Aldosterone and Electrolyte Balance in Human Hypertension

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The exact roles of aldosterone and sodium in the pathogenesis of essential hypertension are still not clear, and it is our intention to discuss in this article some recent advances in this field, as related to human hypertension, emphasising the following three aspects: (1) aldosterone metabolism in human hypertension, especially in the benign, uncomplicated phase of essential hypertension, presenting our new findings on aldosterone plasma levels and metabolic clearance rate and describing recent experiments from other research groups, and indicating a definite disturbance in aldosterone response to various stimuli in patients with benign essential hypertension; (2) the emergence of new hypermineralocorticoid hypertensive syndromes associated with renin unresponsiveness; and (3) disturbances in sodium and potassium regulation in hypertension.

Aldosterone
Our first report (Genest et al., 1956) of a significantly mean increased urinary aldosterone excretion in patients with severe essential and malignant hypertension has been widely confirmed by all research workers using similar or more accurate isotopic methods.

Excessive aldosterone secretion rate or daily excretion have been reported in about 50 per cent of patients with hypertension associated with renal artery obstruction. There has been a good deal of confusion as to the role of the renin-angiotensin system in this field since it has not been appreciated fully that the presence of a renal artery obstruction does not necessarily mean that it is the cause of hypertension in a given patient. The expression 'renovascular hypertension' should be strictly reserved for those in whom the correction of the renal arterial obstruction has resulted in a lowering of blood pressure to
normal levels, which persist without any antihypertensive therapy for at least one year following surgery (Genest et al., 1960). In such patients, Barraclough et al. (1965) have demonstrated marked increases in aldosterone secretion rate in 6 out of 7 patients studied. Kaufmann and his colleagues (1967) have made a more thorough study in similar patients by the simultaneous determination of aldosterone secretion rate, daily excretion, metabolic clearance rate, and plasma levels. In all patients studied, plasma aldosterone levels were above the normal range, whether or not the aldosterone secretion rate was high or normal. These high plasma levels were due to a significant decrease in metabolic clearance rate.

This concept of the metabolic clearance rate of aldosterone (Tait et al., 1962) which is mainly controlled by the liver and closely related to the hepatic blood flow and, also, to the rate at which the liver cells inactivate circulating aldosterone into the tetrahydro-aldosterone glucuronide has been most useful and has been applied by our group to the study of patients with benign, uncomplicated essential hypertension.

This latter group of patients has been the subject of much discussion and confusion concerning the state of aldosterone metabolism. It is of the utmost importance to define clearly the state of aldosterone metabolism and regulation in this early stage of essential hypertension for a better understanding of the role, if any, of this hormone in the physiopathology of human essential hypertension. This group of patients must be well defined as having benign hypertension, normal renal function and plasma electrolyte levels, normal renal arteriogram and rapid sequence intravenous pyelography, absence of vascular complications of retinopathy or microscopic haematuria and absence of any known cause of hypertension.

Our earlier findings of increased urinary aldosterone excretion in about 40 per cent of such patients (Genest et al., 1960), using a physicochemical method of measurement (Nowaczynski et al., 1957), although confirmed by many other workers using similar methods, have not been supported by other groups using more accurate procedures of double isotope dilution techniques for measurement of urinary aldosterone excretion or of its secretion rate. The findings of these groups (Laragh et al., 1966; Kaplan, 1967a, b; Biglieri et al., 1968; George et al., 1968) indicate a normal secretion rate and daily excretion in the great majority of patients with benign, uncomplicated essential hypertension. Based on these latter findings, the prevailing view in the last four to six years has been that, since aldosterone secretion rate and excretion were normal in the great majority of these patients, the disturbances in aldosterone metabolism in the more advanced stages of the disease were secondary and not primary phenomena and that its regulation was normal in
early essential hypertension. Nevertheless, it should be pointed out that Conn and his colleagues (1966–67), using a similar double isotope dilution technique (Kliman and Peterson, 1960) have reported findings of urinary aldosterone excretion identical to those we had previously reported (Genest et al., 1960), with a significantly \( p < 0.001 \) higher mean value in patients with benign essential hypertension when compared to normal subjects.

