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THE ROLE OF ALDOSTERONE
IN THE PATHOGENESIS OF HYPERTENSION

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THE ROLE OF ALDOSTERONE
IN THE PATHOGENESIS OF HYPERTENSION

The high incidence and vast importance of high
blood pressure in the causation of disease and death
today are unquestioned. Hypertension is second only
to arteriosclerosis as the disease with the greatest
fatality rate, and accounts for over one-fifth of
all deaths per year. (1)

The exact incidence of hypertension as quoted
by different investigators varies greatly. It has
been variously computed as twenty million, fifteen
million, and six million persons in the United States
alone. This discrepancy is not due to error, but to
varying criteria used in the selection of cases.
Hypertension, either primary or secondary, occurs in
five to twenty per cent of the total population, and
its incidence rises to over fifty per cent in per-
sons over age fifty.

The term hypertension connotes a systemic arte-
rial pressure consistently above the accepted normal
values. These are customarily established as 140/90.
However, many people today regard fixed criteria for
diagnosis as no longer acceptable. True hypertension

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implies an elevation in both systolic and diastolic blood pressures. Although it is possible for only the systolic pressure to be elevated, this systolic type of hypertension is etiologically distinct, and is a field separate from the realm of this thesis. Here only the true or diastolic hypertension will be considered.

Hypertension has been variously classified by different investigators. Perhaps the most standard one is the classification which is reproduced below.

Etiologic Classification of Hypertension

I. Essential (or Primary)
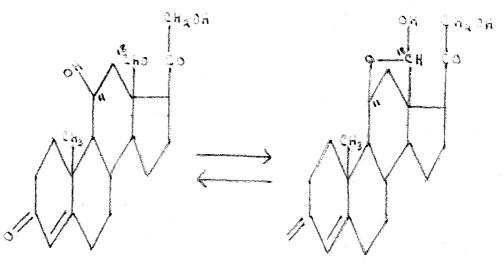
    A. Benign (incidence about ninety per cent)

    B. Malignant (incidence about ten per cent)

II. Secondary

    A. Renal

    B. Endocrine

    C. Neurogenic

    D. Psychogenic

    E. Cardiovascular

    F. Miscellaneous

When there is a persistent elevation of the systolic and diastolic blood pressures without a demonstrable cause, the condition is referred to as essential or

primary hypertension. This is subdivided into the
benign or chronic phase, and the malignant or accel-
erated phase, depending on the rate of progression
of the disease. Benign hypertension is character-
ized by a gradual and often insidious onset, slow
progression, and long duration extending over ten
to forty years. Malignant hypertension refers to
the small per cent of cases (one to seven per cent)
which progress rapidly and are characterized by high
diastolic blood pressure, papilledema, progressive
renal failure, and renal necrotizing arteriolitis
at autopsy. (2) Some workers feel that this clas-
sification is incorrect, as they feel secondary
hypertension may enter a malignant phase. This
argument is beyond the scope of this thesis.

It has been the goal of many investigators
through the years to discover a morphological or
biochemical abnormality which would act as a causa-
tive factor to explain the hypertensive phenomena
now classified as essential hypertension. With
increased knowledge of endocrinology, including the
isolation, purification, and synthesis of adrenal
cortical hormones, many workers feel this is now
possible. To investigate this possibility, this
thesis is dedicated.

In 1952, Simpson and Tait (3) first showed that it was a new steroid which was responsible for the mineral corticoid activity of the adrenals. Two years later, these same workers, in collaboration with Reichstein, Wettstein, and their respective groups, discovered its chemical formula. This mineral corticoid was later named aldosterone.

Aldosterone

The chemical formula of aldosterone shows the important differentiating point between this hormone and cortisone, hydrocortisone, and other steroids. (4) This is the presence of an aldehyde group in position eighteen. In solution, aldosterone is mainly in the form of a hemiacetal between C eleven and C eighteen, as shown above.

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Aldosterone is the major mineral corticoid excreted by the adrenal cortex, but is not the only one. 11-Desoxycorticosterone and dehydroepiandosterone are also mineral corticoids but have much less normal physiological activity than does aldosterone. Comparative bioassays have revealed that adrenal steroids may not act purely as gluco or mineral corticoids, but may have overlapping functional potencies. The comparative action of aldosterone, hydrocortisone, and desoxycorticosterone are listed below. (5)

HORMONE	ESTIMATED POTENCIES	
	GLUCOCORTICOID	MINERALCORTICOID
Hydrocortisone	1	1
Aldosterone	0.5	200-400
DOC (Desoxycorticosterone)	0	25

The functional zonation of the adrenal cortex has been established beyond any reasonable doubt. (6) The zona glomerulosa produces mostly mineral corticoids and is little affected by corticotropin, whereas the zona fasciculata and zona reticularis form predominately gluco corticoids, 17-keto steroids, and estrogens, and are dependent upon corticotropin for growth and secretory stimulation.

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Aldosterone is synthesized mainly by the enzymatic introduction of an aldehyde group in the C eighteen methyl group in the d position. Smaller amounts of aldosterone are synthesized through other pathways. Only the d form is biologically active. There is only very minimal binding in the plasma, and this is to albumin.

