BRITISH MEDICAL JOURNAL

LONDON SATURDAY MARCH 10 1962

ALDOSTERONE SECRETION IN HYPERTENSIVE DISEASES

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Among the many possible causes of hypertension, the role of aldosterone is attracting great interest at the present time. This interest has been stimulated by several findings. First, the state of chronic overproduction of aldosterone which occurs in Conn's syndrome of primary aldosteronism is almost invariably associated with a hypertension, and this hypertension may often be cured by removal of the tumour. Secondly, an increase in the urinary content of aldosterone is often found in hypertensive subjects. Thirdly, the substance angiotensin, which is believed to be an aetiological factor in some types of hypertension, has recently been found to be a fairly powerful stimulator of aldosterone secretion in man (Genest, 1961).

Early Evidence

Genest *et al.* (1956) were the first to suggest that human essential or malignant hypertension might actually be caused by a sustained mild overproduction of aldosterone. Their early evidence was based on the relatively inaccurate results of bioassay of urine extracts for aldosterone content, but they were soon able to apply more precise methods of estimation based on orthodox chemical procedures. With these Genest *et al.* (1958) were able to show that there is a much wider scatter than normal in the concentration of aldosterone in the urine of subjects with hypertension whether this be due to renal disease or be essential or malignant. The mean figure found by this group in normal subjects was 3.6 μg. daily, but in severely hypertensive subjects the mean rose to about 8 μg. daily. About 55% of their hypertensive subjects showed urinary aldosterone figures above the normal range. Later work from their laboratory confirmed these findings, and in addition indicated that subjects with early asymptomatic renal or essential hypertension showed much greater individual fluctuations in urinary aldosterone level from day to day than did normal subjects (Genest *et al.*, 1961).

Confirmation of this general trend has come from several other centres. Thus Venning *et al.* (1961) found the mean urinary excretion of aldosterone in 26 hypertensives to be significantly higher than in normotensive subjects, and they found still higher values in malignant hypertension. Garst *et al.* (1960) obtained somewhat different results. They found that of 38 hypertensive subjects studied the urinary aldosterone excretion was in the normal range in 75%, but that the remaining 25% showed values definitely above the control level, the difference being highly significant.

It may be accepted, therefore, that subjects with essential or malignant hypertension have a tendency to excrete in the urine significantly more aldosterone than do normal persons. But care must be exercised in drawing conclusions from such an observation and caution used in concluding that there is necessarily any aetiological relationship between the two.

Several possible explanations for the increase could be suggested. There might, for instance, be a change in renal physiology in hypertensive subjects whereby aldosterone leaks more readily from blood into urine, for it must be realized that the relationship between blood levels and urinary excretion is quite unknown. Or there might be a change in the extent to which aldosterone is bound to plasma protein producing a similar result. Neither of these possibilities can be investigated adequately at the present time because sufficiently reliable methods for the estimation of the excessively small concentrations of aldosterone in plasma are not yet available. Alternatively there may be a true increase in the secretion rate of aldosterone in hypertensive subjects to account for the increased quantity which appears in the urine. This possibility can now be tested, for the recent availability of isotope-labelled aldosterone has made possible the measurement of aldosterone secretion rates in man. Two general methods of doing this are feasible, the first requiring the isolation in pure form of some of the urinary aldosterone, a method originally developed by Ayres *et al.* (1958). The second method is to isolate from the urine a metabolite of aldosterone, which also needs to be purified. Such a metabolite, believed to be a tetrahydro-aldosterone, was identified in human urine by Ulick and Lieberman (1957) and a method of making use of this to estimate the secretion rate of aldosterone was developed by Ulick *et al.* (1958).

This method has since been used by Laragh *et al.* (1960) to study aldosterone secretion in human hypertension. Their conclusions from these studies were that in advanced hypertensive disease, and in nearly all subjects with malignant hypertension, the secretion rate of aldosterone was significantly elevated, often greatly so. In eight patients with benign essential hypertension, on the other hand, the secretion rate was within normal limits. These workers were rightly cautious in their interpretation of the significance of the raised secretion rate in malignant hypertension, but they thought that "the results . . . make it reasonable to consider the possibility that hypersecretion of aldosterone plays a causal role in malignant hypertension." Their finding of normal secretion rates in essential hypertension was at variance with the finding by the Genest group of frequent increases of urinary aldosterone excretion in such patients.

Because of the apparent importance of these findings and the evident possibility that there may be an aetiological relationship between the raised aldosterone production and at least some forms of hypertension, further information on the behaviour of aldosterone

secretion in hypertensive states is clearly needed, for confirmation of the raised secretion rate in the severer forms would be of great theoretical and practical interest.

