Plasma Renin Concentration in Human Hypertension IV: Renin in Relation to Treatment and Prognosis

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In previous papers we have seen that in clinical hypertension plasma renin concentration is inversely related to plasma sodium, and we have discussed this association from the aspects of aetiology and complications (Brown *et al.*, 1965a, 1965b, 1965c, 1966a). The present paper is concerned with renin in relation to treatment and prognosis. As we shall show, treatment apparently causes changes in renin mainly when alterations in sodium balance are involved.

The clinical material studied and the methods used are as given previously (Brown *et al.*, 1965b, 1965c, 1966a). The relationship between plasma renin concentration and other components of the renin-angiotensin system, such as substrate concentration, angiotensin concentration, and "renin activity," was also discussed in these earlier papers, and will not be considered further here.

Primary Hyperaldosteronism

In this condition overproduction of aldosterone is found, the most common cause being a benign adrenocortical adenoma (or adenomata) (Conn, 1955 ; Mader and Iseri, 1955 ; Milne *et al.*, 1957 ; Luetscher, 1964 ; Conn *et al.*, 1964). Less often the syndrome may occur in the absence of a discrete tumour (Bartter and Biglieri, 1958 ; Relman, 1963). Typically, plasma sodium is increased, and the raised blood-pressure is accompanied by abnormally low plasma renin concentration (Brown *et al.*, 1963, 1964a, 1964b, 1964c).

Surgical removal of the tumour may correct the electrolyte abnormalities, plasma renin concentration then returning to normal (Brown *et al.*, 1964a, 1965b, 1965c, 1965d). The blood-pressure also falls, though it may not always return to strictly normal levels (see Conn *et al.*, 1964). Occasionally the adenoma is difficult to locate ; in these circumstances the adrenals may suffer ischaemic damage during the course of surgical exploration, or the tumour may not be revealed until both adrenals have been removed and sectioned (Relman, 1963 ; Slaton and Biglieri, 1965).

An alternative method of treatment, which avoids damaging the adrenals in cases where a tumour is not apparent at exploration, is the prolonged administration of spironolactone. By blocking the action of the excess aldosterone this drug corrects the electrolyte abnormalities, and, probably as a consequence, the arterial pressure is lowered. The establishment of normal plasma sodium concentration and normal total exchangeable sodium is accompanied by restoration of a normal plasma renin. Aldosterone secretion rate may, however, be unaltered in these circumstances, thus emphasizing the absence of a direct relationship between aldosterone and renin (Brown *et al.*, 1963, 1964a). One such patient, in whom an adrenal tumour was not found on surgical exploration, has been maintained free of symptoms, with normal blood-pressure, electrolytes, and renin concentration, for more than two years on oral Aldactone-A (spironolactone), 300 mg. daily (Brown *et al.*, 1963, 1964a, 1964b, 1964c). Similar results were obtained over a period of 10½ months in another patient, from whom an adrenal adenoma was later removed (Brown *et al.*, 1963, 1964a, 1965d).

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Hyponatraemic Hypertensive Syndrome

This condition provides a contrast to primary hyperaldosteronism. Though increased aldosterone secretion and hypokalaemia may be present, the plasma sodium is low, and renin concentration high (Brown *et al.*, 1965b, 1965c). Renal artery stenosis or a parenchymal renal lesion was found in 25 cases of this syndrome, all of which also had evidence of the malignant phase (Brown *et al.*, 1965b). The syndrome is therefore of concern when considering the treatment of renal artery stenosis, the malignant phase, and chronic renal failure. We shall discuss each of these aspects separately, though it will be evident that they overlap considerably.

Renal Artery Stenosis

Plasma renin concentration was found to be in the normal range in about one-third of the cases of hypertension and renal artery stenosis studied (Brown *et al.*, 1965c, 1965e). The remainder had elevated renin, there being throughout the whole group a close reciprocal relationship between plasma sodium and renin concentration, and definite, though less close, direct relationship between the severity of the stenosis and the renin level (Brown *et al.*, 1965c). The cases with high renin, low sodium, and severe renal artery narrowing frequently had other evidence of the hyponatraemic hypertensive syndrome, such as hypokalaemia, increased aldosterone secretion, and the changes of malignant hypertension. The effects of treatment were most striking in these hyponatraemic cases.

