

# Severe Hypertension in Childhood

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The natural history of hypertension in childhood is poorly documented. More data are required, not only as regards aetiology, but also as a guide to prognosis, and for the assessment of effective hypotensive agents. We have reviewed those children with a raised blood pressure seen at The Hospital for Sick Children, Great Ormond Street, during the 10-year period 1954-64. The normal values of the blood pressure in children of different ages, and their variations due to cuff size and emotion, are well established (Moss and Adams, 1962; Nadas, 1963). Having full regard for these precautions, only those children with severe hypertension were selected for this series. All patients with a sustained diastolic blood pressure of over 120 mm. Hg were included, if this was accompanied by the presence of cardiomegaly on clinical examination, or left ventricular hypertrophy on ECG. Cases of acute nephritis in which the hypertension was a temporary phenomenon were excluded.

An average of 5 patients fulfilling these criteria were seen each year (Fig. 1). The slight increase over the past 5 years may reflect more children being referred for specialized investigations. There was no sex preponderance and the series included 27 girls and 28 boys.

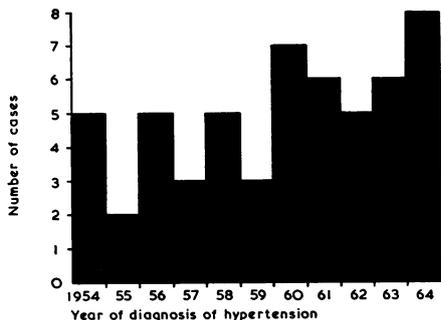


FIG. 1.—Numbers of cases of hypertension diagnosed from 1954-1964.

## Aetiology

Table I shows the aetiological diagnosis in 55 cases of severe hypertension. Ultimately 35 children (64%) had evidence of pyelonephritis, either on renal biopsy or at necropsy. In approximately half (16 cases) there had been a previous history of urinary infection, the original infection occurring under 6 months of age in 50% and under 3 years in 90%.

**Primary pyelonephritis.** We have used this term to describe those patients with evidence of pyelonephritis, in whom there was no preceding obstructive lesion of the urinary tract, or any known structural abnormality of the kidney itself. 18

TABLE I  
*Aetiological Diagnosis in 55 Children With Severe Hypertension*

	Boys	Girls	Total	%
Primary pyelonephritis ..	5	13	18	33
Secondary pyelonephritis ..	9	4	13	26
Glomerulonephritis ..	4	2	6	11
Renal artery abnormalities ..	—	5	5	9
Coarctation of aorta ..	3	3	6	11
Miscellaneous ..	7	—	7	12

patients were considered examples of primary pyelonephritis. They were the largest single group, and consisted of 13 girls and 5 boys with an average age of 9 years. Vesico-ureteric reflux was demonstrated in 9 out of these 18 (50%), but cystograms were not performed in the remainder since they were seen before the micturating cystogram became a routine procedure.

Rosenheim (1963) found 50% of his patients with primary pyelonephritis were aged 10-20; 11 of his 36 cases presented with hypertension; and in 64% evidence of reflux was demonstrated. There is now general agreement that vesico-ureteric reflux in the absence of obstruction is an abnormal finding, and when accompanied by bacterial infection can progress to pyelonephritis (Williams, 1961). On

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reviewing Williams and Eckstein's (1965) series of 276 children with reflux, hypertension (diastolic level greater than 95 mm. Hg) was found in only 3%. This incidence rose to 6% if only those cases with a blood urea greater than 60 mg./100 ml. were selected.

Brod (1956) found hypertension (blood pressure greater than 145/95 mm. Hg) in 40-60% of adults under the age of 40 with chronic pyelonephritis, and this rose to 80% with progressive renal damage. Comparable figures in children tend to be lower as pyelonephritis is diagnosed earlier. Smellie, Hodson, Edwards, and Normand (1964) found an overall incidence of hypertension of 3.5% in a series of 200 consecutive children admitted to hospital with a urinary infection. Kimmel (1942) found that 10% of 75 children with chronic pyelonephritis had hypertension.

**Secondary pyelonephritis.** There were 13 children whose hypertension followed pyelonephritis secondary to some preceding lesion. 5 of these resulted from obstructive anomalies of the urinary tract, while the remaining 8 included examples of hypercalcaemia, the Fanconi syndrome, polycystic kidneys, medullary cystic kidney, and renal ischaemia.