We have therefore investigated a series of hypertensive subjects by methods similar to those used by Laragh *et al.* (1960). Such an investigation involves two separate aspects. First, we have investigated the validity of the method of determination of the aldosterone secretion rate. Secondly, we have made a comparison of the series of hypertensive subjects with suitable control groups.

Before presenting our conclusions it is necessary to consider first the method of estimating the aldosterone secretion rate a little more closely.

The Principle of Estimation of the Aldosterone Secretion Rate

The principle used to measure the aldosterone secretion rate is essentially the same as that employed by Pearlman (1957) for the progesterone secretion rate, and by Cope and Black (1958) for the cortisol secretion rate in man. A very small dose of isotope-labelled aldosterone of negligible weight compared with the body content is introduced into the subject intravenously. This mixes with the body supply of the steroid, and is metabolized in precisely the same way as is the endogenous supply of aldosterone. Eventually the decomposition products of both are eliminated from the body, mostly in the urine. Because the isotope-labelled steroid is handled in the body in the same way as the natural substance it will be converted into the same metabolites as is the naturally produced steroid, and in the same proportion. As a result all the metabolites of the aldosterone which leave the body in the urine or elsewhere will be accompanied by the same proportion of the isotope-labelled compound. When this has happened it becomes possible to estimate the total quantity of aldosterone metabolites in this urine, and surprisingly it does not matter if many of them are still unknown in nature.

It is necessary to make only two measurements: (1) to isolate any one suitable metabolite from the urine and to determine its isotope content per microgram, M; and (2) to measure the total quantity of the isotope present in the whole urine collection, U. The ratio U/M will then indicate the total mass of metabolites in the urine derived from this steroid. Now, if all the metabolites of aldosterone enter the urine, the total mass of metabolites in the daily urine must equal the daily production or secretion rate provided there has been no considerable change in the body content. Measurement of the secretion rate is thus essentially an estimate of the total mass of metabolites. The extent to which the aldosterone metabolites do in fact enter the urine will be indicated in every case by the percentage of the injected isotope dose recovered in the urine collection. For if 100% of the injected isotope can be found in the urine, that may be taken as adequate proof that all the metabolites of the natural aldosterone are also entering the urine in that patient at that time. If, on the other hand, a smaller fraction, perhaps only 70%, of the doses injected can be recovered from the urine, then this is strong evidence that some of the metabolites, the remaining 30%, are leaving the body by other routes. A likely alternative route would be into the faeces via the bile.

These general principles are important ones to bear in mind when considering the measurement of aldosterone secretion rates in disease. The principles on which estimations of the secretion rate are based are simple in concept. They are, however, rather less simple in execution. Many precautions have to be taken before the results obtained can be regarded as valid estimates of the secretion rate. Some of these are of a very technical nature which need not be considered here because the whole subject has been well reviewed by Peterson (1959). But others are of especial importance to the particular problem of aldosterone secretion in hypertensive subjects, and since these may have a big influence on the eventual estimates obtained, and have indeed caused confusion to some workers in the past, they call for more detailed treatment here.

To ensure that a reasonably reliable estimate is obtained three points are especially important: (1) There must be thorough mixing of the injected isotopic steroid within the body. This is ensured if the urine is collected over a sufficiently long period of time. Any period of less than 24 hours may prove insufficient. (2) The metabolite to be analysed must be isolated in a state of sufficient purity to enable its isotope content per microgram, its specific activity, to be measured. This is a matter of chemical technique and is considered further under Methods. (3) The mode of excretion of the metabolite must be known. Since the manner in which aldosterone metabolites are eliminated in diseased human subjects, especially in renal failure, has not been adequately studied, it has been necessary to obtain some such information as an essential preliminary to the estimation of aldosterone secretion rates in subjects with poor renal function. In such persons the secretion rates cannot be reliably calculated without this knowledge.

Methods and Materials

7-^{3}H d-Aldosterone, of activity 20 μc/μg., was obtained through the courtesy of the Division of Research Grants, National Institutes of Health, Bethesda, Md., from the Endocrine Study Committee, U.S. Public Health Service. This was found to be more than 95% pure when analysed by paper chromatography, and proved to be quite stable in ethanol solution.

In aldosterone secretion studies the patient first empties the bladder. About 1 μc of the tritiated aldosterone in 1 ml. of pure ethanol mixed with 15 ml. of normal saline is then injected intravenously. All urine is carefully collected for the next 24 hours. In some studies further daily urine collections have been made. Determination of the specific activity of the aldosterone metabolite, the tetrahydro-aldosterone, in this urine is then made according to the procedure described in detail by Cope *et al.* (1961). This method follows in essentials the original method developed by Ulick *et al.* (1958).

