HYPERTENSION OF RENAL ORIGIN IN CHILDHOOD

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A persistently raised blood pressure is uncommon in children. Essential hypertension is rare, only a few cases having been recorded (Court, 1941). Endocrine causes, such as the hyperadrenalism of phaeochromocytoma (Snyder and Vick, 1947) are also uncommon. Elevation of the systolic pressure occurs in diseases of the heart and great vessels, being most notable in coarctation of the aorta and in severe degrees of aortic incompetence. The majority of cases of hypertension, however, are associated with renal disease.

It had been realized for many years that some connexion existed between renal disease and hypertension. Bright noted the cardiac hypertrophy of renal disease in 1838. How renal disease could affect the blood pressure was not apparent until Goldblatt et al. (1934) showed that in rabbits a pressor substance is liberated from kidneys to which the blood supply has been reduced. This work has since been developed and extended to other animals, and it is thought probable that the findings are applicable also to man, although this has not been proved conclusively.

Butler (1937) was the first to employ nephrectomy deliberately for the relief of hypertension in a child, although Quinby in 1923 found a fall of blood pressure in a case from which a diseased kidney had been removed. Since then many similar operations have been undertaken.

Recently Trueta et al. (1947) have put forward their views on the possible role of the kidney in essential hypertension and in the hypertension of chronic renal disease.

The experiments of Goldblatt et al. and their subsequent elaboration by others have shown the probable mode of production of hypertension in many cases in which there is an organic cause, whereas Trueta and his colleagues describe a possible mechanism in cases in which organic change is absent at the onset of hypertension and only develops later in the disease.

Cases Preceded by Organic Change

The cases in which there is apparent renal disease can be divided into the following three groups.

1) The situation when there is obvious obstruction of the blood flow to the kidney by a lesion of the renal artery.

A case of partial occlusion of the renal artery by a muscle plug is described by Leadbetter and Burkland (1938), and an aneurysm of the renal artery occurred in the case described by Howard (1940). These are rare conditions but their importance lies in their close analogy with Goldblatt's experiments, showing that these can apply to the human as well as to the animal subject.

2) Cases in which the lesions affect smaller vessels within the kidney substance, and probably only localized areas of the kidney become ischaemic.

In polyarteritis nodosa the characteristic lesions occur in the walls of the smaller arteries, producing either partial or complete thrombosis, or dilatation to form tiny aneurysms. Hypertension occurs in 64 per cent. of all cases according to Miller and Daley (1946), and was present in 30 per cent. of twenty-three cases in children reported by Rothstein and Welt (1933).

In amyloid disease the deposition of the hyaline substance in the walls of the arterioles and capillaries obviously restricts the blood flow, but there is, in addition, a second mechanism, which will be discussed later.

Chronic pyelonephritis is frequently found in cases of hypertension, and may be included in this group. Here the focal areas of fibrosis are thought to compress the renal vessels by their contraction as healing takes place. The disease may be unilateral, and nephrectomy for hypertension in these cases has been found to produce good results more often than in other types of unilateral renal disease (Langley and Platt, 1947).

Renal tuberculosis is a cause of hypertension in some cases. Possibly the disease acts by causing a thrombo-angiitis obliterans in the vessels which become involved in the spread of the lesions.

3) In the third group tumours are present. They probably act by occupying space within the relatively rigid capsule, and, as they swell or grow, obstruct the venous return. This group includes cases of polycystic disease, renal neoplasms, and infarcts of the kidney.

Cases Without Early Organic Change

The work of Trueta and his colleagues (1947) provides a possible explanation for the cases in
which histological changes in the kidney do not appear until a later stage of the disease. They demonstrated a mechanism by which the blood supply to the renal cortex, and therefore the formation of urine, is regulated, and showed how overaction of this mechanism could produce cortical ischaemia. They applied these ideas to essential hypertension, suggesting that unknown stimuli, which might even be psychic in origin, caused prolonged overaction of this mechanism. This reduced blood flow to the cortex sufficiently to cause liberation of renin, yet not enough to impair renal function.

