Renin and hypertension in childhood

It is clearly established that hypertension is a major factor in the genesis of arterial disease in adult life (Kannel and Dawber, 1974). Severe hypertension in childhood is a relatively uncommon but important disorder, for in at least 80% of cases it is secondary to some underlying, often treatable, condition (Loggie, 1971; Kaufman et al., 1972). Furthermore, it is increasingly being realized that essential hypertension may have its origins in childhood (Londe et al., 1971). The renin angiotensin system plays an important causative or perpetuating role in many forms of hypertension; for this reason a review of its status in children and its relevance to childhood hypertension is appropriate.

Renin angiotensin system (Fig.)

Renin is a proteolytic enzyme produced by the juxtaglomerular cells of the afferent arterioles in response to a variety of stimuli. The most important of these is a decrease in renal arterial perfusion pressure, but changes in renal tubular fluid sodium concentration and sympathetic nervous system plays an important causative or perpetuating role in many forms of hypertension; for this reason a review of its status in children and its relevance to childhood hypertension is appropriate.

Renin substrate

Renin

Angiotensin I

Converting enzyme (Lungs)

Angiotensin II

Aldosterone

Arterioles

Fig.—The renin angiotensin system.

The renin is released into the circulation and acts on an $\alpha$-globulin, renin substrate, generating the physiologically inactive decapetide, angiotensin I. In the plasma and on passage through the lungs, angiotensin I is converted to the active pressor octapeptide, angiotensin II, which causes arteriolar vasoconstriction and hence an increase in total peripheral resistance. Angiotensin II also has a less well understood direct natriuretic action on the renal tubules, but this effect is overshadowed by its stimulatory action on the production of aldosterone by the adrenal cortex. This in turn promotes sodium reabsorption in exchange for potassium in the distal renal tubules. Renin itself cannot be measured easily, but the activity of the renin system can be gauged by the rate of production of angiotensin I from endogenous substrate during incubation of plasma in the presence of inhibitors of the converting enzyme and angiotensinas; this estimation is known as the plasma renin activity (PRA). A similar measurement is available known as plasma renin concentration, in which excess exogenous substrate is added eliminating the effect of substrate variation. In addition there are assays for determining the levels of circulating angiotensin II (Boyd, Landon, and Peart, 1967).

In children interpretation of plasma renin values has proved difficult because of the limited normal data available. Contributory factors in this dearth of paediatric information have been the large quantities of blood hitherto required for measurement of the various parameters of the renin angiotensin system and the sampling difficulties encountered in young children. Several studies have suggested that in children peripheral venous plasma renin levels were higher than in adults (Godard et al., 1968; Amsterdam et al., 1969; Kotchen et al., 1972). Krause, Schillmöller, and Hayduk (1972) confirmed these findings utilizing a bioassay technique for plasma renin concentration and showed a significant negative correlation between renin concentration and body surface area. More recently, Dillon and Ryness (1974), using a semimicro radioimmunoassay have established normal ranges for peripheral plasma renin activity in infancy.
and childhood and observed a tenfold decline in
PRA with age, falling from 1392 pg angiotensin I/ml
per hr in infancy to 87 pg angiotensin I/ml per hr in
adult life. Plasma aldosterone concentration
similarly declines from 20-2 ng/100 ml to 11-7
ng/100 ml.

Sodium deprivation enhances renin secretion, and
it is established that PRA should be interpreted in
relation to sodium turnover (Laragh et al., 1972) or
total exchangeable sodium (Davies et al., 1973). It
is not obvious how to compare rates of sodium
turnover in infants and adults but the decline of
PRA with age cannot be wholly attributable to
differences in sodium intake. A possible
explanation is that the young infant is more
dependent than the adult upon renin-aldosterone
stimulated distal tubular sodium reabsorption for
the maintenance of salt balance.

Renal hypertension

The conditions in which hypertension is
associated with activation of the renin-angiotensin
system include renal ischaemia due to renal artery
stenosis, many varieties of parenchymal renal disease
especially when hypertension is resistant to saline
depletion (Weidmann et al., 1971; Schalekamp et
al., 1973), rare renin-secreting tumours (Robertson
et al., 1967), occasionally Wilms's tumours (Mitchell
et al., 1970), and malignant hypertension in some
individuals. Secondary hyperaldosteronism with
hypokalaemia may occur in all these situations.

Renovascular disease. Renovascular hyper-
tension can be defined as hypertension caused by
a lesion of the renal artery or its branches which
impairs blood flow to all or part of the kidney
(Leumann et al., 1970). It is a curable disorder that
has recently been recognized with increasing
frequency. It is second only to coarctation of the
aorta as a cause of surgically remediable hyper-
tension in children (Fry et al., 1973). Renal artery
stenosis with hypertension has been reported in
neonates (Ljungqvist and Wallgren, 1962; Schmidt
and Rambo, 1965; Angella et al., 1968; Formby and
Emery, 1969). It is sometimes familial (Bergstein
et al., 1971; Kaufman et al., 1972). Renal artery
stenosis has been associated with idiopathic
hypercalcaemia (Wiltse et al., 1966), Marfan's
syndrome (Loughridge, 1959), the rubella syndrome
(Menser et al., 1966), Takyashii disease (Fry et
al., 1973), and neurofibromatosis (Halpern and
Curringino, 1965; Bourke and Gatensby, 1971;
Klecker and Roth, 1974). A variety of pathological
lesions have been reported, including hypoplasia,
intimal hyperplasia, arteritis, and external
compression. However, the commonest finding is
fibromuscular dysplasia, particularly in older
children (Fry et al., 1973). The disease may be
bilateral, may involve segmental vessels (Kaufman
et al., 1972; Fry et al., 1973), and occasionally the renal
artery is replaced by many smaller vessels (Barratt,
1974).