The method involves the use of two different isotopes. The tritium of the tritium-labelled aldosterone which has been injected marks all the metabolites of natural aldosterone. The chosen metabolite, tetrahydro-aldosterone, is then further labelled with a second isotope ^{14}C, by acetylating it with ^{14}C acetic-anhydride during the process of isolation and purification. This second isotope enables the actual quantity of the metabolite eventually recovered to be determined. The specific

activity, the tritium content per microgram, M, of the metabolite is then calculated directly from the observed ratio of tritium to ^{14}C in the final product. No chemical measurement is involved, therefore, in the determination of the secretion rate of aldosterone once the various reagents have been standardized. Since only physical measurements are involved, the control of the purification of the metabolite, which is essential for accuracy, is much simplified. Only contaminants which have taken up ^{14}C during the acetylation will interfere, and the progressive removal of these is readily followed by the scanning for ^{14}C of all chromatograms used during purification. This checking has been invariably made on all the chromatograms used in this work.

Estimation of Urinary Tritium

A one-hour aliquot of a 24-hour urine collection is concentrated to 25 ml. This usually represents a reduction in volume to about one-third. 0.5-ml. and 0.75-ml. portions of this concentrated urine are each separately mixed with 15 ml. of Kinard's (1957) scintillator solution. The samples are kept in the dark for 24 hours and are then counted for tritium on the Packard Tricarb liquid scintillation spectrometer, using 1,300 volts HV and with discriminator settings between 10 and infinity. Counting is continued on each sample for at least 30 minutes. Background is determined by counting in the same way similar urine samples which contain no tritium. Quenching of each sample is then measured by adding a known further amount of tritium and recounting. With such concentrated urine samples quenching usually averages about 60%. The efficiency of tritium counting in each sample is thereby determined, and the true tritium content is then readily calculated.

The experimental errors involved in these urine counts have been determined both theoretically and by trial. After the injection of tritiated aldosterone the tritium content of the first day's urine can be measured with an error of less than 5%. The smaller quantity of tritium present in the urine sample of the second day involves an average error of about 30%.

Clinical Material

Twenty-two patients with hypertension of sufficient severity to require admission to hospital have been investigated. The aetiology has been very varied. As controls we have used not only convalescent hospital subjects who have not had any metabolic disturbance, but also a second group of patients having various types of metabolic disturbance unassociated with hypertension. Cases of sodium depletion or of hepatic cirrhosis have been excluded from the series.

Elimination of Aldosterone Metabolites

The tritium of the injected aldosterone remains attached to the steroid nucleus during its metabolic breakdown. The route of excretion of the aldosterone metabolites is therefore clearly indicated by the fate of this tritium after the injection.

The metabolites of aldosterone are not excreted in the urine as completely as are those of cortisol. In a series of 10 subjects all of whom had blood-urea concentrations below 50 mg./100 ml. the amount of tritium recovered in the urine in the first 24 hours after the intravenous injection of about 1 μc of tritiated aldosterone varied from 45% to 80% of the dose, the mean recovery being 62.3%. In the second 24 hours a further small quantity of tritium could be detected in the urine, and this varied between 3% and 11% of the dose, with a mean of 6.7%. The total recovered in the first 48 hours varied from 54% to 83%, with a mean of 69% of the injected dose. Tritium excreted in the third day was usually too little to detect and is unlikely to exceed 1% of the dose as a rule. Thus only about 70% of the metabolites of aldosterone appear in the urine in average hospital patients with good renal function.

It may be suspected that the remainder is eliminated through the bile into the faeces. That elimination of adrenal steroids does indeed occur via the bile into the faeces has been shown in experimental animals. Bradlow *et al.* (1954) found 31% of the dose in the faeces of a mouse 24 hours after intravenous injection of tritiated cortisone, and in another animal 0.5% of the dose was found in the gall-bladder as soon as three minutes after the intravenous injection. In a human being Migeon *et al.* (1956) found nearly 4% of an injected dose of ^{14}C-labelled cortisol in the bile obtained in eight hours from a biliary fistula. Since aldosterone metabolites appear in the urine less completely than do those of cortisol, a higher percentage elimination in the faeces is very probable. But for technical reasons it is difficult to detect the presence of this tritium in the faeces. The evidence must therefore remain indirect. Further support for the view than an appreciable fraction is eliminated by routes other than the urine lies in the very low recovery on the second day. It might be expected that if two-thirds of the metabolites are excreted on the first day, as is found, then two-thirds of the remainder—that is, about 22%—would be recovered on the second day. The fact that the actual recovery on the second day is consistently so much less than this supports the belief that some has already left the body by another route.