In one example surgical relief of the renal artery stenosis was followed by restoration of normal blood-pressure, correction of hyponatraemia and hypokalaemia, a fall in aldosterone secretion rate from 1,197 to 142 μg./day, and a fall in plasma renin concentration from 1,920 to 16 units/l. (Barraclough *et al.*, 1965 ; Barraclough, 1966) (Fig. 1).

In another patient the removal of a kidney with a thrombosed renal artery restored normal blood-pressure, while renin dropped from 72 to 17 units/l. (Fig. 1).

In a third case plasma renin concentration fell from 26 to 7.5 units/l. when the blood-pressure was lowered with guanethidine, and the retinal lesions cleared (Fig. 1). At subsequent surgical exploration in this patient a pressure drop of 50 mm. Hg was demonstrated across a renal artery stenosis. After the insertion of a bypass graft from aorta to distal renal artery the blood-pressure, although not restored to normal, was controlled with considerably smaller doses of drugs than were required previously. This last case raises two important points. Firstly, the presence of a renal artery lesion does not necessarily prevent successful drug treatment of the hypertension (see Brown *et al.*, 1960). Secondly, it demonstrates that an elevated plasma renin concentration may in these

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circumstances revert to normal with correction of the arterial pressure before operation.

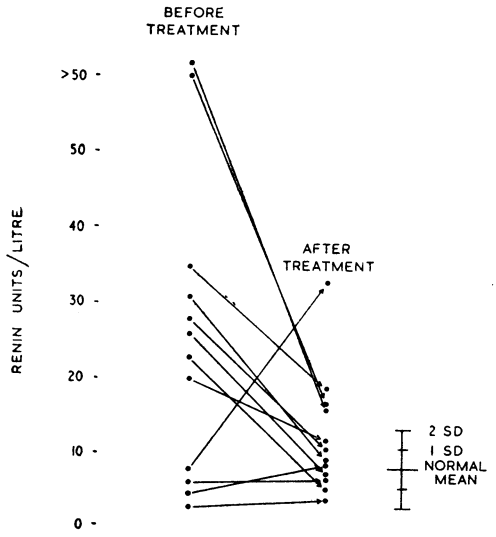

FIG. 1.—Plasma renin concentrations in 12 patients with malignant hypertension before and after treatment. In all cases the retinal lesions had cleared by the time of the second sample. Renal artery stenosis was present in seven of the eight patients initially with elevated renin; in five of these the hypertension was corrected and the retinopathy cleared following surgical repair of the lesion or nephrectomy; hypotensive drugs alone were effective in one patient with renal artery stenosis and in the single case of these eight who did not have renal artery stenosis. Surgical treatment was combined with drug therapy in the remaining patient with a renal artery lesion. Hypotensive drugs only were used in the four patients in whom renin was initially normal or low; the one case showing a marked rise in renin had received thiazides. Additional details are given in the text. The range of plasma renin in normals is also indicated.

Features Indicating a Favourable Response to the Surgical Treatment of Renal Artery Stenosis

Pre-operative plasma renin estimations were available in six patients with renal artery stenosis in whom nephrectomy or correction of a renal artery lesion was followed by a satisfactory reduction in arterial pressure. All these cases had bilateral retinal haemorrhages or exudates or papilloedema before operation, and in all of them the retinopathy subsequently resolved without drug therapy. Renin concentration ranged from 24 to 1,920 units/l. The mean pre-operative plasma sodium was 133.7, S.E. 2.0 mEq/l., and the mean potassium 3.88, S.E. 0.32 mEq/l.

By contrast, six patients with renal artery stenosis who failed to respond to surgical treatment had plasma renin ranging from 3 to 30 units/l. (mean 14.0; S.E. 4.5 units/l.). One of these had unilateral exudates; none of the others had retinal changes. The mean plasma sodium was 139.4, S.E. 1.4 mEq/l., and the mean potassium 3.78, S.E. 0.24 mEq/l., in this group. The differences between the means of both sodium and renin before operation in the two groups were marginally significant (in each $0.02<P<0.05$).

