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The Adrenal Cortex in Internal Medicine*—Part II

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Aldosterone

The same interval elapsed between discovery of aldosterone in 1952 by Tait *et al.* and recognition of the first aldosterone-producing tumour by Conn in 1954, as between recognition of adrenaline and the first adrenaline-producing tumour. If the rate of clinical progress has not changed in 45 years, that of technical progress has been immensely greater, making possible the isolation of aldosterone from human urine, its crystallization, and the determination and proof by synthesis of its chemical structure, all within two to three years. Shortly afterwards isotope-labelled samples of the hormone were prepared, and with this the daily secretion rate was first estimated. This rapid progress was all the more remarkable because the daily production is only about one-hundredth of that of cortisol.

More recently plasma-aldosterone levels have been estimated, though the technique is exacting and the use of isotopes is essential: they average only about a thousandth of the normal plasma cortisol, or about a five-millionth of the normal plasma-glucose content. The now familiar estimations of similar low concentrations of vitamin B_{12} are made possible by the peculiar sensitivity of a living organism, but there is no equivalent specific organism or chemical reaction for aldosterone. Analysis still involves laborious separation by orthodox chromatographic methods, with assay by modern double isotope-derivative techniques, because the quantities are much too small even for classical microchemical methods. But in spite of the difficulties the general dynamics of aldosterone within the body have now been fairly completely worked out.

Aldosterone is secreted into the systemic blood by the zona glomerulosa of the adrenal cortex at a rate which averages 130 μg. a day, but varies from 50 to 200 μg. in normal circumstances. Circulating aldosterone, unlike cortisol, is only mildly bound to plasma protein, the mean being 65% compared with 95% for cortisol (Daughaday *et al.*, 1961). When blood passes through the liver its aldosterone is almost completely removed. The liver is probably the only major site of aldosterone destruction, for indirect isotopic estimates of the amount of blood cleared of aldosterone per minute coincide very closely with the estimated total liver blood-flow (Bougas *et al.*, 1964). This volume of blood has been called the metabolic clearance rate for aldosterone. The rate of removal from the circulation is such that half the blood content is destroyed in about 30 minutes, and under normal circumstances this will be replaced by freshly secreted aldosterone. The plasma concentration at any time reflects the balance between secretion and destruction, the two being in approximate equilibrium. If any two of these three variables can be measured the third can be calculated.

Estimates of total plasma aldosterone obtained either indirectly or directly, by the double isotope-derivative method, give a mean of 0.007 μg./100 ml. (Peterson, 1964). Some of this minute amount leaks into the urine; the renal clearance for free aldosterone is about 14% of the inulin clearance (Gfeller and Siegenthaler, 1965), and that for the 3-oxo-conjugate is about 250% of the inulin clearance (Siegenthaler *et al.*, 1964). If confirmed, this would indicate an active secretion by the renal tubules, but the loss in the urine rarely exceeds 10% of the daily production.

Although most of our knowledge of the behaviour of aldosterone in disease derives from changes in the urinary content, this is not the ideal criterion because of its uncertain relation to the plasma levels, especially in impaired states of renal function, which are frequent in just those conditions where the behaviour of aldosterone is of greatest interest. Direct measurement of plasma concentrations, after a great deal of labour, reflects the state of the internal environment at an instant in time. The aldosterone secretion rate, feasible as a research procedure, is more valuable, giving a mean value for 24 to 48 hours; but it requires the skilled use of isotopes and has the disadvantage of not necessarily reflecting the prevailing plasma levels, because in disease the rate at which aldosterone is destroyed in the liver varies (Luetscher *et al.*, 1965).

Most Useful Index

The most useful index of aldosterone behaviour in the body is likely to be an indirect estimate of the mean plasma-aldosterone concentration over 24 hours. Tait (1963) derives this estimate by dividing the aldosterone secretion rate by the rate of removal of aldosterone from the blood-stream, the latter being measured during constant infusion—the so-called metabolic clearance rate. This index is technically more feasible and probably more valid clinically than most of the others, but as yet few data have been published. In my laboratory Glaz and Pearson have studied the procedure, but it is not yet suitable for routine clinical investigation, calling for considerable patience and technical skill.

Aldosterone production in the body is as labile and variable as that of cortisol, but it rises and falls in response to quite

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different stimuli from those which influence cortisol, and the more important of these should be clearly appreciated.

The greatest single factor in stimulating aldosterone secretion is sodium loss, with the resultant need to conserve this ion; secretion may thereby be raised ten times. The mechanism is not yet well understood, but it is not the result of a fall in plasma sodium. Potassium depletion lowers aldosterone production, but this effect is weaker and easily overruled if both potassium and sodium are depleted, as often happens. Magnesium depletion alone has no significant effect (Cope and Pearson, 1963b), but generous potassium administration tends to increase aldosterone secretion. Other important stimuli seem to be concerned with threats to the extracellular fluid (E.C.F.) volume: if E.C.F. volume is increased, even if plasma sodium is decreased, aldosterone production falls (Bartter *et al.*, 1956). Likewise, reduction in E.C.F.—for example, produced by a potent diuresis or a large haemorrhage—may lead to a sharp increase in aldosterone production, even when plasma sodium is rising (Beck *et al.*, 1955).

