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Analysis of 100 children with severe and persistent hypertension

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Gill, D. G., Mendes da Costa, B., Cameron, J. S., Joseph, M. C., Ogg, C. S., and Chantler, C. (1976). *Archives of Disease in Childhood*, **51**, 951. **Analysis of 100 children with severe and persistent hypertension.** In 100 children with persistent hypertension seen over the past 5½ years the commonest causes of hypertension were chronic glomerulonephritis, reflux nephropathy, coarctation of the aorta, and obstructive uropathy, accounting for some 70% of cases. 17 children have died, but in the remainder hypertension has been controlled by surgery, chronic haemodialysis, or by the use of pharmacological agents. Methyldopa was the commonest drug used, and the children appeared relatively resistant to the side effects of this and of other drugs, even when large doses were used. The improvement in the prognosis of severe hypertension in childhood indicated in this survey is largely due to the availability of chronic haemodialysis and transplantation for end-stage renal disease, but the advances in diagnostic methods and surgical techniques and the introduction of new drugs have also contributed.

There have been many excellent reviews of childhood hypertension in recent years (Loggie, 1971; Lieberman, 1974; Rance *et al.*, 1974). The last major British review was that of Still and Cottom (1967). The purpose of this review is to analyse our experience of childhood hypertension at Guy's Hospital over the last 5½ years, to consider the aetiological factors, to study the outcome, and to review the efficacy of the drugs used to manage hypertension.

This study included children aged 0–15 years inclusive at presentation and seen at Guy's Hospital between 1 January 1970 and 30 June 1975. Hypertension was defined as a blood pressure persistently in excess of the upper limit of 'normal,' defined as the mean plus two standard deviations for children of different ages (Table I). Normal blood pressure values were taken from the data of Haggerty, Maroney, and Nadas (1956), Moss and Adams (1962), Londe (1966), and Mitchell *et al.* (1975). Hypertension was deemed persistent when present for longer than 3 months in a condition unlikely to resolve spontaneously.

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Patients and methods

Age, race, and sex distribution of patients. The ages and the sex distribution of the children at presentation are shown in the Fig.; 12% of the children presented under the age of 1 year. There were 58 boys and 42 girls. 90% were Caucasian, the remainder being immigrants from the West Indies, India, Pakistan, Nigeria, and Malaya. The mean age of the Caucasian children at presentation was 8·1 years, while that of the immigrant children was 5·8 years.

Investigations. The range of investigations performed in a child with hypertension is shown in Table II. The types of investigations and frequency were, of course, related to the initial clinical diagnoses. The relatively noninvasive procedures such as intravenous urography were often carried out, and of 50 performed at Guy's after transfer, 62% were abnormal. Recently dynamic renal scintillography using technetium 99^m diethylene triamine penta acetic acid (DTPA) was added to the diagnostic evaluation and was abnormal in 11 of 13 selected children in whom it was performed. Nine renal arteriograms were done, without complication and all were abnormal. Bilateral renal vein renin activities were measured in 6 children.

Cause related to age groups. Causes of the hypertension are shown in Table III. Guy's Hospital is a referral centre for both paediatric nephrology and

TABLE I

Blood pressure values

Age (years)	Normal children				Present series (mean mmHg)	
	Mean mmHg		Mean + 2SD			
	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
0–2	95	55	110	65	152	106
3–6	100	65	120	70	163	113
7–10	105	70	130	75	166	115
11–15	115	70	140	80	158	113

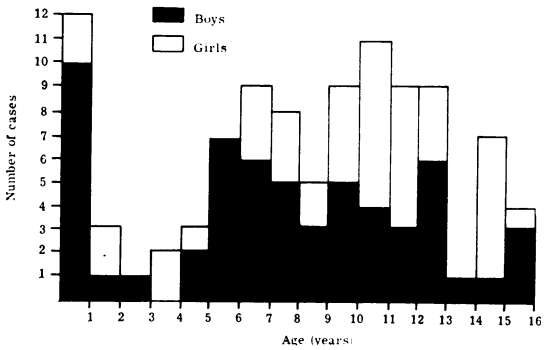

FIG.—*Age of children at presentation.*

TABLE II

Investigations in a child with hypertension

Blood	Full blood picture
	Urea, electrolytes, creatinine
	Glomerular filtration rate
	Calcium, phosphate, alkaline phosphatase
	Cholesterol ± lipoprotein electrophoresis
	Plasma proteins
	Diurnal plasma cortisol
	Peripheral vein renin/aldosterone
	Blood gases
Urine	MSU + microscopy
	Urinary electrolytes
	Urinary protein
	Vanillylmandelic acid (VMA) excretion
	Urinary steroid excretion
X-rays	Bone age
	Chest
	Skull
	Intravenous urography
	Renal arteriography
Other	Electrocardiography
	Dynamic renal scintillography
	Static renal scintillography
	Isotope renography
	Renal vein renin estimation
	Cardiac catheterization

