CONN'S SYNDROME

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An account of Conn's syndrome could begin with the first description of potassium-losing nephritis by Brown, Currens and Marchand in 1944²: or with the discovery of the renal effects of adrenal cortical hormones by Loeb, Atchley, Benedict and Leland 10 years earlier.¹³ This account begins with the sweat glands. It begins in 1950 and it begins with Conn.⁴ In that year he published with L. H. Louis a paper on the production of 'endogenous salt-active corticoids' as reflected in the concentrations of sodium and chloride of thermal sweat. This was the first clear demonstration of the extra-renal actions of adrenal mineralocorticoids. Soon both the salivary glands and the colonic mucosa were found to respond to adrenal stimulation, like the renal tubules, by conserving sodium and secreting potassium. As Conn and Louis pointed out, the ability to observe changes in mineralocorticoid activity promised to be of great value in the investigation of clinical conditions.

Shortly afterwards, in 1952, Grundy and Simpson¹⁰ reported the isolation from beef adrenal extract of a new, highly active mineralocorticoid. This compound, 18-aldo-corticosterone, was later named aldosterone.¹⁹ Its sodium-retaining activity in man was found to be at least 20 times greater than that of desoxycorticosterone (DOC). The effect on urinary potassium excretion was less striking but was still five times greater than that of the same dose of DOC.

Conn foresaw that clinical disorders due to primary over-production of the new hormone might now be recognized. He did not have long to wait. On April 27, 1954, a 34-year-old white woman was admitted to his wards, complaining of intermittent spasms, weakness and paralysis of muscles for seven years. In October, 1947, she had been 'paralysed' from the hips down for two days. Several similar but less severe attacks had occurred since. She had frequent episodes of great muscular weakness. She described other attacks of typical tetany involving the hands and sometimes the feet. Between attacks she was well. The systolic blood pressure was known to have been 180 to 190 mm. for four years. The urine

had repeatedly shown a trace of albumin. For years she had had polyuria and nocturia. She had never had prolonged diarrhoea nor used purgatives to excess.

Physical examination revealed well-developed musculature, positive Chvostek's and Trousseau's signs and hyperactive reflexes. The blood pressure was 170/104. There was no oedema. The most striking chemical abnormalities were a low plasma potassium (1.6 to 2.5 mEq/l.), high plasma sodium (146 to 151 mEq/l.) and alkalosis (plasma bicarbonate 39 m. mol/l., pH 7.62). Plasma calcium concentration was 10.2 mg./100 ml. Urinary 17-ketosteroid and 17-hydroxycorticosteroid excretions were normal. Renal functional studies indicated reasonably normal glomerular and tubular function, except for the presence of a small amount of proteinuria and a low, fixed urinary specific gravity which was unaffected by Pitressin administration. The urine was persistently neutral or slightly alkaline. Urinary potassium concentration was over 30 mEq/l., despite the low plasma values.

These initial findings led Conn to suspect that the abnormality might be due to excessive activity of aldosterone and not to 'potassium-losing nephritis'. Further evidence of increased mineralocorticoid activity was therefore sought. Measurements of the electrolyte composition of sweat and saliva gave consistently low values for sodium and chloride and high values for potassium. Administration of potassium lowered the concentration of sodium still further, indicating greater activity of the abnormal mechanism. Balance studies showed that when an attempt at potassium repletion was made there was at first some retention of potassium and excretion of sodium. After four days, however, resistance to further potassium retention and sodium loss occurred, and it proved impossible to bring plasma potassium values to normal with large amounts of supplementary potassium. Bio-assays of urinary sodium-retaining corticoid gave values four to 30 times greater than those found in normal people.

These studies firmly established the presence of excessive mineralocorticoid activity. To distin-

guish it from heart failure and other oedematous states in which such overactivity was held to be secondary, Conn⁵ designated the new syndrome 'primary aldosteronism'. The term 'Conn's syndrome' is now preferred by most authors in view of the present uncertainty about the part played by aldosterone.

The treatment proposed was total adrenalectomy, followed by substitution therapy. At operation, however, to the surprise and delight of those present, a cortical adenoma 4 cm. in diameter was seen arising from the right adrenal gland and this was removed together with the tumour. Microscopically, the tumour was found to be composed of large lipid-containing cells. Bio-assay of extracts of tumour tissue indicated that it contained 10 to 100 times as much mineralocorticoid activity as normal adrenal, and paper chromatographic studies showed that this activity was almost certainly due to aldosterone. Biopsy of the remaining adrenal revealed atrophy confined to the zona fasciculata. A renal biopsy disclosed a major tubular lesion resembling the 'clear-cell nephrosis' already recognized as being associated with severe potassium depletion.¹⁸

Dramatic improvement followed. Within 14 days of removal of the tumour the electrolyte abnormalities had disappeared and blood pressure had returned to normal values. Polydipsia, polyuria and nocturia ceased, proteinuria disappeared and renal concentrating ability improved, although not to normal. Little or no sodium-retaining activity could now be detected in the urine.⁶