The control of the secretion of aldosterone has not been completely elucidated. Several factors have been recognized as causing an increase in aldosterone secretion. (6)

1. Reduction in intravascular volume
This reduction in intravascular volume as it occurs after sodium restriction, dehydration, or plasma extravasation causes the greatest increase in secretion--ten to forty-fold above normal. Conversely, overhydration with sodium chloride intakes of greater than 5 grams per day, or infusion of blood or albumin lead to a decrease in normal aldosterone secretion. Various baroreceptors in the carotid arteries and the right atrium have been implicated in the regulation of these volume-induced changes, but these have not been proven.

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2. Angiotension II

Angiotension II, the active component formed in
renin may cause an increase in aldosterone secre-
tion.

3. Adrenoglomerulotropin

Adrenoglomerulotropin, a lipid factor extracted
from the pineal gland, may increase aldosterone
secretion.

4. Adrenocorticotropic hormone

Pituitary corticotropin does increase aldosterone
secretion in man, though the rise is smaller than
that sustained by other adrenal steroids, and is not
prolonged.

The physiologic importance and effect of aldo-
sterone in man was not realized until 1955 when Conn
described the syndrome of a potassium losing nephri-
tis which he called primary aldosteronism. (7) This
is now known as Conn's syndrome. Clinically, this
syndrome is characterized by paresthesias, intermit-
tent tetany, polyuria, polydipsia, severe periodic
weakness and "paralyses", arterial hypertension, and
a lack of edema. The biochemical laboratory data in
such cases show an alkalosis with a pH greater than
7.5, a low serum potassium (1.6-2.5 mEq./L), and a

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high serum sodium. The sweat, salivary, and urinary potassium values are low, whereas these values for sodium are high. Pathologically there is usually an adrenocortical tumor (adenoma), or distinct adrenocortical hyperplasia.

With the discovery of aldosterone and the identification of Conn's syndrome, it was not long until investigators were postulating the possible causation of cases of essential hypertension via the aldosterone mechanism. There were many presumptive evidences at that time which might have led investigators to such a hypothesis.

Presumptive Evidences for this Relationship

Such a hypothesis (that essential hypertension was caused by an excess production of aldosterone) could explain many already known clinical and experimental observations.

1. The hypertension in Cushing's syndrome and the hypotension in Addison's disease.

2. The hypertension in the syndrome of primary aldosteronism. (Conn's syndrome)

3. The correlation between the elevation of

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blood pressure in patients, and their
sodium chloride intake. (8)

4. The benefical effect in a certain number
of hypertensive patients of the rice diet
(9, 10, 11) or diets limited to two hun-
dred and fifty mg. of sodium per day.
(12, 13, 14)

5. The increased concentration of sodium in
the muscles and arteries of patients with
essential hypertension, and of animals
made hypertensive by various procedures.
(15, 16)

6. The hypertensive effect of desoxycorti-
costerone acetate in normal subjects and
in Addisonians receiving a diet with normal
amounts of sodium. (17, 18, 19, 20) The
potentiating effect of salt on this DOCA
pressor activity, (21, 22) and the dis-
appearance of this effect when sodium
chloride is removed from the diet. (22)

7. The increase in the DOCA pressor effect
in animals with decreased renal functional
mass. (23)

8. The DOCA pressor effect in nephritic and hypertensive patients. (17, 24)

9. The rise in blood pressure after an increase in dietary salt in hypertensive patients, (22) and the disturbance in salt and water excretion following sodium restriction. (25)

10. The identical appearance of the capillaries of the bulbar conjunctiva in patients with essential hypertension and in patients with Cushing's syndrome. (26)

11. The hypertrophy of the adrenal cortex, especially the zona glomerulosa after angiotensin administration in experimental renal hypertension. (28)

12. The blood pressure fall in patients with essential hypertension following restriction of dietary potassium. (29)

13. The significant decrease in hypertension after complete removal of the adrenal cortex in dogs and rats with acute or chronic experimental hypertension. (30, 31, 32)

This evidence is, however, only presumptive. Before the validity of the hypothesis can be tested, concrete evidence must be obtained.

ALDOSTERONE--AN ETIOLOGIC AGENT IN HYPERTENSION

Evidence Substantiating this Hypothesis

The most extensive investigations of the role
of aldosterone have been made by Genest. (33). His
work was begun in 1948 when only the most basic work-
ing hypotheses were known, and measurements for sepa-
rating and measuring adrenocorticosteroids were very
crude. These first studies used an aluminum oxide
column for eluting the corticosteroid fraction of
urine. With these methods he could detect no dif-
ference between the values obtained for hypertensive
patients with high sodium intakes and high blood
pressure levels, and these same patients during
sodium restriction with blood pressure reduction to
normotensive levels.