Three further cases of the present series had the combination of retinopathy and high renin concentration, and were not cured by surgery. Two of these were responsive to hypotensive drugs after operation, having been refractory before.

These data suggest the possibility that the patients most likely to respond to surgical treatment of renal artery stenosis may be those with features of the hyponatraemic hypertensive syndrome. Evidence of this syndrome appears in varying degrees in numerous reports of cases successfully treated by surgery (Øster, 1947; Deming, 1954; Brust and Ferris, 1957; Connor *et al.*, 1957; Adams and Newman, 1958; Peabody and Gates, 1958; Dollery *et al.*, 1959; Brown *et al.*, 1960; Laidlaw *et al.*, 1960; Yendt *et al.*, 1960; Gowenlock and Wrong, 1962; Goldberg and McCurdy, 1963; Scherlis and Lee, 1964; Slaton and Biglieri, 1965).

While deficiencies of surgical technique may have accounted for a number of failures in both the present cases and in other series when the prospects were otherwise favourable, it must also be recognized that surgical successes have been reported in patients who did not have retinal lesions, and in whom no other evidence of the hyponatraemic hypertensive syndrome is mentioned—for example, Brust and Ferris (1957), Yendt *et al.* (1960), and Stamey *et al.* (1961). Similar examples may well be concealed in the several papers reporting a high incidence of success but lacking detailed information—for example, Rob (1961), Morris *et al.* (1962).

Measurements of plasma renin or angiotensin have often been suggested as pre-operative diagnostic tests in renal artery stenosis, but in the absence of either adequate assay methods or of a clear understanding of the role of the renin-angiotensin system in renal hypertension their value has been limited (see discussions by Øster, 1947; Deming, 1954; Page *et al.*, 1959; Brown, 1962; Helmer, 1963; Itskovitz *et al.*, 1963; Langford, 1963; Morris *et al.*, 1964; Mulrow, 1964). While the point is far from established, the present observations suggest that an elevated plasma renin concentration may help to forecast a favourable response to renal arterial surgery. If this tentative suggestion should be correct the further issue is then raised whether assay of renin or angiotensin is an essential investigation where such surgical measures are contemplated, or whether the relevant information could be more simply inferred either from repeated and careful estimation of the plasma sodium concentration, or from some more precise measure of the state of sodium balance (see also discussion by Brown *et al.*, 1966b).

Chronic Renal Failure

Bilateral nephrectomy in patients with advanced renal disease may be followed by a fall in plasma renin to very low concentrations (Brown *et al.*, 1966a), an observation which accords with earlier experiments in the rabbit (Lever and Robertson, 1964). This has possible therapeutic relevance in that it may provide a method of lowering plasma renin independently of changes in external sodium balance. Some cases of malignant hypertension with advanced renal failure have extremely low plasma sodium levels, and the plasma renin concentration is then correspondingly high (see Brown *et al.*, 1965b). It is theoretically possible that in these circumstances sufficient angiotensin could be generated to have a substantial direct pressor effect; and it has been suggested (see Verniory, 1965) that bilateral nephrectomy, by lowering renin and consequently angiotensin, may be necessary to control the blood-pressure in some instances.

In one patient with chronic renal failure, malignant hypertension, and a plasma sodium of 132 mEq/l. bilateral nephrectomy was followed by a fall in plasma renin concentration from 35 to less than 1.5 units/l. within 48 hours. Over the same period the blood-pressure decreased from 200/140 to 140/80 mm. Hg, while plasma sodium was unchanged. Though these results are interesting, it would be premature on the present evidence to attribute the fall in blood-pressure simply to the drop in plasma renin concentration.

Malignant Phase of Hypertension

As a group, patients with malignant hypertension were found to have a high mean plasma renin, since numerous examples of the hyponatraemic hypertensive syndrome were included. Nevertheless, it must be stressed that both the retinal and histological stigmata of the malignant phase were seen also in patients with normal or low plasma renin concentration, this always

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having a close reciprocal relationship to the plasma sodium (Brown *et al.*, 1965b, 1965c, 1965e) (Fig. 2). The effect of treatment of malignant hypertension varied widely, but in general tended to restore renin to the normal range.