Cardiac Oedema

The sharp responses of aldosterone production to the changes in E.C.F. volume, and its extreme potency in causing sodium retention by the kidney and facilitating potassium excretion, are clearly important in the various forms of oedema.

Although Deming and Luetscher (1950) found generous amounts of the sodium-retaining hormone, which was soon identified with aldosterone (Luetscher *et al.*, 1954, 1956) in the urine of patients with congestive cardiac failure, later work in several laboratories has shown that a raised excretion or secretion is the exception rather than the rule—for example Schröder (1963). In eight such cases we found secretions from 70 to 620 μg., with a mean of 261 μg./day—about 100% above our normal daily mean of 129 μg. (Cope *et al.*, 1961). Although it has been suggested that stretching of the atrium may increase aldosterone secretion, our figures in severe tricuspid incompetence and mitral stenosis have been normal; observations on urinary aldosterone excretion lead to the same conclusion (Wolff *et al.*, 1956). Direct measurements of plasma aldosterone (Wolff *et al.*, 1964, 1965) have been normal in static congestive failure, yet modest changes seem likely. Luetscher *et al.* (1963) found rather slow destruction of aldosterone in congestive failure. Camargo *et al.* (1965) studied plasma levels by the indirect method: the mean aldosterone secretion rate was 178 μg. daily in seven slight-to-moderate cases of failure, and 188 μg. in six advanced cases; their normal mean value, like ours, was 128 μg. Aldosterone removal by the liver was only slightly reduced in the mild cases, but was reduced to a mean of 44% of normal in the severe cases. They calculated that the mean plasma-aldosterone levels were 19 mμg. for the mild and 26 mμg. for the severe cases, compared with the normal mean of 7.7 mμg./100 ml. Aldosterone secretion rates tended to be higher in cardiac patients with an intake of less than 80 mEq of sodium a day, averaging 230 μg. daily compared with 155 μg. when the sodium intake was higher.

Aldosterone production in congestive cardiac failure is thus not at all impressive, being indeed often rather more sluggish than normal. The aldosterone-secreting mechanism, faced with a greatly expanded E.C.F. volume, apparently lets it remain so; when volume changes are produced by outside influences it usually reacts to resist the change. A low-salt diet and any natriuresis produced tend to raise aldosterone secretion. The result should theoretically be a less effective action of the aldosterone antagonist, spironolactone (Aldactone A), which depends on a mass-action effect, since these antagonists were deliberately produced to act as anti-metabolites (Kagawa *et al.*, 1957). To assess this quantitative effect, Ross and Bethune (1959) infused both aldosterone and spironolactone simultaneously in varying proportions into suitable subjects, and concluded that the antagonist inhibited roughly a thousandth part of its own weight of aldosterone. It is common experience that the diuretic and natriuretic effects of the spironolactones are variable and unpredictable, and it is tempting to suspect that this is due either to very low aldosterone secretion, so that there is almost none to inhibit, or to very high secretion, too great for the antagonist to compete with. But in fact neither of these facile explanations seems to be true, and the behaviour of aldosterone continues to baffle our understanding.

Resistant Cardiac Oedema

We have endeavoured to throw light on the problem of resistant cardiac oedema by direct measurement of aldosterone secretion rates.

In 15 cases of congestive cardiac failure the mean aldosterone secretion rate was 185 μg. daily, only three being above the normal range, although the oedema in all of them was resistant to regular administration of chlorothiazide. Resistance to this diuretic is therefore not referable to increased aldosterone secretion. Some of these subjects were studied before and after a five-day course of spironolactone, 100 mg. daily, which was superimposed on the regimen of mild salt restriction, regular chlorothiazide, and intermittent mersalyl, to which all were completely resistant. The mean aldosterone secretion rate before spironolactone was 231 μg./day—a figure rather higher than that found by Camargo *et al.* (1965). After spironolactone, aldosterone secretion rates rose in some and fell in others, so that no uniform trend was evident, but the mean was 271 μg. Four subjects showed negligible weight loss from the spironolactone, and their mean aldosterone secretion rate rose from 210 to 227 μg.—an insignificant change of only 8%. In four others the weight loss with spironolactone was greater than 2 kg., and their mean aldosterone secretion rate rose from 280 to 344 μg. daily—that is, by 23%. Though it is unwise to draw firm conclusions, the results do suggest that response to spironolactone is better in cardiac oedema with higher aldosterone secretion, and, furthermore, that when the drug provokes weight loss aldosterone secretion rises higher, apparently in an effort to resist the beneficial change. The aldosterone secretion seems to respond to the weight change or to the loss of E.C.F., rather than to the presence of the spironolactone itself (cf. Sanders and Melby, 1964). Interference with the action of aldosterone on its target in the kidney does not itself provoke a compensatory rise in secretion to combat its ineffectiveness.

We are here concerned primarily with the role of the adrenal cortex in cardiac oedema, and this seems to be humble and secondary. An as yet undefined factor is the major determinant of cardiac oedema, and without this no amount of aldosterone will produce it. The minor role of aldosterone can be judged from the extreme rarity of oedema in primary hyperaldosteronism, and from the fact that long-term administration of aldosterone fails to produce oedema. Kelly *et al.* (1962) have given doses of aldosterone totalling 80 mg. over periods of four to five days to several healthy medical students without producing oedema or other observable effect.

