Renin Levels in Nephroblastoma (Wilms' Tumour)

Report of a Renin Secreting Tumour

J. D. MITCHELL, THELMA J. BAXTER, J. R. BLAIR-WEST, and D. A. MCCREDIE

From Royal Children's Hospital, Melbourne; Department of Pathology, University of Melbourne; Howard Florey Laboratories, Department of Physiology, University of Melbourne; and Department of Paediatrics, University of Melbourne, Victoria, Australia

Mitchell, J. D., Baxter, Thelma J., Blair-West, J. R., and McCredie, D. A. (1970). *Archives of Disease in Childhood*, 45, 376. **Renin levels in nephroblastoma (Wilms' tumour). Report of a renin secreting tumour.** The case history is reported of a child aged 1 year 10 months with malignant hypertension in association with Wilms' tumour. In addition there was a marked electrolyte disturbance, with hyponatraemia and hypokalaemia, and a blood picture of microangiopathic haemolytic anaemia. All these features resolved after removal of the kidney and tumour. Pre-operative plasma renin concentration was extremely high and had returned to normal 3 months after operation. The renal tumour showed a marked degree of differentiation, with glomerulus-like structures attached to tubules, and significant quantities of renin were found on assay. No renin was detected in the renal cortex of the affected kidney. In two other normotensive patients with Wilms' tumour no renin could be detected in the tumour tissue. We consider that the evidence suggests that this patient had a renin-secreting nephroblastoma.

The association of hypertension with Wilms' tumour was first reported by Pincoffs and Bradley (1937) who described 4 patients, in 2 of whom the hypertension remitted after operation, only to rise again with the recurrence of the tumour. The most severely affected of these patients had a well-differentiated tumour containing both cystic and glomerulus-like structures. Extracts of this tumour were tested for pressor activity in dogs with negative results (Pincoffs and Bradley, 1937; Bradley and Pincoffs, 1938).

A mild to moderate increase of blood pressure is now well recognized in Wilms' tumour though its incidence appears to vary considerably in different series. Bradley and Drake (1949) described hypertension in 10 out of 12 patients. Campbell (1951), reviewing the literature, suggested an incidence of 75–90%. On the other hand many comprehensive reviews do not mention the problem (Jagasia *et al.*, 1964; Lalli *et al.*, 1966; Parkkulainen, Sirola, and Sulamaa, 1965; Schweisguth and Bamberger, 1965), while Howard (1957) in a review of 26 cases states that the blood pressure was normal in all patients in whom it was measured.

Though Lattimer, Melicow, and Uson (1958) found a moderate increase in blood pressure in 19 out of 32 patients in whom it was recorded, the highest diastolic reading was only 110 mm. Hg. Severe hypertension with retinal changes and encephalopathy is certainly an uncommon feature but has been described by Daniel (1939), Bradley and Drake (1949), Hughes, Rosenblum, and Horn (1949), Cox and Smellie (1955–56), and Gooding and Raslavicius (1965).

This report concerns an infant with Wilms' tumour and malignant hypertension. In view of a recent report of a possible renin-secreting tumour (Robertson *et al.*, 1967), we decided to check the possibility that the hypertension was related to production of renin by the tumour in this patient. Renin levels were measured in plasma, kidney, and tumour, and compared with findings in two normotensive patients with nephroblastoma. Some of these findings have been reported briefly elsewhere (Blair-West, McCredie, and Mitchell, 1968b).

Case Report

A 23-month-old girl presented on 17 February 1968, because of failure to thrive. Her birthweight had been 3.38 kg. after uncomplicated pregnancy, labour,

and delivery. From the age of 12 months the child had shown poor appetite and weight loss associated with chronic constipation. Polydipsia and polyuria were noticed at about the same age. Her blood pressure was 110/70 mm. Hg at 17 months, and one month later albuminuria (300 mg./100 ml.) was recorded. Microscopy of the urine at that time was normal. On presentation the patient was a thin, ill-looking child. She was afebrile and weighed 9 kg. A large mass was palpable in the right side of the abdomen. Her blood pressure was 260/200 mm. Hg and retinal exudates, haemorrhages, and moderate oedema of the optic disks were present (Fig. 1).

FIG. 1.—Photograph of optic fundus of patient showing retinal exudate and swelling of optic disk.