Other causes of renovascular hypertension in
children include renal artery aneurysm (Grossman
and Babbit, 1967; Kaufman et al., 1972), arterio-
venous fistula (Long, Javid, and Julian, 1964),
intrarenal vascular anomalies (Leumann et al., 1970;
Chrispin and Scatliff, 1973), and renal artery
disruption after trauma (Fry et al., 1973).

The ischaemic kidney secretes excess renin but
not all cases of renal artery stenosis have raised
peripheral plasma renin activity (Brown et al., 1965)
or angiotensin II concentration (Catt et al., 1971).
On the other hand, Vaughan et al. (1973) found that
if peripheral plasma renin levels were related to the
urinary sodium excretion they were abnormally high
in adults with renal artery stenosis. Dillon and
Ryness (1974) have confirmed that most children
with hypertension secondary to renal vascular
anomalies or renal scarring have higher PRA than
healthy children of equivalent age.

In terms of preoperative prediction of surgical
cure it appears that it is not the peripheral plasma
renin activity but the differential renal vein renin
levels which are of greatest value (Michelakis et al.,
1967; Stockigt et al., 1972). A renal vein renin
ratio of greater than 1:1.5, especially if associated
with evidence of suppression of renin release from
the contralateral kidney, predicts a good response in
terms of surgical treatment for renovascular disease
and is useful in patients with other types of renal
hypertension (Stockigt et al., 1972). However,
renal vein renin determinations in children are even
more prone to error than in adults. False negative
ratios may occur for many reasons (Poutasse et al.,
1973; Vaughan et al., 1973) and it must be
remembered in this context that β-adrenergic
blockers specifically depress renin release and should
be withdrawn at least 3 days, but ideally 2 weeks,
before this investigation is undertaken. Selective
sampling from segmental veins draining under-
perfused areas of kidney may allow the identification
of localized sources of renin secretion which may be
overlooked by main renal-vein sampling
(Schambelan et al., 1974). Successful re-
vascularization of an ischaemic kidney in childhood
offers a good prospect of permanent cure of hyper-
tension (Kaufman et al., 1972; Fry et al., 1973).
**Parenchymal renal disease.** The relation between parenchymal renal disease and hypertension is very complex. Hypertension is regularly associated in children, as in adults, with advanced renal disease and uraemia. However, with some important exceptions, the renin angiotensin system cannot be implicated in this group of patients. In most of the patients the hypertension responds to salt depletion but in the remainder this fails to lower the blood pressure; these individuals have high circulating renin levels in their peripheral blood in relation to their exchangeable sodium (Schalekamp et al., 1973).

Lesser degrees of parenchymal renal damage may be implicated in the causation of renin-dependent hypertension in children. Included within this group are probably segmental renal hypoplasia (Ask-Upmark, 1929; Bonnin et al., 1971), the kidney after renal venous thrombosis (Perry and Taylor, 1940), and also children with localized pyelonephritic scarring and hypertension. In unilateral renal disease with negligible function on that side and with an apparently normal or hypertrophied contralateral kidney, nephrectomy may well be undertaken in the hope that the blood pressure will fall. In bilateral disease in which the disparity of function is less marked, then medical treatment is to be preferred (Barratt, 1974). Renal vein renin studies may well reveal clear lateralization of renin output in this type of case, but it is worth noting that with some pyelonephritic kidneys the hypertension sometimes subsides spontaneously without resort to operation (Barratt, 1974). No clear guidelines have been established in children for deciding which kidney should be removed and if in doubt, a conservative approach is preferable.

**Renal tumours.** It has been reported that Wilms' tumours are occasionally associated with hypertension (Koons and Ruch, 1940; Hughes, Rosenblum, and Horn, 1949) and that this has been associated with increased renin output from the offending kidney (Mitchell et al., 1970). Whether this is due to impairment of vascular supply to part of the kidney or to increased secretion of renin from the tumour itself is not entirely clear, but the findings suggest the latter (Lee, 1971). More recently it has become apparent that specific renin secreting tumours exist, known as haemangio-pericytomas. There have been 7 published reports (Robertson et al., 1967; Kihara et al., 1968; Eddy and Sanchez, 1971; Bonnin, Hodge, and Lumbers, 1972; Conn et al., 1972; Schambelan et al., 1973; Brown et al., 1973) and of these, 3 were in children, the youngest being a girl of 8 years. Characteristically, those affected have hypertension, evidence of secondary hyperaldosteronism, normal renal function, normal IVP, and a normal or only slightly abnormal renal arteriogram. Divided renal vein renin levels reveal clear lateralization to the side affected and nephrectomy results in cure. So far, there is no evidence of malignancy and no metastases have been reported.

In conclusion, it is becoming increasingly apparent that disturbances of the renin angiotensin system in childhood are of considerable importance. An understanding of the physiology and pathology is essential for the satisfactory diagnosis and treatment of many hypertensive disorders which affect children. With development of semimicro methods for measurement of plasma renin activity and more refined techniques of arteriography and reconstructive vascular surgery, there is every reason to expect improvement in the evaluation and treatment of these children.

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**REFERENCES**


