THE VALUE OF PLASMA RENIN CONCENTRATION PER SE, AND IN RELATION TO PLASMA AND EXTRACELLULAR FLUID VOLUME IN DIAGNOSIS AND PROGNOSIS OF HUMAN RENOVASCULAR HYPERTENSION

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SUMMARY

1. Plasma renin concentration (PRC) has been measured in 212 hypertensive patients. In fourteen patients with essential hypertension and in seventeen patients with renovascular hypertension, plasma volume (PV) and extracellular fluid volume (ECFV) were measured.

2. The results obtained have been discussed in three ways:
   (a) PRC in relation to the aetiology of hypertension;
   (b) PRC in relation to the effect on blood pressure of surgery for unilateral renal diseases;
   (c) PRC, PV and ECFV in 'essential' and renovascular hypertension.

3. Excluding patients with ophthalmoscopic signs of malignant hypertension, PRC is significantly higher in renovascular hypertension than in normal subjects and patients suffering from 'essential' hypertension and hypertension associated with bilateral renal disease; but the overlapping of the single values of the patients with these diseases is marked. Thus a normal PRC has no diagnostic value, while a high PRC without sodium deficiency or retinopathy might favour a diagnosis of renovascular disease.

4. In twenty-seven out of thirty-three patients submitted to surgery for unilateral renal disease and followed up for 12 months or longer, blood pressure has been significantly reduced. This group includes twelve patients with a normal preoperative PRC and fifteen patients with a high PRC. These results clearly demonstrate that unilateral renal disease may maintain a high blood pressure without increasing PRC and that PRC has no prognostic value.

5. Concurrent estimations of PRC, PV and ECFV in patients with renovascular or essential hypertension revealed the following differences. In cases of renovascular hypertension with normal PRC, PV and ECFV were significantly increased while in those with raised PRC, PV did not differ and ECFV was barely raised with respect to

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values obtained in patients with essential hypertension. PV of renovascular patients with normal renin was significantly higher than that of renovascular patients with high renin. The analysis of these results with quadratic discriminant functions demonstrated that an integrated evaluation of blood pressure, PV, ECFV and PRC allows a separation between the two types of hypertension. In other words these factors, taken together, in some way seem to reflect a difference between the two diseases. These results may indicate a new type of approach to the diagnosis and prognosis of renovascular hypertension.

The pathogenetic role of renin in many forms of human hypertension is far from clear. The finding of normal levels of this enzyme in the plasma of some patients or animals with renal hypertension is the main argument against a pressor role of renin in this disease (Gross, Schaechtelin, Brunner & Peters, 1964; Lever & Robertson, 1964; Brown, Davies, Lever & Robertson, 1965a; Brown, Davies, Lever, Robertson, Bianchi, Imbs, Johnson, Lawrence, Fraser & James, 1966a; Peart, 1965; Bianchi, Campolo, Riva & Vegeto, 1966a; Bianchi, Brown, Lever & Robertson, 1966b).

Recently interest in the pressor effect of renin has been renewed by the demonstration that changes of plasma renin concentration, induced by intravenous infusion and of the same magnitude as found in some patients with renovascular hypertension, produce marked modifications of the blood pressure of both normal rabbits (Imbs, Brown, Davies, Lever & Robertson, 1967) and dogs (Bianchi, Brown, Lever, Robertson & Roth, 1968; Bianchi, Tenconi & Lucca, 1970).

While 'renin activity' in the plasma of hypertensive patients has been extensively studied (Helmer, 1964; Fitz & Armstrong, 1964; Genest, Boucher, De Champlain, Veyrat, Chretien, Biron, Tremblay, Roy & Cartier, 1964; Meyer, Alexandre, Devaux, Leroux-Robert & Milliez, 1966; Conn, Cohen & Rovner, 1964; Laragh, Sealy & Sommers, 1966; Aida, Maebashi Yoshinaga & Ichinone, 1965; Del Greco, Simon, Goodman & Roguska, 1967; Creditor & Loschky, 1967; Bath, Gunnells & Robinson, 1968; Reubi & Hodler, 1968), reports on plasma renin concentration have been almost exclusively published by the group of Brown, Davies, Lever & Robertson, 1963; Brown et al., 1965a; Brown, Davies, Lever & Robertson, 1965b; Brown, Davies, Lever & Robertson, 1966b, 1966c; Brown, Chinn, Davies, Dusterdieck, Fraser, Lever, Robertson, Tree & Wiseman, 1968), with few exceptions (Verniory, Cuykens, Lotteau & Toussaint, 1967; Skinner, 1967), as far as we are aware.