The publication of Conn's report aroused widespread interest and many similar cases have now been recognized. Ross,¹⁶ in a recent interview, lists 22 well-documented cases. Although one asymptomatic case has been recorded, most patients present with recurrent weakness or paralysis. Thirst and nocturia are very commonly present. Hypokalaemia is almost always severe, in the range 1.4 to 2.5 mEq/l. The degree of hypertension varies, but it may be severe, as in the case reported by the present writer and his colleagues³ and the blood pressure may not fall to normal after removal of the tumour. At least one case of malignant hypertension (with an adenoma) has been reported. Hypernatraemia and alkalosis are less constant features. Most patients at one time or another have plasma sodium concentrations above 145 mEq/l. Plasma bicarbonate and pH have remained normal throughout in several instances: this feature has not been satisfactorily explained. Acidosis never occurs in Conn's syndrome, but is the rule in renal tubular disorders associated with potassium loss.

Except for an impaired capacity to concentrate

and acidify the urine, renal function is usually reasonably normal. The blood urea is therefore normal or only slightly raised, unless severe hypertension or pyelonephritis have caused irreversible renal damage. The potassium-depleted kidney appears to be particularly susceptible to infection.¹⁵

Urinary aldosterone excretion is not increased in every case. For example, normal values were obtained by Barrett *et al.*,¹ by Milne, Muehrcke and Aird (1957, case 2¹⁵), and on two out of three occasions in our patient.³ This is not to say that blood levels and secretion rates may not be increased. The excised tumour in case 2 of Milne *et al.* produced five times as much aldosterone on incubation as did an equal weight of ox adrenal gland. But it is important to realize that urinary aldosterone measurements can be misleading. It may be preferable to measure the secretion rate using tritiated aldosterone.

Urinary 17-hydroxycorticosteroid and 17-ketosteroid excretion rates are always normal. (The one exception is the case described by Foye and Feichtmeir,⁹ who excreted increased amounts of both aldosterone and 17-hydroxycorticosteroids: this patient had a metastasising adrenocortical carcinoma.) There is nonetheless a strong suspicion that increased aldosterone activity is not the whole story. In Mader and Iseri's case¹⁴ the excised tumour contained an excess of corticosterone. The incubated tumour from case 2 of Milne *et al.*¹⁵ produced eight times as much corticosterone as an equal weight of ox adrenal gland. In normal man the pattern of electrolyte excretion characteristic of Conn's syndrome, namely, increased potassium excretion with relatively little sodium retention, can be produced by giving aldosterone together with corticosterone: aldosterone alone causes much greater sodium retention.¹⁷

Far the commonest adrenal finding is an adenoma. Indeed only one case of aldosterone-secreting carcinoma has been reported.⁹ In cases without tumours, that is, with hyperplastic or apparently normal adrenals, it now seems likely that the increased mineralocorticoid activity is always secondary to hypertension or renal ischaemia. The adenoma is usually 3 to 4 cm. in diameter but may be as small as 1 cm. (Hewlett *et al.*, case 2¹¹). Such a tumour cannot be demonstrated radiologically and may be difficult to find even at operation. It contains lipid and is yellow, orange or brown on section. Histologically it resembles normal zona fasciculata. This is a puzzling finding, since there is some evidence both direct and indirect, that aldosterone is produced in the zona glomerulosa and not in the fasciculata. On the other hand, when atrophy of

the normal adrenal occurs in Conn's syndrome, it is confined to the fasciculata.

Removal of the adenoma may be followed by a period of mild aldosterone insufficiency in which the electrolyte abnormalities are reversed, hypotension may occur, and glomerular filtration rate decrease. Sometimes the blood pressure falls to normal after operation but rises again a few months later. In such cases the remission is probably due to hypoaldosteronism.

The differentiation of Conn's syndrome from other causes of hypertension with hypokalaemia may be extremely difficult. Cases of renal tubular acidosis or Fanconi syndrome can now be clearly distinguished by the presence of metabolic acidosis and the absence of increased mineralocorticoid activity. Fitzgerald *et al.*,⁸ however, reported a case of malignant hypertension with potassium depletion, alkalosis and increased urinary aldosterone in whom removal of one hyperplastic adrenal arrested the losses of potassium, but removal of both failed to alter the course of the hypertension. Several other cases of hypokalaemia with hypertension have since been recorded in whom no primary adrenal abnormality (i.e. an adenoma) was present. In one instance reduction of blood pressure by means of hypotensive drugs corrected the hypokalaemia.¹² Recently Dollery, Shackman and Shillingford⁷ have described two patients with malignant hypertension and hypokalaemia who were found to have unilateral obstruction of the renal artery. In both cases the hypokalaemia and in one the hypertension were cured by nephrectomy. The investiga-

tion of such patients should therefore include renal arteriography as well as intravenous pyelography. Urinary pressor amines must also be measured. In doubtful cases surgical exploration of the adrenals is indicated and should be carried out without delay.

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