, the calculations were performed after logarithmic transformation of the values and computation of the mean logarithmic value of each patient (Verniory et al., 1970). Table 1 shows that there is a highly significant difference between the groups due exclusively to the malignant nephroangiosclerosis group.

Variations of plasma renin concentration of individual patients

The results reported in Table 1 allow all cases of chronic glomerulonephritis, chronic pyelonephritis and polycystic disease to be considered as one group and to compare the variances between the patients and in the same patient; in this way a highly significant F test is obtained: 9.96 ($P<0.001$) from which it may be concluded that variations between individual patients are larger than variations between samples taken at different times from the same patient. Thus each patient maintains a characteristic concentration of plasma renin during the whole period of haemodialyses; this may be normal, above normal or even extremely high.

Fig. 1. Comparative evolution of (a) uraemia, (b) body weight, (c) arterial blood pressure and (d) plasma renin concentration after bilateral nephrectomy and kidney transplantation. The patient, a 21-year-old female suffering from chronic glomerulonephritis, was treated by repeated haemodialyses.

Four patients did not follow this pattern. In one of them, a 21-year-old woman suffering from chronic glomerulonephritis, hypertension became more severe 6 months after haemodialysis was started and there was a parallel increase in plasma renin concentration (Fig. 1). In the three remaining patients the reverse was observed; a fall of arterial pressure with regression of
the signs of malignant hypertension was accompanied by a corresponding decrease in plasma renin concentration.

**Correlations of plasma renin concentration with blood pressure, sodium and potassium plasma concentrations**

For the reasons discussed below, patients with a history of acute blood loss in the few days preceding plasma renin determination were excluded from this correlation study.

There is a wide range of the logarithms of plasma renin concentration when plotted against the systolic blood pressure (Verniory *et al.*, 1970). However, the highest plasma renin concentrations were observed in the severely hypertensive patients. The correlations between the logarithm of renin concentration and systolic and diastolic blood pressures are low but highly significant (respectively \( r = 0.177, t = 4.09, P < 0.001 \) and \( r = 0.163, t = 3.72, P < 0.001 \)).

On the other hand, an inverse relationship exists between the logarithm of renin concentration and sodium concentration (\( r = -0.312, t = 7.47, P < 0.001 \)). An inverse correlation also exists between systolic blood pressure and plasma sodium concentration (\( r = -0.238, t = 5.56, P < 0.001 \)). This last relationship suggests that there is a mutual interaction of these two parameters with plasma renin concentration. The interaction may be evaluated by calculating partial correlation coefficients. Examination of Table 2 shows that by this correction the

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>( t )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( r_{xy} )</td>
<td>0.176</td>
<td>4.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>( r_{xz} )</td>
<td>-0.311</td>
<td>7.44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>( r_{yz} )</td>
<td>-0.238</td>
<td>5.56</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>( r_{xy,z} )</td>
<td>0.110</td>
<td>2.51</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>( r_{xz,y} )</td>
<td>-0.282</td>
<td>6.67</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>( r_{yz,x} )</td>
<td>-0.196</td>
<td>4.53</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

There are 518 determinations; \( x = \) logarithm of plasma renin concentration; \( y = \) systolic blood pressure; \( z = \) plasma sodium concentration.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>( t )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( r_{xy} )</td>
<td>0.159</td>
<td>3.62</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>( r_{xz} )</td>
<td>-0.319</td>
<td>7.58</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>( r_{yz} )</td>
<td>-0.167</td>
<td>3.81</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>( r_{xy,z} )</td>
<td>0.113</td>
<td>2.56</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>( r_{xz,y} )</td>
<td>-0.300</td>
<td>7.09</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>( r_{yz,x} )</td>
<td>-0.124</td>
<td>2.81</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

There are 510 determinations; \( x = \) logarithm of plasma renin concentration; \( y = \) diastolic blood pressure; \( z = \) plasma sodium concentration.
correlation between renin concentration and blood pressure is markedly decreased, whereas the inverse relationship between plasma renin and sodium concentrations remains highly significant.