Still further evidence is obtained that this is so when patients with severe renal impairment and grossly raised blood-urea levels are studied. For in such subjects the delayed renal excretion will provide opportunity for a proportionately larger elimination by other non-renal routes.

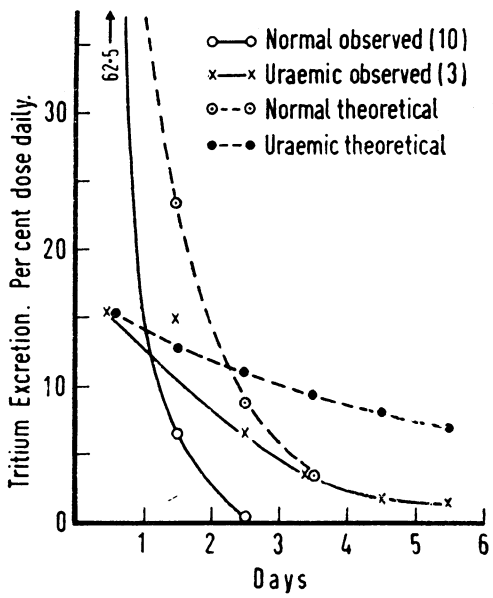

FIG. 1.—Urinary elimination of aldosterone metabolites as indicated by attached tritium. Subjects with normal and impaired renal function.

The mean tritium excretion of three patients whose blood-urea concentrations lay between 125 and 355 mg./100 ml. is shown in Fig. 1, and is there compared with the theoretical curve to be expected if all tritium is excreted by the kidneys. All these excretion data are in agreement with the view that about 65% of the daily aldosterone metabolites enter the urine, and that about 25% is daily eliminated in the stools. The curve of urinary excretion calculated on this assumption coincides almost exactly with the observed excretion curve shown in Fig. 1.

Calculation of the Aldosterone Secretion Rate

When all the metabolites of the injected dose have left the body the secretion rate will be indicated by the ratio Dose/M, for then Dose=U. We have seen that in the average patient the total leaving the body in the first 24 hours by urine and other routes is about 90% of the tritium dose administered. In general, therefore, the secretion rate will be indicated by the ratio 0.9×Dose/M (formula A). But in disease deviations from this mean figure must be expected, and the urinary excretion of tritium, U, must be determined. A much closer approximation of the true secretion rate will be obtained by the ratio $\frac{U+25}{100} \times \frac{Dose}{M}$ (formula B) where 25% represents the proportion excreted in the stools.

These two formulae differ essentially in only one point. Formula A assumes that the usual average rate of excretion of metabolites has occurred. Formula B uses reliable estimates of the total mass of urinary metabolites but assumes the usual rate of elimination by faecal or other non-renal route.

In practice the deviation of the estimate obtained by formula A from the more representative estimate obtained by use of formula B will be small when there is no renal impairment. In a series of 24 comparisons in persons without raised blood urea, the difference exceeded 10% in only one case, and the mean figure for the series obtained by one method of calculation differed from the mean obtained by the other by only 0.5%.

But renal impairment is particularly likely to be found in severely hypertensive subjects. In such conditions failure to base the estimate on the observed tritium excretion by the use of formula A instead of formula B will always lead to erroneous results.

The extent of the error which can be incurred in this way is well indicated by the estimates of the secretion rate in uraemic subjects shown in Table I.

TABLE I

Case No.	Blood Urea (mg./100 ml.)	U % Dose	Dose/M	Apparent Secretion Rate	
				Formula A	Formula B
1	215	12·5	1,900	1,710	712
2	218	11·9	1,590	1,431	588
3	125	19·7	690	621	313
4	120	13·5	1,335	1,201	373
5	355	16·0	448	403	183

In these estimates the simple calculation Dose/M will give results which may be as much as three times the truer figure estimated by formula B.

In making our estimates of the aldosterone secretion rate we have invariably used formula B in patients with blood urea above 50 mg. It has been used in 17 of the 22 hypertensive subjects and in 10 of the 22 normotensive subjects. The remainder of the estimates were obtained by the use of formula A, the data on these patients having been obtained before we were able to estimate the urinary tritium sufficiently well.

In developing formula B we have been most grateful for the penetrating mathematical analysis of the situation when excretion is imperfect which has been carried out for us by Dr. E. H. Belcher. The formula is based on this analysis.