Hypertension

The role of the adrenal cortex in hypertension has been studied ever since the discovery of adrenaline and the clinical features of phaeochromocytomata. But for many years lack of suitable methods prevented profitable investigation, and this accounted for what Janeway (1913) called the "beautiful dream of adrenalinaemia." The 17-ketosteroids were soon found to be normal in the great majority of hypertensive disorders. Recognition that Cushing's syndrome was due almost entirely to overproduction of cortisol, with a high level of this hormone in the plasma, naturally revived interest in the possible role of cortisol in other forms of hypertension, but exploratory studies met with little encouragement. Kornel (1960) showed that the plasma levels of 17-hydroxycorticosteroids were unchanged in other hypertensive disorders, the mean plasma level being 13.4 μg./100 ml. in normotensives, and 13.6 μg. in hypertensives. Nor was the response to corticotrophin significantly different in the two groups. Vermeulen and Van Der Straeten (1963) have

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since found normal cortisol secretion rates. Clearly cortisol is an uncommon factor in the pathogenesis of hypertensive disorders, and any beautiful dream of hypercortisolaemia has been shattered.

The dramatic recognition of aldosterone-secreting tumours (Conn, 1955) not only presented a major diagnostic challenge but also sharpened interest in the possible role of aldosterone in other forms of hypertension. Adrenaline and cortisol had both proved disappointing ; aldosterone might be more rewarding. Wrong (1961) pointed out that a mild degree of hypokalaemia was frequent in the commoner types of hypertensive disorder—a discovery made by De Wesselow and Thomson (1939) more than 20 years earlier—and Dollery *et al.* (1959) showed that in some subjects both hypokalaemia and hypertension could be cured by unilateral nephrectomy.

Genest *et al.* (1958) in Montreal claimed that urinary aldosterone excretion was raised in uncomplicated essential hypertension: they found that 32 out of 64 estimations of urinary aldosterone in essential hypertensives were above the normal, the mean being 12 μg. daily compared with a normal of 5 μg. But further study showed a much wider fluctuation in day-to-day output than is normal. A number of groups have confirmed this variability, notably Venning *et al.* (1961), who also found a raised output of the main aldosterone metabolite, tetrahydroaldosterone, its mean value in seven patients with essential hypertension being 38.4 μg. daily compared with 23.1 μg. in 34 normotensives. But further work does not support the conclusion that the aldosterone secretion or plasma level is raised in essential hypertension. Both we (Cope *et al.*, 1962) and the main American workers (Laragh *et al.*, 1960b) agree that in uncomplicated essential hypertension aldosterone secretion remains entirely within the normal range. In our series the mean value for subjects with essential hypertension was 130 μg. daily compared with a mean for normal subjects of 129 μg., both groups being on a normal diet and salt intake (Cope, 1964). In these subjects aldosterone clearly plays no part in pathogenesis, and, since there is no reason to suspect impaired liver function or faulty aldosterone breakdown, we must conclude that plasma aldosterone was also within the normal range.

Changed Pattern in Other Types of Hypertension

In other types of hypertension the pattern changes. All agree that high aldosterone secretion is much more frequent.

Venning *et al.* (1961) found a mean urinary aldosterone excretion of 19.4 μg. in hypertensives with primary renal disease, the highest figures being in the most severely ill. Laragh *et al.* (1960b) found well-increased aldosterone secretion rates in nearly all (93%) their patients with malignant hypertension. We (Cope *et al.*, 1962) have found high aldosterone secretion in half of a small group of malignant hypertensives. The proportionate differences in frequency need not worry us unduly: they are readily explained by the type of clinical material. The point is that, whereas in essential and uncomplicated hypertension the rise is small or absent, in malignant hypertension it is large and frequent (Fig. 11). There is similar variability and tendency to high values in renal artery stenosis,

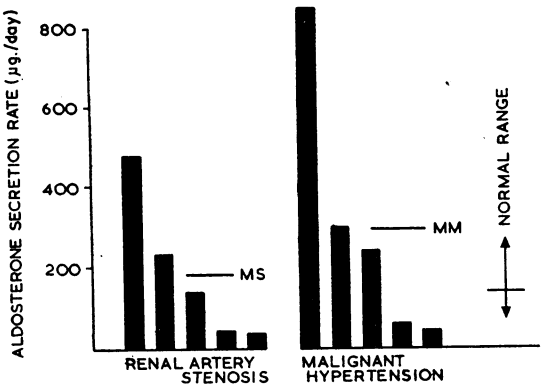

FIG. 11.—Range of aldosterone secretion rates encountered in renal artery stenosis and in malignant hypertension.

which can simulate the clinical picture of primary hyperaldosteronism in a remarkable way (Laidlaw *et al.*, 1960, 1964). We have found high aldosterone secretion rates in two or five proved cases of renal artery stenosis (Fig. 11). More recently Sambhi *et al.* (1963) found a normal aldosterone secretion rate in five further cases, but nevertheless the hypertension was cured by nephrectomy. These differences probably reflect no more than the hazards of case selection in an uncommon and complex disorder.

