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Plasma Renin Concentration in Human Hypertension II: Renin in Relation to Aetiology

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In previous papers (Brown *et al.*, 1965a, 1965b) we have demonstrated, in clinical hypertension, a close inverse relationship between renin concentration and plasma sodium which appears to be independent of aetiology, the height of the arterial pressure, complications, and treatment. The present communication is concerned with an analysis of renin and sodium in hypertension in relation to aetiology. The methods used in this study are as given previously (Brown *et al.*, 1965b, 1965d); data on additional cases have been included, but the series is basically that described earlier. Plasma renin concentrations in a total of 276 hypertensive patients have been compared with those in 125 normal subjects having a mean renin concentration of 8.2; S.D. 2.7 units/l. (Brown *et al.*, 1964d).

Overactivity of the Adrenal Cortex

Primary Aldosteronism due to Adrenal Tumour

In this condition hypertension is caused by an aldosterone-secreting adrenal cortical adenoma (Conn, 1955; Mader and Iseri, 1955; Milne *et al.*, 1957; Conn *et al.*, 1964b). Plasma sodium and total exchangeable sodium are often raised, while potassium is low. Whether all the features of the syndrome can be attributed solely to the excess aldosterone, or whether other hormones produced by the tumour are necessary, has been the subject of discussion (see Ross and Hurst, 1965).

The hypertension and increased exchangeable sodium are accompanied by depression of plasma renin concentration; after removal of the tumour, with correction of the hypertension and electrolyte abnormalities, renin rises into the normal range (Brown *et al.*, 1963b, 1964a–c, 1965d) (Fig. 1).

Alternatively, the administration of spironolactone to patients with this syndrome may correct the hypertension and electrolytes without affecting aldosterone secretion (Brown *et al.*, 1963b, 1964a, 1964b, 1964c, 1965d); plasma renin concentration rises to normal as the sodium falls, emphasizing the inter-relationship between renin and sodium, and showing that the effect of the adrenal overactivity on renin concentration is not a direct one but is mediated by the electrolyte abnormalities (Brown *et al.*, 1963b, 1964a, 1964c).

Estimations of other components of the renin-angiotensin system have been handicapped by relative insensitivity, but in

several cases have given results in general agreement with these measurements of renin concentration. Thus circulating angiotensin has usually, though not invariably, been undetectable in primary aldosteronism (Biron *et al.*, 1962; Morris *et al.*, 1964).

Measurements of "renin activity"¹ have been less consistent. Thus Yoshinaga *et al.* (1963), who used a modification of the method of Helmer and Judson (1963), reported high normal levels in this disease. Kirkendall *et al.* (1964), with a basically similar technique, found plasma "renin activity" variously low or undetectable before operation in a patient with primary aldosteronism, the values rising after removal of the tumour. Findings similar to those of Kirkendall *et al.* (1964), but with an occasional result well in the measurable range before operation, were later published by Conn *et al.* (1964a), who used the extraction procedure of Boucher *et al.* (1964).

Thus, while these tests may sometimes add support to the pre-operative diagnosis of primary aldosteronism, the limits of their reliability are uncertain. In the patients we have studied renin concentration and plasma sodium have appeared closely linked. Sodium values are not given in the case reports of Biron *et al.* (1962), Yoshinaga *et al.* (1963), Conn *et al.* (1964a), Kirkendall *et al.* (1964), and Morris *et al.* (1964), and it therefore remains uncertain whether estimations of renin concentration, renin activity, or angiotensin are capable of providing diagnostic information which cannot be inferred from repeated and accurate measurement of plasma and exchangeable sodium. Leutscher (1964) refers to cases of primary aldosteronism with persistently normal sodium, but we have not so far encountered one. Renin measurements in such patients would be of considerable theoretical and practical interest.

FIG. 1.—Plasma renin concentrations before operation in four patients from whom aldosterone-producing tumours were later removed. Post-operation values also shown in two. Normal mean $\pm$ 1 and 2 S.D. indicated.

¹ The meaning of this term has been discussed previously (Brown *et al.*, 1965b).