Aldosterone Secretion in Hypertensive Subjects

Since the conditions which stimulate aldosterone secretion are still imperfectly understood, it is difficult to define a truly normal group. But in a series of 10 representative hospital patients who had no known reason for any metabolic disturbance, and who were on normal dietary intake, the range of aldosterone secretion rates has been from 62 to 275 μg. a day, with a mean secretion rate of 143 μg.

In a series of 22 severe hypertensive subjects of mixed aetiology the range of aldosterone secretion rates found has varied from 832 down to 31 μg. daily, the full range being shown in Fig. 2.

The mean secretion rate for the whole group is 227 μg. daily, but it is clear that with such a wide scatter the mean figure has little significance. If we take the upper limit of normal arbitrarily as 200 μg., then 8 of the 22 cases exceed this figure, and six of them exceed 250 μg. But it will be noted that the series includes five cases below 60 μg. daily. Thus although the hypertensive series contains some cases with aldosterone secretion rates above the normal range, it equally contains several with secretion rates below the normal range.

It is of interest to subdivide the series according to aetiology or pathogenesis.

Seven of the cases studied could be regarded as uncomplicated essential hypertension. They are marked E in Fig. 2. Their symptoms were of minor degree. They showed secretion rates ranging from 163 down to 53 μg. daily, with a mean figure for the group of 107 μg. daily. This small series is in agreement, therefore, with the findings of Laragh *et al.* (1960) that the aldosterone secretion rate is not raised in essential hypertension without complications.

Of the whole group, four were suffering from severe malignant hypertension. They are indicated by the letter M in Fig. 2. The secretion rates for these were found to be 650, 343, 49, and 44 μg. daily respectively. It is apparent, therefore, that although some patients with malignant hypertension may show very high aldosterone secretion rates, this is by no means invariable, and subnormal values may be encountered.

In view of the great interest shown at the present time in the role of pyelonephritic lesions and of vascular anomalies, especially renal artery stenosis, in the pathogenesis of hypertension, it is of interest to compare the aldosterone secretion rates of those hypertensives with normal pyelogram patterns with the group with a clearly abnormal pyelogram.

The mean secretion rate for nine consecutive hypertensive patients with a normal pyelogram was 235 μg. a day, the range being from 832 down to 42 μg. The mean secretion rate for nine consecutive hypertensive patients with clearly abnormal pyelogram was 186 μg., ranging from 498 down to 31 μg. In view of the wide scatter in both groups, the difference between the two

means cannot be regarded as significant. They are marked respectively N and A in Fig. 2.

Five of the patients were proved to have a renal artery stenosis, and these showed aldosterone secretion rates varying from 498 down to 31 μg. daily, the mean figure for the five being 188 μg. Two high, one normal, and two low secretion rates are found in these five cases, which are marked S in Fig. 2.

In one case an adrenal cortical adenoma was found which had the morphological characteristics of an aldosterone-secreting tumour. Secretion rates of 623 and 270 μg. were recorded in this man.

A patient with severe hypertension due to long-standing periarteritis nodosa showed a normal aldosterone secretion rate, and so also did a patient with severe unilateral hydronephrosis and hypertension.

No correlation at all has been found between the height of the blood-pressure, either systolic or diastolic, and the aldosterone secretion rate.

In this series three cases had serum potassium concentrations below 3.5 mEq/l. They are marked K in Fig. 2. Two of these had secretion rates of 832 and 691 μg. respectively, but the third showed a secretion rate of only 44 μg. daily. The mean secretion rate for five patients whose serum potassium lay between 3.5 and 4 mEq/l. was 132 μg. daily. The mean for another five patients whose serum potassium level was above 4 mEq/l. was 177 μg. daily.

