Essential Hypertension and Aldosterone

By Eleanor H. Venning, Ph.D., Inge Dyrenfurth, Ph.D., John B. Dossetor, B.M. (Oxf.), and John C. Beck, M.D.

Many factors have been implicated in the etiology of essential hypertension and at present the primary cause of this disease remains obscure. The relationship of sodium to the development of hypertension and the question of involvement of the adrenal cortex has been the subject of numerous investigations. Efforts by earlier investigators to show a hypersecretion of corticosteroids in this condition were conflicting and the general conclusions were that there was no consistent abnormality in adrenal cortical function in this disease. With the isolation of aldosterone, a highly active, naturally occurring sodium-retaining hormone, interest has been renewed in the relationship of the adrenal cortex to hypertension. An elevated blood pressure is the usual finding in patients with primary aldosteronism, and the administration of aldosterone to normal individuals and to patients with Addison's disease over periods of 2 to 3 weeks results in a rise in blood pressure. Genest et al. have reported that 55 per cent of patients with essential, renal, and malignant hypertension, excrete amounts of aldosterone in the higher range or above normal levels. In a more recent study, using an isotope-dilution technic, Laragh and co-workers found the secretion rate of aldosterone to be within the normal range in patients with benign essential hypertension. In hypertensive patients with renal or vascular complications, the secretion was significantly increased.

In the present study a survey was made of the levels of urinary aldosterone and its reduced metabolite in normal individuals and in patients with essential hypertension in whom the sodium intake was known. A small group of patients with malignant and renal hypertension was also investigated. Most of the patients were followed from 2 to 6 days in the hospital. The response of plasma and urinary 17-hydroxy corticosteroids and urinary aldosterone to the administration of adrenocorticotrophic hormone (ACTH) was investigated and in addition the steroid content of the adrenal glands obtained at autopsy from two patients with malignant hypertension was determined.

Methods

Aldosterone was extracted from urine after hydrolysis at pH 1.5 at room temperature for 48 hours. The fraction containing aldosterone was purified on paper in four chromatographic systems as outlined by Dyrenfurth and Venning and was measured by reduction with blue tetrazolium.

The tetrahydro derivative of aldosterone was hydrolyzed by means of β-glucuronidase and was isolated and determined after acetylation by the reduction of blue tetrazolium according to a modification of the procedure of Ulich and Lieberman. The details of this method will be published by Dyrenfurth et al.

Urinary 17-hydroxy corticosteroids were determined by the Porter-Silber method and the plasma 17-hydroxy corticosteroids by the method of Bush and Silber. The pattern of corticosteroid excretion was examined in two patients with essential hypertension, and the steroid content of adrenal tissue from two patients with malignant hypertension by procedures previously outlined by Dyrenfurth and co-workers.

The functional capacity of the adrenal gland to respond to the administration of adrenocorticotrophic hormone was determined in 5 patients with essential hypertension and was compared with responses obtained in normotensive individuals. The normal subjects and the hypertensive patients were studied either in the metabolic unit or in the general medical wards of the Royal Victoria Hospital. In the former instance complete metabolic balance technics were followed and the dietary composition was determined from food tables with periodic checking of sample diets. The dietary intake of patients studied on the general wards was supervised by a dietitian who calculated the

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electrolyte content on the basis of the actual daily food intake.

Clinical Material

It has been customary to classify hypertension into a primary and a secondary form, the former being largely a diagnosis of exclusion. The patients described in this study were carefully investigated from the clinical point of view. Meticulous inquiry into the family history as well as into a previous history of renal disease was made. In all patients urinalysis and routine hematologic studies were performed as well as an electrocardiogram, a radiologic examination of the chest, and an intravenous pyelogram. Nonprotein nitrogen or serum creatinine, serum sodium, potassium, chloride, and bicarbonate determinations were carried out in all patients. In most of the individuals studied a phenolamine (Regitine) test was carried out as a screening procedure for pheochromocytoma, as well as a tetraethyl ammonium chloride test (TEAC) as a screening procedure for unilateral renal vascular disease. Urinary catecholamines were determined when indicated, as were repeated urine cultures when clinical or laboratory evidence suggested the presence of a pyelonephritis. In many patients an endogenous creatinine clearance, as an index of glomerular filtration rate, was determined, as well as a 10 ml. intravenous phenolsulfonphthalein test with collection of urines at 15, 30, 60, and 120 minutes. In patients in whom hypertension secondary to a unilateral renal vascular lesion was suspected, aortography and differential renal function studies as described by Howard23 were performed. Although the pitfalls of any attempt to classify patients with hypertension are well recognized, it was considered that there was some merit in subdividing these hypertensive subjects into the following categories:

1. Essential hypertension without clinical and laboratory evidence of renal disease.

2. Essential hypertension with renal disease. These were patients with a previous diagnosis of essential hypertension who developed laboratory evidence compatible with arteriolar nephrosclerosis.

3. Hypertension secondary to renal disease. These patients had previously recognized glomerulonephritis, pyelonephritis, or periarteritis nodosa. A clear-cut separation of categories 2 and 3 may be impossible in some patients with the clinical laboratory procedures available at the present time.

4. Malignant hypertension. These individuals had an accelerated form of hypertension associated with progressive renal damage, retinopathy, and papilledema.

The distinctions made in these four categories were based on the belief that they probably represent a progressive advance in the severity of the disease. There is as yet a lack of information concerning the effect of alterations in renal functional capacity upon aldosterone excretion by the adrenal cortex.

5. Hypertension associated with generalized arteriosclerosis.

6. Hypertension with associated heart failure. This group was separated because it was thought that the syndrome of congestive heart failure in itself elevates the urinary aldosterone excretion.

7. Hypertension associated with pheochromocytoma.

The sodium intake in these cases was controlled but only a limited number were placed on complete metabolic studies, the results of which will be reported in a subsequent communication.

The clinical report of the two cases with malignant hypertension whose adrenal glands were analyzed for their steroid content (table 1) is as follows:

Case 1 was an obese man, aged 42 years, with severe hypertension, who had been treated for several months with reserpine, chlorothiazide, and a low-sodium diet. Since he was unreliable, he probably did not follow his treatment. He suffered a cerebral hemorrhage, was admitted to the hospital in an unconscious state, and died that night. An autopsy was performed 20 hours after death and showed the following pathologic changes: subarachnoid hemorrhage, hypertrophy and dilatation of the heart, malignant nephrosclerosis, arteriolar sclerosis and necrosis of the adrenal glands, liver, and spleen, and adrenal cortical hyperplasia, nodular in part.

Case 2 was a woman aged 53 years, with a history of severe hypertension for at least 6 months,
congestive heart failure, and pyelonephritis. Her blood pressure did not respond to hypotensive drugs. She developed hypokalemia on chlorothiazide and the sodium intake was reduced to 86 mEq. per day with supplementary potassium chloride, 2.5 mg. of mecamylamine hydrochloride daily, and frequent mersalyl injections. After a week on this therapy she was discharged. She was readmitted 2 days later following a fall. At this time serum electrolytes were within normal range. On the second day the blood pressure dropped and convulsions occurred, and an emergency neurosurgical procedure was performed. This was followed on the third day by a tracheotomy. The patient died that night. An autopsy performed 10 hours after death showed brain contusion and laceration with subdural hemorrhage, severe bilateral chronic pyelonephritis with marked vascular sclerosis, hypertrophy of the heart, and hyperplastic adrenal glands with a large adenoma of the right adrenal gland.* There was no clinical evidence to suggest that this might have been a case of primary aldosteronism nor did the patient show any symptoms of Cushing's syndrome.

*We are indebted to Dr. Sean Moore of the Department of Pathology, Montreal General Hospital, for the supply of adrenal tissue.

Results

The results of the survey are shown in table 2. Forty-six patients with hypertension were studied and a total of 147 assays of aldosterone was made. Twenty-six of these patients presented a picture of essential hypertension without clinical and laboratory evidence of renal disease. They were divided into two groups, depending upon their sodium intake. This varied from 100 to 150 mEq. per day in the first group and from 70 to 85 mEq. per day in the second group. In the normotensive group the estimated sodium intake was between 100 and 170 mEq. per day.