TABLE III

Conditions associated with hypertension

	Age (years)			
	0–1	1–5	6–15	All
Chronic glomerulonephritis		2	33	35
Coarctation of aorta	8	5	2	15
Chronic pyelonephritis/reflux nephropathy			14	14
Obstructive uropathy	1	1	4	6
Haemolytic-uraemic syndrome	1	2	3	6
Renovascular	1	3	2	6
Polycystic kidneys		1	3	4
Dysplastic kidneys			3	3
Cystinosis			3	3
Hypoplastic kidneys		1	1	2
Nephronophthisis			2	2
Wilms's tumour	1			1
Papillary necrosis		1		1
Essential			1	1
Obesity			1	1
Total	12	16	72	100

cardiology and the high proportion of renal and cardiac patients may be influenced by this factor. To ascribe a single cause for hypertension is an over simplification, as several factors such as chronic renal failure, transplant rejection, and corticosteroids may be implicated in any one patient. The aetiology at different ages is given in Table III, showing that under the age of 5 years coarctation of the aorta and renovascular lesions account for 60% of cases. Chronic glomerulonephritis and chronic pyelonephritis or reflux nephropathy accounted for 65% of cases in the 6 to 15-year-old group. Only one child aged 12 years (with young hypertensive parents) was thought to have essential hypertension, and severe obesity was the only acceptable explanation for hypertension in one child.

Presenting features. The presenting features which prompted measurement of blood pressure are shown in Table IV. 49% of the children had symptoms, 19% became hypertensive while under observation for chronic renal failure, 16% presented with a cardiac

TABLE IV

Clinical presentations

Headache	16
Cardiac murmur	16
Tiredness	8
Enuresis	5
Epistaxis	4
Cardiac failure	4
Convulsions	4
Abdominal pain	3
Haematuria	2
Anorexia	1
Short stature	1

murmur, and in 17% raised blood pressure was an incidental finding.

Complications of hypertension. 11% of the children had hypertensive fits. In 9 the fits occurred in untreated hypertension; only 2 children had fits while on hypotensive therapy. As a consequence of hypertensive encephalopathy, 2 children experienced temporary cortical blindness, and one developed a hemiplegia; one boy suffered a small subarachnoid haemorrhage while on warfarin for chronic progressive nephritis.

Results

Results of follow-up to date are shown in Table V. 17 children died, 10 as a result of chronic renal failure, 4 after failed renal transplantation, 1 while on chronic dialysis, and 1 after repair of bilateral renal artery stenosis. One child had multiple peripheral renal arterial stenoses which were not amenable to surgical correction; the hypertension failed to respond to drugs, and the child died of a cerebral haemorrhage. The mean age of the children who died was 6·3 years.

Of the 39 children treated by dialysis or transplantation 34 are still alive. 43 of the 100 children have either stable or improving renal function over the period of follow-up while in 6 children glomerular filtration rate is slowly declining. 71 children were treated for a prolonged period with antihypertensive drugs. This group includes some children who became hypertensive after transplantation; children not included in this group were either taken immediately onto dialysis or operated on for coarctation of the aorta.

Management of hypertension. 15 children had operative repair of coarctation which in all cases corrected the hypertension. The remainder of this report concerns those 71 children who received antihypertensive drugs for prolonged periods and includes children with renal artery stenosis all of whom required vigorous antihypertensive treatment before operation.

The policy for treatment and the drugs used are shown in Table VI. In 40 of the 71 children blood pressure was adequately controlled by the use of one or two drugs—either a diuretic or methyldopa alone, or a combination of both. The range of dosage used is shown in Table VII. It is our policy to increase each drug to maximally tolerated dosage before introducing another drug. As the drug dosages are not normally distributed, the mean dose tends to be higher than the median. Frusemide was the most frequently used diuretic, as there is evidence (Wrong, 1973; Loggie, 1971) that frusemide is a more potent diuretic and a more useful hypotensive agent than the thiazides in hypertension associated with chronic renal failure.