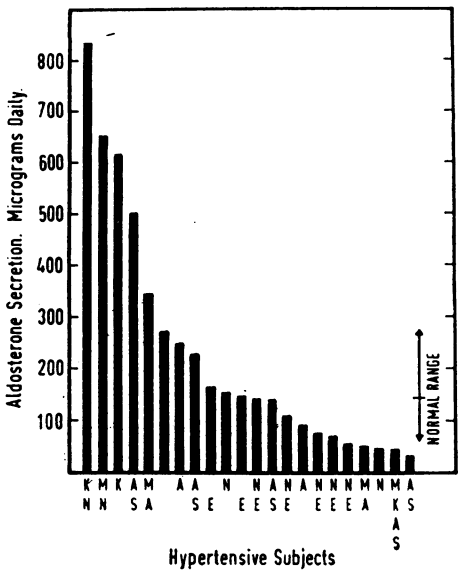

FIG. 2

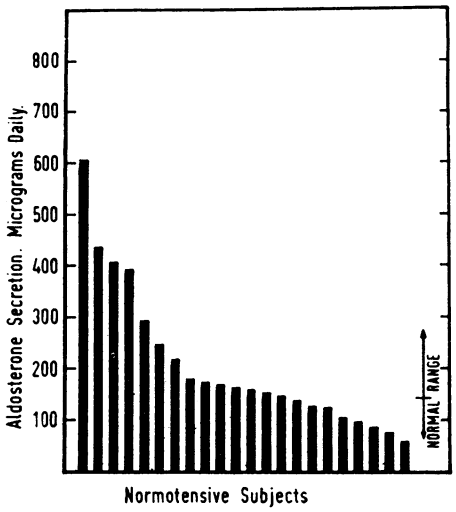

FIG. 3

FIG. 2.—Daily aldosterone secretion rate in 22 hypertensive subjects. Letters below each case have the following significance: E=Essential hypertension. M=Malignant phase. S=Proved renal artery stenosis. N=Normal pyelogram. A=Abnormal pyelogram. K=Low serum potassium. (See text.) FIG. 3.—Daily aldosterone-secretion rate in 22 normotensive patients with metabolic disturbance but without sodium deprivation. (See text.)

Normotensive Subjects

In seeking to compare the secretion rate of aldosterone in hypertension with control subjects, it is not sufficient to choose only normal persons. Many patients with severe hypertension, especially in the malignant phase, are ill in various ways. It is desirable, therefore, to compare the hypertensive subjects with other ill persons who differ essentially only in that they are normotensive.

Our control group of ill normotensive patients therefore comprises a consecutive series of 22 estimations of aldosterone secretion rate on normotensive subjects who had various metabolic disturbances. None had fever or any malignant disease, and in none was there any detectable degree of sodium depletion due either to the disease or to the use of natriuretic drugs, for sodium depletion is probably the strongest known stimulus to aldosterone secretion. All showed a normal urinary sodium excretion. The results are shown in Fig. 3.

The range of secretion rates found in this series of similarly ill but normotensive patients has been from 604 down to 56 μg. daily, the mean for the whole group being 209 μg. The scatter is perhaps rather less than in the hypertensive group, and in this series only one case shows a secretion rate below 60 μg. daily. The mean for this normotensive group is thus only slightly lower than in the hypertensive group. In the normotensive group 7 of the 22 have secretion rates above 200 μg. daily, and five above 250 μg. The secretion rate data are summarized in Table II.

The general picture shown by comparisons of the secretion rate is also evident when the daily excretion in the urine of the amount of tetrahydro-aldosterone is compared in the two groups. The scatter of values in both groups is shown in Fig. 4. There is a somewhat larger scatter in the hypertensive group than in the normotensive group, just as there is with the secretion rates. But the mean of all the 22 estimations in the normotensive series is 39.7 μg. daily, the mean for the 22 estimations of the hypertensive series is

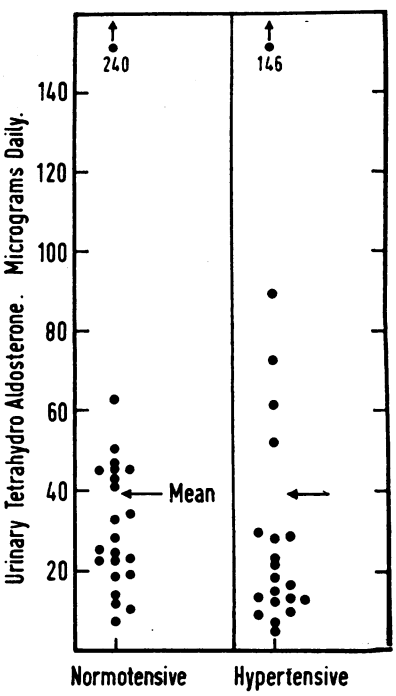

FIG. 4.—Comparison of urinary excretion of tetrahydro-aldosterone in normotensive and hypertensive subjects. The mean is the same in both groups.

38.8 μg. daily. There is thus a surprising degree of agreement between the two groups.