Clearly, hypertensive disorders with renal and possibly other complications are much more likely to be associated with raised aldosterone secretion than are those without such complications. The first suggestion that ischaemic renal disease might stimulate aldosterone secretion, giving a form of secondary aldosteronism, was apparently made by Wrong (1957) at a meeting of the Association of Physicians of Great Britain and Ireland.

Yet high aldosterone secretion rates are not peculiar to hypertensive disorders ; they may be encountered in hepatic cirrhosis with ascites or in nephrotic oedema, and associated for long periods with normal blood-pressure. Comparing ill normotensive subjects with hypertensives, Cope *et al.* (1962) found the scatter of aldosterone secretion rates was equally wide, and the mean for the two groups was not significantly different.

One woman, observed over several years, was a psychopathic purgative addict, who exposed her kidneys and cardiovascular system to severe hypokalaemia, which caused widespread and complete muscle paralysis several times. She had had recurrent pyelonephritis, and after an emergency abdominal operation much haemorrhage led to severe lower-nephron necrosis, from which she eventually recovered almost completely. She had an aldosterone secretion rate of at least ten times the normal for many months on end ; yet, despite these multiple insults to the renal and cardiovascular systems, she remained completely normotensive and eventually died of an unrelated disorder. Overproduction of aldosterone does not necessarily cause hypertension at all (see Clinicopathological Conference, 1966).

Aldosterone-stimulating Factor

The impression is that overproduction of aldosterone is a by-product of the true cause of the hypertension rather than a direct cause itself. From purely clinical analysis one cannot determine what the aldosterone-stimulating factor may be. It is apparently provoked by the complications of hypertension, such as renal ischaemia and the malignant phase ; yet in our experience the incidence of hyperaldosteronism in hypertensives is not higher when the pyelogram is clearly abnormal, as might be expected (Cope *et al.*, 1962), though one must concede that the pyelogram is a very crude index of renal damage.

Severe functional renal damage might be expected to throw light on the clinical factors leading to increased aldosterone secretion. But the principle by which such secretion rates are determined normally requires good renal function, with prompt excretion of hormonal metabolites for validity. To overcome this problem we developed a somewhat indirect method of estimating the secretion rates that depends on certain assumptions for which there is at present only strong circumstantial evidence. Nevertheless, these estimates are likely to be of the right order of magnitude. We found (Cope and Pearson, 1963) as great a range of secretion rates of aldosterone in uraemic subjects as in those with normal function, and the mean was practically the same. Here again no significant difference emerged between renal failure in normotension and hypertension, the ranges being similar (Fig. 12). Thus clinical analysis has provided no adequate clue to the factor determining aldosterone variability and stimulation.

But, on the experimental side, two groups of workers have found independently that angiotensin is a potent stimulator of aldosterone secretion without much effect on cortisol production (Laragh *et al.*, 1960b ; Genest, 1961). This is clearly an important clue.

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Laragh (1962) showed that continued infusion of angiotensin will augment aldosterone secretion for as long as 11 days; the effect is specific, it does not involve cortisol production, and it can be observed with doses which are only very mildly pressor. These doses of angiotensin are insufficient to raise the diastolic blood-pressure appreciably (Genest, 1961). This is very important, for if it is true, then we must conclude that angiotensin plays no part in the pathogenesis of hypertension when the aldosterone secretion rate is normal. This would apply to essential hypertension, where no stimulation of aldosterone secretion is apparent: angiotensin could be a possible factor in pathogenesis only if doses exist which can raise the blood-pressure significantly without at the same time stimulating aldosterone secretion. So far as I know no such claim has been made, and it has indeed been specifically denied by Laragh (1964).

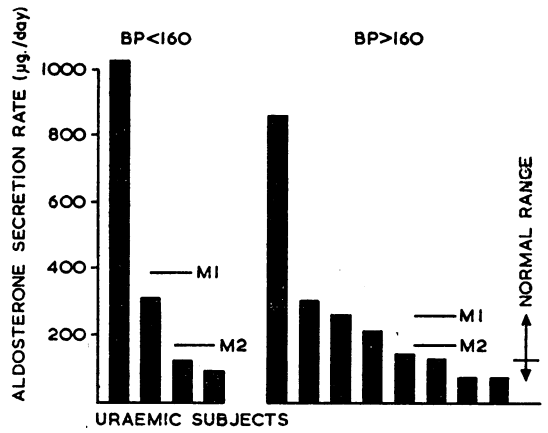

FIG. 12.—Range of aldosterone secretion rates encountered in severe renal failure with and without hypertension. (From Cope and Pearson, 1963a.)

Direct measurements of the angiotensin level in the blood in various hypertensive conditions ought to solve this problem, but so far they have only produced conflicting results.

Genest *et al.* (1964a) found values above the upper limit of their normal range in 32% of 50 essential hypertensives, yet only one of eight malignant hypertensives had a raised angiotensin level. Morris *et al.* (1962) failed to find angiotensin in 20 essential hypertensives and also in five cases of malignant hypertension, yet it was present in all their 13 cases of renovascular disease. These results are difficult to reconcile with those for aldosterone, suggesting that the two aspects are more independent than one is inclined to think. (See also Genest *et al.*, 1964b).