The healthy individuals excreted amounts of aldosterone ranging from 2 to 12 µg. per day, with a mean value of 5.1 ± S.E. 0.22. The patients with essential hypertension showed values ranging from 3.3 to 18.9 µg. per day, with a mean value of 8.8 ± S.E. 0.43. The difference between these two means was statistically significant, p < 0.001. A distribution curve of the urinary aldosterone values

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**Table 1**

<table>
<thead>
<tr>
<th>Steroid Content of Adrenal Glands in Malignant Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenal weights</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
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<td>Case 1, male</td>
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<td></td>
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</table>

**Table 2**

<table>
<thead>
<tr>
<th>Excretion of Aldosterone in Hypertension</th>
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<td>Cases</td>
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<td>-----------------------------------------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Normotensive Individuals</td>
</tr>
<tr>
<td>1. Essential hypertension with renal disease</td>
</tr>
<tr>
<td>2. Essential hypertension with renal disease</td>
</tr>
<tr>
<td>3. Hypertension secondary to renal disease</td>
</tr>
<tr>
<td>4. Malignant hypertension</td>
</tr>
<tr>
<td>5. Hypertension and arteriosclerosis</td>
</tr>
<tr>
<td>6. Hypertension and heart failure</td>
</tr>
<tr>
<td>7. Pheochromocytoma</td>
</tr>
</tbody>
</table>

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Figure 1
Distribution of 24-hour excretion rates of aldosterone in normotensive individuals and patients with essential hypertension.

in normotensive individuals and in patients with essential hypertension is shown in figure 1. Approximately 75 per cent of the normal subjects showed values between 2 and 6 µg. per day whereas 82 per cent of the patients with essential hypertension excreted amounts greater than 6 µg. aldosterone per day.

In four patients with essential hypertension in whom the sodium intake had been restricted to 70 to 85 mEq. per day, the urinary aldosterone values ranged from 5.7 to 19.6 µg. per day, with a mean value of 12.0 ± S.E. 1.14 µg.

The patients with essential hypertension and secondary renal disease, on a normal sodium intake, showed a higher mean value of 10.1 ± S.E. 0.88 µg. per day than those with benign essential hypertension, and in the group in which the hypertension was associated with primary renal disease the mean value was 19.4 ± S.E. 1.75 µg.

Prior to the collection of urine, the patients with malignant hypertension had been in the hospital for a few weeks and had received ganglion-blocking agents and reserpine in an effort to control the blood pressure. In two patients on a normal sodium intake the mean value for aldosterone excretion was 15.0 µg. per day, whereas that obtained in two patients on a lower sodium intake was 23.3 µg. Two older women, aged 68 and 72 years, with mild hypertension and arteriosclerosis, had values for urinary aldosterone within the normal range and one patient with hypertension and heart failure also showed a normal output of aldosterone. A second patient in this group on a sodium intake of 70 to 85 mEq. had values ranging from 11.6 to 18.7 µg. per day. In the two patients with proved pheochromocytoma, the aldosterone output was within the normal range.

In each group of hypertensive patients the mean aldosterone excretion was always higher with the lower sodium intake. In general the severity of the disease tended to be greater, so that it is perhaps not justifiable to attempt to assess the influence of the lower sodium intake on aldosterone excretion in these cases.

When hypertensive patients were followed daily for periods of 4 to 6 days, it became evident that many showed wider fluctuations in aldosterone excretion than normotensive individuals. Approximately 30 per cent of the cases studied showed these fluctuations. The daily aldosterone excretions in five hospitalized normotensive and five hypertensive subjects that showed these fluctuations are depicted in figure 2.

The amount of aldosterone extracted from urine at pH 1.5 represents only a small fraction of the amount elaborated by the adrenal gland. Part of the hormone is metabolized in the body and is excreted as a tetrahydro derivative. The values found by Dyrenfurth and co-workers in 34 normotensive persons (17 males and 17 females) was 23.1 µg. ± S.E. 1.49 (ranges 6.8 to 38 µg.) In 11 determinations carried out on seven patients with essential hypertension on a normal sodium

Figure 2
Fluctuations in daily urinary aldosterone levels in normal subjects and in patients with essential hypertension on a known sodium intake.