**Glomerulonephritis.** Including all types of glomerulonephritis and the nephrotic syndrome, there were only 6 children who developed severe hypertension from this cause. 2 followed the Henoch-Schönlein syndrome and 1 also showed evidence of coincident pyelonephritis. It was occasionally difficult to evaluate those patients who were receiving corticosteroids and in whom the raised blood pressure might in part be steroid induced. Corticosteroid therapy frequently caused considerable rises in blood pressure, and in several instances this coincided with marked deterioration and subsequent death in renal failure.

**Renal artery anomalies.** Five confirmed cases of abnormalities of the renal artery causing hypertension are included and the relevant findings are shown in Table II. Cases 1 and 5 are examples of

renal artery stenosis in which operation resulted in a lowering of blood pressure, and pyelonephritis was absent on histology. In the other 3 cases pyelonephritis was present, and it is possible that these were originally hypoplastic kidneys; the renal arteries were certainly abnormal, but their contribution to the hypertension must remain questionable.

Leadbetter and Burkland (1938) were the first to describe a child with renal artery stenosis, in whom nephrectomy resulted in cure of the hypertension. Royer, Habib, and Mathieu (1963) reviewed the published material, and found 27 instances in children in whom anomalies of the renal artery were associated with hypertension.

**Other causes.** It is of interest that among more than 300 cases of coarctation seen at the hospital during the period under review, only 6 had a diastolic pressure greater than 120 mm. Hg in the arms, and 3 of these were infants.

In the miscellaneous group are included 3 children who were diagnosed as having essential hypertension. Each underwent extensive investigation including open renal biopsy without any cause being found. Other cases were phaeochromocytoma (1), Cushing's syndrome (1), and polyarteritis nodosa (1). A case of particular interest was a 1-year-old haemophilic who became hypertensive following a renal haematoma. At necropsy, a year later, both kidneys were small and contracted, presumably the result of renal ischaemia. The production of hypertension under these circumstances closely resembled the experimental work of Page (1939) when he wrapped a cellulose film envelope around the kidney.

### Clinical Findings

The presenting signs are set out in Table III. There were 19 patients who were already under observation at the time that they developed hypertension, and 36 (65%) in whom the various manifestations of hypertension were responsible for the initial illness. Headache, convulsions, haematuria, and cardiac failure are well-recognized symptoms of

TABLE II  
*Renal Artery Abnormalities*

Case No.	Age of Presentation of Hypertension	Blood Urea (mg./100 ml.)	Renal Artery Stenosis	Pyelonephritis	Outcome
1	7 wk.	41	Bilateral	Absent	Surgical death aged 2½ yr.
2	2½ yr.	30	Unilateral	Present	Nephrectomy: cure
3	5 yr.	31	Bilateral	Present	Alive: hypertensive
4	7 yr.	30	Unilateral	Present	Post-operative death
5	10 yr.	37	Unilateral	Absent	Nephrectomy: hypertensive

TABLE III  
Clinical Presentation in 55 Cases of Hypertension

Presenting Symptom	No.
Headaches .. . . . .	20
Already under observation .. . . . .	19
Convulsions .. . . . .	12
Haematuria .. . . . .	7
Cardiac failure .. . . . .	5
Facial palsy .. . . . .	3
Abdominal pain .. . . . .	1

hypertension. Facial palsy of the lower motor neurone type was the presenting feature in 3 patients, and has been discussed recently by Lloyd, Jewitt, and Lloyd Still (1966).

Irritability and weight loss were other prominent symptoms, while generalized abdominal pain was a later symptom in 6 children. This pain was often extremely severe and was quite unrelated to uraemia. It is thought to be due to a vasculitis (Court, 1941; Chaptal, Jean, Pagès, and Bonnet, 1961).

Of the 54 children, 20 had papilloedema, and hence by definition malignant hypertension; all patients included in this series had evidence of cardiomegaly. Neurological complications occurred in 18 children (convulsions in 12, lower motor neurone facial palsies in 6, and cerebrovascular lesions in 5).

Hypertension can occur at any age, as is shown in Fig. 2. There were 12 cases under the age of 4 years, only 3 of which were due to coarctation of the aorta. No particular clinical pattern is characteristic of the younger age-groups.

### Investigations

**Renal function.** Table IV shows the levels of blood urea when the diastolic blood pressure reached 120 mm. Hg; and it is of interest that 29 cases (53%) had values within the normally accepted range. This lack of correlation between the gravity of the hypertension and the degree of disturbance of renal function in cases of pyelonephritis has been frequently stressed (Butler, 1937; Weiss and Parker, 1939; Kimmel, 1942; Chaptal *et al.*, 1961).