The reasons for the conflicting results with angiotensin assays are not certain, but some can be suspected. Angiotensin assays are still in an early stage of development: they require a relatively large sample of arterial blood (the concentrations are much lower in venous blood); they are dependent on a bio-assay; and plasma is known to contain angiotensinase enzymes bent on its destruction, which seem to vary at different times (Khairallah *et al.*, 1963; Hickler *et al.*, 1963). These assays, therefore, are fraught with many real handicaps, and as Peart (1965) has said: "It is easy to predict that there will be a large mass of confusing and inaccurate data produced by methods which are not quantitative."

Variable Sensitivity

An indirect but more promising way of assessing the effective circulating angiotensin level has been proposed by Kaplan and Silah (1964), who have collected much evidence to explain the variable sensitivity of different hypertensives to a constant infusion of angiotensin. They find high sensitivity in states where the renin content of the plasma—and by inference the angiotensin content—is low. Primary hyperaldosteronism and salt administration in normal subjects are both associated with low plasma-renin contents, and both show high sensitivity to infused angiotensin. Conversely, conditions of secondary hyperaldosteronism—for example, salt restriction or cirrhosis with ascites—show reduced responsiveness to angiotensin. Raising the plasma content by direct infusion of angiotensin also reduces the sensitivity to further administration, and the effect is likely to be a simple one of mass action.

With different groups of hypertensive subjects, the conclusions agree much better with expectations from the aldosterone data. Subjects with essential hypertension or acute glomerulonephritis were uniformly sensitive, and so were 11 out of 12 chronic nephritics, implying a low circulating level of angiotensin in all these groups. In contrast, 5 out of 10 cases of near-malignant hypertension and 8 out of 16 with established renal vascular disease were angiotensin-resistant and presumably had high plasma-angiotensin levels (Goorno and Kaplan, 1965). These figures for the frequency of raised aldosterone secretion compare better with ours than do the angiotensin assays. However, there is no agreement on the place of this test, and serious discrepancies occur. Breckenridge (1965), for example, found that some subjects with apparent essential hypertension were relatively resistant. This approach seems logical for obtaining a very rough estimate of the mean angiotensin-like activity to which the receptor organs are exposed; but at present it is only in the stage of indirect inference, and neither the validity of a real assay nor diagnostic value can be claimed.

Angiotensin II, which we have been considering, is an octapeptide derived in the blood-stream from a less active decapeptide called angiotensin I. This precursor in turn is formed by the action of the enzyme renin, released into the blood-stream from the kidney and there reacting with a specific substrate. This substrate is an alpha-2 globulin (Green and Bumpus, 1954), of which there are probably several varieties, all of them glycoproteins of molecular weight about 57,000; a large part of the chemical formula is known, and one substrate at least has been synthesized (Skeggs *et al.*, 1964). In suitable circumstances renin can be detected in both arterial and venous blood by its ability to form angiotensin *in vitro*; very sensitive and apparently specific methods of assay have been developed, notably by Lever *et al.* (1964).

Plasma Renin

The enzyme renin is probably itself inactive (Denton, 1964), but the amount detectable in plasma is likely to influence the quantity of angiotensin II produced, especially when the specific renin substrate is in generous excess in the plasma, as seems usual. However, the relation between the two has not yet been fully established.

The behaviour of renin, or renin-like activity in the plasma, correlates much better with the known behaviour of aldosterone than does the directly determined apparent angiotensin content itself. Thus low-salt diets increase plasma renin and also aldosterone secretion. A high salt intake depresses both (Brown *et al.*, 1964), and pregnancy increases both (Brown *et al.*, 1963). These similarities in behaviour towards physiological changes also apply in the hypertensions. The plasma-renin concentration, like the aldosterone secretion, is generally regarded as normal in uncomplicated essential hypertension (Brown *et al.*, 1965b; Fasciolo *et al.*, 1964; Veyrat *et al.*, 1964). We must conclude that neither aldosterone nor renin is a factor in the pathogenesis of so-called essential hypertension. Gross *et al.* (1964), working with rats, came to the same conclusion.

Data on behaviour of plasma renin in the malignant forms of hypertension contrast sharply. Brown *et al.* (1966b) record values above the normal range in 57% of such cases, and Helmer (1965) found high plasma-renin activity in all his cases. But we have much more information about proved renal artery stenosis, in which there is a 20–50% chance of raised aldosterone secretion. Veyrat *et al.* (1964) found high values for plasma renin in three of seven cases, and Brown *et al.* (1956b) observed

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high figures in 32 (73%) of 44 assays; those with associated retinopathy all had high values, in contrast to 7 (37%) of 19 of those without. We found increased aldosterone secretion in 40% of a small series of renal artery stenoses.