For this reason and in order to define more definitely the role of aldosterone in early benign essential hypertension, Nowaczynski and I have recently terminated an intensive study of the aldosterone metabolism in such patients by the direct measurement of plasma aldosterone levels, its metabolic clearance rate, and its secretion rate. All patients were carefully selected on the basis of the above criteria for benign essential hypertension and were studied after four days of a fixed daily dietary intake of 135 mEq of sodium and 90 mEq of potassium in our clinical investigation unit. Their mean age was 37 years, with a range of 17 to 55 years. Older patients with overt signs of arterio-atherosclerosis and a wide pulse pressure were not studied. All patients had blood pressure levels above 140/90 mm Hg at the time of the study, and those in whom the effect of rest and reassurance resulted in a decrease of blood pressure to levels below 140/90 mm Hg were rejected and not studied.

Plasma levels of aldosterone were measured by the method of Nowaczynski et al. (1967) and the metabolic clearance rates were determined by the procedure of Tait et al. (1962), modified by Nowaczynski et al. (1970).

Mean plasma aldosterone levels in the group of 42 patients with benign uncomplicated essential hypertension were 17.2 ng\% ± SD 14.5 as compared to the mean value in a group of 20 normal subjects of 7.5 ng\% ± SD 4.8 (Fig. 1). This difference between the means is significant at a \( p < 0.01 \). Of the 42 hypertensive patients, 14, or one third, had plasma levels above the upper normal range.

This group of patients was divided into two subgroups depending on the plasma renin activity. Subgroup A consisted of 25 patients in whom plasma renin activity was normal. Mean aldosterone plasma levels were 20.2 ± SD 17.8 and the difference, when compared to that of normal subjects, is significant \( p < 0.01 \). Half of the patients had levels above the normal range. Subgroup B of 17 patients had undetectable plasma renin activity in the recumbent position and at rest. Mean plasma aldosterone levels were lower (12.7 ng\% ± SD 7.2) than in Subgroup A, but the difference, when compared to the group of normal subjects, is still significant \( p < 0.02 \). Three patients had values above the normal range.

The study of aldosterone metabolic clearance rate in 10 of these 42 patients
with benign essential hypertension shows a significant (p < 0.001) mean decrease when compared to that of a group of 7 healthy subjects (Fig. 2). The mean metabolic clearance rate in those patients was 867 litres of plasma/day/square metre of surface area + SD 270, as compared to a mean of 1484 ± SD 265 in normal subjects. It is of interest to point out that many of these patients with benign essential hypertension with decreased metabolic clearance rates also presented aldosterone secretion rates in the low range of normal, between 60 and 90 µg/day.

These findings indicate a definite disturbance in aldosterone metabolism, mainly in the rate of removal of aldosterone by the liver. Whether this disturbance is due to a decrease in hepatic blood flow or in the rate of degradation of aldosterone by liver cells remains to be determined. The second possibility appears more likely in view of a previous report indicating a normal hepatic blood flow in groups of hypertensive patients (Wilkins et al., 1952).
Our studies of aldosterone secretion rate in this group of patients are in agreement with those previously reported by Laragh, Biglieri, Bartter, Kaplan and their respective groups.

Other evidence of disturbances in aldosterone regulation have recently been reported by several groups of workers. Helmer and Judson (1968) observed no change in daily aldosterone excretion during severe sodium restriction in 13 patients with essential hypertension and suppressed plasma renin activity. These findings were confirmed by Streeten et al. (1969), and José et al. (1970). In the patients studied by Streeten et al., no distinction was made concerning the levels of plasma renin activity (PRA). The aldosterone excretion of these patients in response to severe sodium restriction was significantly decreased \( p < 0.001 \) when compared to that of normal subjects. José and his group obtained very similar results and found, in addition, that this decreased aldosterone responsiveness was accompanied by a significantly \( p < 0.01 \) greater loss of urinary sodium in the ‘PRA-nonresponders’ than in the ‘PRA-responders’.

Williams et al., (1970) extended these observations to the effects of acute sodium loss by administration of large doses of frusemide (200 mg orally in
one day) and of severe bleeding. They found that the administration of frusemide, while producing a marked rise in PRA was not accompanied by any change in aldosterone secretion rate in patients with benign essential hypertension in contrast to a significant increase in normal subjects. The same observation was also made in similar patients following the removal of 500 to 700 ml of blood over a period of 20 to 30 minutes.