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Cushing's Syndrome

The distinctive clinical features of this condition are the result of excessive production of glucocorticoids (see Paschkis *et al.*, 1958). In some cases, as in primary aldosteronism, hypertension may be associated with hypokalaemia and hypernatraemia. The possible mechanisms by which steroid excess produces the electrolyte abnormalities in the two conditions are discussed by Mills *et al.* (1960), Bartter and Fourman (1962), Gwinup *et al.* (1964), Bagshawe *et al.* (1965), Gantt (1965), Ross (1965), Ross and Hurst (1965), Tashima (1965). Moore *et al.* (1954), while emphasizing the difficulty of assessing total exchangeable sodium and potassium (NaE and KE) in conditions where body weight is altered, found NaE (in mEq/kg.) and serum sodium normal in a case of Cushing's syndrome with hypertension. Similarly, Arons *et al.* (1958) found NaE normal and KE low in four of five cases; NaE was raised in only one of the five. Renin measurements are thus of considerable theoretical interest in this disease.

So far we have measured renin concentration in four cases of Cushing's syndrome with hypertension. All had clinical stigmata of the disease, together with raised plasma cortisol and/or increased cortisol secretion rate and/or increased urinary 17-hydroxycorticosteroids. Blood-pressures varied from 200/130 to 148/100 mm. Hg. The plasma renin concentrations found in these patients are shown in Fig. 2.

FIG. 2.—Plasma renin concentrations in four cases of Cushing's syndrome with hypertension. Normal mean $\pm$ 1 and 2 S.D. indicated.

The lowest plasma renin (3 units/l.) was found in the case with the highest plasma sodium (145 mEq/l.). The highest plasma renin (9 units/l.) was close to the normal mean of 8.2 units/l. This patient had a normal NaE (39.0 mEq/kg.), low KE (30.2 mEq/kg.), plasma Na 143 mEq/l., and plasma K 2.2 mEq/l. In the two remaining patients, both of whom had renin concentrations of 7 units/l., plasma electrolytes were not strikingly abnormal (Na respectively 143 and 139; K 3.8 and 4.5 mEq/l.).

Although these observations permit only limited interpretation, they are not discordant with the theme of inverse relationship between plasma renin concentration and plasma sodium.

"Essential" Hypertension

Of 123 untreated patients with diastolic pressures of 100 mm. Hg or more only 11 could be strictly described under this heading. None of these had retinal haemorrhages or exudates attributable to the hypertension; none had proteinuria or urinary infection; and none had a renal abnormality revealed by intravenous pyelography. Renal arteriography was performed in four, and was normal. None had evidence of aortic coarctation or adrenal pathology, and all had a blood urea below 40 mg./100 ml., plasma potassium between 3.9 and 5.2 mEq/l., and a plasma sodium between 135 and 144 mEq/l.

The mean plasma renin concentration in this group (10.0; S.E. 1.5 units/l.) did not differ significantly from the normal mean of 8.2 units/l. ($t=1.07$; $P>0.1$).

The first column of Fig. 3 shows the relation between plasma renin concentration, sodium, and potassium in these 11 patients with "essential" hypertension. The remaining three columns show the relation between renin and plasma sodium in hypertensive patients without retinal lesions when progressively lower categories of plasma potassium are considered. These groups include increasing numbers of patients with primary aldosteronism and Cushing's syndrome, and it can be seen that plasma renin falls and plasma sodium rises in the groups with lower potassium levels. It is possible that similar abnormalities could result from lesions other than primary tumour or hyperplasia of the adrenal cortex (Brown *et al.*, 1964a, 1965d).

FIG. 3.—Hypertension without retinopathy. Shows rise in sodium and fall in renin as groups with progressively lower plasma potassium are considered. The first column comprises the 11 cases considered to have "essential" hypertension (see text). Mean values and S.E. of mean shown for renin and plasma sodium.

Coarctation of the Aorta

Plasma renin concentrations in four cases of hypertension with coarctation of the aorta were in the normal range (Fig. 4). A further estimation made in one of these patients four months after surgical correction of the lesion, with consequent reduction of the arterial pressure, showed no marked change in renin concentration (Fig. 4). The number of patients studied was too small to reveal any slight but systematic difference in plasma renin which might exist in coarctation as a group, compared with normal. It is notable that Morris *et al.* (1964) found arterial angiotensin higher in coarctation than in "essential" hypertension.

FIG. 4.—Plasma renin concentrations in (a) four patients with coarctation of aorta; (b) four patients with pheochromocytoma; and (c) 41 patients with various diseases of the renal parenchyma. Normal mean $\pm$ 1 and 2 S.D. indicated.