It is evident, however, that the stimulus to renin overproduction and aldosterone secretion is not constantly acting. We had noted and speculated about the fact that, although aldosterone secretion is often high in the hypertensions with complications, some cases have aldosterone secretions below the normal range; and Brown *et al.* (1964) showed an equally wide range of plasma-renin values in similar hypertensive subjects, with a considerable proportion well below the normal range. High day-to-day variability of aldosterone excretion was found by Genest *et al.* (1958) and Venning *et al.* (1961). One possible reason for such wide fluctuations could be a poorly damped feed-back control mechanism between renin and aldosterone. Such a reciprocal link between the two can scarcely be doubted (Table I), and this probably accounts for the low

TABLE I.—*Correlations Suggesting a Feed-back Mechanism*

	Aldosterone Secretion	Plasma Angiotensin (Indirect)*	Plasma Renin
Addison's disease	Low	—	High
Aldosterone injection	High	—	Low
Conn's syndrome	„	Low	„

* Estimate based on angiotensin sensitivity (Goorno and Kaplan, 1965).

plasma renin in Conn's syndrome (Conn *et al.*, 1964a) and after aldosterone injection into animals (Gross, 1960), and also for the very high plasma-renin values in untreated Addison's disease which fall after treatment has been instituted (Brown *et al.*, 1964). But we must also suspect that liberation of renin itself is variable and intermittent from the kidney, just as is aldosterone secretion (Brown *et al.*, 1966a).

So far we have been considering frequency of occurrence but not individual cases. A major gap is the direct correlation of individual plasma—renin values with aldosterone secretions. We urgently need to know whether cases with high circulating renin levels are the same as those with high aldosterone secretions, and how often (if at all) there is an inverse relation between the two activities. Barraclough *et al.* (1965) have now made direct comparisons in seven patients with renal lesions: in six of these both renin and aldosterone secretion were high, and in the other both were normal. Preliminary evidence thus encourages belief that this correlation will prove close.

The known sensitivity of both renin and aldosterone to the sodium intake has suggested to some that changes in plasma sodium may prove to be a major factor in this variability (see Laragh *et al.*, 1964). Brown *et al.* (1965b) believe that they have shown a general relationship between plasma sodium and renin content, but in their studies potassium concentration, which also varies, seems equally likely to be involved. Certainly there is no clear relation between the plasma sodium and the aldosterone secretion in either congestive cardiac failure or advanced renal failure. Even if sodium or potassium derangement eventually emerged as a recognizable factor in this variability, one would still have to explain why it is not a factor in essential hypertension. Much more careful and critical evidence is needed before a clearer assessment can be made. But the evidence for a close link between renin and aldosterone secretion is steadily growing, even though it is not yet related to the plasma sodium. The similarities in behaviour between aldosterone secretion, sensitivity to angiotensin, and plasma-renin levels are summarized in Table II.

If renin were to stimulate aldosterone production by a mechanism similar to that whereby corticotrophin stimulates cortisol production, then we might expect an aldosterone-producing adenoma severely to inhibit renin production, just as a cortisol-producing adenoma inhibits corticotrophin production. This appears to be so. Conn *et al.* (1964a) found absence of plasma renin in 10 out of 11 pre-operative blood samples from three patients with primary aldosteronism, even after severe sodium restriction, and their renin values all returned to normal after treatment. Brown *et al.* (1965b) also found subnormal plasma-renin values in four such cases, two of which returned to normal after treatment.

TABLE II.—*Correlations Suggesting Aldosterone Stimulation by Renin/Angiotensin*

	Aldosterone Secretion	Plasma Angiotensin (Indirect)*	Plasma Renin
Pregnancy	High	—	High
Cirrhosis with ascites	„	High	„
Salt restriction	„	„	„
Salt-feeding	Low	Low	Low
Essential hypertension ..	Normal	Normal	Normal
Chronic nephritis	Normal–high	Low	Low–high
Malignant hypertension ..	50% high	>50% high	57%–high
Renal vascular disease	Low–50% high	50% high	Low–30 to 70% high

* Estimate based on angiotensin sensitivity (Goorno and Kaplan, 1965).

Primary versus Secondary Aldosteronism

Normal to high aldosterone secretions can occur for various reasons in normotensive subjects. A precisely similar range of values may be encountered in hypertensives, especially if they are hypokalaemic. This is the same in malignant hypertension or renal artery stenosis as in proved cases of aldosteronoma—that is, Conn's syndrome.

Our first case of Conn's syndrome—studied simultaneously with Conn's own first case—was recognized only when its true nature was pointed out in a letter from Conn himself in 1954, because at that time we were not aware of the profound effect of aldosterone on potassium metabolism, and therefore we interpreted the patient's high aldosterone excretion as secondary to, rather than the cause of, the electrolyte disturbance. In fact ours was the first direct demonstration of overproduction of aldosterone in this disorder. Difficulty may still arise today in distinguishing between primary and secondary forms of hyperaldosteronism, and this confusion is much greater with aldosterone than with cortisol.

Primary and secondary forms cannot be distinguished by measuring either urinary aldosterone or the aldosterone secretion rate, and most of the clinical features are unhelpful. Patients with primary aldosteronism tend to be markedly hypernatraemic, but the scatter of values is wide and so heavily overlaps the range found in secondary hyperaldosteronism that the point is rarely of diagnostic value. The degree of hypokalaemia and alkalosis is about the same in both groups also, but a few features can aid the distinction. Malignant hypertension with papilloedema practically excludes primary aldosteronism, only one doubtful case having been recorded (Kaplan, 1963), but a history of renal or urinary trouble going back into childhood makes congenital and primary hyperaldosteronism very probable even with papilloedema and malignant hypertension (Conn and Conn, 1961). Renal artery stenosis or a misshapen or shrunken kidney makes a secondary cause highly probable. In spite of these clinical aids the number of ambiguous cases is considerable.

