correlation with vascular diseases has also been shown in adults, particularly women, with myxoedema and premyxoedema.[22 23]

The other organ-specific pancreatic antibodies, glucagon- and somatostatin-cell antibodies, are sometimes found in diabetics together with islet-cell antibodies, and also in some non-diabetics with a family history of type I or insulin-dependent diabetes mellitus.[25] They tend to persist in the serum and might thus represent another marker of the genetic tendency to pancreatic autoimmunisation.

Healthy relatives with islet-cell antibodies also belonged to "autoimmune" families, and in at least three out of nine cases the diabetic member had had these antibodies for 10-12 years. Patients with polyendocrine autoimmune disease may develop islet-cell antibodies as long as ten years before clinical diabetes.[12 24 26] This may also happen in people who have relatives with serological evidence of organ-specific autoimmunity. Follow-up studies are needed to confirm that islet-cell antibodies are a marker for potential diabetes. Our data suggest that any search for people with these antibodies should be concentrated in families with an autoimmune predisposition. Identifying such individuals will be particularly important if it ever becomes possible to prevent diabetes in those who are susceptible. The suggestion from our data that autoimmune diabetes may have a stronger tendency to run in families and be more likely to cause complications than in non-autoimmune families needs to be confirmed by further investigations.

We thank Professor I M Roitt for his interest and support, Maura O'Kane and the technicians of the autoimmune serology laboratory for their help, and Ms Philippa Peck and Mrs Ann Read for typing the manuscript. Our thanks are also due to Mrs Alison Smith and Dr G Werther for help in the paediatric diabetic clinic and Dr R R Holman, Dr W G Hughson and Mr R Gelfs for help in collecting blood samples and Miss Jane Hornecastle for interviewing the diabetic patients and their relatives. Financial support was received from the British Diabetic Association, the Medical Research Council, and the World Health Organisation.

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(*Accepted 4 May 1978*)

CONDENSED REPORT

Renal vein renin measurements in children with hypertension

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British Medical Journal, 1978, **2**, 168-170

Summary and conclusions

Renal venous renin activity was measured in 50 children with hypertension. Main renal vein and segmental renal vein sampling was feasible in children as young as 15 months. In all cases in which there was a clear difference in renin secretion between the kidneys—that is, a main vein renin ratio above 1·5—surgery, when undertaken, successfully restored normal blood pressure. Most of the children with main renal vein renin ratios below 1·5 had bilateral disease or apparently normal kidneys. Segmental renal vein sampling contributed useful information additional to that provided by main renal vein measurements and permitted identification of local sources of renin production.

In children with renal transplants who developed hypertension renal vein renin measurements helped in determining the cause and facilitating the management of the raised blood pressure.

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Introduction

The use of renal vein renin measurements in identifying surgically curable forms of renal hypertension in adults is well established.[1-3] Nevertheless, only limited data are available on their use in evaluating hypertension in children. This is due to the large quantities of blood needed for plasma renin assays and the difficulties in taking samples from young children. Some reports indicate that renal vein renin measurements aid assess-

ment of childhood renovascular disease,[1-7] but doubt has been cast on their value in investigating children with various types of renal hypertension.[8 9] We have therefore reviewed our experience of divided renal vein renin measurements in assessing children with various types of renal hypertension.

Patients and methods

We measured differential renal venous renin activity in 50 patients (24 boys and 26 girls) with sustained hypertension. Apart from one 18-year-old transplant recipient their ages ranged from 1 to 16 years (mean 8·8 years). The cause of hypertension in each case was ascribed to one of four groups of disorder—namely, renovascular disease, renal parenchymal disease, essential and other non-renal hypertension, and hypertension after renal transplantation. Thirteen children (mean age 6·7 years) had renovascular disease (five unilateral renal artery stenosis (RAS), seven bilateral RAS, and one intrarenal vascular anomaly). Twenty-six children (mean age 9·2 years) had renal parenchymal disease (11 unilateral, 12 asymmetric bilateral, and three symmetric bilateral), and in most coarse renal scarring was present. Five children (mean age 7·0 years) had essential or other non-renal hypertension; of these, one had an intracranial vascular anomaly and one a neuroblastoma, and in three the cause of hypertension was not found. Six children (mean age 13·5 years) had renal transplants and were investigated with their original kidneys in situ.