After aldosterone was discovered in 1952 by
Simpson and Tait, using the newest techniques of
paper chromatography and the biological assay for
sodium-retaining activity which they suggested,
Genest was able to isolate the purified aldoster-
one fraction. When this fraction of the purified
extract obtained from the urine of hypertensive
patients was then injected into adrenalectomized

rats, a significant decrease (p is less than 0.001) in the urinary sodium potassium ratio could be seen, in comparison with those rats which received injections of urine fraction extracts from normotensive patients. Thus this finding suggested first, in 1956, that more aldosterone was excreted in the urine of hypertensive patients than of normotensive ones. (34)

This method was soon found to lack specificity and accuracy, and in 1958, Genest reported studies on this problem using a new physico-chemical method of aldosterone determination. (35) With this he demonstrated a two-fold increase in mean urinary aldosterone excretion in patients with essential, renal, and malignant hypertension, as compared to normal subjects. This difference was statistically significant with p less than 0.001. Also he demonstrated an excessive daily variation in the aldosterone content of the urine of hypertensive patients. This was in marked contrast to the relatively stable excretion of aldosterone in normal subjects. He could find no reason to account for these variations--such as the presence of acute stress, a chronic anxiety state, or the level of sodium or potassium intake.

In 1960 he completed two hundred forty-seven determinations of urinary aldosterone in one hundred forty-three normal subjects and hypertensive patients. (36) In this study, patients with essential, renal, and malignant hypertension showed a two-fold to four-fold increase in average urinary aldosterone excretion as compared to normotensive patients. Forty-three per cent of all aldosterone determination in patients with essential and malignant hypertension were greater than the upper normal limit (two to ten micrograms per day). In each of the three groups the differences between the means were statistically significant. For essential hypertension as compared to normotension, p was less than 0.001. For renal hypertension as compared to normotension, p was less than 0.005. For malignant hypertension as compared to normotension, p was less than 0.001.

These results are from spot determinations on hypertensive patients. However, Genest realized that such determinations could not reflect the marked overlapping which might occur between normal and hypertensive patients. For this reason he introduced a continuous study of the urinary aldosterone secretion of hypertensives and normals for periods of five to twenty consecutive days. In some cases the subjects

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were placed on fixed sodium and potassium intake diets, while in others, the diets were self-selected. Normal subjects' daily urinary aldosterone excretion remained well within normal limits even when these subjects were undertaking their usual activities, and despite marked variations in dietary sodium intake. However, all of the hypertensives but one showed excess fluctuation of daily urinary aldosterone above normal range despite hospitalization. These fluctuations were more marked in the malignant phase of hypertension but were also present in asymptomatic essential hypertension. No edema was present in these subjects.

There are several plausible explanations for the wide fluctuations of urinary aldosterone noted. This may be a variation in excretion rate, or an alteration in the metabolic degradation of aldosterone and its consequent urinary excretion. Fluctuations may occur as a result of emotional disturbances. Increases have been observed in medical students during examinations when anxiety was present. (37) Also one should consider the fact that the adrenal glands of hypertensive patients might be more responsive to adrenocorticotropic hormone. This possibility may be considered rather unlikely, due to the fact that ACTH is thought by most observers to have only a slight tropic action on aldosterone.

Genest's results with essential hypertension were confirmed by Garst. (38) She initiated a study whose primary aim was to determine the incidence of aldosteronism in hypertensive patients. In this statistically well-documented study she found that about twenty-five per cent of the patients with essential hypertension had significantly elevated levels of urinary aldosterone, using a paper chromatography method for determination. In none of these patients, however, were the abnormal serum electrolyte changes seen such as occur in primary aldosteronism.

Venning (39) studied aldosterone in hypertensives by a similar method with special emphasis on aldosterone changes as correlated with specific etiologies. She found that, although the majority of the patients with essential hypertension on a normal sodium diet excreted amounts of aldosterone within normal range, the mean value was statistically significantly higher than that seen in normotensive patients. She noticed also that most of the hypertensive patients were in an older age than the normotensive ones. The effect of age on aldosterone excretion is not known, but if it declines with

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advancing years as does the excretion of the other adrenal hormones—17-hydroxycorticoids and 17-ketosteroids—the difference between the two groups would be even greater.

She noticed that when renal disease was a secondary complication of essential hypertension, the mean value of aldosterone excretion was higher, even though the individual values were still within normal limits. But, if the hypertension were due to primary renal disease, the aldosterone excretion values were beyond normal range.

In addition to studying the physiologic effects of aldosterone, Genest studied its relationship to another normally occurring steroid, pregnanetriol. (Pregnane 3a, 17a, 20a-triol) This steroid is derived mainly from progesterone after 17-hydroxylation. Several authors (40, 41) feel that progesterone is an aldosterone antagonist because it inhibits the sodium retaining effect of aldosterone. Therefore, in hypertensives one might expect the pregnanetriol values to be decreased. Genest found a highly significant decrease (p is less than 0.001) in average pregnanetriol excretion values for essential, renal, and malignant hypertension patients as compared with normal subjects. Similar results were obtained by Bongiovanni and Eberlein. (42)

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The ratio of pregnanetriol to aldosterone has been proposed by Genest as an even more sensitive index of cardiovascular disease. This is true, he feels, whether there is an absolute increase in aldosterone, or a relative increase over a decreased progesterone. This ratio in all three groups of hypertensive patients is below the lower limits of normal range in ninety-two per cent of all patients studied in this regard.

Since the excretion of pregnanetriol is seemingly affected by the presence of hypertension, one might expect that other steroid values would also be affected. However, Genest has found no difference in the mean excretion of cortisol, cortisone, and their tetrahydro derivatives, etiocholanolone, and the tetrahydro derivative of 17-hydroxyl, 11-desoxycorticosterone in patients with hypertension--essential, renal, or malignant--and normal subjects.