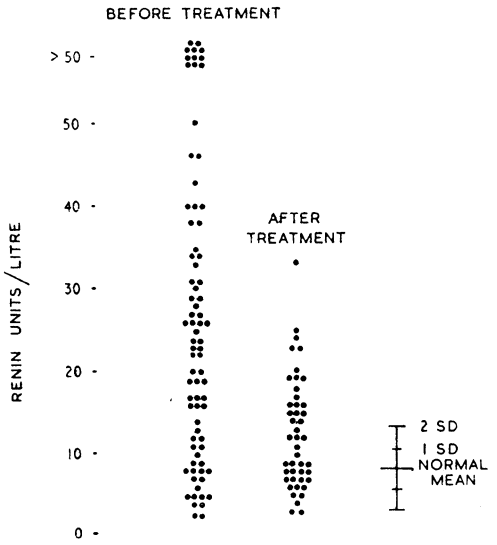

FIG. 2.—Plasma renin concentrations in 78 patients with uncontrolled hypertension and severe retinopathy, compared with values in 45 cases of previous malignant hypertension after reduction of the arterial pressure and clearing of the retinal lesions. The 12 patients from Fig. 1 are the only individuals to appear in both columns of Fig. 2. Normal mean and 1 and 2 S.D. are also shown for renin.

The first column of Fig. 2 shows plasma renin concentrations in 78 patients with severe hypertension and bilateral retinal haemorrhages and exudates. These are compared in the second column of the figure with renin levels found after reduction of the arterial pressure and disappearance of the retinal lesions in 45 patients who had previously had such retinopathy. Only 12 individuals (see Fig. 1) appear in both columns. Successful treatment included correction of renal artery stenosis, unilateral nephrectomy, partial nephrectomy, and a variety of hypotensive drugs both singly and in combination. The distribution of the results after treatment was very close to that for normal subjects. When the patients receiving diuretics were eliminated the renin concentration in the remaining 37 did not differ significantly from the normal mean of 8.2 units/l. ($t=0.89$; $P>0.3$).

The points are illustrated by Fig. 1, which shows plasma renin concentrations in the 12 patients who were studied both before and after clearing of the retinal lesions. In eight the renin was high initially. The mean plasma sodium in these was 136.2 mEq/l., compared with a mean of 140.0 mEq/l. in the four with normal renin. After treatment the respective means were 140.3 and 139.5 mEq/l. Where renin was high before treatment it subsequently reverted to normal. Where renin was normal at the outset it remained virtually unchanged, except in one case where it rose to 33 units/l. Thiazide diuretics were part of the treatment in this last case, and at the time of the second sample plasma potassium had fallen from 4.2 to 3.0 mEq/l., and sodium from 140 to 137 mEq/l.

Diuretics apart, the evidence suggests, therefore, that the correction of the retinal lesions, plasma electrolytes, and renin concentration is largely independent of the method of treatment provided the blood-pressure is lowered satisfactorily.

Effect of Hypotensive Drugs on Plasma Renin Concentration

Apart from the hyponatraemic hypertensive syndrome, discussed earlier, we found no evidence in the present series of a specific change in plasma renin concentration as a result of treatment with a variety of ganglion-blocking or sympatholytic drugs, or with methyldopa. The series did not, however, include observations on patients made frankly hypotensive by therapy, or instances where oedema developed on reducing the blood-pressure.

Thiazide Diuretics

We have previously described how the use of thiazides as an adjunct to hypotensive therapy may lead to an increase in plasma renin concentration. There was a highly significant inverse relationship between plasma renin and plasma sodium concentration in these cases ($r=-0.495$; $n=75$; $P<0.001$), while no significant relationship was found between plasma renin and plasma potassium ($r=-0.079$; $P>0.1$) (Brown *et al.*, 1965b).