In the absence of renal functional impairment or revealable renal abnormality the diagnosis can be relatively straightforward, as Conn *et al.* (1964c) have pointed out. But recurrent or persistent hypokalaemia can itself damage renal function and increase liability to pyelonephritis. Conn *et al.* (1964b) found that 27 (37%) of 73 recorded cases of primary aldosteronism had impaired renal function. With evident renal damage, either functional or anatomical, as revealed by radiography, the differential diagnosis can become extremely difficult and sometimes practically impossible.

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In this dilemma Conn *et al.* (1964a) suggest that additional observation of the plasma-renin level may give a sharp distinction: whereas this is either normal or much raised in the secondary forms, it has been low or completely indetectable in all the recorded examples of primary aldosteronism so far studied. A difficult case in which combination of the two assays was of diagnostic help, leading to the successful removal of an aldosteronoma, was reported by Brown *et al.* (1965a). The suggestion is logical and is likely to prove valuable, especially if the sensitivity of the renin assay is enhanced by drawing the blood sample after a few days of sodium restriction.

Proceeding further from this suggestion, Conn (1964) entered the realms of speculation and prediction. Shamma *et al.* (1958) and Sherwin (1964) found that 20% of the adrenals of hypertensive subjects show true adenomata which are morphologically indistinguishable from true aldosteronomata, and Conn suggests that 20% of patients with so-called essential hypertension may prove to have an aldosteronoma and thus be curable. This clearly presents a diagnostic challenge which has attracted wide interest. In the experience of Conn *et al.* (1965a) in primary aldosteronism hypertension may exist for many years before that hypokalaemia develops which would normally alert one to the possibility of such a diagnosis. Brown *et al.* (1964) also found that some 20% of 48 hypertensive subjects without renal-artery stenosis had plasma-renin levels below the lower limit of the normal range; and a further cogent point is their observation that 5 out of 13 hypertensives with plasma potassium below 3.1 mEq/l. had plasma-renin values below the lower limits of the normal range, and so would qualify as suspects. But we have not found raised aldosterone secretions in all hypertensive hypokalaemics (Fig. 13). Conn announced his

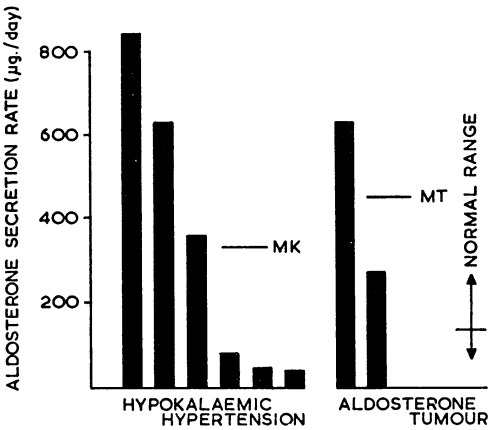

FIG. 13.—Range of aldosterone secretion rates found in hypokalaemic hypertension and in aldosteronoma.

first diagnostic and therapeutic success by this means in April of last year (Conn *et al.*, 1965b), and Conn *et al.* (1966) reported the detection of five more examples of aldosteronoma among cases of apparent essential hypertension Yet my view is that the yield from such a search will be considerably less than the 20% optimistically anticipated, for suspicion of an aldosteronoma is aroused not by a low renin titre alone but by its association with an increased aldosterone secretion rate. We failed to find high aldosterone secretion rates in any of 15 essential hypertensives, and the experience of Laragh *et al.* (1960b) seems to be similar.

Meyer *et al.* (1965) offer some data by which to judge the frequency of unsuspected aldosteronoma in apparent essential hypertension: 119 such patients were explored, and a cortical adenoma was found in seven. All these had shown evidence of hyperaldosteronism, but this had for various reasons been regarded as secondary. They estimate the incidence as perhaps 7% of severe hypertensives, and about 7.5 per thousand of a random and unselected group of hypertensives. We await eagerly the diagnostic yield of the combined assays, but the technical challenge of Conn's proposals is great. Both renin and aldosterone secretion assays are difficult, and no appreciable simplification of the latter has appeared in the world literature in the past five years.

Simpler methods for screening suspects are urgently needed. Technical errors can readily lead to false high values in secretion-rate assays, and presumably also to failure to detect renin in plasma samples. But simplifications which reduce the reliability of either assay are likely to increase, and not reduce, the number of suspects.

Ambiguous Cases

The suggestion that renin assays might distinguish between primary and secondary forms of hyperaldosteronism implies a rigid difference between the two; but this is by no means always so, and we have studied two cases with proved hyperaldosteronism in which no final decision could be reached.

The first of these had a daily aldosterone secretion rate of 660 µg.—that is, about five times the normal—associated with severe hypokalaemia. Clear radiological evidence of pyelonephritic scarring led to nephrectomy, and at operation a typical aldosteronoma 2 cm. in diameter was found. Since it seemed unjustifiable to remove only one of the abnormal organs, both the grossly scarred pyelonephritic kidney and the adrenal adenoma were removed, with great improvement; but it was then not possible to determine which was the major contributing cause.