TABLE IV  
Blood Urea Values When Diastolic Pressure First Reached 120 mm. Hg

Urea (mg./100 ml.)	0-40	40-60	60-120	120-200	>200	Total
Pyelonephritis .. . . . .	12	6	5	6	6	35
Glomerulonephritis .. . . . .	3	1	1		1	6
Others .. . . . .	14					14
Total .. . . . .	29	7	6	6	7	55

**Urine findings.** Albuminuria was present in every case of renal hypertension; in 9 out of 11 children without renal disease no albuminuria was present despite severe hypertension. The degree of protein loss varied considerably, the highest values exceeding 1%; the degree of albuminuria paralleled the height of the blood pressure, falling with control of the latter. A positive urine culture was obtained in 39 patients at some time during their illness.

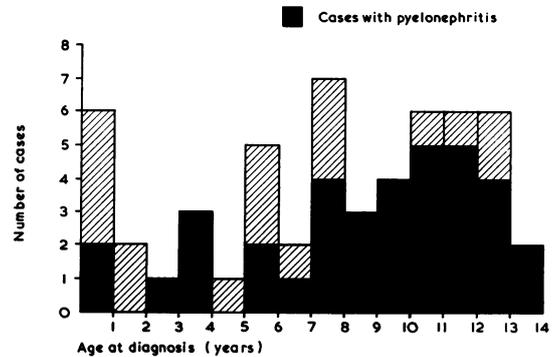


FIG. 2.—Age incidence of hypertension (diastolic pressure > 120 mm. Hg) with and without pyelonephritis.

**Other investigations.** The haemoglobin values showed wide variation correlating with the level of blood urea. Vanilylmandelic acid estimations were performed on 22 patients and were always normal, including the patient with phaeochromocytoma. Divided renal function studies were usually disappointing owing to technical difficulties. 8 children (all with renal hypertension) presented with plasma sodium levels under 130 mEq/l. It is interesting to speculate whether the plasma renin levels would have been raised in these patients, as they were in the series reported by Brown, Davies, Lever, and Robertson (1965).

### Outcome

Table V shows that only 6 cases in this series were cured. These all resulted from operation and

TABLE V  
Outcome in 55 Cases of Severe Hypertension

Died .. .. .	31
Cured .. .. .	6
Alive (treated) .. .. .	18
Total .. .. .	55

consisted of 4 children who had coarctations repaired, 1 nephrectomy, and 1 child who had a phaeochromocytoma removed. 31 (56%) of the patients have died (Table VI); and the average duration of survival in these from the onset of hypertension was 14 months. The majority (18 cases) died of uraemia. Of the remaining patients, 4 died within a few days of major operation, emphasizing the extreme dangers of performing any surgical manoeuvre in the presence of severe hypertension. Medical therapy caused irreversible hypotension in another child; and 3 children died of bleeding complications. Altogether, 11 children died with a normal blood urea, which is a surprisingly high incidence when compared with adult series. The outlook for children with malignant hypertension is similar to that of adults, and 90% will die within 1 year of diagnosis unless some form of treatment can be effective.

TABLE VI  
Causes of Death in 31 Fatal Cases

Causes	No.
Uraemia (cardio-renal failure) .. .. .	18
Surgery .. .. .	4
Hypotensive therapy .. .. .	1
Steroids .. .. .	2
Haemorrhage (other than uraemia) .. .. .	3
Miscellaneous .. .. .	3
Total .. .. .	31

### Treatment

Butler (1937) was the first who deliberately performed nephrectomy for the cure of hypertension in a child. Since then the role of surgery in the treatment of hypertension has fluctuated considerably. Evelyn (1961) discussed the types of hypertension amenable to surgery; amongst conditions listed were 'Goldblatt' lesions of the kidney, coarctation of the aorta, Cushing's syndrome, primary aldosteronism, and phaeochromocytoma. Unfortunately these conditions account for only a small proportion of the total number of hypertensive children. (For example, in our series, though performed on 18 children, operation cured only 6 out of a total of 55 cases.)