It is now apparent from the work in rats of Wilson and Byrom (1941) that one of the effects of prolonged hypertension is to produce arteriolar lesions. When this occurs in the renal vessels a vicious circle is completed. Narrowing of the vessels, which is now organic, leads to further ischaemia and liberation of renin, and the resulting hypertension causes further arterial lesions.

With reference to the hypertension of plumbism, Fishberg (1939) expresses the view that generalized arterial spasm is a major factor in the early stages before histological changes occur in the kidneys. He attributes this spasm to direct action of the lead on smooth muscle, and considers that the kidney plays no part. In view of the instability of the cortical arterioles demonstrated by Trueta et al., it seems likely that the kidney may after all play a part in raising the blood pressure to a higher level. Later, arteriosclerotic changes develop in the kidney and maintain the hypertension during the chronic stages of the disease.

In cases of chronic renal disease of various origins Trueta et al. have shown that prolonged use of the bypass through the medulla results in permanent dilatation of these pathways. This in turn leads to the formation of 'arteriae rectae verae' running from arterial to venous sides of the medullary circulation, and permanently diverts blood from the cortex. The best example is amyloid disease, where the cortical circulation is mechanically obstructed by the hyaline deposits, and the bypass is forced to dilate.

The relationship between hypertension due to gross organic renal disease and that probably ascribable to vasospasm is intimate, and some examples may be regarded as borderline instances, for example, acute and chronic glomerulonephritis.

The most striking histological feature in the early stages of acute glomerulonephritis is the absence of blood from most of the glomerular capillaries, indicating gross diminution in blood flow; it is not surprising that hypertension frequently occurs. Although mechanical obstruction by endothelial thickening of the capillaries may be the cause of the ischaemia, Volhard (1931) suggests that vasospasm in the renal vessels is responsible.

In chronic glomerulonephritis also the histological picture of glomerular lesions and fibrous tissue replacement of the atrophic areas of parenchyma makes it easy to visualize reduced blood flow with resultant anoxia, liberation of renin, and hypertension.

It has been shown experimentally in dogs by Levy et al. (1937) that obstruction of the ureter causes a marked diminution of the blood-flow through the kidney, thus affording a possible explanation of the occurrence of hypertension in uncomplicated hydronephrosis.

Case Reports

Case 1. This child, Maureen McC., was admitted at the age of nine years with an acute exacerbation of a chronic pyelonephritis. She presented with haematuria and her blood pressure was 150/130 mm. Hg. Blood, pus, and Bact. coli were found in her urine. The right kidney was enlarged and easily palpable. The optic fundi showed some blurring of the discs, and a slight increase in light reflex from the arteries.

Previous illnesses included measles, pertussis, chicken-pox, mumps, and jaundice, and there had been frequent attacks of tonsillitis for four years, the most recent being eight weeks previously. There were no relevant points in the family history.

A course of sulphanilamide temporarily sterilized the urine, but pyuria recurred a few days later and persisted. The blood urea varied between 39 and 46 mg. per cent. The blood pressure rose to 180/140 mm. Hg.

After six weeks she was transferred to a convalescent home where her urine continued to show
varying amounts of albumin, pus, and Bact. coli despite two further courses of sulphonamides. It was still infected on discharge nine months later. Although her general condition was much improved her blood pressure had risen to 210/150.

The child was readmitted at the age of twelve years with gross haematuria, actual clots being passed. Her general condition was good but her blood pressure was 255/230 mm. Hg. The urine was still infected. Blood urea now ranged between 48 and 75 mg. per cent. Pyelography showed a moderate degree of bilateral hydronephrosis with dilated ureters (fig. 1).