The differences between the methods measuring renin activity and those measuring renin concentration have been illustrated and discussed elsewhere (Brown, Davies, Lever & Robertson, 1966d; Lever, Robertson & Tree, 1964; Bianchi & Riva, 1965).

From the clinical point of view the major interest in plasma renin estimations in hypertensive patients are (Brown, Davies, Lever & Robertson, 1966d; Lever, Robertson & Tree, 1964; Bianchi & Riva, 1965).

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(a) the diagnosis of renovascular hypertension and primary aldosteronism;
(b) the prognosis of hypertension after surgery in cases with unilateral renal disease.

It has clearly been demonstrated that renin produces at least two types of effects (Brown et al., 1966a): (1) a modification of the salt and water metabolism through both a direct effect on the kidney and an increase of aldosterone secretion, (2) an increase of the blood pressure. It is also well established that changes of sodium and water metabolism influence both plasma renin level (Brown et al., 1966d; Brown, Davies, Lever & Robertson, 1966e; De Champlain, Genest, Veyrat & Boucher, 1966) and its pressor effect (Bianchi et al., 1968).
Therefore any evaluation of the pathogenetic role of this enzyme in arterial hypertension and thus its diagnostic value should also involve the assessment of the state of the sodium and fluid balance.

The purposes of this communication are to describe our own experience concerning three aspects of these problems: firstly, the plasma renin concentration in relation to the aetiology of the hypertension; secondly, the prognostic value of this estimation in predicting the effect of surgery on arterial hypertension associated with unilateral renal disease; and thirdly the relationships between renin and plasma and extracellular fluid volumes measured in patients with renovascular and 'essential' hypertension.

Some of these results have been published in brief elsewhere (Bianchi et al., 1966a; Bianchi, Campolo, De Ponti, Vegeto & Pietra, 1969; Bianchi, Campolo, Riva & Vegeto, 1966c).

MATERIALS AND METHODS

Techniques

Plasma renin concentration was measured by the method of Brown, Davies, Lever, Robertson & Tree (1964a) without modifications. In a previous paper (Bianchi & Riva, 1965), the characteristics of this method in our laboratory have been described. In brief, we obtained a renin recovery of 41.8% SEM 2.7. We measure renin in thirty samples simultaneously and to evaluate the error of the method we include in each batch of thirty samples two aliquots taken from a standard plasma pool, with a known renin concentration, stored at -20°C. The mean of twenty determinations made in ten batches is 24.4 unit/l, SD 2.27 (range from 19.2 to 27.4 unit/l). While the mean difference among the ten duplicates is 6%, SD 4.24, range 0%–12%.

The blood for renin estimation was always taken from a peripheral vein between 08.00 and 11.00 hours with the patient in the supine position for at least 1 h and without any drugs for at least 15 days, and on a normal salt intake. Where stated, plasma and extracellular fluid volume estimations were performed on these occasions.

Twenty-four hour urinary excretion of 17-ketosteroids and 17-hydroxycorticosteroids was estimated according to the MRC Committee on Endocrinology (1963) and Silber & Porter (1954). Plasma and urinary sodium and potassium were determined by flame photometry.

Plasma volume was measured with the Evans blue dye method. In thirteen patients the plasma volume was also estimated simultaneously with $^{131}$Ialbumin (Schultz, Hammarsten, Heller & Ebert, 1953): the mean plasma volume with albumin was 2541 ml (SD 379.5) and with the dye was 2471 ml (SD 294). The mean difference of 70 ml was not significant ($t = 0.52, P<0.5$).

Extracellular fluid volume was measured as thiocyanate space after 90 min of equilibration.

The statistical analyses were performed with a General Electric Time Sharing System.

Patients

303 renin estimations were performed in 212 patients. The number of patients in the various diagnostic groups is shown in Table 1.

Benign essential hypertension—this group includes fifty-five patients in whom the following investigation revealed a normal or negative result: sodium and potassium in plasma and in 24-h urine, blood urea and glucose, urinalysis, creatinine clearance, phenol red excretion, concentration test, phentolamine test, intravenous pyelogram, including films made at 1, 2, 3 and 4 min, and isotope renogram. Where some of these tests gave an equivocal response or
the history and the physical examination suggested some particular type of hypertension, the following additional tests were performed: aortography, split renal function tests, kidney biopsy, 24-h 3-methoxy-4-hydroxy-mandelic acid (VMA) urinary excretion and 24-h 17-hydroxycorticosteroid and 17-ketosteroid urinary excretion. None of these patients had retinal haemorrhages, exudates or papilloedema.