Spironolactone

The results of spironolactone treatment in primary hyperaldosteronism have already been described. In other forms of hypertension effects on sodium, renin, and blood-pressure very similar to those caused by thiazides were produced. Thus in three patients the administration of spironolactone, though associated with only a mild fall in blood-pressure, caused distinct hyponatraemia, while renin concentration became abnormally high.

Summary

Plasma renin concentration in hypertensive patients was studied in relation to treatment. Generally changes in renin resulting from treatment were such as to suggest that these probably resulted from changes in sodium balance.

The highest initial plasma renin concentrations were found in the hypertensive syndrome characterized by hyponatraemia, the malignant phase, a renal arterial or renal parenchymal lesion, hyperaldosteronism, and, frequently, hypokalaemia.

In one instance, where this syndrome was accompanied by severe renal disease and chronic renal failure, bilateral nephrectomy caused plasma renin to fall to very low levels.

In other cases, with less advanced renal disease, the raised plasma renin concentration returned to normal with correction of the plasma sodium after either surgical treatment of a renal lesion or the use of hypotensive drugs. This suggests, but does not prove, that renin fell because sodium was raised by treatment in these patients. Retinal evidence of the malignant phase simultaneously resolved.

In other cases of malignant hypertension, where sodium and renin were initially normal, renin concentration remained normal after treatment unless sodium was lowered by diuretics, when renin rose.

In primary hyperaldosteronism with hypernatraemia the low plasma renin concentration could be returned to normal either by removal of an adrenal tumour or by spironolactone therapy, each of which also corrected plasma sodium.

No evidence was seen of a specific effect on renin due to ganglion-blocking or sympatholytic drugs, or to methyldopa.

Thiazides or spironolactone, which caused sodium loss, led to corresponding increases in plasma renin, irrespective of the aetiology of the hypertension.

The possibility is suggested that the cases of renal artery stenosis most likely to respond to surgery may be those with the hyponatraemic hypertensive syndrome, and thus with raised plasma renin concentration.

The pathogenesis of the hyponatraemic hypertensive syndrome, and some of the possible stimuli govering plasma renin concentration, are discussed more fully elsewhere (Brown *et al.*, 1966b).

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Effect of Hydramitrazine (Lisidonil) in the Treatment of Neurogenic Bladder Dysfunction

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Bladder dysfunction is a serious problem in many patients with neurological disorders. Such symptoms as frequency, urgency, and urge incontinence may compromise the patient's well-being and social adjustment. There is thus every reason to give energetic treatment to the neurogenic bladder.

The experience gained in urological treatment of patients with traumatic paraplegia has to some extent been applied to other groups of patients, such as those suffering from multiple sclerosis or non-traumatic paraplegia. This actually marks a big step forward.

However, there is some divergence of opinion on the value of medical treatment of the neurogenic bladder, and several writers have expressed fairly pessimistic views. As a recent example may be cited McAlpine (1965), who states that drugs may be given a trial, but that patients with a tendency to incontinence must be advised to use a urinal, which—as is well known—involves special problems for females.

In our opinion this pessimistic assessment of the value of medical treatment of the uninhibited neurogenic bladder is not justified. We shall try to demonstrate our reasons for this view by reporting our experience of seven years' work with the problems of bladder dysfunction. Lisidonil has occupied a central position in our programme of treatment.

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Material and Results

Chemical Data and Animal Pharmacology

Chemically Lisidonil[1] (Hydramitrazine) is 2-hydrazino-4,6-*bis*-diethyl-amino-1,3,5-triazine-D-tartrate. Animal experiments have shown that the drug inhibits the polysynaptic much more than the monosynaptic reflexes, which indicates that the substance has an inhibitory effect on spinal interneurones. The drug has no effect on neuromuscular transmission. Its action is of the same type as that exerted by mephenesin, but as distinct from the latter hydramitrazine has scarcely any pronounced effect on the brain ; it is thus ineffective in the treatment of convulsions provoked by strychnine or leptazol. Hydramitrazine has no structural resemblances to mephenesin or any other available muscle relaxant. Further details of the pharmacology of Lisidonil are given by Bein (1959).

[1] Lisidonil is manufactured by Ciba Ltd. (Basle). It is not at present marketed in Great Britain.

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