Gross haematuria occurred intermittently, and her blood pressure continued to rise. Exudates, haemorrhages, and sclerotic changes could be seen in the retinae. Her condition began to deteriorate rapidly. The blood pressure rose to over 300/150 mm. Hg. and bilateral detachment of the retinae occurred. Haematuria was so gross that a waxy pallor developed. Haemoglobin fell to 28 per cent. and the plasma proteins to 3·3 per cent. with an albumin:globulin ratio of 1:1. She developed uraemic symptoms as the blood urea rose to 204 mg. per cent., and a pericardial friction rub developed over the whole praecordium. Slight oedema of the face appeared, becoming more generalized later. Death occurred two months after her admission.

Pathology. The pericardial sac was seen to be covered with shaggy, blood-stained exudate and contained about 200 ml. of blood-stained fluid. There was generalized hypertrophy of the heart, especially of the left ventricle. Both kidneys were slightly enlarged and soft, and the capsule was adherent over areas of scarring. There were numerous small abscesses in the cortices. The cut surface was hyperaemic and oedematous, with scars of fibrous tissue and streaks of pus extending from medulla to cortex. The ureteric pelves were moderately dilated and inflamed containing purulent urine. There was slight dilatation of the ureters. The bladder also contained purulent urine, and its mucosa was inflamed. The para-aortic glands were enlarged.

Histology. On histological examination the sections of the kidney showed areas of scarring in which most of the glomeruli had become hyalinized and others showed periglomerular fibrosis. The tubules were dilated and many contained hyaline eosinophilic material. Some of the tubules contained pus, almost forming small abscesses. Scattered areas of round cell infiltration could be seen. Vascular changes were present, consisting of hypertrophy of both media and adventitia of the arterioles, extending into the afferent arterioles of the glomeruli. There was intense congestion and round cell infiltration of the subepithelial layers of the ureteric pelvis.

The picture was that of chronic pyelonephritis, with superimposed acute pyelonephritis.

Case 2. This child, Clara J., aged thirteen years, was admitted with pains in her joints accompanied by haematuria of eleven days' duration. Two weeks before admission an abscess had appeared in her left axilla and had ruptured spontaneously. During the previous two years she had suffered with increasingly severe attacks of headache and vomiting and occasional attacks of abdominal pain. Previous illnesses included measles, chorea, and jaundice. There was nothing of note in the family history.

Examination showed a thin child, below normal height. There was tenderness in the left renal angle and along the line of the left ureter, and the kidney on that side was palpable. The urine showed gross haematuria and albuminuria and a few leucocytes and Bact. coli were found. The blood urea was 31 mg. per cent. and the Wassermann reaction was negative. The blood pressure was found to be 270/215 mm. Hg. The retinae showed exudates and oedema to a marked degree with minute haemorrhages. The retinal arteries were narrowed and tortuous. Intravenous pyelography showed complete lack of excretion on the right side, but the left kidney appeared to be hypertrophied.

She continued to lose blood by haematuria, epistaxis, and finally, by a brisk haemorrhage into the bowel; her haemoglobin fell to 44 per cent.
At the same time her blood pressure fell, reaching 180/160 at the time of the rectal bleeding, but it rose again afterwards.

The child now began to complain of painful tingling sensations in her left arm, and a false aneurysm of the third part of the axillary artery rapidly developed and had to be ligatured off leaving an arm partly paralysed and with poor function. (Later this arm recovered almost completely.)

Retrograde pyelography was then performed and clearly outlined the right ureteric pelvis showing blunting and bunching together of the calyces (fig. 2). It was therefore decided to remove whatever might be remaining of this kidney, although the child had gradually lost weight and had become extremely emaciated.

At operation a small atrophic kidney was found and removed, and there was an immediate fall in blood pressure (fig. 3). There was also a rapid improvement in her general condition. Blood urea was 29 mg. per cent., and urea clearance 64 per cent. (standard).