Renovascular disease—the diagnostic criteria used for the diagnosis of renal artery stenosis were the arteriographic demonstration of the arterial lesion, a decrease of at least 50% in urinary flow on ureteric catheterization with an increased urinary creatinine concentration of at least 50% and a decreased urinary sodium concentration of at least 15%. This group includes ten patients with bilateral papilloedema and/or retinal haemorrhages and exudates. The possibility has been suggested that arteriolar disease may produce a functional ischaemic pattern of one kidney without any demonstrable arterial lesion on arteriography (Brown, Owen, Peart, Robertson & Sutton, 1960; McDonald, 1968) and that the hypertension was cured by nephrectomy (McDonald, 1968). For these reasons we included in this group three patients where such diagnostic criteria were fulfilled on arteriography, divided renal function studies, intravenous pyelogram and isotope renography. We have no histological demonstration of the arteriolar stenosis; thus the diagnosis in these three patients should be considered unproved.

‘Malignant’ hypertension—this diagnosis has been made on the basis of either bilateral retinal haemorrhages or exudates with or without papilloedema. This group includes eleven patients with ‘essential’ hypertension and seven patients in whom primary renal or adrenal disease could not be excluded because it was not possible, for various reasons, to perform some of the diagnostic tests.

Parenchymal kidney diseases—this group includes thirty-one cases of bilateral disease having one of the following pathological conditions: acute or chronic glomerulonephritis; chronic pyelonephritis; polycystic disease; acute renal failure and terminal renal disease. All these patients had a blood urea above 43 mg/100 ml and were hypertensive; five patients had ophthalmoscopic evidence of malignant hypertension. The diagnosis of chronic glomerulonephritis or pyelonephritis was made in twenty-five patients on the following basis: history, urinalysis, creatinine clearance, intravenous pyelogram, phenol red excretion, concentration test, isotope renogram, urine culture and kidney biopsy. Four patients underwent aortography and six had split renal function tests. Another group of eleven patients were receiving haemodialysis treatment; none of these patients had malignant hypertension. Thirteen patients had unilateral disease: twelve a small hypoplastic or pyelonephritic kidney and one tuberculosis. The diagnosis has been made with intravenous pyelography, aortography, split renal function tests and kidney biopsy. In seven cases the diagnosis was confirmed by surgery. We shall consider together the cases of small hypoplastic or pyelonephritic kidney owing to the difficulty of distinguishing these two pathological conditions (Heptinstall, 1966).

RESULTS

Plasma renin concentration in relation to the aetiology of arterial hypertension

Table 1 shows the plasma renin concentration in the various groups of patients, with the range of the single patient’s values and the number of patients with renin level outside the normal range.
Renin and body fluids in human hypertension

Normal patients—Our plasma renin concentration figures in normal subjects (mean 10.24 units/l; SD 4.4, range 4.5–20.5 units/l), are near to the values of Brown et al. (1964a) (mean 8.2 units/l; SD 2.7, range 4–18 units/l) and of Verniory et al. (1967) (mean 9.4 units/l SD 5.8, range 4–22 units/l).

Essential hypertension—Six patients in this group had a subnormal level of renin, without any abnormalities in plasma or urinary electrolytes. Aldosterone had not been measured in any

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of patients</th>
<th>Renin (units/l) mean ± SEM</th>
<th>Range of the values of single patients</th>
<th>Patients out of the normal range</th>
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<td>below</td>
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<td>n</td>
</tr>
<tr>
<td>Normals</td>
<td>35</td>
<td>10.24 ± 0.75</td>
<td>4.5–20.5</td>
<td>4-5</td>
</tr>
<tr>
<td>Benign essential hypertension</td>
<td>55</td>
<td>10.66 ± 0.67</td>
<td>2.6–23.8</td>
<td>6</td>
</tr>
<tr>
<td>Malignant hypertension</td>
<td>18</td>
<td>39.50 ± 17.46</td>
<td>3.6–32.8</td>
<td>1</td>
</tr>
<tr>
<td>Parenchymal disease of the kidney</td>
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<tr>
<td>unilateral</td>
<td>13</td>
<td>23.40 ± 7.30</td>
<td>3.3–84</td>
<td>2</td>
</tr>
<tr>
<td>bilateral</td>
<td>31</td>
<td>11.40 ± 1.27</td>
<td>3.0–30.6</td>
<td>3</td>
</tr>
<tr>
<td>bilateral on haemodialysis</td>
<td>11</td>
<td>18.00 ± 3.53</td>
<td>6.9–38</td>
<td>0</td>
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<tr>
<td>Renovascular disease</td>
<td></td>
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<tr>
<td>Renal artery stenosis:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>unilateral</td>
<td>41</td>
<td>22.96 ± 2.59</td>
<td>4.5–90</td>
<td>0</td>
</tr>
<tr>
<td>bilateral</td>
<td>5</td>
<td>22.10 ± 4.20</td>
<td>12.5–33.6</td>
<td>0</td>
</tr>
<tr>
<td>Functional ischaemic kidney without renal artery stenosis</td>
<td>3</td>
<td>9.35 ± 2.4</td>
<td>6.0–16.4</td>
<td>0</td>
</tr>
</tbody>
</table>

