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Primary Excess and Deficiency of Renin

Diseases of endocrine glands characteristically are associated with syndromes both of overproduction and deficiency of the relevant hormone. Study of such cases is important for an understanding of the normal working of the gland and the nature or even existence of its hormone. Renin was amongst the first of the hormones to be described: R. Tigerstedt and P. G. Bergman[1] suggested in 1898 that renin might be released from the kidney into blood and thus influence peripheral blood vessels. This preceded by several years E. H. Starling's[2 3] definition of the hormone as a blood-borne chemical messenger. Even so, 60 years then elapsed before renin appeared in endocrinology texts. The neglect may have been due in part to the lack of syndromes associated with primary hyper- and hyporeninism. Both have been described recently.

During the last six years at least six cases with supposed renin-secreting haemangiopericytoma of the kidney have been reported.[4-9] The first was a full description[4] of a young man whose hypertension was relieved by surgery which included the removal of a kidney with a renin-containing vascular tumour. This case is perhaps the least certain because renin was not measured in blood before operation, and the fall of blood pressure may have been partly due to removal of adrenal tissue. Nevertheless, the remaining five patients are remarkably similar: their age varied from 13 to 37, and most presented with severe hypertension and hypokalaemia, leading at first to a suspicion of primary hyperaldosteronism (Conn's syndrome). At least two were subjected to laparotomy with this diagnosis in mind. However, high circulating levels of renin, renin activity, or angiotensin II preoperatively[5-9] were strongly against the diagnosis. Instead they pointed more to one of the secondary forms of hyperaldosteronism in which overactivity of the renin-angiotensin system occurs with increased aldosterone. This was borne out by the raised aldosterone levels in three out of four patients. The exception[9] had been subjected previously to subtotal adrenalectomy.

At this stage of the investigations most physicians would justifiably suspect either malignant-phase hypertension[10] or renal vascular disease[11] as the cause of secondary hyperaldosteronism. But not all patients had evidence of the malignant phase, and in none of the five subjected to arteriography was there evidence of renal vascular disease, though in four[6-9] a renal tumour was suspected. This, coupled with the demonstration of high renin activity in venous plasma from the affected kidney, led to the preoperative diagnosis of a renin-secreting tumour in at least three cases.[7-9]

All six patients were subjected to unilateral nephrectomy. In one[5] the tumour was not found until after operation. In each instance it appeared to be a benign haemangiopericytoma or neoplasm of juxtaglomerular cells. Histochemical characteristics were in accord, as were antibody[8 9] and tissue culture studies.[8] A renin-like enzyme was extracted in large amounts from the tumour,[4 6 8] considerably more than from adjacent kidney tissue. Characterized in various ways, the enzyme seemed indistinguishable from renin.[4-8] It is unlikely that these were false positive results, because similar data were obtained by bioassay and by wholly different radioimmunoassay techniques.

After operation blood pressure fell to normal in all patients without further treatment. Hypokalaemia was corrected, and, when measured, both renin and aldosterone decreased to normal or subnormal. There is therefore a strong case for suggesting that renin-secreting haemangiopericytoma of the kidney may lead to severe hypertension with secondary hyperaldosteronism.

Other commoner renal tumours may sometimes be asssociated with high blood pressure,[12] and high circulating levels of renin together with increased renin in tumour tissue have been noted in hypertensive children with Wilms's tumour.[12-14] As with the haemangiopericytoma, excision of the kidney was followed by a fall of renin and blood pressure.[13 14]

It is impossible to say at this stage whether renin-secreting tumours are common or rare. This diagnosis is difficult and may well be overlooked when renin measurements are not made. Radiological diagnosis does not seem easy, and, though positive when tested, renal-vein renin estimations could be falsely positive in conditions where renin release was normal but renal blood flow was reduced. Recognition of the disease is nevertheless important for the positive reason that it represents an identifiable and (so far) curable cause of hypertension in young people, and for the negative reason that without renin measurements hypokalaemia with hypertension and increased aldosterone

may wrongly lead to the diagnosis of primary hyperaldosteronism and even to the excision of the wrong endocrine gland.

The opposite clinical syndrome—primary lack of renin or hyporeninism—has also been recognized recently. In this disease primary lack of renin (and hence of its active product angiotension II) apparently leads to selective deficiency of aldosterone associated with normal cortisol production. The literature contains reference to some 20 cases of isolated analdosteronism, the first a report by J. B. Hudson and his colleagues[15] in 1957. Only recently however has the primary deficiency been recognized as renin lack in at least some of these patients. At page 650 of this issue of the *B.M.J.* we publish what appears to be the first report of a case in Britain.