It seems reasonable to assume from the patient's course during a long period of observation that she would soon have died if nephrectomy had not been performed. The eye changes showed that the hypertension had reached a malignant stage and there was no tendency for it to fall except temporarily following haemorrhages. The improvement which followed nephrectomy was most dramatic: the child became much brighter, her appetite returned, and emaciation rapidly decreased. She has now maintained this improvement for two years, and so far shows no return of the hypertension. Her eyes show interesting changes: the oedema of the retinæ has subsided, but the central retinal arteries are protruding forwards on what seems to be the remains of some exudate. There are pinhead points of retinal atrophy with some pigmentation, probably due to resolved haemorrhages. Vision is: R. 6/6; L. 6/9. The fields of vision are normal.

Pathology. The right kidney measured 5½ cm. and consisted of a thin shell of tissue two to three mm. thick, surrounding dilated calyces. The kidney section showed practically no functioning renal parenchyma. The glomeruli were almost wholly hyalinized and some of the tubules were completely atrophied while others appeared to be open but were filled with hyaline eosinophil material. There was a marked interstitial fibrosis with infiltration of lymphoid elements. Subacute pyelitis was also apparent. The arteries and arterioles showed well marked hypertensive changes. The renal artery showed hypertrophy of the media, but no fibrosis. There was also a little proliferative endarteritis.

Case 3. This child, Peter B., aged thirteen years, presented with a severe epistaxis of three days' duration associated with a 'cold'. He had had similar attacks six months and one year before. Later a history was elicited of frequency of micturition for several years, but there was no definite history of pyelonephritis or nephritis. For the previous two years he had been suffering from headaches which were becoming more frequent. Chronic cough and a pale complexion had been noted since infancy. Previous illnesses included pertussis. There was nothing of note in the family history.

Examination revealed a very pale, anxious boy, small for his age. He was still bleeding post-nasally but no local cause could be found. Bleeding continued for four days, but stopped after a blood transfusion had been given. Apart from a haemoglobin of 41 per cent. and red blood count of 2,060,000, blood investigations showed no abnormality. The blood pressure was found to be 220/130, but it fell as bleeding continued, rising again later.

The optic fundi showed slight oedema of the discs, accentuated light streak of the arteries generally, and irregular contractions of some of the vessels. These changes increased slightly during the period of observation, and a few small areas...
of retinal exudate appeared to the nasal side of the right disc.

Repeated examination of the urine showed no abnormality except on one occasion when some albumin and a few hyaline casts were found. Nevertheless it was felt that the urinary system should be fully investigated. The blood urea varied between 34 and 45 mg. per cent. Blood calcium, phosphorus, and phosphatase were normal. Urea clearance (maximum) was 74 per cent. The urea concentration test was in the lower limits of normal, and the urine concentration test (Fishberg's modification) showed a maximum specific gravity of 1.016. Phenolsulphonephthalein excretion was 20.4 per cent. in the first hour, 16 per cent. in the second hour, and 2.5 per cent. in the third hour. These tests suggested impairment of renal function.

Intravenous pyelograms showed a similar concentration of dye on both sides. The right kidney shadow appeared small and irregular, the calyces were deformed, and the ureter slightly dilated. The left kidney appeared to be uniformly enlarged with elongated calyces. Retrograde pyelograms confirmed the abnormal shape of these calyces (fig. 4). On injecting indigo-carmine intravenously during cystoscopy the dye appeared first at the left ureteric orifice in four minutes in high concentration, but it did not appear at the right ureteric orifice until three and a half minutes later and was in poor concentration.

The child's blood pressure had risen again to over 200/150 mm. Hg., the haemoglobin percentage was also rising, and attacks of headache had recurred, accompanied by vomiting. In view of these symptoms and the increase in the eye changes it appeared as though his hypertension had entered upon the malignant stage. After consultation it was decided to remove the right kidney.

At operation the peritoneum was opened to allow the left kidney to be palpated. It was large, firm, and smooth. The peritoneum was closed and the right kidney was removed.