of these cases; thus normokalaemic primary aldosteronism (Conn, Edwin, Cohen, Rovner & Nesbit, 1965; Conn, Rovner, Cohen & Nesbit, 1966) could not be excluded.

All the other patients but one had normal plasma renin concentration. These results are in agreement with the results of Brown et al. (1965b).

Malignant hypertension—In three out of eight patients in this group, with a renin level above the normal range and in four out of ten patients with normal renin, it was impossible to exclude a primary renal or adrenal disease; hence the percentage of patients with high renin level in the malignant phase of ‘essential’ hypertension may lie between 28 and 57%. Brown et al. (1966b) found high renin levels in approximately 45% of patients with hypertensive retinopathy and without renal artery stenosis. No efforts were made by these authors to separate patients with primary renal parenchymal diseases.

Renovascular hypertension—Twenty-one patients out of forty-six with a lesion in the main
renal arteries had a renin level above normal. Six of these patients had ophthalmoscopic signs of malignant hypertension, hence the percentage of patients without retinopathy and with an increased plasma renin concentration is 37.5%. These data are similar to the results of Brown et al. (1965b) (31.5%). As we have demonstrated that renin is normal or subnormal in all patients except one with essential hypertension in the absence of retinal signs of malignancy, a high renin level in such a patient might favour the diagnosis of renovascular disease, provided that all other causes of increased renin (Brown et al., 1966d) can be ruled out. Conversely it is clear that a normal renin level does not exclude a diagnosis of renal artery stenosis. Brown et al. (1965b) found a high plasma renin concentration in all patients with retinopathy and renal artery stenosis, while in our series four patients with retinopathy had a renin level in the normal range.

**Parenchymal renal diseases**—The incidence of high renin levels in our patients with bilateral renal parenchymal disease and hypertension (6.4%) is definitely lower than in the series of Brown et al. (1965b). In our group there are no cases of hyponatraemic hypertensive syndrome; this fact could explain the discrepancy. It is of interest to note the difference in plasma renin concentration between patients with parenchymal disease and patients with renovascular disease (see Table 2).

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of patients</th>
<th>Plasma renin concentration (Units/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normals</td>
<td>35</td>
<td>10.24 4.48</td>
</tr>
<tr>
<td>Renal artery stenosis and hypertension</td>
<td>36</td>
<td>23.08* 17.14</td>
</tr>
<tr>
<td>'Essential' hypertension</td>
<td>55</td>
<td>10.66 4.99</td>
</tr>
<tr>
<td>Bilateral parenchymal renal disease</td>
<td>26</td>
<td>10.79 5.69</td>
</tr>
</tbody>
</table>

* F test = 16.20, P < 0.001.

Plasma renin concentration tends to be higher in patients receiving haemodialysis treatment. The incidence of high renin levels in our patients is similar to the figures of Verniory et al. (1967).