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intake the values ranged from 22.3 to 66.7 μg. per 24 hours, with a mean value of 38.4 ± S.E. 4.3 (fig. 3).

The daily excretion of aldosterone and its metabolite is shown for two patients with hypertension in table 3. Case 1, a man, age 40 years, with chronic glomerulonephritis and hypertension was receiving a sodium intake of 100 mEq. per day. Despite treatment with hydralazine the patient's blood pressure stayed at a mean of 210/110 mm. Hg. At the time of the assays the nonprotein nitrogen and edema were increasing and the patient died 6 days later. With deterioration in the patient's condition, the levels of urinary aldosterone rose from 11.7 to 28.7 μg. and its metabolite from 68.9 to 185 μg. per day.

A second case, a man, age 41 years, with malignant hypertension, was followed for 10 days. One week prior to admission to the hospital a subarachnoid hemorrhage had occurred and the blood pressure at that time was 204/130. Bilateral grade IV hypertensive retinopathy was present. The patient was given a 10 mEq. sodium diet; reserpine and hydralazine were administered. The blood pressure fluctuated considerably during the first 3 weeks and finally reasonably good control was achieved with reserpine, 0.2 mg. three times a day by mouth and hydralazine every 6 hours in alternating doses of 50 and 75 mg. The assays were carried out after relative control of the blood pressure had been achieved at a level of 140/90. At the beginning of the study, both aldosterone and its metabolite were excreted at high levels and gradually decreased although the low-sodium intake was maintained throughout. During this period there was also an improvement in the patient's clinical condition although the blood pressure changes could not be correlated with the level of aldosterone excretion.

Table 3

<table>
<thead>
<tr>
<th>Case</th>
<th>Sodium Intake (mEq./24 hr.)</th>
<th>Treatment</th>
<th>Blood Pressure (mm. Hg)</th>
<th>Aldosterone (μg./24 hr.)</th>
<th>Aldosterone metabolite (μg./24 hr.)</th>
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<tbody>
<tr>
<td>1.</td>
<td>100</td>
<td>apresoline</td>
<td>210/110</td>
<td>11.7</td>
<td>68.9</td>
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<tr>
<td></td>
<td>100</td>
<td>apresoline</td>
<td>135/82</td>
<td>29.8</td>
<td>124.2</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>apresoline</td>
<td>138/110</td>
<td>28.0</td>
<td>174.0</td>
</tr>
<tr>
<td>2.</td>
<td>10</td>
<td>reserpine &amp; apresoline</td>
<td>150/85</td>
<td>14.8</td>
<td>67.3</td>
</tr>
<tr>
<td>Malignant hypertension*</td>
<td>10</td>
<td>reserpine &amp; apresoline</td>
<td>140/90</td>
<td>24.0</td>
<td>125.0</td>
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<tr>
<td></td>
<td>10</td>
<td>reserpine &amp; apresoline</td>
<td>148/88</td>
<td>18.0</td>
<td>144.0</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>reserpine &amp; apresoline</td>
<td>165/100</td>
<td>11.2</td>
<td>62.0</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>reserpine &amp; apresoline</td>
<td>172/100</td>
<td>18.0</td>
<td>70.0</td>
</tr>
</tbody>
</table>

*On admission to hospital blood pressure was 240/130. Assays were carried out 3 weeks later during continued therapy.
Excretion of 17-Hydroxycorticosteroids

The excretion of 17-hydroxycorticosteroids measured by the Porter-Silber method in patients with essential hypertension was within the range observed in healthy individuals and was not affected by hospitalization (table 4). In two patients with this disease the corticosteroids were fractionated on paper and a pattern was obtained of the ultraviolet-absorbing and blue tetrazolium-reducing urinary corticosteroids. The patterns were essentially normal. Figure 4 shows the results obtained on a woman, age 63 years, who maintained herself on a normal and a low-sodium intake and also following the administration of adrenocorticotrophin.