The second case of hypokalaemic hypertension had an aldosterone secretion of 500 µg. daily, and a normal pyelogram. An aldosteronoma was therefore suspected, and the abdomen was explored: both kidneys were seen to be normal, and subtotal adrenalectomy was carried out. A month later the patient died of massive pulmonary embolism. At necropsy the normality of both kidneys was confirmed. The excised adrenals showed only a mild degree of patchy hyperplasia affecting mainly the zona glomerulosa.

Thus in neither case was a clear distinction between primary and secondary hyperaldosteronism possible, in spite of full histological investigation of both organs. Others have experienced examples of similar ambiguity. Wrong (1964) commented on the association of true adrenal adenoma with renal ischaemia. Laidlaw *et al.* (1960) recorded a case in which malignant hypertension and hypokalaemia were found at necropsy to be associated with a small cortical adenoma. In another case, reported by Hoet and Molineaux (1960), an atrophic left kidney was associated with an adrenal adenoma weighing 15 g. In all, four examples of renal ischaemia with either adrenal adenoma or gross adenomatous hyperplasia have been recorded, which seems to exceed the expectation of random probability. In two of these cases removal of the adrenal adenoma failed to reduce the severe hypertension.

The frequency of such dual aetiology is likely to increase with the spread of the necessary diagnostic methods and awareness among clinicians. These cases have aroused suspicion that persistence of the aldosterone-secreting stimulus from the ischaemic kidney may lead eventually to autonomous hypersecretion by the adrenal cortex, manifested histologically by either adenomatous hyperplasia or frank adenoma formation. Additional renin assays may help to resolve many ambiguous cases, but they are unlikely to differentiate them all.

To the clinician the practical implications of these developments are fairly clear. An abnormal pyelogram or demonstration of renal artery stenosis in a case of suspected hyperaldosteronism does not remove the need for careful search for adenoma formation in both adrenals. Likewise, the firm diagnosis, and even removal, of an adenoma does not exclude the possible coexistence of renal ischaemia. After 12 years the distinction between primary and secondary forms of hyperaldosteronism is still blurred in some cases. They are likely to be a minority, but the clinician should be aware of their existence.

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Conclusion

To construct a working hypothesis of the role of the adrenal in the pathogenesis of hypertension one has to be somewhat selective with the rather conflicting data. Overproduction of aldosterone causes hypertension only when it is in excess of the needs of the prevailing conditions. What precisely determines these needs is still uncertain. Two known factors can lead to an "inappropriate" secretion of aldosterone: a cortical adenoma producing aldosterone and an excessive production of renin from a damaged kidney. Such inappropriate secretion needs to be long sustained for it to produce hypertension, and for a considerable time it is reversible. The damage is probably not due to the hypokalaemia which may be produced. Severe progressive and malignant forms of hypertension are commonly associated with excessive renin formation. Such renin excess will produce, as a by-product, excessive secretion of aldosterone, and if long maintained this may contribute further to vascular degeneration as a secondary factor. Liberation of renin is probably intermittent. Circumstances which provoke increased aldosterone secretion are not normally present with congestive cardiac failure, and they are not produced by pronounced expansion of extracellular fluid or hyponatraemia.

Thus aldosterone, like cortisol, but in a different sphere, is a source of fascination to research workers. The stimuli to which it responds are still very inadequately understood. Clearly, when overproduced, it can become a major cause of hypokalaemia, but it seems to be a relatively weak factor in the pathogenesis of hypertension. Because the factors which stimulate its production are poorly understood, the primary and secondary forms cannot be distinguished by aldosterone assays alone, either in urine or in plasma. The diagnostic help of these very exacting assays is relatively small. In this respect aldosterone contrasts sharply with cortisol.

Knowledge of the adrenal androgens is only just beginning. The techniques necessary are at least as exacting as those for aldosterone, and we have not yet reached the stage where such assays can give useful clinical guidance. But increasing knowledge indicates ever more clearly the insidious way in which infinitesimal amounts of certain steroids formed in this small organ can profoundly influence the body. The discovery of further steroids with equally profound effects is by no means excluded: indeed, they are being very actively sought in several research centres. It may be realized by future generations that the story of the adrenal steroids has only just begun. It is well that we should be humble, and remind ourselves that we still have no idea how these hormones act at the cellular level, nor of the true reason for their emergence in evolution. Cogent claims are being made that aldosterone (Edelman *et al.*, 1964; Dingman and Sporn, 1965), as well as cortisol (Lang and Sekeris, 1964), acts at gene level in the chromosome, and affects messenger ribonucleic acid just as the insect hormone ecdysone has been shown to do (Clever and Karlson, 1960; Karlson, 1963).

The Académie des Sciences de Bordeaux 250 years ago offered a prize on the subject "What is the use of the suprarenal glands?" Many essays were submitted, but none was considered worthy of the prize (Shumacher, 1936). It is most unlikely that this could be won by anyone today, for though we know much about the harm which results from disturbances of these glands we still know little about the benefits they bestow when allowed to pursue their natural functions undisturbed.

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