Whether or not a cause amenable to operation is discovered, hypotensive therapy is becoming increasingly important; however, in spite of the vast literature in adults, adequate controlled trials have yet to establish their place in childhood. Caligiuri, Shapiro, and Holliday (1963) reported remarkable clinical improvements in 4 children with chronic renal disease, whose hypertension was controlled over long periods by hypotensive therapy; none of their children had significant azotaemia. These authors thought the prognosis for these children was better than was generally supposed. In our series the average duration of treatment of the 16 patients who are still alive is almost 4 years from the time that their diastolic pressure first reached over 120 mm. Hg. When the glomerular filtration rate is under 20 ml./min. hypotensive therapy is usually ineffective. We now think that some form of hypotensive therapy is indicated in children when the diastolic blood pressure is persistently greater than 95 mm. Hg, and before there is much reduction in the glomerular filtration rate; only in this way can treatment be maximally effective.

Reserpine is useful as the initial drug in children, and if ineffective can be replaced by guanethidine or methyl dopa. Most workers seem agreed that it is the effect on lowering the blood pressure rather than any specific drug used for this purpose that is important (Smirk, 1954; Harington, Kincaid-Smith, and McMichael, 1959). Initially, the dose can only be assessed by titrating it against the level of the blood pressure. If one drug causes unpleasant side-effects, then an alternative drug or often the combination of a hypotensive agent together with a diuretic is useful. At the same time, measures should be taken to relieve anxiety both in the child and in the parents, for emotion can lead to marked fluctuations in the blood pressure and resultant difficulty in control.

### Discussion

The most difficult cause of malignant hypertension to diagnose in adults is pyelonephritis (Kincaid-Smith, McMichael, and Murphy, 1958). In our paediatric series pyelonephritis was frequently only recognized at a late stage of the disease, though in many instances the original attack could be traced back to infancy. Increasing attention has now focused on the periods of infancy and childhood when the high incidence of congenital defects, and abnormalities of function of the renal tract (in particular vesico-ureteric reflux) predispose to permanent damage to the kidneys.

Among conditions that are particularly vulnerable to pyelonephritis are renal malformations (Camp-

bell, 1951), tubular defects (Russell and Barrie, 1936), hypercalcaemia (Schlesinger, Butler, and Black, 1956), acute glomerulonephritis (Kassirer and Schwartz, 1961), and potassium deficiency (Milne, Muehrcke, and Heard, 1957). Any kidney that is damaged by the effects of hypertension will also have a similar predisposition.

Primary pyelonephritis was the commonest cause of severe hypertension in our series, and evidence of vesico-ureteric reflux was invariably present in this group when looked for. The importance of reflux in the aetiology of pyelonephritis is at present the subject of much debate. Our findings show that children with recurrent urinary tract infections and evidence of reflux stand a slight but definite risk of subsequently developing hypertension, and that this risk increases with the degree of renal damage present. At present there are insufficient data to assess the outcome of the hypertension in these children, but it is our impression that no sustained rise in the blood pressure in a child can necessarily be regarded as safe and non-progressive. Two children in the series of Williams and Eckstein developed hypertension several months after a successful reflux-prevention operation. It is well known that many years may elapse before the onset of hypertension in a scarred kidney, but this complication should become rarer if pyelonephritic scarring can be prevented by the earlier use of antibiotics and surgery.

The chances of finding a remediable cause for hypertension in children is greater than in adults. The relatively high incidence of renal artery abnormalities (9% of this series) emphasizes the importance of detailed investigation in any child with undiagnosed hypertension. The techniques of renal biopsy, aortography, the micturating cystogram, the radioactive renogram, hormonal assays, and divided renal function studies, have demonstrated that the spectrum of differential diagnosis of hypertension is just as wide in children as in adults. So-called 'essential' hypertension is rare in childhood; some of our cases had abnormal patterns of steroid excretion, but their significance is still unknown, and this may turn out to be a heterogeneous group.

Hypertension is common in young adults (Robinson and Brucer, 1939) and we have demonstrated that it is not a rarity in childhood. The appalling prognosis of untreated malignant hypertension in children is similar to that in adults, and since hypotensive therapy has been shown to prolong survival in adults (Smirk, 1954; Harington *et al.*, 1959), its application seems only logical to children. However, the greatest challenge still

remains, and that is to prevent the disease that gave rise to the hypertension.

### Summary

A series of 55 children with severe hypertension seen between the years 1954-64 is reviewed.

Pyelonephritis was the commonest predisposing cause and was invariably accompanied by evidence of vesico-ureteric reflux.

Although many cases were first seen at a late stage of renal failure, the onset of hypertension in pyelonephritis does not correlate with the degree of renal function.

Investigation in children is more rewarding than in adults. The probability of finding a surgically treatable cause is appreciably higher.

Hypotensive therapy is of value and should be energetically pursued.

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