Patients undergoing renal vein catheterisation were either basally sedated or anaesthetised and remained horizontal throughout. At no time was renin activity pharmacologically stimulated. When blood pressure was difficult to control antihypertensive treatment was continued. Catheters were introduced through the femoral vein and their positions identified by fluoroscopy. Samples for plasma renin determinations were drawn from both main renal veins and from the caudal inferior vena cava (IVC) below the entry of the renal veins. This sequence of sampling was repeated in each patient, so that two samples were obtained from each site. Nineteen children also underwent segmental venous catheterisation, and samples were obtained when possible from the upper, middle, and lower segmental veins of each kidney. The six patients with renal transplants underwent sampling from the renal veins of the original kidneys, the graft vein, the vena cava or iliac vein above the graft, and the iliac or femoral vein below the graft. When indicated, renal arteriography was combined with renal vein catheterisation after the renal vein samples had been obtained.

Plasma renin activity (PRA) was determined by semi-micro-radioimmunoassay on 0·25 ml plasma.[10 11] The within-assay variation was ±5% in duplicates ranging through the standard curve, and hence the maximum PRA ratio between identical samples caused by imprecision in the assay was 1·1.

The ratio between the renin activity in the renal vein from the diseased kidney (R) and that in the vein from the contralateral normal or less-affected kidney (Rc) was determined. In addition, the ratio between the PRA in the contralateral kidney and that in the caudal IVC (P) was calculated to indicate the degree of inhibition of renin secretion in the contralateral kidney.

Results

Figure 1 shows the R:Rc and Rc:P ratios in the children according to the type of hypertension. The patients were divided into three groups according to their R:Rc ratio and response to treatment (fig 2). The children with transplants were excluded as their results had to be analysed differently.

Fifteen children with R:Rc ratios above 1·5 were treated surgically, 12 by nephrectomy and three by revascularisation. Of these, 13 remained normotensive without drug treatment after operation, and in the other two there was definite improvement in blood pressure and drug dosages could be reduced. In 13 of these children evidence suggested contralateral renin suppression (Rc:P < 1·3). In the remaining two children Rc:P was 1·68 and 1·73 respectively. The first of these children had bilateral RAS and was cured surgically by a two-stage procedure; the other was thought to have unilateral reflux nephropathy but underwent nephrectomy despite the Rc:P ratio because of difficulty in controlling the blood pressure medically.

In 10 children with R:Rc ratios above 1·5 the blood pressure was easily controlled medically, although surgery might subsequently have been necessary. Of these 10 children, one had unilateral RAS, one bilateral RAS, one a complex intrarenal vascular anomaly, two

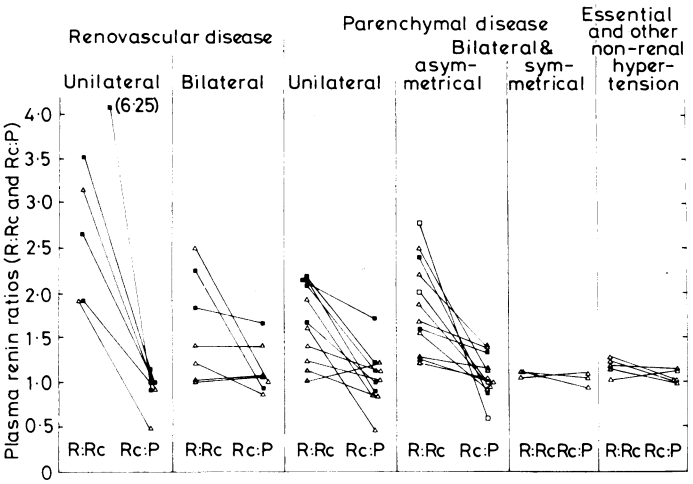

FIG 1—Renal vein plasma renin ratios in children with hypertension caused by renovascular and parenchymal disease and with essential and other non-renal hypertension.

■ = Hypertension cured by surgery. □ = Hypertension improved by surgery. △ = Medical or no treatment.