Isolated hypoaldosteronism usually occurs in elderly patients and is characterized by attacks of loss of consciousness, cardiac arrhythmias, muscle weakness, and weight loss. It should be considered when severe hyperkalaemia occurs with only a moderate rise of blood urea and where cortisol production is normal. The symptoms are due to the electrolyte derangements, since treatment with ion exchange resins leads to a prompt clinical remission, which is maintained when plasma electrolytes are kept normal with mineralocorticoid replacement therapy. While the selective deficiency of aldosterone in a few of these patients may have been due to a block in the biosynthetic pathway leading to aldosterone,[16-18] primary lack of renin now seems a likely explanation in the remainder. This idea was put forward originally by D. R. Jacobs and J. B. Posner[16] in 1964, but remained unsupported until recent reports in the syndrome of low plasma levels of renin[18-21] and angiotensin II,[18] persisting even during the stimulus of sodium deprivation. Evidence that the lack of aldosterone in these patients is secondary to the low circulating levels of angiotensin II is provided by the Glasgow group (this week), who report a distinct increase of plasma aldosterone when plasma angiotensin II was raised in their patient by infusion of synthetic angiotensin.

These reports of primary hyper- and hyporeninism are of interest in several ways. For the clinician primary hyperreninism becomes another potentially remediable cause of hypertension, while hyporeninism should be considered in all cases of unexplained hyperkalaemia, particularly since treatment is so simple and effective. In pathophysiological terms hyper- and hyporeninism shed considerable light on the role of the renin-angiotensin system in the regulation of aldosterone secretion and blood pressure. Primary hyperreninism is a condition in which an excess of circulating renin apparently leads to a reversible increase of aldosterone secretion and blood pressure, while primary hyporeninism leads to a reversible deficiency of aldosterone persisting in the presence of hyperkalaemia, otherwise a potent stimulus to aldosterone production.

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Pruritus Vulvae

Vulval irritation, or pruritus vulvae, is a distressing and sometimes baffling and intractable symptom. It can have a variety of local or general causes. A careful search for them is an essential prelude to treatment, since elimination of the cause usually brings relief.

Among the common causes are irritating discharges, which may come from the cervix, vagina, or urethra. Particularly common and readily recognized by bacteriological examination are those due to infection by *Trichomonas vaginalis* or *Candida albicans*. Vulval irritation may sometimes be the result of urinary incontinence. Special mention must be made of diabetic vulvitis, when to some extent the vulvitis may be due to irritation by the heavily sugar-laden urine, but *Candida albicans* infection is a frequent accompaniment of it.

Local disease of the skin may be part of a general skin disease such as psoriasis, eczema, or herpes. Lichen sclerosis may be present, a condition which may affect other parts of the body but very frequently affects the vulva. Here the vulva and perianal regions show patchy, white, atrophic changes. Histologically there is hyperkeratosis, atrophy of epithelium, and flattening of rete pegs and Malpighian layer. Usually it does not progress, but occasionally leukoplakia can supervene.

Leukoplakia and kraurosis vulvae are specific lesions which may be associated with pruritus vulvae. The characteristic white patches of leukoplakia are associated with hyperkeratosis and thickening of the epidermis, with overactivity of the Malpighian layer and degeneration of the corium. The hypertrophic form of leukoplakia is of particular importance because of its pronounced premalignant tendencies. Traditionally, a late atrophic stage of leukoplakia has been described too, the histological features of which are identical with those of lichen sclerosis.

The term kraurosis is reserved for a condition whose main features are atrophy and shrinkage of tissues, with flattening of epithelium, affecting the labia and particularly the vaginal introitus. But it should be noted that the clinically helpful distinctions drawn here between lichen sclerosis, leukoplakia, and kraurosis are not universally accepted. T. N. A. Jeffcoate and A. S. Woodcock,[1] for example, consider there is no good evidence that lichen sclerosis and leukoplakia are separate entities. There are in addition other cases, variously named Bowen's disease, Paget's disease, and carcinoma in situ, in which the features of intraepithelial carcinoma exist.

Ulcerative vulval lesions include some venereal conditions not often seen in Great Britain—namely, granuloma venereum and lymphogranuloma inguinale. Behçet's syndrome