The higher than usual excretion rates in hypertensive patients with associated renal disease seem to indicate a possible renal-adrenal interplay in this disease. This possibility has been variously considered in the medical literature since 1934, when Goldblatt and his colleagues produced hypertension

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experimentally in animals by clamping the renal artery. (43) Their findings, and later work by Houssay and Fasciolo of Buenos Aires, suggested that a humoral substance might be responsible for such an elevation. This substance was later isolated and found to be renin, an enzyme which reacted on a substrate in plasma to produce a vasoactive substance. (It is interesting to note that in 1898, Tigerstedt and Bergman of Stockhold first demonstrated the presence of a humeral substance in the kidney. This substance had remained dormant for thirty-six years until Goldblatt attempted his classical experiment.)

This vasoactive substance was named variously hypertensin and angiotonin. To avoid this confusion in names, the name angiotensin I has been accepted for this substrate. (44) Angiotensin I is a polypeptide. A converting enzyme, also present in the blood, breaks off two terminal amino acids to form angiotensin II--an extremely potent octapeptide vasoconstrictor. This substance has been shown to be ten times as vasoconstrictive as l-epinephrine. (45)

The exact nature of this renal-adrenal interplay has not yet been completely elucidated. However, it has been shown (46, 47) that renin infusion in dogs

producing experimental hypertension, will increase
the rate of aldosterone secretion. Carpenter, Davis,
and Ayers have shown that the infusion of renin into
hypophysectomized-nephrectomized dogs will increase
not only aldosterone, but also corticosterone. Like-
wise, the infusion of synthetic angiotensin II into
similar dogs has been shown to increase both of these
steroids. In fact, with doses of angiotensin II too
small to elicit a blood pressure response, physio-
logically significant increases in aldosterone secre-
tion were occasionally observed. Whereas in dogs
with benign hypertension the kidney renin content was
only slightly increased and aldosterone secretion was
within normal limits, in dogs with malignant hyper-
tension, there was a ten-fold increase in renin con-
tent of the kidneys and aldosterone output was markedly
increased.

Hardy and his colleagues report the case of a
fourteen year old girl with marked hypertension asso-
ciated with renal artery muscular hypertrophy. An
adrenal vein blood sample prior to nephrectomy (which
abolished the hypertension) showed a markedly elevated
aldosterone content which was statistically signifi-
cant as compared with that of nonhypertensive patients
undergoing laparotomy. Postoperatively, the urinary

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aldosterone was less than half of the value obtained preoperatively. They hypothesize that the renal ischemia in this case was responsible for the production of the increased aldosterone levels via a renin-angiotensin type mechanism.

Genest has also studied extensively the renal-adrenal relationships. (33, 49) His experiments consisted of acute and long-term intravenous infusions of synthetic angiotensin, which is identical to that isolated from oxen, except that the aspartic acid is replaced by asparagine in the synthetic material. In these experiments he studied urine volume, sodium and potassium excretion, glomerular filtration rate as approximately measured by creatinine clearance, urinary aldosterone, cortisol, cortisone, and their tetrahydro derivatives, in both normotensive and essential hypertensive individuals maintained on fixed sodium and potassium intakes. His results are summarized below.

I. Effects of Angiotensin on Urinary Electrolytes and Creatinine Clearance (Angiotensin administered at rates to produce an increase of eighteen to thirty millimeters of mercury diastolic pressure above control levels)

A. Results in Normal Subjects

    1. Marked sodium retention but with decrease in both sodium and potassium excretion.

    2. Decrease in urinary sodium potassium ratio.

    3. Creatinine clearance variable. (Thus the decrease in sodium and potassium excretion can occur without change in glomerular filtration rate.)

B. Results in Hypertensive Subjects

    1. Marked sodium excretion but with increase in both sodium and potassium excretion.

    2. Increase in urinary sodium potassium ratio.

    3. Increase in creatinine clearance. (Too few patients to be too significant.)

II. Effects of Angiotensin on Aldosterone and Other Corticosteriods. (Angiotensin administered at rates to increase diastolic pressure fifteen to thirty-five millimeters of mercury above control levels.)

A. Results in Normal Subjects

1. Two and one-half to eleven-fold increase in urinary aldosterone.

2. Parallel rise in aldosterone's reduced metabolite, tetrahydroaldosterone.

3. In two of four patients, a two to three-fold rise in urinary cortisol and tetrahydrocortisone. (A rise of this magnitude is small in terms of physiologic significance in comparison to the rise of aldosterone.)

It is interesting that in two cases where angiotensin was infused at low levels where the effect was still subhypertensive, there was a significant degree of aldosteronuria. This appears to indicate the great sensitivity of the aldosterone response to angiotensin. Control infusions of five per cent glucose, epinephrine, norepinephrine, and phenylephrine were administered to these patients to see if the increased urinary aldosterone was the result of the stress of the infusion experiment. In all cases except one, the aldosterone level did not undergo any significant change. (In one instance with phenylephrine, there was a small rise, but this was quite small in comparison to that obtained during the infusion of angiotensin.) Venning

(50) has shown an increase in urinary aldosterone
during emotional stress situations. These experi-
ments show that this increase in aldosterone in such
situations is not mediated through catecholamines.