Luetscher et al. (1969) observed a total lack of suppression of plasma levels, secretion rate and daily excretion of aldosterone by administration of an oral salt load (urinary sodium excretion above 300 mEq/day) to patients with benign essential hypertension, whether their PRA was normal or suppressed. Recently, Luetscher and his colleagues (1970) have reported the extension of these studies to 50 patients with benign essential hypertension and found that 41 of them failed to reduce aldosterone excretion to the normal range on a daily intake of more than 300 mEq of sodium per day. Their mean secretion rate was twice that of normotensive controls on the same high sodium intake. This led Luetscher et al. to 'conclude that many hypertensive patients have moderately increased basal secretion of aldosterone'. On the other hand, Kem et al. (1970) reported the suppression of plasma aldosterone levels following acute intravenous administration of 2 litres of isotonic saline in patients with benign essential hypertension similar to that observed in normal subjects. This difference in response of hypertensive patients between intravenous versus oral salt loads may be a consequence of the acute expansion of plasma volume and the sudden rise in plasma sodium concentration.

Our data on plasma levels of free aldosterone, metabolic clearance rates, and responses of aldosterone to various stimuli indicate definite disturbances in aldosterone metabolism and regulation in patients with benign, uncomplicated essential hypertension. A possible explanation of the latter finding could be, as suggested by Williams et al. (1970), a defect in the angiotensin II action on the adrenocortical production of aldosterone.

**HYPERMINERALOCORTICOID HYPERTENSIVE SYNDROMES**

In this group we include primary aldosteronism, whether hypo- or normokalaemic (Conn, 1966-67), Biglieri's syndrome (1968), the hypertensive form of adrenal virilising hyperplasia (New and Seaman, 1970), the glucocorticoid-remediable hyperaldosteronism (Salti et al., 1969; Sutherland et al., 1966), the corticosterone hypertensive syndrome (Fraser et al., 1968) and two new syndromes recently described by Küchel et al. (1970b) in hypertensive patients with ovarian agenesis. These hypermineralocorticoid hypertensive syndromes are almost always associated with suppression of PRA and its unresponsiveness to the stimuli of upright posture and severe sodium
restriction. Many occur without any signs of hypokalaemia and may be associated with an excessive secretion of mineralocorticoid hormones other than aldosterone, such as deoxycorticosterone, corticosterone and their 18-hydroxy derivatives, and of compound ‘S’. Several show excellent response in blood pressure to the suppression of ACTH by administration of a glucocorticoid hormone.

The latest figure of the incidence of normokalaemic primary aldosteronism given by Conn is about 7 per cent. This incidence is queried by others and, although Conn’s view that normokalaemia exists in some patients with essential hypertension who are cured by the removal of an aldosteronoma is now well accepted, we believe that it will still take two or three more years to have a clearer indication of the incidence of the normokalaemic primary aldosteronism.

Biglieri’s syndrome, characterised by 17-hydroxylase deficiency and the new hypertensive syndrome described by Küchel et al. (1970b) in three siblings with severe hypertension, advanced renal insufficiency, decreased hearing, decreased platelet adhesiveness and enlarged thymus, and the hypertensive form of adrenal virilising hyperplasia are due to the excessive secretion of deoxycorticosterone, corticosterone and/or compound ‘S’ with very low levels of aldosterone secretion and excretion.

Melby et al. (1970) have recently reported excessive urinary excretion of 18-hydroxy-tetrahydro-11-deoxycorticosterone in 3 out of 4 patients with essential hypertension. It is of interest that Rapp and Dahl (1970) found that the 18-hydroxy-11-deoxycorticosterone production and adrenal venous blood concentration of a salt-sensitive hypertensive strain of rats were twice that of the salt-resistant normotensive strain, whereas there was no difference in deoxycorticosterone or aldosterone secretion between the two strains. Preliminary experiments in our laboratory (Küchel et al., 1970a) have shown an increased 18-hydroxy-11-deoxycorticosterone secretion rate in 8 out of 12 patients with benign, uncomplicated essential hypertension. Whether or not the hypersecretion of these steroids with mineralocorticoid activity weaker than that of aldosterone may be associated with the pathogenesis of hypertension remains to be demonstrated, although it can be argued that excessive secretion for prolonged periods and with a high sodium intake may be sufficient to increase blood pressure to hypertensive levels.