R = Renal vein affected. Rc = Renal vein contralateral. P = Inferior vena cava.

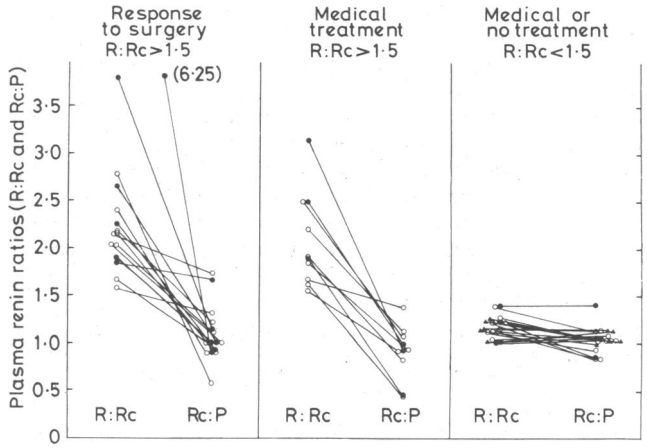

FIG 2—Renal vein plasma renin ratios divided into groups according to R:Rc ratio and response to treatment.

● = Renovascular disease. ○ = Parenchymal disease. ▲ = Essential and other non-renal hypertension.

unilateral renal scarring, and five bilateral renal scarring. Rc:P was below 1·2 in all these patients except one: in this girl, who had bilateral parenchymal disease, Rc:P was 1·39.

Nineteen children had R:Rc ratios below 1·5. None was treated surgically. Four children had complex bilateral RAS; six had bilateral renal scarring; one child had neuroblastoma, which had erroneously been considered to be compressing the left renal artery; and in four children the cause of the hypertension was uncertain. The remaining children had radiological evidence of unilateral disease—three children had unilateral renal scarring and one a small left kidney after a renal venous thrombosis. Rc:P was below 1·2 in all these children except one, who had bilateral RAS and whose Rc:P was 1·4.

Of the 19 children who underwent segmental vein sampling, 10 had bilateral renal scarring, three bilateral main or segmental RAS, one unilateral main RAS with possible segmental artery stenosis, one a unilateral intrarenal vascular anomaly, one unilateral renal scarring with possible hypertensive damage to the contralateral kidney, and three hypertension of unknown aetiology. In most cases in which the appropriate segmental vein could be entered high renin activity was found in segmental samples draining areas of radiological scarring or ischaemia. There was also evidence of renin suppression in samples from intervening radiologically normal areas of kidney. In one child with bilaterally scarred kidneys and malignant hypertension, however, the radiologically normal lower pole of one kidney had the highest

level of renin activity, possibly due to damage caused by the hypertension.

In the six transplanted patients the renal vein renin studies implicated the graft as the cause of hypertension in two children, and the original kidneys in two. In the remaining two children, despite stenosis of the graft artery visible radiologically, the renin data were equivocal.

One child died after renal vein catheterisation combined with cardiac catheterisation and angiocardiography. She had an embolus in the vertebral artery, and death was considered to be a complication of the cardiac investigation.

Discussion

Renal vein renin measurements may be carried out (*a*) to predict the feasibility of correcting the hypertension surgically; (*b*) in patients with bilateral renovascular disease to indicate which kidney should be revascularised first; (*c*) as a diagnostic investigation in children with hypertension and raised peripheral PRA in whom no obvious cause for the raised blood pressure can be found; and (*d*) in transplanted patients to establish whether hypertension is due to the graft or original kidneys. Even though divided renal vein renin measurements have been much used in investigating adult renal hypertension, doubt remains about the interpretation of renin ratios.[1 3] There is also controversy about whether the increased renal vein renin activity—for example, in cases of RAS—reflects increased renin secretion or decreased renal blood flow.[12] The procedure is useful, however, in predicting the likelihood of a surgical cure of hypertension in adults with renovascular disease and of some other types of renal hypertension.[2 13]