TABLE II.—*Aldosterone Secretion in Hypertensive States, μg. Per Day*

	Range	Mean	Percentage Over 200 μg.
Normal subjects (10)	62–275	143	10
Essential hypertension (7) ..	53–163	107	0
Malignant hypertension (4) ..	44–650	281	50
Normal pyelogram (9)	42–832	235	22
Abnormal pyelogram (9) ..	31–498	186	44
Uraemia (5)	183–712	440	80
Renal artery stenosis (5) ..	31–498	188	40
Adrenal cortical adenoma (2) ..	270–623	450	100
Normotensive controls (22) ..	56–604	209	32

Discussion

From these data it may be concluded that a raised aldosterone-secretion rate will be encountered in hypertensive subjects in about one-third of the cases. There is evidence of a much greater range of values than is seen in normal subjects. But when the figures are compared with aldosterone-secretion rates encountered in other ill but normotensive patients, then no great difference can be detected, for neither the range nor the mean secretion rate of the normotensive group is significantly different from the hypertensive group.

From the data obtained from the hypertensive subjects it seems justifiable to make the following generalizations: (1) Patients with uncomplicated essential hypertension have aldosterone-secretion rates within the normal range. (2) Patients with malignant hypertension may have greatly elevated aldosterone-secretion rates, but do not always do so. (3) Hypertensive patients with an abnormal pyelographic picture are no more likely to show raised aldosterone secretion than are those with a normal pyelogram. (4) Patients with a proved renal artery stenosis may show a raised aldosterone secretion, but may equally show normal or low secretion rates.

These conclusions suggest strongly that the factors considered above are not the ones which determine whether aldosterone secretion is raised or not. Some other determining factor or factors seem to be acting independently of these aetiological subdivisions of the hypertensive state.

As to the nature of this factor only speculation can at present be offered. But it seems clear that many types of metabolic derangement can increase aldosterone secretion to some degree just as many types of stress can increase cortisol production. Since our consecutive series of normotensive metabolic disorders shows a similar scatter and a similar mean figure to the hypertensive series, it seems likely that some at least of the aetiological factors acting in the normotensive group are also operative in the hypertensive series. If this be so, then it would seem desirable to regard at least some of the raised aldosterone-secretion rates encountered in hypertensives as incidental manifestations of associated metabolic disturbances.

It seems most improbable that a mild chronic overproduction of aldosterone is concerned in the pathogenesis of essential hypertension as Genest *et al.* (1956) suggested, for neither Laragh *et al.* (1960) nor we have found any evidence of raised aldosterone production in essential hypertension. Moreover, Genest (1961) has shown that angiotensin acts as a stimulant to aldosterone production even in doses too small to produce detectable hypertension. This claim therefore suggests that raised aldosterone secretion should be a sensitive indicator of circulating angiotensin, more sensitive indeed than the blood-pressure itself. Since aldosterone secretion is not increased in uncomplicated essential hypertension it is difficult to believe that angiotensin is circulating in increased amount in this disorder.

The absence of raised aldosterone secretion in essential hypertension indicates that the raised blood-pressure itself is not the determining factor in provoking a raised secretion, and the inconsistent rises found in malignant hypertension and in renal artery stenosis support the same view.

Angiotensin has been proved to be a potent stimulant to aldosterone secretion in man (Genest *et al.*, 1961), and Davis (1961) has shown that the kidney is necessary to the initiation of the raised aldosterone secretion in dogs after a severe blood loss. But the frequency with which angiotensin provokes the raised aldosterone secretions seen in a proportion of hypertensive subjects can be determined only when further information about the frequency of high plasma angiotensin levels in such subjects has become available. At the present time such information is lacking. There is no reason to believe that angiotensin is the only stimulus to aldosterone secretion (Farrell and McIsaac, 1961).

Genest (1961) has suggested that the aldosterone production may be only intermittently raised in these hypertensive subjects so that "spot tests" of secretion rate may fail to reveal the rises. While this possibility may be conceded, there is little reason to believe that intermittent rise in aldosterone secretion alone will produce hypertension. Such increases are often encountered in nephrosis and in cirrhosis of the liver with ascites, and in both conditions the increase may persist for long periods without rise in blood-pressure. Furthermore, chlorothiazide and similar natriuretic drugs often stimulate increased aldosterone secretion as sodium is lost, yet these drugs tend to reduce rather than to raise blood-pressure

There is a little indirect evidence that some other aspect of illness than the hypertension is the determining factor in the raised aldosterone secretions encountered in some hypertensive subjects. In their original study Laragh *et al.* (1960) had already observed that there was no relation between the height of the blood-pressure and the aldosterone-secretion rate. But they did notice that "in general the hypersecretion of aldosterone was more impressive in the seriously ill patients."