Initial investigations disclosed Hb 16.2 g./100 ml.; leucocytes 20,600/cu.mm. (73% polymorphs, 20% lymphocytes, 6% basophils, 1% monocytes); blood film and platelet count normal; blood urea 72 mg./100 ml.; serum electrolytes—sodium 126 mEq/l., potassium 2.8 mEq/l., chloride 79 mEq/l.; blood pH was 7.43, PCO_2 41 mm. Hg; standard bicarbonate 26.0 mEq/l., total CO_2 27.6 mEq/l., and base excess + 2.7 mEq/l. Urine showed moderate albuminuria and glycosuria but no cells or bacteria. X-ray of the chest indicated clear lung fields and the cardiac outline appeared normal in size. No abnormalities were detected in a skeletal survey.

A selective renal arteriogram on day 2 showed stretching of the main branches of the right renal artery around a large renal mass with some 'tumour circulation', confirming the diagnosis of Wilms' tumour. Some functioning renal tissue was present at the upper pole. The left renal system appeared normal (Fig. 2). An inferior vena cavogram showed a constant filling defect in the region of the renal veins.

Dactinomycin therapy was begun, and, the following day (day 3), blood was drawn for plasma renin, after which antihypertensive treatment with intramuscular pentolinium tartrate was started. Surgical removal was planned after three daily doses of dactinomycin, but was postponed because of severe haematological disorder and persisting electrolyte imbalance. Progress serum electrolytes, blood urea, diastolic blood pressure, Hb, and platelet levels are shown in Fig. 3. Serum electrolytes tended to remain low despite vigorous intravenous replacement including hypertonic (3%) saline. The blood pressure remained raised though, for the most part, diastolic blood pressure was close to 100 mm. Hg.

By day 4, Hb had fallen to 7.3 g./100 ml. and platelets to 16,000/cu.mm. Dactinomycin therapy was tem-

FIG. 2.—Selective renal arteriography. (a) Early phase with stretching of the main branches of the renal artery around a large mass. Note the areas of tumour circulation scattered through most of tumour. (b) Later phase with some excretion of dye from upper pole.

FIG. 3.—Clinical progress of the patient. Arrows on abscissa represent blood transfusion. Dactinomycin was given on days 2, 3, 4, 10, 12, 14, 16, and 19.

porarily discontinued, 400 μ g. having then been given. The blood picture at that stage was that of a micro-angiopathic haemolytic anaemia with numerous burr cells, micro-spherocytes, and fragmented cells (Fig. 4). Fibrinogen index and prothrombin levels were normal. Acute renal insufficiency was indicated by a rising blood urea and reduced urine output, despite adequate hydration. Fresh blood was transfused producing a further rise in blood pressure to 300/260 mm. Hg with the onset of a triple rhythm and some hepatic enlargement. The patient was then digitalized and intravenous frusemide given. This produced a rapid improvement in urinary output. By day 6 platelets had fallen to 3000/cu.mm. and hydrocortisone therapy was begun, together with ampicillin and methicillin. By day 10 her condition had improved: serum electrolytes were normal, blood urea had fallen to 40 mg./100 ml., and platelets had risen to 42,000/cu.mm. Dactinomycin was again administered on the 10th and 12th days, and laparotomy

was performed on the 14th day, after a further injection of 140 μ g. dactinomycin. In all 5 doses of dactinomycin (totalling 670 μ g.) were given over a period of 12 days before operation, together with a further 140 μ g. at the time of operation. Antihypertensive agents were discontinued 12 hours before operation.

At operation a large encapsulated spheroidal mass was found occupying the outer part of the right kidney about its middle, and compressing the renal pelvis. Blood pressure rose to high levels during operation, but removal of the right kidney and tumour produced an immediate fall in blood pressure which was unrecordable for 45 minutes, despite noradrenaline infusion, but which then rose to supranormal values, necessitating further antihypertensive treatment. The post-operative course was otherwise uneventful, the platelet count rising to 78,000 within 48 hours, and the serum electrolytes and blood urea remaining normal.

Deep x-ray therapy was given for 3 weeks after operation (1850 rads anteriorly and 1850 rads posteriorly to the tumour bed), and a further 2 injections of 140 μ g. dactinomycin were given over the succeeding 6 days. Methylodopa was continued for approximately 6 weeks after operation, and then discontinued without recurrence of hypertension. 12 months later she appears a normal healthy child with blood pressure of 75/50 mm. Hg.