B. Results in Benign Hypertensive Patients

1. Increase in urinary aldosterone.

These studies give strong clinical support to
the renal-adrenal hypothesis and seem to correlate
well with the experimental studies of Tobian (51)
which link the granulations of the renal juxta-
glomerular cells to the adrenal zona glomerulosa and
sodium regulation. He feels that the width of the
zona glomerulosa, which secretes aldosterone, the
granularity of the renal juxtaglomerular cells, which
probably secrete renin, and the renin content of the
kidney vary in parallel. They increase in response
to low sodium intake, or high renal artery pressure
such as seen in cases of hypertension and after admini-
stration of renin or desoxycorticosterone.

The angiotensin studies of Genest do not solve
all problems, however. In particular they do not
explain why the increased aldosterone levels during
angiotensin infusions in normal patients are accom-
panied by marked sodium restriction and lowering of
the urinary sodium potassium ratio; whereas in patients

with hypertension, these same aldosterone increases are accompanied by marked decreases in the urinary sodium potassium ratio. This appears to suggest a basic difference between normal subjects and hypertensive subjects in response to angiotensin.

Selye, (23) in 1942, was the first to experimentally produce nephrosclerosis through the use of desoxycorticosterone acetate. His first experiments were in chicks, but later similar findings were obtained in the dog, rat, and monkey. In 1943 he repeated his experiments in rats, and also determined that this experimentally induced renal disease would be accompanied by a rise in blood pressure and structural changes in the systemic blood vessels such as those seen in the malignant hypertensive patient. He noted that this was particularly pronounced when the rats were kept on a high sodium chloride diet.

This presumptive evidence of the effect of a mineral corticoid has been repeated using aldosterone by Gross. (55) He found that aldosterone, if given in relatively higher amounts than DOCA, would produce a comparable increase in blood pressure in rats. However, it did not produce the severe renal lesions which Selye and Gross both observed with

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DOCA. This, then, is strong experimental proof of
the effect of aldosterone in an experimental animal.

Evidence Not Substantiating This Hypothesis

In a subject which is exceedingly complex, and
in which there are many different factors occurring,
it is inevitable that there should not be unanimity
of opinion between various authors. This is cer-
tainly true of this field.

Laragh (53) and his group in 1960 completed a
study of the secretion of aldosterone in hypertension.
His method of analyzing the aldosterone content was
entirely different from that of Genest. In this
method he utilized the technique of radioactive iso-
tope dilution. This involved the injection of a
tracer of tritium labeled aldosterone, and the deter-
mination of the specific activity of its metabolite,
tetrahydroaldosterone in the subsequent twenty-four
hour urine. The difference between the specific
activity of the injected tracer and that of the uri-
nary metabolite is a measure of the endogenous contri-
bution. This permits estimation of the actual daily
secretion of aldosterone, thus obviating, he feels,
the inherent difficulty in studies which have been
based on measurement of the small fraction of aldo-
sterone excreted unchanged in the urine. By this
technique normal subjects produce one hundred-fifty

to three hundred-fifty micrograms of aldosterone per day, and this value may rise to one thousand micrograms per day with sodium deprivation. However, feeding of excess sodium can suppress the normal aldosterone secretion to as low as fifty micrograms per day.

In this study he classifies hypertensives in three groups--(1) primary hypertension, which represents patients with benign essential hypertension, (2) advanced hypertension, which includes those patients with either nitrogen retention or retinal hemorrhages, and (3) malignant hypertension, in which the patients had papilledema. He found that in patients with benign hypertension, the rate of aldosterone secretion was normal. In addition, these patients responded normally to sodium depreivation by increasing the aldosterone secretion. However, he also found that in patients with primary hypertension, as in normals, increased aldosterone secretion is not necessary for normal sodium conservation. In addition, both of these groups showed that the plasma potassium, or the state of potassium balance, is an important stimulus to aldosterone secretion. This might account for the increased excretion ascribed to sodium or volume changes in other studies.

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In contrast to patients with benign hypertension, those with malignant hypertension showed definite increases in the aldosterone secretion rate. These values ranged from six hundred to ten thousand micrograms per day. At autopsy, the adrenal glands of these patients were at or above the upper limits of normal in weight. Thus, these patients differ from patients with primary aldosteronism not only in their clinical features, but also in that in no instance has an adrenal adenoma been discovered. These patients further differed from those with benign hypertension in that variations in the sodium intake did not modify the aldosterone secretion rate. However, in these subjects as well as in normals, the aldosterone secretion rate was related to potassium balance.

In addition to these studies, Laragh measured the aldosterone secretion rates of patients with Conn's syndrome. In these cases, aldosterone values ranged from five hundred ten to sixteen hundred ninety micrograms per day. Thus, in both malignant hypertension and primary aldosteronism were excessively high values obtained. Laragh concludes that this hypersecretion of aldosterone might be a secondary or a concomitant phenomenon. However, the possibility that aldosterone might be of causal significance cannot be excluded.

The most damaging criticism of the work of Genest was written by Cope (54) in 1962. He accepts the fact as stated by Genest that subjects with essential or malignant hypertension have a tendency to excrete significantly more aldosterone than do normal subjects. However, he cautions against drawing the conclusion from these observations that there is necessarily any etiological relationship between the two.