Venning *et al.* (1961), who studied only urinary excretion, observed two patients who had greatly raised urinary excretions of aldosterone and of tetrahydroaldosterone at a time when their general condition was deteriorating. It has been known for many years that there is an increased urinary excretion of aldosterone, and therefore presumably an increased secretion, in such a non-specific disturbance as a surgical operation (Llaurado, 1955). Laragh (1961) thinks that in essential hypertension "increased aldosterone secretion may be encountered inconsistently as these patients develop renal or cardiac complications." With the suggestion that when raised aldosterone secretion occurs in essential hypertension it is likely to be due to some other complicating factor we would concur. We think the same may prove to be true in some patients with malignant hypertension, possibly in the majority. It is interesting that, whereas Laragh *et al.* (1960) found

that in malignant hypertension "marked hypersecretion of aldosterone almost invariably occurs," two of our four cases had low secretion rates. These low values cannot be attributed to technical errors, for practically all the many possible errors which can creep into an analysis of this complexity will raise, not lower, the secretion rate estimate obtained. It is curious also that, whereas Laragh *et al.* found raised secretion usual in malignant hypertension, Genest (1961) finds a raised urinary excretion of aldosterone in only 50% of such cases.

It is clearly important to determine the true frequency with which subjects with malignant hypertension do show secretion rates of aldosterone higher than may be encountered in normotensive subjects having a comparable degree of illness. Until this can be done it would seem unwise to suggest an aetiological relationship between the aldosterone secretion and the malignant phase. We have indeed been impressed with the very low secretion rates recorded in some of these hypertensive patients, but can only speculate as to the cause. We have found similar figures in normotensive subjects only when they have been given a high salt intake or generous doses of 9α-fluorohydrocortisone with a resultant increase in body weight due to sodium retention. It seems possible that some degree of sodium retention was present in these hypertensive cases, although it was not apparent in the serum sodium concentration, nor was there any oedema. It is recognized that some hypertensive subjects respond to treatment with chlorothiazide and the response may well be due to reduction of the retained sodium.

Thus it seems likely that the aldosterone-secretion rate is the resultant of two groups of factors, the one tending to raise it and the other to lower it. If this be so, then both types of influence may be operative simultaneously in some persons with resultant normal secretion rate. This could explain normal secretions in situations such as malignant hypertension where a rise is often seen, but could scarcely explain the normal secretion in essential hypertension, since no evidence of a stimulant factor has been obtained.

It is clear that much more information is needed about the factors determining aldosterone secretion before the precise role of this steroid in the pathogenesis of hypertension can be elucidated. Aldosterone would seem to be unconnected with the development of essential hypertension. When increased secretion is found in hypertensive subjects it is likely to be due to complicating factors which are not always necessarily the same.

Summary

By the use of tritium-labelled aldosterone the aldosterone-secretion rate has been compared in hypertensive and in normotensive patients.

The mode of estimating the secretion rate is reviewed and its application to patients with poor renal function is discussed.

Six of the series of 22 hypertensive subjects had aldosterone secretion rates higher than 250 μg. daily. Five of a series of 22 normotensive patients had secretion rates in excess of this figure.

Patients with uncomplicated essential hypertension have aldosterone secretion rates within the normal range.

Either high or low secretion rates may be found in subjects with malignant hypertension, in those with a normal or with an abnormal pyelogram, and in patients with proved renal artery stenosis.

Uncomplicated hypertension does not raise the aldosterone-secretion rate.

It is probable that when aldosterone secretion is found high in hypertensive subjects the cause may often be one also encountered in normotensive subjects. It seems unlikely that the cause of the increased secretion is always the same.

It is suggested that factors tending to lower the aldosterone secretion rate may also be operative in some cases of hypertension.

There is no reason to believe that aldosterone plays any part in the pathogenesis of uncomplicated essential hypertension.

This work was in part supported in its early stages by the U.S. Department of Army (Contract No. DA.91.591. EUC.1407). We are also grateful to the Medical Research Council for a personal grant for Miss M. Harwood. We are indebted to the U.S. Public Health Service, National Institutes of Health, Bethesda, Md., for a generous supply of tritiated aldosterone, and to Miss Valerie Hughesden for valued technical assistance.

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More courses are to be started to provide a general training in social work on the lines recommended in the Younghusband Report. The first three were started last autumn in London, Birmingham, and Liverpool, and the colleges concerned are now ready to consider applications for entry to further two-year courses on the same pattern, to start next September. Similar courses will start in the autumn in Bristol, Manchester, and Leeds and possibly in other centres in England and Wales. These courses are designed to meet the urgent need for further trained staff in the local authority health and welfare services, including the mental health service, and similar services of voluntary organizations, by providing at colleges of further education a two-year full-time training, in which the study of theory and practice will be closely linked.