Pathological examination of kidney and tumour.

The tumour was a spherical, encapsulated mass occupying the outer part of the kidney about its middle, and compressing the renal pelvis. It weighed approximately 160 g. and measured 9 × 7 × 6 cm. (Fig. 5). The renal vein was thin and free of tumour. There was no marked distortion of the arterial pattern. On section the mass was yellowish tan in colour. Several areas of haemorrhage and necrosis were apparent and two fluid-filled cysts.

Histological examination showed considerable differentiation of the tumour, with numerous structures closely resembling glomeruli, including capsules, 'Bowman's space', capillaries, and a vascular pedicle. Irregular tubules appeared to be associated with these bodies and the whole was embedded in a moderately dense fibromuscular stroma (Fig. 6). The kidney showed marked tubular dilatation and atrophy, with fibrosis and fibrinoid changes in some glomeruli (Fig. 7). There was some fibrinoid necrosis of afferent arterioles, and larger vessels showed muscular hypertrophy. No juxtaglomerular cells were shown in either renal tissue or tumour.

Microdissection of tumour (Fig. 8). The various parenchymal units dissected free from the tumour mass were heavily embedded in dense fibrocollagenous connective tissue. These ranged from solid little aggregations of cells, many of which were spherical in shape, to well-differentiated renal corpuscles with their attached proximal tubules. The short lengths of proximal tubules dissected free were brittle and rigid and therefore easily fractured. In addition, some renal

FIG. 4.—Blood film of patient, showing burr cells, poikilocytes and microspherocytes.

FIG. 5.—Operative specimen of kidney and tumour.

corpuscles were observed which were isolated structures, except for their attachment to vessels, while others were attached to small blindly-ending tubules; some were of cystic proportions.

Dissection of the kidney showed a marked range of variation; many of the nephrons were small atrophied units while others closely approached the normal. Most of the proximal convoluted tubules were tightly and rigidly coiled making manipulation difficult. Almost without exception the distal convoluted tubules

were cystically dilated for most of their length. Most arterioles were thickened and Ludwig's vessel was frequently observed.

Renin assay. Plasma renin concentration (PRC) was measured by enzyme kinetic assay (Blair-West *et al.*, 1967), similar to the method described by Skinner (1967). The normal range for this method is 10–35 ng./hr. per ml. (i.e. ng. angiotensin produced per hr. of incubation per ml. plasma) for sodium replete adults after 12–16 hours' bedrest. The renin content of kidney cortex and tumour tissue was determined by the method previously described for sheep kidneys (Blair-West *et al.*, 1967). At the present time no data are available for normal human kidneys by this method, though 11–238 Goldblatt units/g. cortex have been detected in the cortex of kidneys removed from adult patients with renal disease. Renin content is expressed in Goldblatt units/g. tissue by comparison with porcine (Nutritional Biochemicals Corporation) and ovine renin preparations. Because much work remains to be done to establish normal levels and appropriate units, the results in this report are interpreted on the basis of the presence or absence of renin in the tissues studied.

PRC was measured in this patient before starting antihypertensive therapy, but 20 hours after the first dose of dactinomycin. Serum Na^+ was then 111 mEq/l. A further blood sample was obtained three months after operation when the patient was clinically well, normotensive, and off all treatment. PRC was 430 ng./hr. per ml. in the pre-operative sample and 23 ng./hr. per ml. post-operatively. Specimens of the tumour and of the kidney were also assayed for renin content. No renin was detected in two samples of kidney cortex, but significant amounts (2.0 and 3.6

FIG. 6.—(a) Low-power view of section of tumour ($\times 65$). (b) High-power view of glomerulus-like structure ($\times 260$).

Goldblatt units/g. tissue) were found in two samples of the tumour.

At the same time two other patients with Wilms' tumour were investigated. Results together with those of our patient are shown in the Table. Neither of these two patients was hypertensive and the tumours showed no differentiation into glomeruloid structures. PRC of Case 1 was 80 ng./hr. per ml. This is above the normal adult range and similar to the increased levels found in normal subjects on a low sodium diet. Renin was undetectable in both tumours but detectable in small amounts in the renal cortex.