There is a weak inverse correlation between the logarithm of plasma renin concentration and the logarithm of plasma potassium concentration (the distribution of the latter is lognormal for our patients) \( r = -0.095, t = 2.16, P<0.05 \).

| \( r_{xy} \) | 0.152 | 3.38 | <0.001 |
| \( r_{xz} \) | -0.277 | 6.31 | <0.001 |
| \( r_{yz} \) | -0.180 | 4.00 | <0.001 |
| \( r_{xy,z} \) | 0.108 | 2.39 | <0.02 |
| \( r_{xz,y} \) | -0.257 | 5.81 | <0.001 |
| \( r_{yz,x} \) | -0.145 | 3.21 | <0.01 |

There are 482 determinations; \( x = \) logarithm of the plasma renin concentration; \( y = \) systolic blood pressure; \( z = \) plasma sodium concentration.

| \( r_{xy} \) | 0.144 | 3.15 | <0.01 |
| \( r_{xz} \) | -0.285 | 6.46 | <0.001 |
| \( r_{yz} \) | -0.124 | 2.71 | <0.01 |
| \( r_{xy,z} \) | 0.114 | 2.49 | <0.02 |
| \( r_{xz,y} \) | -0.272 | 6.13 | <0.001 |
| \( r_{yz,x} \) | -0.087 | 1.91 | >0.05 |

There are 474 determinations; \( x = \) logarithm of the plasma renin concentration; \( y = \) diastolic blood pressure; \( z = \) plasma sodium concentration.

Several patients were treated with antihypertensive drugs such as guanethidine, reserpine and hydralazine with, in general, a slight effect on their blood pressure. As these drugs could have influenced the plasma renin concentration, the calculations were repeated after excluding the values obtained during antihypertensive therapy (Table 3). The correlation coefficients generally become slightly lower but they retain about the same degree of significance.

**Correlation of plasma renin concentration with size and granulation of the juxtaglomerular apparatuses**

The relationship between the last renin determination preceding nephrectomy or autopsy and the state of the juxtaglomerular apparatus as estimated by a size index and a granulation index was determined in forty-one patients.
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There is no correlation of the logarithm of the plasma renin concentration with the size index \((r = 0.031, P>0.80)\) but there is a significant correlation with the granulation index \((r = 0.420, P<0.01)\). This last result is consistent with previous observations made mainly in animals and with the experiments of Bing, Eskildsen, Faarup & Frederiksen (1967) demonstrating that renin is synthesized in granulated muscle cells of the juxtaglomerular apparatus.

**Effect of acute haemorrhage on plasma renin concentration**

In four patients plasma renin was measured within a few hours to 5 days after an acute haemorrhage. Three patients developed acute blood loss from the gastro-intestinal tract; their plasma renin concentrations were 128, 71 and 52 units/l respectively. In the last of these cases the plasma renin concentration was normal (19 units/l) 30 days later.

In the fourth patient monthly determinations of renin during a period of 11 months had been normal (6–25 units/l). During a pericardiotomy the myocardium was accidentally torn and the patient lost 4 litres of blood. Five days after this mishap the plasma renin concentration had risen to 97 units/l; one month later it had fallen to a nearly normal value (24 units/l).

The two of these four cases with the highest plasma renin also had a very low plasma sodium concentration (115 and 124 mEq/l).

**Effect of haemodialyses on reninaemia**

Plasma renin concentrations were measured before and after dialysis in twenty-one patients undergoing a total of thirty-seven haemodialyses. The mean difference of plasma renin concentration from the initial value was +1.16±9.51 units/l (SD). Changes of blood urea and plasma renin concentration caused by dialysis were significantly correlated \((r = -0.6854; P<0.001)\); a less significant correlation exists between variations of plasma renin concentration and systolic blood pressure \((r = -0.4151; P<0.02)\). No statistically significant correlation was observed between variations in plasma renin concentrations and other parameters such as diastolic blood pressure, weight, plasma sodium and potassium concentrations.

**Effect of bilateral nephrectomy on arterial blood pressure**

The effect of bilateral nephrectomy on arterial blood pressure was studied in thirty-one patients who were operated upon because of uncontrolled malignant hypertension or chronic urinary infection. The values of blood pressure before nephrectomy represent the means of the pressure readings taken at the commencement of each dialysis, during the month preceding surgery. The values after nephrectomy are the means of the pressure readings taken in similar conditions during the period extending from 15 to 75 days after surgery; this interval was sometimes shorter when a kidney was grafted before the seventy-fifth day. The plasma renin concentrations were registered either during the periods considered or in a few cases, during a period as near as possible to the one considered. When more than one determination was made in the same period, only the mean value is recorded.