**Prognostic value of plasma renin concentration**

So far forty-one patients with hypertension and both renovascular and parenchymal unilateral renal disease have been submitted to nephrectomy or renal artery reconstruction. Thirty-three of these patients have been reviewed at 12 months or longer, four were lost to further observation and four have been followed for a period less than 12 months. The present report will deal only with the first group of patients. All patients except four were seen at intervals of 3 months by one of us for 1 year and yearly thereafter. For the other four patients the follow-up examinations have been carried out by the family physicians.
The patients were classified as cured if the blood pressure was 140 systolic and 90 diastolic or below without hypotensive drugs throughout the study period. The patients were classified as improved if the diastolic blood pressure was at least 25 mmHg less than preoperative levels without hypotensive therapy. The other patients who did not fulfill these criteria were classified as failure. Fig. 1 shows the plasma renin concentration of the three groups of patients. Eight of the twenty-one patients cured and four out of six patients improved by surgery had a plasma renin concentration in the normal range. Three out of six failures had renin levels above the normal range. Renin has been measured in fifteen patients after surgery (six revascularization and nine nephrectomy) and found normal in all but one; this patient will be discussed later (Fig. 2). The retinal signs of malignant hypertension were seen in four out of thirteen patients cured and with high renin, and in two out of three patients unimproved and with renin above the normal level. The other patients had no retinal haemorrhages, exudates or papilloedema. Patency of the by-pass was demonstrated in only one of the three patients who failed to respond to revascularization; this patient had a normal renin level. In the other two patients aortography was not performed. Although the presence of bilateral haemorrhages and exudates may explain the slight increase in renin levels in the two patients who did not respond to nephrectomy and technical surgical failure may account for the failure in the other patient, the restoration of normal blood pressure (eight patients) or reduction of blood pressure (three patients) in patients with normal renin levels clearly demonstrates that renal artery stenosis may maintain a high blood pressure without increasing plasma renin concentration. Brown et al. (1966c) reported that blood pressure was satisfactorily reduced by surgery in six patients with renal artery stenosis and renin concentrations ranging from 24 to 1920 units/l; while in another six patients, with renin ranging from 3 to 30 units/l, surgery did not influence blood pressure.
Verniory et al. (1967) did not find any plasma renin concentration differences between four patients cured by surgery and four patients unimproved by surgery; in both these groups, renin was distinctly above the normal. The series are too small to make comparisons. However there is agreement that surgical failure may occur even in patients with high renin levels.

**Relationship between renin, plasma and extracellular fluid volumes in essential and renovascular hypertension**

It is clear from the preceding paragraphs that the estimation of renin per se in the peripheral venous plasma is of little diagnostic and prognostic value in this disease. These negative findings could be foreseen from the experimental observations quoted in the introduction, indicating that evaluation of the diagnostic and prognostic role of renin should also take into account the state of sodium and fluid balance.

For these reasons we include the data on the simultaneous estimation of sodium and renin plasma concentration, plasma and extracellular fluid volumes in fourteen patients with essential hypertension and in seventeen patients with renovascular disease; the latter were divided into two groups according to whether the renin figures were normal or high (see Table 3).

We choose plasma and extracellular fluid volumes mainly because the bulk of evidence indicates that these volumes are linked in some way to sodium balance, blood pressure, renin and some kidney functions (Gauer & Henry, 1963; Brown et al., 1966b; Pickens & Enoch, 1968; Romero, Staneloni, Dufau, Dohmen, Binia, Kliman & Fasciolo, 1968; Mayerson, 1965; Brown et al., 1966d; Black, 1967; Chobanian, Burrows & Hollander, 1961; Biglieri & Forsham, 1961; Teng, Shapiro & Grollman, 1954; Tarazi, Frohlich & Dustan, 1968; Blumberg, Nelp, Hegstrom & Scribner, 1967; Ledingham & Cohen, 1964).

Of the several factors (Tibblin, Bergentz, Bjure & Wilhelmson, 1966; Eisenberg & Wolf, 1965; Cranston & Brown, 1963; Muelheims & Broun, 1962; Mayerson, 1965; Nicholson & Zilva, 1964; Tarazi et al., 1968) affecting plasma and extracellular fluid volumes, some (exercise, posture, time of day, diet, therapy) have been kept as identical as possible for the two groups by precautions indicated in the Methods section. Other factors (body weight, height and body surface) are not statistically different in three groups of patients (see Table 3) though essential hypertensive patients were, on average, heavier than the others. Age is significantly higher in the essential hypertensive group, but Chien, Usami, Simmonds, McAllister & Gregersen (1966) found no difference of plasma volume with age. Blood pressure is significantly higher in the renovascular hypertensive group with high renin than in the patients with normal renin. None of these patients had clinical signs of cardiac failure or renal insufficiency. All the patients included in the essential group underwent aortography and/or split renal function studies.