He hypothesizes several possible explanations. There might be an alteration in renal physiology in patients with hypertension, whereby aldosterone is excreted more readily from the blood into the urine, for with Genest's techniques, the relationship between blood levels and urinary excretion is unknown. Or, he hypothesizes, there might be a change in the extent to which aldosterone is bound to a plasma protein, thus producing a similar situation. Although methods are not yet available to estimate the excessively small concentration of aldosterone found in plasma, and thus answer these questions, the newly available isotopicly labeled aldosterone has made possible the measurement of aldosterone secretion rates. Such a measurement was attempted by Laragh and the results reported earlier in this paper. Cope has repeated these studies. The isotope dilution effect makes it possible to estimate

the total quantity of aldosterone metabolites in the urine, even if many of them are unknown in nature.

This study, in contrast to the one of Laragh, took cognizance of the fact that patients with severe renal impairment have a delayed renal excretion of the tritium labeled aldosterone. This delayed renal excretion provides opportunities for proportionately larger elimination by non-renal routes (ie. feces), in which the radioactive metabolite cannot be detected. To correct for this fact, a mathematical formula was devised and used in his series.

Cope found that for normotensive patients, the rate of aldosterone secretion was sixty-two to two hundred seventy-five micrograms per day, with a mean secretion rate of one hundred forty-three micrograms per day. For hypertensive patients of mixed etiology, the rates varied from thirty-one to eight hundred thirty-two micrograms per day, with a mean value of two hundred twenty-seven micrograms per day. However, he feels that the wide scatter of values (eight cases above two hundred, five below sixty) make the mean value of little significance. Thus, although in some cases the aldosterone secretion rates are above normal, the series also contains those with rates below normal.

After subdividing his cases according to patho-
genesis, he finds that of seven cases with essential
hypertension, the rates varied from fifty-three to
one hundred sixty-three micrograms per day, with a
mean value of one hundred seven micrograms per day.
These findings are in agreement with Laragh, in that
the aldosterone secretion rates are not raised in
essential hypertension. Of nine patients with a
normal pyelogram, the mean secretion rate was two
hundred thirty-five micrograms per day, with a range
of forty-two to eight hundred thirty-two micrograms
per day. For nine patients with abnormal pyelograms,
the mean secretion rate was one hundred eighty-six
micrograms per day, with a range of thirty-one to
four hundred ninety-eight micrograms per day. In
view of this wide scatter, the difference is of no
significance. Of four patients with malignant
hypertension, two had high secretion rates, while
two were subnormal. Thus, very high secretion rates
are by no means invariable in malignant hypertension.

In addition, his study included control patients
who did not have hypertension, but were ill in vari-
ous ways. It is known that many patients with severe
hypertension are ill in various ways other than with
hypertension. Thus, it is desirable to compare

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hypertensive subjects with other ill persons who differ essentially only in that they are normotensive. None of these ill normotensive patients had fever or any malignant disease, and in none was there any detectable degree of sodium depletion due to disease of natriuretic drugs. In these control patients the range of secretion was found to be fifty-six to six hundred four micrograms per day, with a mean value of two hundred nine micrograms per day. It is seen, therefore, that there is a high degree of correlation between the secretion rates of aldosterone in these two groups.

From these extensive studies Cope concluded that a raised aldosterone secretion rate will be encountered in hypertensive subjects in about one-third of the cases. The range of values is much greater than that seen in normals. But, in comparison to other ill normotensive patients, no detectable differences can be seen--neither in range of values or mean secretion rate.

From these conclusions Cope makes three generalizations:

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

2. Patients with malignant hypertension may have greatly elevated aldosterone secretion rates, but do not always.

3. Hypertensive patients with an abnormal pyelogram are no more likely to show raised aldosterone secretion rates than those with a normal pyelogram.

Thus, these conclusions suggest that the factors in these studies are not the ones which determine whether aldosterone secretion is raised or not. It appears, therefore, that some determining factor or factors must be acting independently of the etiological classification of the hypertensive condition. He feels the nature of such factors can only be speculated upon. However, these studies seem to indicate that many types of metabolic derangement can increase aldosterone secretion, just as many types of stress can increase cortisol production. And, since the comparison of aldosterone secretion in normotensive metabolic disorders to hypertensives is so similar, it seems suggestive that at least some of the etiological factors acting in the normotensive group are also operating in the hypertensive group. Thus, some of the aldosterone overproduction seen in hypertensives

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might be incidental manifestations of associated
metabolic disturbances.

He states, "it seems most improbable that a
mild chronic overproduction of aldosterone is con-
cerned in the pathogenesis of essential hypertension
as suggested by Genest, for neither Laragh nor we have
found any evidence of raised aldosterone production
in essential hypertension. Moreover, Genest has
shown that angiotensin acts as a stimulant to aldo-
sterone production even in doses too small to pro-
duce 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."
(54) This is very doubtful, and can only be deter-
mined when plasma angiotensin levels can be easily
ascertained. There is no reason to think that angio-
tensin is the only stimulus to aldosterone production.