A plasma renin concentration above the normal range was found in eight patients, all of whom had uncontrolled hypertension and who all had a significant fall of their systolic blood pressure after nephrectomy. In the twenty-three patients who had normal renin concentrations, the changes in blood pressure were variable: blood pressure fell in five cases, rose in five others and did not change significantly in the remaining thirteen cases.
Statistical analysis of the results shows a significant inverse correlation between the logarithm of the plasma renin concentration recorded before nephrectomy and the difference in systolic blood pressure occurring after the operation \( (r = -0.544, t = 3.49, P < 0.01) \) (Fig. 2).

![Graph showing the relationship between plasma renin concentration before bilateral nephrectomy and variation of systolic blood pressure after this operation in thirty-one patients.](image)

**Fig. 2.** Relationship between plasma renin concentration before bilateral nephrectomy and variation of systolic blood pressure after this operation in thirty-one patients.

**Persistence of renin in the blood of anephric patients**

Plasma renin concentration was measured in 186 blood samples taken from thirty-six anephric patients: twenty men (with a total of 100 determinations) and sixteen women (with a total of eighty-six determinations). A measurable amount of renin (3–15 units/l) was found in ninety-four samples, fifty-six having been taken from male patients and thirty-eight from female patients. The presence of renin in the blood bore no relationship with the time elapsed after nephrectomy \( (r = -0.054, P > 0.40) \); it could remain detectable even 1 year after removal of the kidneys.

Analysis of the variance demonstrates that differences between individual patients exceed the variations existing between samples taken from the same patient and that there is no significant difference according to sex of the patients (Table 4).
Blood renin in patients bearing a kidney graft

Plasma renin concentration was determined in 360 blood samples taken from sixty-four patients during the course of seventy-five renal transplantations. The statistical study was limited to the forty-four patients who had no renal tissue other than the grafted kidney; in this group a total of fifty kidneys were transplanted and 233 renin determinations were made.

Table 4. Analysis of variance of the plasma renin concentration in anephric patients

<table>
<thead>
<tr>
<th>Source of variation</th>
<th>Degrees of freedom</th>
<th>Sum of squares</th>
<th>Mean square</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>35</td>
<td>578.38</td>
<td>16.525</td>
<td>3.36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Samples</td>
<td>150</td>
<td>736.98</td>
<td>4.913</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>185</td>
<td>1315.36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>1</td>
<td>11.36</td>
<td>11.36</td>
<td>0.68</td>
<td>NS</td>
</tr>
<tr>
<td>Patients of same sex</td>
<td>34</td>
<td>567.02</td>
<td>16.68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
<td>578.38</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Correlation of plasma renin concentration with arterial blood pressure and with sodium and potassium plasma concentrations and urinary excretions. There is a significant correlation between the logarithm of the plasma renin concentration and systolic and diastolic blood pressure \( (r = 0.233, t = 3.61, P < 0.001 \) and \( r = 0.291, t = 4.60, P < 0.001 \)). There is an inverse correlation between the logarithm of the plasma renin and plasma sodium concentrations \( (r = -0.221, t = 3.41, P < 0.001 \). The partial correlation coefficients between these three parameters are lowered but remain highly significant. The correlation between the logarithm of the plasma renin and plasma potassium concentrations is direct and slightly significant \( (r = 0.154, t = 2.28, P < 0.05) \).

There is a significant inverse correlation between the logarithm of the plasma renin concentration and the daily urinary excretion of sodium \( (r = -0.448, t = 7.29, P < 0.001) \) (Fig. 3). Conversely, there is no significant correlation between the plasma renin concentration and urinary potassium \( (r = -0.083, t = 1.10, P > 0.10) \).

To determine whether antihypertensive drugs do not introduce bias in the correlation values, the same calculations were repeated after exclusion of fifteen results obtained during the periods of antihypertensive treatment. This correction leads to slightly lower correlations; their significances, however, remain essentially unchanged.