The renovascular group includes one case with bilateral renal artery stenosis (patient 17). The other patients had unilateral renal artery stenosis. In ten of these patients the causal relationship between stenosis and the hypertension has been proved by blood pressure returning to normal or by an improvement in hypertension after surgery (patients 3, 6, 7, 10, 11, 12, 13, 14, 15 and 16). In one patient (No. 2) a nephrectomy performed 1 year after the volumes and renin estimations failed to reduce blood pressure. During this period the creatinine clearance had fallen to 35 ml/min. In three cases surgical treatment is too recent to evaluate the effect on blood pressure (patients 4, 8 and 9) while the other patients have not yet come to operation.

Plasma volume of renovascular hypertensive patients with normal renin is significantly increased compared with the other two groups of patients, while statistics demonstrate a
significant difference of extracellular volume only between essential and renovascular hypertensives with normal renin. These data could explain the conflicting results obtained by Frohlich, Ulrych, Tarazi, Dustan & Page (1967, 1968), who found no difference of plasma volume between renovascular and essential hypertensives, and by Streeten, Schletter, Clift, Stevenson & Dalakos (1969) who found higher plasma volume in renovascular patients. In fact, the renovascular group of Frohlich et al. (1968) might have included more patients with high renin level than the group of Streeten et al. (1969).

The heavier weight of the essential hypertensive patients, although not statistically different, may contribute to the decrease in volume values expressed as ml/kg of these patients with respect to the other two groups. As Tarazi et al. (1968) demonstrated that plasma volume correlated inversely with the level of diastolic blood pressure in a group of normal and 'essential' hypertensive patients, the possibility that the higher pressure values of renovascular patients with high renin may affect the comparison of plasma volume with normal renin patients cannot be excluded, even though from the data of Tarazi et al. it does not seem that there is any decrease of plasma volume with increase of diastolic pressure over 110 mmHg.

With such limitations these results might indicate that, at least in some patients with normal renin, a relative sodium retention with an expansion of plasma and extracellular fluid volume could favour an increase of blood pressure either by direct effect or by increase of the pressor sensitivity towards angiotensin, and conversely inhibit the rise of plasma renin concentration. This could be the case of the patient illustrated in Fig. 2 where surgery restored normal blood pressure and the previously expanded fluid volumes while plasma renin concentration slightly increased.

In considering the single renin and fluid volume values of the renovascular patients it is not always possible to find an inverse relationship, and regression analysis demonstrated negative correlations which were not however statistically significant between the fluid volumes and renin; thus the relationship, if any, between these variables in some individual patients may be overridden by other factors.

In order to evaluate whether a combination of the blood pressure, sodium, renin and fluid volume figures could differentiate the behaviour of renovascular hypertensive patients from that of essential hypertensive patients, the quadratic discriminant function has been calculated. The discriminant function analysis has been introduced by Fisher (1936) for separating two species of plants with a linear combination of four variables on the assumption that the sets of correlation coefficients between the variables were not significantly different. Subsequently, to overcome the limitation of the correlation coefficient differences, the quadratic discriminant function has been developed (e.g. see Johnson & Leone, 1964). In this analysis, the coefficients representing the discriminant capacity of the variables are estimated. Then, based on these coefficients, a discriminant value is calculated as a function of the mean values of the two groups and of the correlation matrices. In addition, the function is calculated on the values of each component of the two groups and the result subtracted from the discriminant value.

In the present analysis, on a conventional basis, the quadratic discriminant function values of each patient have been further codified in order to have zero as the discriminant value so that the values for essential hypertension will have a positive sign while those of renovascular hypertension will have a negative sign. Patients whose values have a sign opposite to the one of their own group are considered errors of classification. The greater the number of the errors of classification, the poorer the discriminant capacity of the variables considered.
### Table 3. Blood pressure, renin, plasma and extracellular fluid volume and quadratic discriminant functions in patients with 'essential' and renovascular hypertension