Phaeochromocytoma

Plasma renin concentrations in four patients with hypertension due to adrenal medullary tumours were in the normal range (Fig. 4). All of these patients had an increased urinary excretion of catecholamines. The highest renin was in the only case in which retinal haemorrhages and exudates were present. Again the group was too small to show whether or not renin concentration differs systematically from normal in this condition, but if any such difference exists it appears to be slight.

Renal Artery Stenosis

The minimum requirements for this diagnosis for the present purposes were the arteriographic demonstration of a renal artery lesion, together with a persistently lower urine flow and increased urinary creatinine (or inulin) concentration on the suspect side on ureteric catheterization. The presence of a stenosis by these criteria does not, of course, imply that the renal artery narrowing was necessarily the cause of the hypertension.

Fig. 5 shows the plasma renin concentration in 44 untreated cases of renal artery stenosis. Nineteen had no retinal lesions. In most of these renin was in the normal range, though the mean value (12.7; S.E. 1.5 units/l.) was significantly higher than the normal mean ($t=5.1$; $P<0.001$). The distribution of renin concentration in these patients without retinopathy was similar to that found in rabbits with experimental renal artery stenosis and hypertension (Lever and Robertson, 1964).

The 25 cases with renal artery stenosis and retinopathy (bilateral retinal haemorrhages and exudates and/or papilloedema) were in marked contrast, plasma renin concentration ranging from the upper limit of normal to values a hundred times higher (highest, 1,920 units/l.). There was a significant inverse relation between plasma sodium and renin concentration both in the patients with and in those without retinopathy (respectively $r = -0.89$ and -0.63 ; $P<0.001$ and <0.01).

Plasma sodium concentration was significantly lower in the patients with renal artery stenosis and retinopathy than in those without renal lesions (respective means, 135.3 and 140.8 mEq/l.; $P<0.005$). Several of the former group were examples of the hyponatraemic syndrome of severe hypertension, and have been discussed in more detail previously (Brown *et al.*, 1965b). A

raised aldosterone secretion rate was found in a number of these (see also Barraclough *et al.*, 1965).

The unusual combination of renal artery stenosis, hypokalaemia, and increased aldosterone secretion, with raised plasma sodium and low plasma renin concentration was seen in one patient previously reported (Brown *et al.*, 1963b, 1964b, 1964c), who was found to have a renin concentration of 6.5 units/l. in peripheral plasma taken at operation for the correction of renal artery stenosis. After operation the hypertension, excess aldosterone secretion, hypernatraemia, and hypokalaemia persisted, and plasma renin was abnormally low. This conforms closely to the pattern seen in primary aldosteronism, and, as we suggested earlier (Brown *et al.*, 1963b, 1964b), the patient probably has either an adrenal tumour which was not discovered at operation, or autonomous adrenal overactivity in the absence of a tumour (see van Buchem *et al.*, 1956; Bartter and Biglieri, 1958; Relman, 1963). (This case is not included in Fig. 5.) The possible causal relationship between renal or renal artery lesions and adrenal cortical autonomy in this and other instances has been discussed previously (Stanbury *et al.*, 1958; Gowenlock and Wrong, 1962; Wrong 1963, 1964; Conn, 1964a, 1964b; Cope, 1964; Laragh, 1964; Brown *et al.*, 1963b, 1964b, 1964c, 1965c, 1965e). The concept is an interesting one, but conclusive evidence for or against is wanting.

The plasma renin concentrations found in the patients with renal artery stenosis were compared with the severity of stenosis as shown by ureteric catheterization studies.

In seven cases no urine was obtained from the affected kidney on ureteric catheterization, four of these being found at subsequent operation to have thrombosed renal arteries. All seven had severe retinopathy, and their plasma renin concentrations included six of the highest in the whole series (respectively 24, 72, 82, 83, 95, 146, and 1,920 units/l.). In the remaining cases the ratio between urinary inulin (or creatinine) concentration from the post-stenotic and normal kidneys was taken as a measure of the severity of the stenosis. Excluding two patients with renal artery branch constrictions, the ratio had a mean value of 1.9 (range 1.1 to 4.0) in the group without retinal lesions, compared with a mean of 2.5 (range 1.1 to 6.6) in those with retinal lesions. Thus, although there was an appreciable overlap between the groups, those with severe retinopathy and high renin had generally the more severe renal artery stenosis.