Relationship between plasma renin concentration and graft function. The function of the transplant was estimated by the clearance of endogenous creatinine which, except during the immediate first transplantation period, gave a good indication of graft rejection. Statistical calculation shows an inverse correlation between the logarithm of the plasma renin concentration and creatinine clearance \( (r = -0.169, t = 2.34, P < 0.05) \).

Thirty-one transplants were subjected to histopathological examination; according to the different states of rejection which were found they were distributed into three groups (Table 5). A rise in plasma renin concentration is found chiefly during acute rejection. Only one patient
Fig. 3. Relationship between plasma renin concentration and daily urinary output of sodium in forty transplanted patients (177 determinations).

Table 5. Correlation between plasma renin concentration and histology of the graft

<table>
<thead>
<tr>
<th>Nature of rejection</th>
<th>Always normal</th>
<th>Transiently high*</th>
<th>High at last determination</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>6</td>
<td>4</td>
<td>7</td>
<td>17</td>
</tr>
<tr>
<td>Subacute or chronic</td>
<td>1</td>
<td>6</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Minimal or absent</td>
<td>2</td>
<td>3</td>
<td>1†</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>13</td>
<td>9</td>
<td>31</td>
</tr>
</tbody>
</table>

* Plasma renin concentrations were elevated at one or more determinations during the period of transplantation but returned to normal at the last determination before histological examination.
† Stenosis of renal artery by a diaphragm.
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had a high plasma renin concentration without exhibiting clinical signs of rejection; pathological examination confirmed the absence of rejection and demonstrated the existence of a stenosis of the kidney artery supplying the graft.

In the other seventeen cases the diagnosis of rejection was made on clinical grounds: elevation of temperature, decrease of urine volume, proteinuria, swelling and painfullness of the transplant. The comparison with plasma renin concentration values was limited to the first month period after transplantation. Ten of these seventeen patients developed signs of acute rejection; in four of them there was an increase in plasma renin concentration; it was most marked in one patient who had a fulminant rejection crisis accompanied by severe hypertension. In this case hyponatraemia followed the increase of plasma renin concentration. In the other six patients who had signs of rejection, plasma renin concentration remained normal. All seven patients who did not appear to reject their graft had a normal plasma renin concentration.

Relationship between plasma renin concentration and granulation index of the juxtaglomerular apparatuses. The granulation index was determined in eight transplanted kidneys that had to be removed because of their rejection. The correlation coefficient between granulation index and plasma renin concentrations, observed at the nearest time before graft removal, was of a magnitude \( r = 0.434 \) comparable with that found in the group of patients who were in the end stage of chronic renal failure \( r = 0.420 \).

DISCUSSION

Renin and arterial blood pressure

In diffuse renal disease the plasma renin concentration may be high, normal or low, an observation that is in agreement with other reports (Brown, Davies, Lever & Robertson, 1966; Brown et al., 1969b).

The aetiology of the kidney disease bears no relationship to plasma renin concentration, except in a small group of patients suffering from malignant nephroangiosclerosis; they were characterized by an extremely high plasma renin concentration with malignant hypertension.

The correlation between blood pressure and plasma renin concentration is weak but significant. However, plasma renin concentration is not an accurate measure of the activity of the renin–angiotensin system. The blood concentration of angiotensin II might be a better index as it takes into account not only renin but also substrate concentration and the presence of inhibitors. There are few reports concerning angiotensin II plasma concentration in the end stage of chronic renal failure (Catt, Zimmet, Cain, Cran, Best & Coghlan, 1971; Brown, Dümsterdieck, Fraser, Lever, Robertson, Tree & Weir, 1971). Catt et al. (1971) did report a significant positive correlation in hypertensive patients between plasma angiotensin II concentration and arterial blood pressure that was more marked in the malignant phase of hypertension; it would be of value to know whether blood pressure correlates better with the angiotensin II concentration rather than with the renin concentration.