There was an immediate fall in blood pressure which was not maintained (fig. 5). A year later the blood pressure was 230/140 mm. Hg. Symptoms, however, have been completely relieved and the child's general condition is much improved. There has been no increase in the blood urea, though the phenolsulphonephthalein excretion has fallen to 21.7 per cent, in two hours.

His fundi still show hypertensive changes, though there has been slight improvement. Fields of vision and colour vision are normal.

**PATHOLOGY.** The kidney measured 7 x 3.5 x 3 cm. and showed externally a number of grooves dividing it into three main portions. The capsule was thickened and adherent at these grooves and
to a lesser extent elsewhere. One small cyst was present beneath the capsule at the lower pole. On section the cortico-medullary pattern was seen to be maintained on the whole in the upper and lower portions, but was less distinct in the central zone. The peripelvic fat was increased, with some haemorrhages at the lower end, probably due to operative trauma. Vessels at the cortico-medullary junction were congested and prominent.

Microscopic examination of the portion of muscle removed for section showed only a few small vessels whose appearance was normal. In the kidney the appearance of the upper and lower thirds was similar. The capsule was normal except over scanty areas of fibrosis where it was thickened. The glomeruli were normal, occasionally separated from the periphery of Bowman’s capsule by albuminous fluid, which was also present in the moderately dilated tubules. The glomerular afferent arterioles were normal. There was no intertubular infiltration. There were a few, wedge-shaped areas of fibrosis, sharply defined from surrounding tissue, in which the glomeruli were hyalinized, the tubules atrophied and dilated, and interstitial tissue increased and infiltrated with small round cells. There was a moderate degree of hyperplasia of the media of medium sized arteries, with musculo-elastic hyperplasia of the intima, but without gross narrowing of the vessels. In the middle zone of the kidney changes were similar, but there was more distortion of pattern by a greater number of zones of fibrosis. The appearance was that of the late result of pyelonephritis.

**Case 4.** This child, William N., aged three years and eight months, was admitted to the Royal Liverpool Children’s Hospital with a subarachnoid haemorrhage of spontaneous onset. Since the age of eleven months he had had attacks of vomiting, preceded by headaches and lasting two to five days; they occurred at intervals of one to four months. The onset of the subarachnoid haemorrhage was about four days after the beginning of one of these attacks when he complained of unusually severe parietal headache and was more drowsy than normal.

Previous illnesses included two attacks of bronchitis during the year before admission to hospital, and tonsillitis three weeks before. He had not had any of the infectious diseases, and was not considered to have suffered from any kidney disease, although pus and albumin had been found in his urine seven weeks before admission.

On examination there was marked neck rigidity and Kernig’s sign was positive. The optic fundi were normal. The heart sounds were loud and forceful and there was accentuation of the aortic second sound. Some cardiac hypertrophy was present, and a blood pressure of 210/170 mm. Hg. was noted. Lumbar puncture showed a xanthochromic fluid under a pressure of 280 mm. of cerebrospinal fluid, containing protein to an extent of 100 mg. per cent. and numbers of red blood cells. The urine contained albumin and pus cells.

Blood urea was 25 mg. per cent. at first, but rose later. The Wassermann reaction and Mantoux tests were negative.

Neck rigidity and headaches subsided following a period of complete rest, but the blood pressure remained at a high level.

Intravenous pyelography revealed a normal left kidney, but there was no excretion of the dye on the right side. Retrograde pyelography showed the presence of a normal-looking pelvis on the right side, but intravenous indigo carmine was not excreted from this side (fig. 6).

**Fig. 6.—Composite tracing of retrograde right and excretory left pyograms. (Case 4.)**

It was decided to remove the useless right kidney. The day before operation the blood pressure rose to 260/190 mm. Hg. and vomiting occurred, and on the day of operation the systolic pressure was even higher and could not be recorded. Clamping of the renal artery was followed by an immediate fall in blood pressure.

Following operation there was a rapid improvement in the boy’s general condition. The decline in blood pressure (fig. 7) has been maintained, but it is not possible to say whether the improvement will continue. Eight months after operation his systolic pressure is 120 mm. Hg. He still has attacks of cyclical vomiting.