TABLE
Renin Levels in Patients with Wilms' Tumour

	Renin Levels		
	Plasma (ng./hr./ml.)	Kidney (U/g. cortex)	Tumour (U/g.)
This patient Pre-op.	430	< 0.3 (2 samples)	3 (mean of 2 samples)
3 mth. after op.	23		
Case 1	80	6.5	< 0.3
Case 2		0.5	< 0.3
Normal range (adult)	10-40		

Discussion

Severe hypertension with encephalopathy and/or retinal changes is an uncommon sequel of Wilms' tumour, but has been described by a number of authors. Possible origins of hypertension in this condition are renal arterial obstruction (Goldblatt *et al.*, 1934), perirenal compression as in the cellophane-wrap kidney (Page, 1939), or production of a humoral agent by the tumour itself. In each circumstance it seems likely that the renin-angiotensin system is the cause of the high blood pressure. However, recent clinical (Mulrow, Lytton, and Stansel, 1966; Brown *et al.*, 1967; Meyer *et al.*, 1967), and experimental (Gross, Brunner, and Ziegler, 1965; Brown *et al.*, 1966; Blair-West *et al.*, 1968a) studies have failed to show consistently raised plasma levels of renin or angiotensin in unilateral renovascular hypertension. A more consistent increase has been reported in malignant hypertension with severe renal disease (Mulrow *et al.*, 1966; Brown *et al.*, 1964a; Massani *et al.*, 1966).

If hypertension associated with Wilms' tumour is in fact due to a humoral factor released from the kidney or tumour, it is likely that this factor is

FIG. 7.—(a) Low-power view of kidney ($\times 65$). (b) High-power view of glomerulus ($\times 260$), stained with PTAH. Arrows point to fibrin deposits in wall of afferent arteriole and in glomerulus.

renin. The investigations in the three children included in this report are not sufficient to settle this point, but there are several pertinent findings.

- (1) Only one child was hypertensive. This child had a very high plasma level of renin pre-operatively and a renin-containing tumour.
- (2) This child also had a severe electrolyte disturbance, such as may be seen with increased activity of the renin-angiotensin-aldosterone system (Bartter *et al.*, 1962; Cannon *et al.*, 1968).
- (3) Hypertension was abolished by removal of the kidney and the tumour, and PRC was normal when measured 3 months after operation.
- (4) The severity of the hypertension in association with the raised PRC is consistent with the relation reported in malignant hypertension.
- (5) The pre-operative PRC was much greater than that seen after severe dietary sodium restriction, which approximately doubles PRC as measured by the present method.
- (6) The histology of the kidney and tumour suggest that either or both might have produced high circulating renin levels. Renal

histology, was that of a microangiopathic haemolytic anaemia, with fibrosis and fibrinoid changes in the glomeruli and some fibrinoid necrosis of the afferent arterioles. A similar picture has been reported in malignant hypertension (Brain, Dacie, and Hourihane, 1962), and also in association with Wilms' tumour (Denys *et al.*, 1967). Both histology and microdissection of the tumour revealed a very advanced degree of differentiation, consistent with the possibility of a renin-secreting tumour.

- (7) Significant quantities of renin were seen in the tumour, but not in the kidney, of the hypertensive patient, while no renin was found in the tumours of two normotensive patients. The low level of renin shown in the kidney in all 3 patients may have resulted from pre-operative dactinomycin treatment, as dactinomycin, by virtue of its effect on messenger RNA protein synthesis, would be expected to decrease renin production.

A number of reports has suggested that the hypertension results from compression of the renal artery by the tumour (Daniel, 1939; Koons and

FIG. 8.—Microdissection of tumour. (A) Two solid aggregations of cells dissected free from dense interstitial tissue ($\times 120$). (B) Montage: Proximal convoluted tubule with its attached renal corpuscle. This was the longest of the nephron components seen. It was rigidly coiled and was broken when manipulation was attempted ($\times 140$). Renal corpuscle $186 \times 160 \mu$. Tubule diameter range $50\text{--}100 \mu$. (C) Upper portion of proximal convoluted tubule attached to a large transparent renal corpuscle. Renal corpuscle $225 \times 211 \mu$. Tubule diameter range $74\text{--}87 \mu$. (D) Upper portion of proximal convoluted tubule and its attached renal corpuscle ($\times 140$). Renal corpuscle $161 \times 136 \mu$. Tubule diameter range $50\text{--}87 \mu$. (E) Group of renal corpuscles, unattached except to a blood vessel and to small remnants of tubules. One small blindly-ending tubule is seen here ($\times 50$). (F) Enlargement of tubule in Fig. E clearly seen to terminate in a small diverticulum ($\times 120$).