TABLE V

Present status and results of treatment of hypertensive children

Diagnosis	No.	Stable renal function	Dialysis/ transplant	Dead	Treated with drugs	Blood pressure controlled by drugs
Chronic glomerulonephritis	35	10	18	5	29	27
Coarctation of aorta	15	15	0	0	2	2
Chronic pyelonephritis	14	2	11	2	12	11
Obstructive uropathy	6	3	0	3	5	5
Haemolytic uraemic syndrome	6	2	2	2	5	3
Renovascular	6	4	0	2	6	4
Polycystic kidneys	4	3	0	1	3	3
Dysplastic kidneys	3	0	3	0	2	2
Cystinosis	3	0	2	1	2	2
Hypoplastic kidneys	2	0	1	1	0	0
Nephronophthisis	2	0	2	0	1	1
Wilms's tumour	1	1	0	0	1	1
Papillary necrosis	1	1	0	0	1	0
Essential	1	1	0	0	1	1
Obesity	1	1	0	0	1	1
Total	100	43	39	17	71	64

TABLE VI

Treatment policy and drugs used

Treatment policy	Drug	Number of occasions used
(1) Diuretic alone	Methyldopa	64
Methyldopa alone	Frusemide	31
(2) Methyldopa + diuretic	Thiazide	25
Methyldopa + bethanidine	Bethanidine	26
	Propranolol	19
(3) Methyldopa + bethanidine + diuretic	Hydrallazine	6
(4) Other combinations	Diazoxide	5
	Reserpine	4
	Spironolactone	4
	Minoxidil	4
	Amiloride	2
	Practolol	1
	Guanethidine	1
	Prazosin	1

TABLE VII

Drug dosages (oral) (mg/kg per day)

Methyldopa	6–60 mean 27
Bethanidine	0·4–11·0 mean 4
Propranolol	0·8–15·0 mean 6·3
Frusemide	0·6–16·0 mean 5
Bendrofluazide	0·08–0·71 mean 0·2
Chlorothiazide	10·0–42·0 mean 26
Hydrallazine	1·0–7·4 mean 3·3
Diazoxide	3·4–28·0 mean 14·0

In addition, the parents' and children's attention was drawn to the importance of a restricted salt diet, though this was often difficult to achieve.

Thirteen children required 3 drugs to control hypertension, and our usual policy was to combine methyldopa, bethanidine, and a diuretic. In 17 children blood pressure was extremely difficult to control, requiring repeated drug manipulation and in 7 a normal blood pressure could not be achieved. Interestingly, 4 of the 6 children with renovascular hypertension had particularly severe hypertension. As can be seen from Table VI, the 'fourth line' drugs included propranolol, diazoxide, reserpine (in the earlier days; this drug is now rarely used), hydrallazine, minoxidil, and spironolactone. Amiloride, practolol, guanethidine, and prazosin were rarely used and for short periods only, and will not be commented on. Many of these 17 children had very labile hypertension and needed to be seen frequently (weekly or fortnightly) in the ward or as outpatients to monitor blood pressure. In addition, the patients of a few of the children were trained in the use of a sphygmomanometer at home and advised to notify the hospital if designated pressures were exceeded.

Oral hydrallazine and diazoxide were the most successful agents in controlling refractory hypertension. We have recently used minoxidil on 4 children as part of a prospective trial which will be reported in detail elsewhere; 2 of the children responded to minoxidil in combination with frusemide and propranolol after failure of all other drugs to control the hypertension.

No precise comments can be made on the side effects of drugs in a retrospective review such as this. On starting therapy methyldopa frequently induced drowsiness, lethargy, somnolence, and occasionally depression. These symptoms subsided either on continuing treatment or on reducing dosage. Bethanidine occasionally caused postural hypertension, and this was an indication for not increasing or lowering the dosage. Propanolol induced excessive bradycardia in several children, and cardiac failure in 2 children. One child while on propranolol developed a high pyrexia secondary to a virus infection; the pulse rate remained low and acute tubular necrosis occurred, presumably due to a fall in renal perfusion. As expected, the long-term use of diazoxide was complicated by hirsutism and hyperglycaemia.

One brief example may emphasize the effect on renal function of control of severe hypertension. A 9-year-old girl had severe hypertension (blood pressure 220/140 mmHg) and was in renal failure (^{51}chromium EDTA clearance 15 ml/min per 1·73 m^2) secondary to reflux nephropathy. With control of blood pressure achieved by a combination of frusemide, methyldopa, bethanidine, and diazoxide, chromium EDTA clearance doubled to 30 ml/min per 1·73 m^2, 2½ years later.