Choosing a significant renal venous renin ratio—the minimum that will clearly identify asymmetric renin secretion—is arbitrary and varies among laboratories. When R:Rc is above 1·5 there is a high probability that blood pressure will be improved after operation.[2] Moreover, suppressed renin release from the contralateral kidney (Rc:P $<1{\cdot}3$) has additional value in predicting the response to surgery.[2] There are several reports of false-negative ratios, however, in which R:Rc ratios below 1·5 (or below a slightly higher figure, depending on the chosen significant ratio) have been associated with favourable responses to surgery.[1 9 14 15] Attempts to improve the reliability of the test in adults have included the use of more complex methods of identifying renal ischaemia by relating renal venous renin activity to arterial activity[16] and the use of segmental vein sampling to identify localised sources of renin production.[17 18]

The study of hypertension in children has lagged behind that in adults, but the development of semi-micromethods for measuring plasma renin activity[10] and more refined techniques of arteriography has allowed young hypertensive children to be investigated by techniques that previously could be used only on adults. Our data emphasise the feasibility of obtaining main renal vein and segmental vein samples for renin measurement in children as young as 15 months. The small quantity of blood needed allows multiple samples to be taken without the risk of exsanguination. When coupled with arteriographic and other radiological findings the procedure contributed data that were useful in planning treatment of children with renal hypertension.

In all cases in which there was a clear difference in renin secretion between the kidneys (R:Rc over 1·5) surgery, when undertaken, successfully restored normal blood pressure, although two children required minimal but greatly reduced hypotensive medication after operation. This gave a 100% surgical success rate and a zero incidence of false-positive ratios. Of the 15 children who underwent surgery, apart from the one with bilateral renovascular disease, only one had an Rc:P ratio above 1·3, which could not be explained. The children whose R:Rc ratio was over 1·5 and who received medical treatment did so because either surgical treatment was technically impossible or their hypertension was so easily treated with drugs that surgery was postponed. Interestingly, most of the children with R:Rc below 1·5 had bilateral disease or apparently normal kidneys. Three patients in this group had unilateral disease, however, and two of these had unusual features. The first had evidence of hypertensive damage to the contralateral kidney, and in the second the left renal vein was so small that sampling had to take place at its point of entry into the IVC and the specimen was probably contaminated with caval blood. Adequate segmental vein sampling might have been helpful in the third child, in whom unilateral disease was associated with an R:Rc ratio of 1·22. No child whose R:Rc ratio was below 1·5 underwent surgery, and therefore the incidence of false-negative ratios cannot be identified. Only two children in this group had surgically amenable lesions, however, and in both cases there was doubt about the adequacy of the samples obtained.

Segmental vein sampling contributed useful additional information to that provided by the main vein renin ratios, as has been shown in adults.[17] In view of the incidence of segmental arterial stenosis in childhood renovascular disease, and of localised areas of renal scarring in many children with parenchymal disease, this technique may identify local sources of renin production and decrease the incidence of false-negative main-vein ratios.[9]

Our limited experience with transplanted patients suggests that renal vein renin measurements may help in determining the cause and hence facilitate the management of hypertension.

We thank the paediatricians who referred specimens and patients to us for investigation; the department of cardiology at the Hospital for Sick Children for undertaking the renal vein catheterisation of patients under our care; and the Buttle Trust, the National Kidney Research Fund, and the joint research board of the Hospital for Sick Children and the Institute of Child Health, London, for financial support.

Requests for reprints should be addressed to MJD. Tabulated clinical details, main and segmental renal venous renin values, and the treatment given to these 50 patients will be supplied by MJD on request.

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(*Accepted 9 May 1978*)

ONE HUNDRED YEARS AGO An inquest was held on Wednesday, before the deputy coroner for Manchester, upon the body of John Pritchard, aged five years, who, two months ago, was playing in the street, when a cat bit him on the right arm with great ferocity and was with difficulty got off the boy. He was taken to the infirmary, and in course of time the wound healed. On Thursday last, he began raving. He was taken to St Mary's Hospital, when symptoms of hydrophobia appeared, and he was placed under treatment for that disease, and got better; but the attacks returning, he gradually sank and died on Monday. A verdict of "Death from hydrophobia from the bite of a cat" was returned. (*British Medical Journal*, 1878.)