Ruch, 1940; Cox and Smellie, 1955-56). Increased tension within the renal capsule producing a 'cellophane' wrap effect has also been postulated as a possible cause (Koons and Ruch, 1940; Hughes *et al.*, 1949; Cox and Smellie, 1955-56). On the other hand Pincoffs and Bradley (1937) reported two patients in whom hypertension subsided with removal of the tumour and kidney, only to recur with the development of metastases. In a subsequent patient Bradley and Drake (1949) found that hypertension was relieved by pre-operative irradiation, and blood pressure remained normal after nephrectomy until the development of metastases, when hypertension recurred. These observations suggested the production of a humoral agent by the tumour, but these workers were unable to show pressor activity in tumour extracts (Bradley and Pincoffs, 1938; Bradley and Drake, 1949). Several cases reported showed well-differentiated tumours with the presence of glomeruloid and tubular structures (Bradley and Drake, 1949; Hughes *et al.*, 1949; Cox and Smellie, 1955-56; and Gooding and Raslavicius, 1965). Such marked differentiation is compatible with production of renin by the tumour. More recently Robertson *et al.* (1967) described a 16-year-old boy with severe hypertension associated with a small renal tumour of haemangiopericytoma type. Hypertension remitted after removal of the tumour and large quantities of renin were found in tumour extract. It appears possible that this was a renin-secreting tumour, and as such may have been responsible for the hypertension in this patient. In our patient other causes of high plasma renin levels may be suggested. The main branches of the right renal artery were stretched around the tumour and this could have produced renal ischaemia. However, the renal arteries did not appear abnormal on pathological examination, and the histological changes in the kidney resembled those seen in malignant hypertension rather than those in renal ischaemia, where the affected kidney is generally spared the ill effects of severe hypertension (Heptinstall, 1966). Another important feature in our patient was the severe electrolyte disturbance. Salt depletion is a potent cause of stimulation of the renin-angiotensin-aldosterone system (Brown *et al.*, 1964b; Veyrat *et al.* 1964; Binnion *et al.*, 1965), and marked hyponatraemia was present when the original plasma renin estimation was made. On the other hand plasma renin was considerably higher than that seen with severe salt depletion. Moreover a severe salt-wasting condition appears commonly to result from malignant hypertension rather than to be the cause of it (Barracrough, 1966).

A major difficulty in the study of these patients is the urgency of treatment. There is little time for preliminary studies of electrolyte balance before the start of anti-tumour therapy and preparation for operation, though clearly a more comprehensive study of electrolyte balance in relation to plasma renin levels would assist assessment of the role of the tumour in renin production. In particular the response to sodium loading would help determine autonomy of renin production (*British Medical Journal*, 1968).

The biochemical and haematological features of this child's illness rapidly reverted to normal after operation. The blood pressure returned to normal rather more slowly, suggesting that secondary hypertensive changes in the opposite kidney may also have been playing a role.

The fact that appreciable quantities of renin were found in the tumour but not in renal cortex appears to confirm that our patient had a renin-secreting tumour. Though the actual concentration was not high, because of the large size of the tumour, this would still represent a large quantity of renin. Dactinomycin, moreover, reduces tumour mass and may have inhibited renin production by the tumour as well as by the kidney. The failure to reveal any characteristically staining juxtaglomerular cells is perhaps not surprising in a tumour of this nature despite the very advanced degree of differentiation seen. The combination of a high PRC reverting to normal after operation, the presence of renin in the tumour but not in the affected kidney, and the absence of renin from the tumours of two normotensive patients, suggest a renin-secreting tumour.

Thanks are due to Drs. A. Murray Clarke and T. G. Maddison for referral of patient and permission to report this case.

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Correspondence to Dr. D. A. McCredie, Royal Children's Hospital, Flemington Road, Parkville. Victoria 3052, Australia.