Genest has also suggested that the aldosterone
levels may be only intermittently raised in hyper-
tensive studies, thus explaining why spot tests
of secretion rate may not reveal this rise. Cope
feels there is little evidence to support this assump-
tion. He also presents additional evidence against
the role of aldosterone in the causation of hypertension.

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He relates that chlorothiazide and other like natriuretics often stimulate increases in aldosterone excretion as sodium is lost. However, in these cases, the blood pressure falls rather than rises.

There are other factors which seem to be unfavorable to the basic assumption of the importance of the role of aldosterone in the pathogenesis of hypertension. It is well known that the highest values of aldosterone secretion occur in conditions other than hypertension. Dr. Ralph Peterson has found values up to three thousand micrograms per day in the states of cirrhosis and heart failure. Luetscher (55) and his group confirm these findings of very high aldosterone levels in conditions of ascites, renal, and hepatic failure. Gross (56) points out that one of the most famous examples of increased aldosterone secretion is in a normal pregnancy. This is not due to an increased production of aldosterone, but a changed metabolism. And, in normal pregnancy, the blood pressure remains normal. However, in toxemia of pregnancy, when the blood pressure is elevated, the same values are seen as in a normal pregnancy.

The well-taught fact that aldosterone is independent of pituitary control cannot be stated too dogmatically. Several authors, including Venning (57) and her colleagues, have found significant increases in the excretion of aldosterone after administration of ACTH. Venning's work suggested that ACTH may act synergistically with a specific aldosterone stimulating factor to enhance the secretion of aldosterone. These observations suggest caution in interpreting aldosterone secretion rates in stressful situations. This effect is much less important than in the synthesis of glucocorticoids.

Dawson (58) and his group attack the basic problem from a different standpoint. He reasons that if aldosterone hypersecretion does influence malignant hypertension, it might be expected that an inhibition of aldosterone secretion should lower the blood pressure in these patients. Such an inhibition can be achieved by the administration of SU 4885, which blocks the 11-hydroxylation step in the biosynthesis. The use of this drug was first reported by Jenkins (59) and his group. In high dosages this causes a general suppression of steroid biosynthesis. In addition, the metabolic excretion product, tetrahydro-desoxycorticosterone, also having mineral corticoid properties, is similarly blocked.

In this study a thirty-seven year old male with malignant hypertension was treated with SU 4885 and prednisone. Prednisone was to act as a replacement for the glocucorticoids suppressed. In this patient, the institution of therapy was associated with an increased rate of urine sodium and chloride excretion, a fall in serum sodium, and a rise in serum potassium. During the treatment the aldosterone excretion fell to minimally detectable rates. An ACTH test performed during the treatment showed marked adrenal impairment with very low cortisol levels. However, there was no significant change in the patient's blood pressure nor any improvement in his symptoms. These studies suggest that aldosterone hypersecretion is not the cause of, or the primary event in the pathogenesis of malignant hypertension.

Hollander and Chabonian (60) explain the increased aldosterone found in malignant hypertension via another method. They have found that patients with primary aldosteronism and patients with malignant hypertension have significant increases in total exchangeable sodium, as determined by the $S^{35}O_4$ space. Normal controls and patients with essential hypertension did not have these findings, although the patient with benign

hypertension in congestive failure did. Also, these investigators noticed that the total exchangeable potassium space was decreased severely in patients with primary aldosteronism, but only slightly decreased in patients with malignant hypertension. They postulate that the increase in sodium and extracellular fluid volume may be manifestations of a state of precongestive heart failure, and this state may be responsible for the increased aldosterone excretion seen.

Not all investigators have been able to produce hypertension in experimental situations by the administration of aldosterone. It is interesting to note that in patients with Addison's disease, treatment with large doses of aldosterone normalizes the blood pressure, but does not cause hypertension. Gross (61) observed hypertension in rats sensitized by unilateral nephrectomy only when he injected five hundred micrograms of dl-aldosterone daily for four weeks. However, Gaunt noted no signs of hypertension in intact rats when administering the same dose over seven months. In man, Thorn (62) has found that a dose of six thousand micrograms of aldosterone daily provokes a rise in blood pressure of only ten to twenty-two millimeters of mercury.

Warter (63) and his co-workers feel that aldo-
sterone may provoke hypertension only in the presence
of renal lesions. They suggest, also, that there
may be great differences in sensitivity of the renal
tubules to aldosterone in hypertensive patients. They
cite the example of one hypertensive patient in which
the administration of one thousand micrograms of aldo-
sterone for three days had no noticeable effect on
either blood pressure or electrolyte balance.

Perhaps the most significant evidence against
the role of aldosterone in the pathogenesis of hyper-
tension can be found in the report of Bartter (64)
in 1962. In this report he described three cases of
a new clinical syndrome, hyperaldosteronism and hypo-
kalemic alkalosis without hypertension. These patients
were examined because of varied, nonspecific reasons,
and were found to have four important aspects in com-
mon. Each had a hypokalemic alkalosis with potas-
sium values of 1.2 -2.3 mEq/L. Each had an elevated
aldosterone level--up to seven hundred fifty micro-
grams per day, but none of these patients had elevated
blood pressures after many readings and an extensive
study. Because of the hyperaldosteronism, each patient
had a kidney biopsy which revealed a unique lesion of
the juxtaglomerular apparatus. This lesion consisted

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of hypertrophy of the juxtaglomerular apparatus which, from fixed preparations appeared to comprise four stages:

1. hypertrophy of the macula densa

2. thickening of the juxtaglomerular cells with hyperplasia of the juxtaglomerular apparatus

3. hyperchromatism of the vascular wall of part of the glomerulus

4. atrophy of the glomerulus

The development of hypokalemia was associated with urinary loss of potassium in excess of intake. This loss was decreased but not prevented by restriction of sodium intake. It was also prevented by the infusion of serum albumin (which decreased the urinary sodium to zero) and aldosterone antagonists. The blood pressure remained normal, even when the extravascular spaces were expanded with albumin, so the absence of hypertension cannot be attributed to hypovolemia.