**PATHOLOGY.** No abnormality was found in the kidney either macroscopically or on microscopic
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examination. It is interesting to speculate on the possibility of some form of stenosis or partial occlusion of the renal artery having been present, but there was no actual evidence.

Discussion

It seems reasonable to assume that in the first three cases the initial lesion was pyelonephritis which became chronic and resulted in progressive renal damage and gross scarring. The inflammation was still very active at death in case 1. In case 2 the infection had almost died out on the grossly damaged side, but the second kidney was becoming involved. In case 3 the disease was temporarily inactive.

Diagnosis. Absence of pus or albumin in the urine of a case of hypertension does not exclude renal disease as found in case 3 nor does a normal blood urea as in case 2 in which there was total loss of function of one kidney. The most valuable aid to diagnosis is the excretory pyelogram which should be obtained in all cases of hypertension in childhood. The result must be interpreted with caution since temporary obstruction of the ureter by clots of pus may prevent excretion of the dye. Moreover, complete absence of one kidney is by no means rare, seven such cases having been found in the Alder Hey Children's Hospital in two and a half years. Hydronephrosis of the single kidney was confirmed in three cases, and the presence of hypertension was established by the resultant post-mortem cardiac hypertrophy in two of them. Retrograde pyelography is essential to distinguish between a non-functioning kidney and its complete absence. Cystoscopy alone is insufficient as a ureteric orifice may be present in spite of the absence of the kidney on that side. Intravenous injection of indigo carmine during cystoscopy may be of help in determining which kidney is more affected. This was invaluable in case 3, where both kidneys appeared to be abnormal on x-ray examination.

None of these cases showed any evidence of obstruction in the urinary tract, nor of congenital malformation which would predispose to stasis and maintenance of infection, but all had foci of infection elsewhere. In case 1 the tonsils were unhealthy, and the child had been having frequent sore throats since the age of five. Case 2 had a chronic vaginal discharge at the age of four, and at present has chronic sinusitis. Case 3 has a chronic lung infection. The association of these foci and the hypertension is probably indirect, but they may possibly have served as the source from which the infection in the kidney originated, or was maintained and renewed.

Effect upon growth. In all these cases there was interference with growth. In case 1 weight was about normal for a child of nine and a half years, namely 62½ lb., although even then her blood pressure had risen to 180/140 mm. Hg. At the time of her second admission to hospital her weight had risen to 67 lb. only, a gain of under five pounds in two and a half years. Unfortunately her height was not recorded.

In case 2 there was gross emaciation. The lowest weight recorded was 45 lb. at the age of thirteen years, her height being 51 in. This was 9½ in. below the average for her age. Over the past year her weight has steadily improved, and she now weighs 84 lb., still 30½ lb. below normal. Her height is now 57 in., a gain of 6 in. in thirteen months.

Case 3 had a weight of 78 lb. and height of 56 in. before operation, 35 lb. and 8½ in. respectively below normal. Five months later, although his blood pressure was still high he was clinically very well and had gained 5½ lb. and almost an inch in height. These figures for height and weight by no means qualify for the description renal dwarfism, being on the low side of normal extremes, but they do suggest a certain retardation of growth, probably occurring in the last year or two.

Prognosis. Complete success in the treatment of hypertension by nephrectomy can only be anticipated in the presence of one normal or only slightly damaged kidney. If both are affected there may be slight improvement as in case 3, and operation is perhaps justified, but if there is one good kidney a successful result may be obtained, even in the presence of a hypertension of over 200/160 mm. Hg of long duration and showing gross retinopathy.
Summary

The possible etiology of hypertension in cases of renal origin is briefly discussed.

Four cases of severe hypertension in children are described. One case is cured and one slightly improved following nephrectomy. Another case appears to be cured, but has not yet been followed up for a sufficiently long period.

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