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>Systolic Blood pressure (mmHg)</th>
<th>Diastolic Blood pressure (mmHg)</th>
<th>Renin (u/l)</th>
<th>Plasma volume (ml)</th>
<th>Extracellular fluid volume (ml/kg)</th>
<th>Sodium concentration (mEq/l)</th>
<th>Values of quadratic discriminant function</th>
</tr>
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<tbody>
<tr>
<td><strong>Benign essential hypertension</strong></td>
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<tr>
<td>1</td>
<td>F</td>
<td>54</td>
<td>72.2</td>
<td>162</td>
<td>245</td>
<td>140</td>
<td>7.2</td>
<td>2113</td>
<td>29.3</td>
<td>13715</td>
<td>190</td>
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<tr>
<td>2</td>
<td>F</td>
<td>43</td>
<td>56.8</td>
<td>162</td>
<td>220</td>
<td>135</td>
<td>9.3</td>
<td>2197</td>
<td>38.7</td>
<td>13180</td>
<td>232</td>
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<tr>
<td>3</td>
<td>F</td>
<td>52</td>
<td>62.0</td>
<td>159</td>
<td>180</td>
<td>115</td>
<td>11.2</td>
<td>2230</td>
<td>36.0</td>
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<td>4</td>
<td>F</td>
<td>42</td>
<td>56.0</td>
<td>150</td>
<td>160</td>
<td>105</td>
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<td>1511</td>
<td>27.0</td>
<td>9734</td>
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<td>5</td>
<td>F</td>
<td>50</td>
<td>58.0</td>
<td>162</td>
<td>200</td>
<td>110</td>
<td>7.0</td>
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<td>6</td>
<td>M</td>
<td>39</td>
<td>72.6</td>
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<td>195</td>
<td>120</td>
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Mean 38 61.7 162 209 131 35.8 2342 38.5 14763 241 141
SD 10.3 9.3 7.5 21.8 16.8 22.6 221 5.3 2328 36.0 3.4
Scheffé Test* 7.3 9.8 3.9 12.3 9.6 24.2 150 3.7 1381 15.4 2.27
P n.s. n.s. n.s. n.s. <0.001 n.s. n.s. n.s. n.s. n.s. n.s.
Scheffé Test† 4.9 0.4 1.8 35.4 17.3 23.3 536 8.02 2159 33.6 0.24
P n.s. n.s. n.s. <0.01 <0.05 <0.01 n.s. n.s. n.s. n.s. n.s.

* Comparison with essential hypertension.
† Comparison with renovascular hypertension (normal renin).
(1) Calculated with six variables (systolic and diastolic blood pressure, renin, Na, plasma and extracellular volume expressed as ml/kg) on the essential hypertensive patients and the ten patients in whom surgery cured or improved blood pressure.
(2) Calculated with six variables as in (1) on all the patients.
(3) Calculated with nine variables (age, weight, height, systolic and diastolic blood pressure, renin, Na, plasma and extracellular volume expressed as ml) on all the patients.
Table 3 shows the discriminant values found for each patient in the three types of analysis made according to the key at the bottom of the Table. It is clear that, comparing the values of column 2 with column 3, the discriminant capacity of this analysis (i.e. the possibility of distinguishing patients with essential hypertension from those with renovascular hypertension) is enhanced by increasing the number of variables taken into account or by more appropriate evaluation of them. In fact, the inclusion of the absolute fluid volume figures with weight, height and age permits a better estimate of the fluids volume values. Moreover, the comparison of columns 1 and 2 indicates that the analysis made with six variables can also discriminate very well if only the ten patients with a renovascular hypertension cured or improved by surgery are considered.

The values of columns 1 and 3 of Table 3 demonstrate that the quadratic discriminant function calculated on the variables indicated at the bottom of Table 3 may differentiate essential hypertension from renovascular hypertension. In fact all the single values of the former group have a positive sign while all the values of the latter have a negative sign.
DISCUSSION

These results demonstrate that the estimation of renin, *per se*, in the peripheral venous plasma has a poor diagnostic and prognostic value in renovascular hypertension. On the other hand it has been stressed already that, excluding patients with ophthalmoscopic signs of malignant hypertension, plasma renin concentration is significantly higher in renovascular hypertension than in normal subjects, or in essential hypertension or in hypertension associated with bilateral renal disease (see Table 2). Furthermore, in eleven patients with renal artery stenosis, surgery returned both blood pressure and plasma renin concentration to normal levels.

This particular behaviour of plasma renin concentration in renovascular hypertension, demonstrated also in rabbits (Lever & Robertson, 1964), may have some meaning even though it might appear to contrast with the fact that surgery also decreases blood pressure in patients with a normal renin concentration.

The following observations may be useful before attempting an explanation of the discrepancy, if any, between these observations. The constriction of one renal artery increases renin 'secretion' (Vander, 1967) which, in turn, produces sodium and water retention. The positive sodium balance decreases plasma renin concentration (Brown, Davies, Lever & Robertson, 1964b) and increases the pressor effect of renin (Bianchi *et al.*, 1968). Furthermore increased sodium retention may itself favour an increased blood pressure, either through an expansion of body fluids or through a more direct effect on the arterial wall smooth muscle. This effect is particularly evident in renoprival man (Onesti, Swartz, Ramirez & Brest, 1968; Carlberger & Collste, 1968; Dustan & Page, 1964) or animals (Giovannetti, Bigalli & Balestri, 1965; Orbison, Peters & Christian, 1956).