Another factor that may obscure the relationship is the variable response of blood vessels to the action of circulating angiotensin. Sodium depletion decreases the pressor effect of renin and angiotensin (Davis, Hartrotf, Titus, Carpenter, Ayers & Spiegel, 1962; Kaplan & Silah, 1964; Bianchi, Brown, Lever, Robertson & Roth, 1968; Brown et al., 1971) and potassium depletion has an even stronger action (Traeger et al., 1969).
More information is given by the changes of blood pressure and plasma renin concentration after repeated haemodialysis of patients who have reached the end stage of renal failure. Among such patients one group, in which renin is unlikely to play a major role in the causation of their hypertension, had normal plasma renin concentrations and their hypertension was easily controlled by inducing water and salt depletion. Conversely, in a group of twelve patients who did not respond to these measures, plasma renin concentration was high in eight cases; in all of the latter, bilateral nephrectomy was followed by a significant decrease of systolic blood pressure and of renin concentration. However, of the four patients who had normal plasma renin concentrations, three benefited by the nephrectomy, a finding which raises the possibility that other renal factors than renin may be implicated in the maintenance of hypertension.

The variations in plasma renin concentration which occur in individual cases are not always easy to explain. It appears there is a relationship between high plasma renin concentration and severe alteration of the renal vasculature, as the highest renin values were found in patients with malignant nephroangiosclerosis. Metabolic factors must also be considered. Depletion of sodium and water as a consequence of intensive haemodialysis, may cause a rise in plasma renin concentration (Brown et al., 1969b). Furthermore, in man and dog potassium depletion produces the same effect (Abbrecht & Vander, 1970; Brunner, Baer, Sealey, Ledingham & Laragh, 1970). Patients in the end stage of renal failure usually have a decreased pool of exchangeable potassium (Cremer & Toussaint, 1964); their depletion may easily be aggravated by repeated haemodialyses with a low concentration of potassium in the baths and by other therapeutic measures directed against hyperkalaemia, for instance administration of ion-exchange resins. Occasionally, therefore, a rise of plasma renin concentration may be a secondary effect of therapy (Brown et al., 1969b).

Renin and sodium homeostasis

An inverse relationship between plasma concentrations of renin and sodium has been reported in various types of hypertension (Brown, Davies, Lever & Robertson, 1965a) and in different pathological conditions (Brown, Lever & Robertson, 1967). It was also found in those of our patients who were in the end stage of renal failure or had a kidney graft.

In our grafted patients whose sodium balance was maintained by adjusting sodium intake to sodium urinary output, an inverse relationship between plasma renin concentration and daily sodium urinary excretion was observed. However, there was a much smaller correlation of plasma renin concentration with plasma potassium concentration and urinary excretion of potassium.

The relationship between renin concentration and sodium homeostasis is still a matter of controversy. Three theories have been proposed: (1) the elevation of plasma renin is caused by sodium depletion and/or hyponatraemia; (2) the elevation of plasma renin is responsible for the lowering of plasma sodium concentration; (3) the inverse variations in blood renin and sodium result from a common cause.

The first view is supported by several observations. A salt-poor diet produces a rise in plasma renin together with a lowering of urinary sodium excretion (Brown, Davies, Lever & Robertson, 1964a); in severe sodium depletion, for instance in Addison's disease, very high plasma renin concentrations are associated with marked hyponatraemia (Brown, Davies, Lever & Robertson, 1964b). The mechanism by which sodium depletion enhances renin secretion could depend on a decrease of either plasma volume or filtered sodium load. The stimulation might
be transmitted to the juxtaglomerular apparatus, in the former case through baroreceptors located in arteriolar walls within the juxtaglomerular apparatus or, in the latter case, through the maculae densae.

Our finding, in patients bearing a kidney graft and maintained in sodium balance, of an inverse correlation between plasma renin concentration and sodium urinary excretion would be more in keeping with the second possibility.