Three other points should be emphasised: (1) patients with Turner’s syndrome and hypertension (found in 25 per cent of patients with this syndrome) should be thoroughly screened for hypermineralocorticoid activity and chromosomal patterns as suggested by the new syndrome recently described by Küchel et al. (1970c); (2) patients with essential hypertension and
low renin were reported by Luetscher et al. (1969) to have serum sodium concentrations generally higher than those with high or normal renin and to have serum potassium concentrations frequently at the lower limits of normal; (3) patients with essential hypertension and suppressed PRA were shown by Woods et al. (1969) to have higher exchangeable sodium than other hypertensive patients with normal renin responsiveness. José et al. (1970) found higher extracellular fluid volumes in similar patients when compared to normal subjects.

These findings suggest that hypertension in patients with suppressed PRA is frequently associated with increased mineralocorticoid secretion and emphasise the need to study a complete mineralocorticoid hormone spectrum: aldosterone, deoxycorticosterone, corticosterone, their 18-hydroxy derivatives, and compound ‘S’.

**SODIUM AND POTASSIUM REGULATION**

It is a clinical fact that most patients with hypertensive disease, except those in renal failure and those with essential hypertension and low renin, as recently demonstrated by José et al. (1970), can maintain sodium balance. This has been well established by the classical studies of Kempner, Dole, and Dahl. Although hypertensive patients can maintain sodium balance even during most severe and prolonged sodium restriction, there is ample evidence

| Table 1. Disturbances of Sodium Regulation in Patients with Essential Hypertension |
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| 1. Greater and more rapid rejection of salt loads. Blockage of this effect by propranolol. |
| 2. Higher incidence of hypertension in populations with high salt intake. |
| 3. Increased arterial sodium content in various types of hypertensive states and preceding the rise in blood pressure in DOCA hypertension. |
| 4. Antihypertensive effectiveness of: (a) Severe sodium restriction (or rice-fruit diet) in 30 to 50% of patients with essential hypertension. (b) Natriuretic agents and spironolactone. |
| 5. Natriuretic effects of angiotensin despite aldosterone stimulation. |
| 6. Potentiation of hypertensive effects of steroids by administration of sodium. |
| 7. Production of hypertension in salt-sensitive strain of rats or by high salt intake in humans. |
| 8. Prevention of toxæmias of pregnancy by low sodium intake and/or thiazide drugs. |
| 9. Pressor response to cross-transfusion of blood from a renal hypertensive rabbit to a high salt-fed rabbit. |
of 'dys-regulation' of sodium in human hypertension as well as in experimental animals. Some of the disturbances are described in Table 1.

Progress in this field has recently been made by the demonstration that the excessive and more rapid natriuresis following administration of salt loads to patients with essential hypertension could be completely blocked by the administration of propranolol (Mroczek et al., 1970). This finding, if confirmed, would indicate that this excessive natriuresis could be due to increased sympathetic nervous system activity and disturbance in intrarenal blood flow distribution. The observations of José et al. (1970) concerning the greater sodium loss in 'PRA-nonresponder' essential hypertensive patients during severe sodium restriction are in agreement with our observation of a tendency in similar patients to orthostatic hypotension when given thiazide drugs (Genest, unpublished observations).

A significantly (p < 0.01) lower salivary Na/K ratio was observed (Adlin et al., 1969) in a group of patients with essential hypertension and suppressed PRA when compared to that of a group of normal subjects or of patients with essential hypertension and normal PRA, indicating increased mineralocorticoid action.

Frankel et al. (1970) have recently reported that the average total body potassium in a group of 60 hypertensive patients was significantly (p < 0.001) decreased by 7.5 per cent when compared to the normal curve established by the whole body counting of 40K in 1,400 normal subjects.

A wise observation was made by Brown et al. (1969) concerning the use of serum instead of plasma for potassium determination and the avoidance of arm exercise preceding or during venipuncture. Hypokalaemia, when present in a hypertensive patient without a history of chronic diarrhoea, thiazide or liquorice ingestion, is always associated with a state of hyperaldosteronism or of excessive secretion of other mineralocorticoid hormones.

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