The lesions of the juxtaglomerular apparatus suggest a hypersecretion of renin which should lead to hypertension. In addition, these patients on bioassay showed increased amounts of a pressor agent resembling angiotensin in the serum. There is little reason to believe that aldosteronism or the resulting potassium depletion produced the renal lesion, since

similar lesions have not been found in patients with primary or secondary aldosteronism, or in the kidneys of potassium-depleted rats. In fact, administration of aldosterone or DOCA to rats on average or high sodium diets causes a _decrease_ in the prominence of the juxtaglomerular apparatus, and a decrease in the renin content of the kidney. It is possible also that the aldosteronism and the juxtaglomerular apparatus lesion are both results of an unidentified common cause. However, it is more likely that the renal lesion should have led to the adrenal one.

Although available evidence does not make a definite explanation possible in this syndrome, Bartter has proposed a working hypothesis. In normal patients, he feels that angiotensin II, after its production via renin, has three functions: (1) a direct effect of blood pressure, (2) retention of sodium via the kidney, and (3) stimulation of aldosterone secretion. Normally, some function of blood pressure or pulse acts as a negative feedback to inhibit renin production. However, he suggests that in these patients, for reasons unknown, there is a primary impairment in the vascular response to angiotensin. This results in a decreased inhibition of renin production, therefore increased production of

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renin, angiotensin I, angiotensin II, and an increase
in aldosterone secretion. He hypothesizes that in
these cases, even though the angiotensin II is unable
to induce hypertension due to the primary defect, it
might still stimulate the adrenal cortex to the over-
production of aldosterone.

Cope (54) attempts to explain raised aldosterone
secretions encountered in some hypertensive subjects
by postulating that there must be some other aspect
of illness rather than the hypertension which is the
determining factor. He states that Laragh (53) and
his group had observed that there was no apparent
relation between the height of the blood pressure and
the increased secretion rates of aldosterone which he
found. However, Laragh did notice that in general,
the hypersecretion of aldosterone was more impressive
in the seriously ill patients. Other investigators
have noted similar phenomena. Venning (65) noted an
increased urinary excretion of aldosterone and tetra-
hydroaldosterone in hypertensives when their general
condition was deteriorating. Llaurado (60) has shown
an increased urinary excretion of aldosterone due to
a non-specific disturbance such as a surgical opera-
tion. Laragh (61) feels also that increased aldoster-
one secretion may be seen in essential hypertension

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patients as renal or cardiac complications develop.
Cope agrees with this general thesis, and feels when
increased aldosterone secretion occurs in essential
hypertension, it is probably due to a complicating
factor. He feels this is probably also true in
malignant hypertension.

SUMMARY

1. The scope of the problem of hypertension is discussed, and a classification stated.

2. The physiologic and chemical properties of aldosterone are presented.

3. Presumptive evidences for the relationship of aldosterone to hypertension are stated.

4. The body of the thesis is used to present affirmative and negative evidence in regard to a basic hypothesis--that aldosterone is an etiologic agent in hypertension. Included in this evidence are views of various investigators as to aldosterone urinary excretion studies, experimental production of hypertension, and a new syndrome of hyperaldosteronism and hypokalemic alkalosis without hypertension.

CONCLUSION

It is difficult to reconcile the differing
results obtained by separate investigators in study-
ing the same aspects of a given problem, unless one
considers differences in techniques and methods used.
The major differences in opinion as to the urinary
excretion of aldosterone as presented in this thesis
are represented by Genest and Garst on one hand, and
Laragh and Cope on the other. These must be inter-
preted in this manner. Whereas the former investi-
gators used a paper chromatographic method in their
findings of an increased urinary excretion of aldo-
sterone in hypertensives (and implied from this an
increased secretion), the latter men used a radio-
active isotopic dilution technique in their finding
of no increased secretion of aldosterone in hyper-
tension. Although it is not possible to be dogmatic
on this point, is appears most logical that the
radioactive isotopic dilution method would be the
more accurate.

It would be false for one to say that there is
not a large body of presumptive evidence which tends
to associate increased aldosterone levels with essen-
tial hypertension. However, this presumptive evidence

of association is much different from true concrete evidence of causation. The recently described syndrome of hyperaldosteronism without hypertension does much in negating such presumptive evidence.

For these reasons, this author must, in conclusion, agree with Cope, that hyperaldosteronism is not a causative factor in either essential, renal, or malignant hypertension, but its frequent presence in such cases is probably due to secondary complicating factors, the exact nature of which is not yet known.

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