Response to Adrenocorticotrophic Hormone

Twenty units of adrenocorticotrophic hormone were administered every 6 hours over a period of 48 hours to five patients with essential hypertension. The daily excretion of urinary corticosteroids and aldosterone was determined (table 5) and plasma 17-hydroxycorticosteroids were measured at 0, 4, and 48 hours (fig. 5). Both groups included male and female patients. The responses were compared with those obtained in healthy subjects previously reported. Although there were variations in response in the two groups, the mean values for both urinary 17-hydroxycorticosteroids and aldosterone were in the same range after the administration of adrenocorticotrophic hormone. The plasma levels of 17-hydroxycorticosteroids before and after adrenocorticotrophic hormone in both groups fell within the same range. These studies indicate that the adrenal glands of patients with essential hypertension are not more responsive to adrenocorticotrophin than those of normotensive individuals.

Steroid Content of Adrenal Glands of Patients with Malignant Hypertension

Adrenal glands from the two patients with malignant hypertension were analyzed for

Table 4

<table>
<thead>
<tr>
<th>Cases</th>
<th>Sex</th>
<th>(yr.) Age</th>
<th>(mg./24 hr.) Range</th>
<th>(mg./24 hr.) Mean</th>
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<tbody>
<tr>
<td>Normotensive, not hospitalized</td>
<td>male</td>
<td>22-35</td>
<td>3.0-8.5</td>
<td>5.3</td>
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<tr>
<td>Normotensive, hospitalized</td>
<td>male</td>
<td>22-29</td>
<td>3.3-8.8</td>
<td>6.1</td>
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<tr>
<td>Essential hypertension, hospitalized</td>
<td>male</td>
<td>27-62</td>
<td>4.8-7.9</td>
<td>6.2</td>
</tr>
<tr>
<td>Normotensive, not hospitalized</td>
<td>female</td>
<td>20-50</td>
<td>2.0-6.0</td>
<td>3.5</td>
</tr>
<tr>
<td>Essential hypertension, hospitalized</td>
<td>female</td>
<td>44-63</td>
<td>2.9-6.8</td>
<td>4.2</td>
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</tbody>
</table>

Table 5

<table>
<thead>
<tr>
<th>Cases</th>
<th>17-Hydroxycorticosteroids mg./24 hr.</th>
<th>Aldosterone mg./24 hr.</th>
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<tbody>
<tr>
<td></td>
<td>ACTH Day 1</td>
<td>ACTH Day 2</td>
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<tr>
<td>Normotensive</td>
<td>8</td>
<td>5.2</td>
</tr>
<tr>
<td>Essential hypertension</td>
<td>5</td>
<td>4.7</td>
</tr>
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</table>
Figure 5
Response of plasma 17-hydroxycorticosteroids to adrenocorticotrophin in patients with essential hypertension and in normotensive individuals.

their content of adrenocortical steroids. At autopsy the glands were removed and frozen and later homogenized and extracted. The corticosteroids were separated by paper chromatographic procedures and measured. The amount of the various steroids present in the tissue is expressed in micrograms of steroid per gram of adrenal tissue (table 1).

Although changes must have occurred in the steroid content between the time of death and freezing of the tissue, the high aldosterone content, 2.6 μg./Gm. in case 1 and 2.9 μg./Gm. of tissue in case 2, was increased many times above the values reported by Neher in normal adrenal glands. The value for hydrocortisone was low in the first case and in the second case within the range given for the normal gland by Neher and by Hudson and Lombardo. Corticosterone was within the limits reported by these investigators.

Discussion
Although the majority of patients with benign essential hypertension, on a normal sodium intake, excreted amounts of aldosterone within the normal range, the mean value found in a group of 26 patients was significantly higher statistically than that observed in normotensive individuals. Whether this difference is of clinical significance in the etiology of the disease is not clear at the present time. Most of the patients were in an older age group than the normotensive individuals and little is known regarding the effect of age on aldosterone excretion. The excretion of other adrenal hormones, 17-hydroxycorticosteroids and 17-ketosteroids, declines with advancing years. If this same phenomenon occurs with aldosterone, then the difference between the two groups might be even greater. When renal disease was a secondary complication, the mean value was higher; when it was a primary factor, most of the values were above the normal range. Similar observations were observed in two patients with malignant hypertension on a normal sodium intake. These findings are essentially in agreement with those of Genest et al. Laragh et al. were unable to find any increase in the secretion rate of aldosterone in patients with benign essential hypertension; however, they did find significantly increased rates in patients with renal complications and in malignant hypertension.