In summary, division of the cases with renal artery stenosis into two groups on the basis of the presence or absence of severe retinopathy split them also into two almost distinct ranges of plasma renin concentration (Fig. 5). Together these cases provided a continuous distribution of renin concentration from the lower part of the normal range to levels a hundred times normal. The rise in renin values along this series was closely followed by a progressive fall in plasma sodium, and, rather less closely, by increasing severity of renal artery stenosis.

Patients with Radiological Evidence of Fibromuscular Hyperplasia

Fourteen patients had the appearances of fibromuscular hyperplasia on renal arteriography (see Bernatz *et al.*, 1962; Sutton *et al.*, 1963). All except one were female. Renal artery stenosis was confirmed by ureteric catheterization studies in nine, and the histological nature of the lesion by biopsy in five. The scatter of renin concentration did not differ greatly in this group from that in renal artery stenosis as a whole (mean 17.4; S.E. 3.8 units/l.).

Hyperplasia of the Juxtaglomerular Apparatus

Hyperplasia of the juxtaglomerular cells, usually accompanied by increased granularity, was found on renal biopsy in 12 cases. Eleven of these had renal artery stenosis and one had Cushing's

FIG. 5.—Plasma renin concentration in renal artery stenosis. ("Retinopathy" = bilateral haemorrhages and exudates and/or papilloedema). Normal mean $\pm$ 1 and 2 S.D. indicated.

syndrome. Plasma renin in this group tended to be high (mean 32.9 ; S.E. 6.7 units/l.).

The findings thus support the suggestion that hyperplasia of the juxtaglomerular cells is related to increased secretion of renin, though it must be recognized that an elevated plasma renin concentration could well be achieved by mechanisms other than increased secretion (see Brown *et al.*, 1965f). In the patient with Cushing's syndrome the renal biopsy showing juxtaglomerular hyperplasia was performed at operation for adrenalectomy after spironolactone treatment had been given. This had been accompanied by an increase in plasma renin concentration from 9 to 16 units/l., and clearly could have caused the juxtaglomerular changes.

Renal Lesions other than Renal Artery Stenosis

Forty-one patients had renal lesions other than renal artery stenosis (chronic glomerulonephritis in 15 ; polycystic disease in 4 ; hydronephrosis in 6 ; renal calculi in 2 ; urinary infection with cellular infiltration of the renal parenchyma in 11 ; and tuberculosis, nephrocalcinosis, and hamartoma of kidney one instance each). Renin concentration in these cases was scattered over a wide range (Fig. 4). Several of the cases in this group in which renin was found to be high were examples of the hyponatraemic hypertensive syndrome (see Brown *et al.*, 1965b). It is clearly possible that disease of the renal parenchyma could produce this syndrome by mechanisms similar to those resulting from stenosis of the main renal artery.

Renin in Relation to Haemoglobin Concentration in Renal Artery Stenosis

Polycythaemia has been found in association with a variety of renal diseases (see *Brit. med. J.*, 1961 ; Hillas Smith, 1963 ; Brandt *et al.*, 1963). Although Cotes and Lowe (1963) did not find a significant increase in haemoglobin concentration in patients with renal artery stenosis, Luke *et al.* (1965) described a case of renal artery stenosis with increased haemoglobin concentration and red-cell volume in which nephrectomy cured the hypertension and restored the haemoglobin concentration to normal. This case had severe retinopathy, but the concentrations of the plasma electrolytes were not reported.

Evidence relating hyperplasia of the juxtaglomerular cells to increased erythropoietic activity has been presented by Osnes (1958), Hirashima and Takaku (1962), Reeves *et al.* (1963), and Mitus and Toyama (1964). Hansen (1964) found increased erythropoietic activity in the urine and in extracts of the post-stenotic kidney of rabbits with experimental renal artery constriction. An increase in haemoglobin concentration and in red-cell volume occurred in some animals. However, Cotes and Lowe (1963) did not find an increase in circulating red-cell volume in rabbits with renal ischaemia and associated hypertension.

In 34 untreated patients with renal artery stenosis in the present series the relationship between renin and haemoglobin concentration was not statistically significant ($r=0.244$; $P>0.1$). As pointed out by Cotes and Lowe (1963) and by Jones *et al.* (1965), however, haemoglobin concentration is not always a reliable index of red-cell volume.