Discussion

The experience of childhood hypertension, with particular reference to its causes and treatment, in a paediatric nephrology and cardiology centre has been reviewed. In this series primary renal disease caused persistent secondary hypertension in 83% of cases. Still and Cottom (1967) found that 70% of their patients were hypertensive secondary to renal disease. Both theirs and the present series are affected by referral selection. Aderele and Seriki (1974), Rance *et al.* (1974), McCrory and

Nash (1952), and other reviewers of childhood hypertension all concur that primary renal disease is its commonest antecedent. In the present series, acquired rather than congenital renal disease accounted for 57% of cases. 6% of children became hypertensive after survival from severe haemolytic uraemic syndrome—it is expected that the increasing number of survivors from this syndrome will make a growing contribution to childhood hypertension (Gianantonio *et al.*, 1968). 26% of children developed hypertension in association with a congenital urinary tract anomaly and renal insufficiency. Many of these children had, in addition, an acquired urinary tract infection.

Blaufox (1971) suggested that coarctation of the aorta was the cause of hypertension in about 10% of children. Still and Cottom detected this in 11% of their series, whereas coarctation accounted for 15% of our cases. Rance *et al.* (1974) found renal artery stenosis in 13% of their series; Still and Cottom's (1967) incidence of renal artery anomalies was 9%, while ours was 6%.

The prevalence of childhood hypertension, and the detected incidence of essential hypertension appears to be greater in the United States than in Europe (Lieberman, 1974), but published reports are scanty in Europe. Londe *et al.* (1971) reported on 74 asymptomatic hypertensive children, of whom 69 were designated as essential. There were strong correlations between a family history of obesity and hypertension and hypertension among children. Zinner, Levy, and Kass (1971) suggested a strong familial aggregation of blood pressure in childhood. Loggie (1971) could find no definable cause for hypertension, except obesity, in about 20% of her cases. The paucity of cases of essential hypertension in both this and in Still and Cottom's (1967) series is probably explained by racial differences and by referral selection.

Symptoms in children with hypertension are very variable, ranging from none at all (Blaufox, 1971), to 'classical' symptoms of headaches, convulsions, and cardiac failure, to symptoms not directly attributable to, or suggestive of, hypertension. Sheth, Duke, and Rance (unpublished, quoted by Rance *et al.*, 1974) found that more than one-third of children with hypertension had no symptoms resulting from the hypertension. In the present series we noted that17% of children were asymptomatic, while others had symptoms, for example, tiredness, abdominal pain, and short stature, which might not altert one to measure the blood pressure. Indeed, the only symptoms in one boy with a blood pressure of 270/180 mmHg, secondary to bilateral renal artery stenosis, were lethargy and abdominal pain.

The precision and safety of diagnostic methods have been much improved by the advances in renal arteriography and the introduction of dynamic renal scintillography and plasma and renal vein renin estimations. One child in this series had no obvious renal arteries at aortography but selective renal angiography showed bilateral severe stenosis with poststenotic dilatation. Reconstructive surgery on the left and autotransplantation on the right was successful in reducing the blood pressure to normal. A full report has been presented elsewhere (Gill, 1975).

Plasma renin determinations are useful in excluding a nonrenal cause for hypertension (Dillon and Ryness, 1975) and selective renal vein renins are valuable in determining whether the hypertension of a child with bilateral disease is likely to be ameliorated by surgery to one kidney. One child had bilateral pyelonephritic scarring and renal scintillography showed poor arterial perfusion of the upper and middle part of the left and lower part of the right kidney; branch renal vein renin activity was raised in these areas and it was decided that surgery was not feasible. She has responded to minoxidil after other drugs failed to control her hypertension. These advances and the possibility of treating uraemia by dialysis and transplantation may account for the smaller mortality (17%) of this series compared with the series of Still and Cottom (56%) and Aderele and Seriki (27%).

There is little information on the effectiveness, safety, and combination of drugs in childhood hypertension (Loggie, 1969a, b, 1971). The maximum drug dosages reached in this series are larger than those recommended elsewhere (Rance *et al.*, 1974; Blaufox, 1971), and reflect our policy to increase drug dosage to maximally tolerated levels before changing therapy. A diuretic or methyldopa are the drugs of first choice. Pickering (1974) states that most of his adult hypertensives find the side effects of methyldopa intolerable. Though our experience in many adult patients confirms this, it has not been our experience or that of Loggie (1971) in children; propanolol may be of greatest value when there is excessive renin secretion (Bühler *et al.*, 1972). Hydrallazine, diazoxide, and α-blocking vasodilators may be reserved for children with refractory hypertension. Current problems with practolol and prazosin in adults probably preclude any prospective trials of their use in children.

In conclusion, while much can be learnt from present experience, our knowledge of the incidence

and spectrum of childhood hypertension will remain incomplete until measurement of the blood pressure becomes routine in the examination of infants and school-age children and the results of population surveys become available.

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