Although the determination of the tetrahydro derivative does not appear to have the same accuracy as that for aldosterone, the mean value in a group of six patients with essential hypertension was considerably higher than that observed in normotensive individuals, 40 per cent of the values being above the highest value obtained in the normal group. The number of patients studied, however, was small compared to the number of normal individuals, and this ratio might change with an increasing number of assays. Very high amounts of the tetrahydro derivative were found in the urine of a patient with glomerulonephritis on a sodium intake of 100 mEq. per day.

Several possible explanations for the wide fluctuations in the urinary excretion of aldosterone that occur in some patients with hypertension can be suggested. These may reflect a variation in the secretion rate or an alteration in the metabolic degradation of aldosterone and its urinary excretion. If the former be so, then single determinations of an aldosterone secretion rate may not truly reflect the amount of aldosterone elaborated by the adrenal gland over a period of time,
and repeated parallel measurements would seem necessary until this matter is clarified. Fluctuations may also occur owing to emotional disturbance, and this certainly was a factor in a few cases. Similar increases have been observed in medical students during examinations when anxiety was present. The possibility that the adrenal glands of patients with hypertension might be more responsive to adrenocorticotrophic hormone was considered. This did not appear to be the case, however, as both normotensive individuals and hypertensive patients showed comparable increases in urinary aldosterone as well as plasma and urinary 17-hydroxycorticosteroids following the administration of similar amounts of adrenocorticotrophic hormone. These observations do not exclude mediation by another humoral pathway.

Several studies with a variety of methods have failed to show an increase in the excretion of corticosteroids in essential hypertension, and in the present study the Porter-Silber corticosteroids were within the normal range. Fractionation of the individual steroids also failed to show any gross abnormality in the ratio of the different urinary corticosteroids.

The high amount of aldosterone found in the adrenal glands of the two patients with malignant hypertension suggests that these glands have been secreting excessive amounts of this hormone at the time of death. These amounts are higher than those reported by Neher in tumors from patients with primary aldosteronism and only slightly lower than that observed by Genest in a case of primary aldosteronism and adrenal hyperplasia. In this case the adrenal gland was removed surgically, and a content of 3.6 µg. aldosterone per gram of tissue was found.

These studies suggest that aldosterone may play some role in the etiology of essential hypertension but a direct causal relationship seems unlikely. The high excretion rates found in hypertensive patients with associated renal disease, whether of a primary or secondary type, would indicate a possible renal-adrenal interplay in this disease. The elevated values observed in malignant hypertension, with a subsequent fall on reversal of this syndrome, together with the increased concentration in the adrenal glands of patients examined post mortem, suggest that hypersecretion of aldosterone may play an important role in its pathogenesis.

Summary

Serial determinations of the urinary excretion of aldosterone have been made in hypertensive patients. Although the majority of patients with benign essential hypertension excrete amounts of aldosterone within the normal range, the mean excretion of 26 patients was significantly higher than that observed in normotensive individuals. When renal complications were present, the mean excretion was still further increased and in patients with malignant hypertension all the values were above the normal range.

The mean excretion of the tetrahydro metabolite of aldosterone was also found to be higher in patients with essential hypertension.

These patients have a normal response to adrenocorticotrophic hormone stimulation, urinary and plasma corticosteroids, as well as urinary aldosterone, showing comparable increases.

The aldosterone content of adrenal glands obtained post mortem from two patients with malignant hypertension was within the range observed by other investigators in primary aldosteronism.

References

5. Genest, J., Kow, E., Nowaczynski, W., and Le Boeuf, G.: Further studies on urinary

An Editor's Prayer to Contributors

Brevity in writing is the best insurance for its perusal.—VIRCHOW