Against this theory, the increased plasma renin concentration is not always associated with hyponatraemia and in certain circumstances it may precede the lowering of plasma sodium concentration. For instance, in antidiuretic hormone (vasopressin) oversecretion the plasma sodium concentration falls to very low values whilst the renin concentration remains normal and may even decrease (Brown et al., 1965b). However, in this situation, plasma volume is increased together with a relatively high urinary excretion of sodium, two factors which would tend to suppress juxtaglomerular apparatus activity. As observed in one of our cases of graft rejection, plasma renin may rise before plasma sodium concentration decreases. Hyponatraemia results from either a loss of sodium or a retention of water. Although angiotensin II is able to increase the urinary excretion of sodium and water in hypertensive subjects (Brown & Peart, 1962) it is unlikely that this effect applies to patients who have almost no remaining kidney function and who, even when their plasma sodium concentration is low, have an increased pool of exchangeable sodium (Toussaint & Cremer, 1964). It appears more likely that the hyponatraemia is a consequence of an increase in body water, probably due to excessive water intake. Polydipsia has been described in a case of malignant hypertension with a very high plasma renin concentration (Brown et al., 1969b). Further, the injection of crude renin (Nairn, Masson & Corcoran, 1956) or of angiotensin (Fitzsimons & Simons, 1968) increases water intake in animals and this effect is not mediated by urinary loss of water, since it persists after bilateral nephrectomy. Also, angiotensin injected into the hypothalamus stimulates thirst (Epstein, Fitzsimons & Simons, 1969).

Adaptation of renin secretion

It is of interest to determine whether a kidney which has suffered almost total loss of excretory function can secrete renin in response to appropriate stimuli. For ethical reasons such patients cannot be subjected to procedures devised to enhance renin secretion.

However, four patients gave us the opportunity to follow the effect of an acute haemorrhage on plasma renin. In all cases heavy blood loss was followed by the finding of high renin concentration which returned to normal in the two cases where subsequent determinations were made.

Haemodialysis is another factor that may influence the secretion of renin by altering the volume and composition of the extracellular fluid. Brown et al. (1969b) observed that after haemodialysis changes in plasma renin concentration depended on the magnitude of body weight loss; under the value of 2 kg plasma renin decreased, whereas above that value it increased, the latter effect probably being mediated by hypovolaemia. In our series the correlation was better with the decrease in uraemia than with the loss of weight. Two mechanisms are seemingly involved; first hypovolaemia, which is an expected consequence of particularly efficient dialyses, and secondly the rapid lowering of blood urea which may provoke intracranial hypertension (Sitprija & Holmes, 1962) with, as possible consequences, systemic hypertension and renin secretion.
From these observations it appears that in severe renal failure the kidney retains the capacity to adapt its renin production to various stimuli, notably in response to acute blood loss.

Presence of renin in anephric patients

The presence of renin in the blood of anephric patients has been repeatedly demonstrated (Blaufox, Birbari, Hickler & Merrill, 1966; Verniory et al., 1967; Capelli, Wesson, Aponte, Faraldo, & Jaffe, 1968; Brown et al., 1969b; Meyer, Worcel, Angles d'Auriac & Milliez, 1969).

In our series of 186 determinations in the blood of thirty-six anephric patients, renin was detected in ninety-four samples from twenty-nine patients. In contrast with the results of Capelli et al. (1968), renin concentration was independent of sex and of time elapsed since nephrectomy. The presence of renin in the blood of anephric patients cannot be explained by the persistence of a residual renin of renal origin and the conditions of blood collection preclude any contamination by transfused blood. It seems that the renin is of extrarenal origin. A renin-like enzyme has been found in salivary glands (Werle, Vogel & Goldel, 1957), placenta (Stakemann, 1960), uterus (Gross, Schaechtelin, Ziegler & Berger, 1964), adrenals (Ryan, 1967) and artery walls (Dengler, 1956; Gould, Skeggs & Kahn, 1964).

In nephrectomized pregnant rabbits, plasma renin originates probably from the uterus (Gorden, Ferris & Mulrow, 1967). In the case of our anephric patients, the uterus cannot be the source of renin, since renin concentration is slightly lower in women than in men.

Renin in transplanted patients

In case of rejection of the transplant, plasma renin concentration is often but not invariably elevated; our observations are consistent with the results of Blaufox et al. (1966) and of West, Turcotte & Vander (1969). However, in very acute rejection the rise of plasma renin is constant and important, and accompanies severe hypertension and hyponatraemia. The transplanted kidney is able to respond to sodium depletion by an increased secretion of renin (Lewis, Blaufox, Jagger, Lauler, Qureshi & Merrill, 1966; Toussaint et al., 1968; Greene, Vander & Kowalczyk, 1968); the stimulation of renin secretion is most probably produced by a humoral mechanism although a regeneration of renal nerves cannot be excluded (Blaufox, Lewis, Jagger, Lauler, Hickler & Merrill, 1969).

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