While this interrelationship between renin, sodium balance and fluid volumes in influencing blood pressure is well established, it remains obscure:

(a) whether such mechanisms may account for the pathogenesis of renovascular hypertension, and, if so,

(b) why the new equilibrium among these factors achieved with hypertension produces, in a limited percentage of patients, an increased plasma renin concentration.

As evidence against a role of such mechanisms in renovascular hypertension, we might consider not only the already cited normal renin levels in some animals or men but also the findings of normal values of both plasma and extracellular fluid volumes in chronic experimental renal hypertension in rats (Ledingham, 1957; Ledingham & Cohen, 1964) or a lack of difference between the plasma volume of renovascular hypertensive patients and that of essential hypertensive patients (Frohlich *et al.*, 1967, 1968) although others (Streeten *et al.*, 1969) have found that the former have higher plasma volumes than the latter.

But these points are far from established. Firstly, because there is other evidence that might indicate that plasma and extracellular fluid volume are involved in chronic experimental renal hypertension (Grollman & Shapiro, 1953; Teng *et al.*, 1954), and secondly, because it is important to keep the following considerations in mind in evaluating the role of fluid volumes in hypertension:

(a) Many factors may affect plasma volume; the blood pressure, for instance, is inversely correlated with plasma volume (Tarazi *et al.*, 1968; Hollander, Chobanian & Burrows, 1961). Thus the comparison between the plasma volume of normotensive and hypertensive animals may be affected by the influence of the blood pressure itself. In comparing plasma volume of
different groups of patients the height, body weight, age, sex, blood pressure and possibly many other aspects should be properly matched. As far as we are aware, no reports where such requirements have been fulfilled have been published.

(b) If we admit a reciprocal influence of renin, sodium state and body fluids in regulating blood pressure, we should measure all these factors concurrently before drawing any conclusion about their pathogenetic role. We are unaware of reports where all these factors have been measured simultaneously.

The results of the simultaneous estimation of renin and of plasma and extracellular fluid volumes indicate the renovascular hypertensive patients with normal renin levels tend, on average, to have higher plasma and extracellular volumes than patients with raised renin levels. Similar findings have been recently obtained in the dog (Bianchi et al., 1970) where the following variables have been measured before and during the development of renovascular hypertension: plasma and extracellular fluid volume, sodium balance, cardiac output, plasma renin concentration, pressor sensitivity to exogenous angiotensin and blood pressure. In fact in the dog with plasma volume expanded by renal artery constriction, renin tends to return to normal levels while in animals with plasma volume unchanged it tends to remain high.

These observations might offer a tentative explanation of the causal relationship between renal ischaemia and hypertension in some patients with normal renin levels. The high blood pressure in these patients could be maintained mainly by a relative expansion of body fluids, which conversely, might also inhibit the plasma renin concentration increase. As has already been stressed, not all patients show an inverse relationship between fluid volumes and renin. The result of the discriminant analysis demonstrates that the combination of fluid volumes and renin figures with some factors which might have some influence on the relationship between these two variables permits a clear separation of renovascular from essential hypertension which, on the other hand, could not be made by the single factors taken separately. In other words, all these factors taken together in some way reflect a difference between the two diseases.

The physio-pathological meaning of this difference is not clear even though it might support the view that in renovascular hypertension the homeostatic equilibrium between renin, blood pressure, sodium balance and body fluids is set at a different level from essential hypertension. From the diagnostic point of view, the possibility of distinguishing renovascular from essential hypertension with simultaneous estimation of renin, plasma and extracellular fluid volume might offer a new safe screening procedure for selecting patients to undergo potentially harmful aortography and split renal function studies.

Evaluation of the prognostic value of this approach will have to await confirmation on larger groups of patients. These preliminary results, indicating that all the ten patients where surgery cured or improved hypertension had a negative value of the discriminant function, are very promising. Only in patient 2 of Table 3 did nephrectomy fail to modify the hypertension, but the renal insufficiency at the time of surgery might explain the failure.

As has been stressed above, the slight differences of body weight, blood pressure and age among the groups of patients might limit the value of these conclusions.

ACKNOWLEDGMENTS

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REFERENCES


Renin and body fluids in human hypertension


G. Bianchi et al.