Renin in the Hypertensive Disease of Pregnancy

Plasma renin concentration is increased in normal pregnancy (Brown *et al.*, 1963a). In "pre-eclamptic toxemia" ("specific hypertensive disease of pregnancy": Pickering, 1955) we have found renin concentration to be no higher than in normal pregnancies of similar duration, and to be rather lower in the more severely affected cases. This condition has been excluded from the present series, and will be analysed and discussed in detail separately (Brown *et al.*, to be published).

Discussion

These results amplify the previous reports of an inverse relationship between plasma sodium and renin concentration in hypertension (Brown *et al.*, 1965a, 1965b). Renin has been consistently low in hypertension with elevated sodium, as may be found in primary aldosteronism and in Cushing's syndrome. In Cushing's syndrome with normal plasma sodium, renin concentration has been in the normal range, while measures which reduce the increased sodium in primary aldosteronism raise renin concentration to normal.

Many cases of hypertension with renal artery stenosis or parenchymal renal lesions have been found to have normal plasma renin concentration. When such renal lesions have been accompanied by retinal evidence of the malignant phase, however, hyponatraemia and high plasma renin concentrations have been common. This hyponatraemic syndrome is the one form of untreated hypertension in man in which we have consistently found renin concentration to be abnormally high.

These findings in clinical hypertension suggest that plasma renin is governed by changes in sodium balance, and confirm that the relationship is independent of the aetiology of the hypertension. As we have previously shown, however (Brown *et al.*, 1965a, 1965b), this does not exclude other influences on plasma renin, nor does it imply that the low plasma sodium is *per se* the stimulus causing increased renin concentration.

Summary

Plasma renin concentration has been examined in relation to aetiology in a series of patients with hypertension.

The findings are in agreement with the earlier demonstration of an inverse relationship between plasma renin and sodium concentration.

Renin concentration did not differ significantly from normal in uncomplicated hypertension without determined cause.

Where hypertension was accompanied by hypernatraemia, as in Cushing's syndrome and primary aldosteronism, renin concentration was low. Renin was normal in three cases of Cushing's syndrome with normal sodium. In primary aldosteronism renin was increased by a variety of measures which reduced sodium.

Plasma renin was often normal in hypertension with renal disease or renal artery stenosis. Where these lesions were accompanied by severe retinopathy, however, plasma sodium was usually low and renin concentration high. Raised aldosterone secretion and hypokalaemia were found in several of these latter cases.

Plasma renin was normal in patients with aortic coarctation or pheochromocytoma.

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Observations on an Apparent Chloroquine-resistant Strain of *Plasmodium falciparum* in West Africa

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Since their development as synthetic antimalarial drugs during the second world war the 4-aminoquinolines have enjoyed a role of expanding importance throughout the world and are now regarded as the drugs of choice, both for suppression and for therapy, in malaria (Coatney, 1963). Though resistance of human plasmodia to pyrimethamine and proguanil has long been known, the recognition of 4-aminoquinoline-resistant strains of *Plasmodium falciparum* is of relatively recent occurrence. Since 1961, strains showing abnormal response to chloroquine have been reported from Colombia (Young and Moore, 1961; Young, 1962; Moore and Lanier, 1963; Powell et al., 1963), and Brazil (Rodrigues Da Silva et al., 1961; Box et al., 1963) in South America, and from Thailand (Young et al., 1963), Vietnam (Powell et al., 1963), Cambodia (Contacos et al., 1963), and Malaya (Montgomery and Eyles, 1963; Sandosham et al., 1963) in South-east Asia. To date, chloroquine resistance, though suspected (Chemotherapy of Malaria,

1961), has not been reported from the African Continent, where the use of chloroquine as an antimalarial drug is widespread.

In this paper we report the results of some observations which, while not pretending to furnish an absolute and final proof of resistance of *P. falciparum* to chloroquine, do tend to strengthen suspicion of its existence. These observations lead us to believe that there exists in this part of West Africa (Upper Volta) a strain or several strains of *P. falciparum* less sensitive to chloroquine than usually admitted.

Material and Methods

The present report is based on a study of 15 patients from Upper Volta, West Africa, who either developed malignant tertian malaria while taking chloroquine sulphate (Nivaquine) as a suppressive (nine cases) or failed to respond to treatment by this drug or by chloroquine phosphate (Aralen) (six cases).

The patients were children hospitalized in the paediatric ward of the Ouagadougou Hospital. All are African children

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