PARKLAND MEMORIAL HOSPITAL

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# HYPERTENSION: THE ROLE OF RENIN, ANGIOTENSIN AND ALDOSTERONE

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## I. The Mechanism of the Control of Aldosterone Secretion

### A. The effects of changes in intravascular volume

Peters, long before aldosterone was identified, postulated that changes in effective circulating blood volume stimulated volume receptors which might control the production of a salt-retaining hormone.

1. Peters, J. P.: The problem of cardiac edema. Am. J. Med. 12:66, 1952.

After aldosterone was recognized as the important salt-retaining hormone, the prime role of a decrease in vascular volume as a stimulus for aldosterone secretion was shown by Bartter, et al.

2. Liddle, G. W., Duncan, L. E., Jr. and Bartter, F. C.: Dual mechanism regulating adrenocortical function in man. Am. J. Med. 21:380, 1956.

3. Bartter, F. C., Mills, I. H., Biglieri, E. G. and Delea, C. S.: Studies on the control and physiologic action of aldosterone. Rec. Prog. Horm. Res. 15:311, 1959.

### B. The site of the volume receptor

Receptors somewhere within the head or neck have been considered. One was suggested by Bartter:

4. Bartter, F. C., Mills, I. H., and Gann, D. S.: Increase in aldosterone secretion by carotid artery constriction in the dog and its prevention by thyrocarotid arterial junction denervation. J. Clin. Invest. 39:1330, 1960.
   The baroreceptor responsive to changes in vascular volume in the dog was said to be in the thyrocarotid artery.

5. Carpenter, C. C. J., Davis, J. O. and Ayers, C. R.: Concerning the role of arterial baroreceptors in the control of aldosterone secretion. J. Clin. Invest. 40:1160, 1961.
   Conclusive evidence that central arterial baroreceptors (including the thyrocarotid) are not involved in the physiologic control of aldosterone secretion.

Various other possible receptors have been proposed, including the carotid sinus, aortic arch (Barger) and right atrium (Farrell).

### C. The role of a hormonal stimulus (not ACTH) to aldosterone secretion and the absence of a direct neural control

While the search for the volume receptor continued, the mode of stimulation of aldosterone secretion was being studied:

6. Yankopoulos, N. A., Davis, J. O., Kliman, B. and Peterson, R. E.: Evidence that a humoral agent stimulates the adrenal cortex to secrete aldosterone in experimental secondary hyperaldosteronism. J. Clin. Invest. 38:1278, 1959.

7. Carpenter, C. C. J., Davis, J. O., Holman, J. E., Ayers, C. R. and Bahn, R. C. Studies on the response of the transplanted kidney and the transplanted adrenal gland to thoracic inferior vena caval constriction. J. Clin. Invest. 40:196, 1961.

8. Denton, D. A., Goding, J. R. and Wright, R. D.: Control of adrenal secretion of electrolyte-active steroids. Brit. Med. J. 2:447 and 522, 1959.

The possibility of an intracranial source (the pineal, no less) of this stimulus was proposed and repeatedly emphasized by Farrell. The hormone was named Adrenoglomerulotropin, but its nature remains unknown and its physiologic importance remains questionable.

9. Farrell, G.: Adrenoglomerulotropin. Circulation 21:1009, 1960.

10. Davis, J. O., Anderson, E., Carpenter, C. C. J., Ayers, C. R., Haymaker, W. and Spence, W. T.: Aldosterone and corticosterone secretion following mid-brain transection. Am. J. Physiol. 200:437, 1961.

D. The role of the J-G cells

Independent of the search for the stimulus to aldosterone secretion, the relation of the J-G cells to electrolyte, hormonal and blood pressure alterations was being studied. The importance of the J-G cells was first suggested in 1939 by Goormaghtigh who thought they were secretory in nature and contained renin.

11. Goormaghtigh, N.: Existence of an endocrine gland in the media of the renal arterioles. Proc. Soc. Exp. Biol. Med. 42:688, 1939.

His suggestion has been amply confirmed:

12. Hartroft, W. S. and Hartroft, P. M.: New approaches in the study of cardiovascular disease: Aldosterone, renin, hypertension and juxtaglomerular cells. Fed. Proc. 20: 845, 1961.

The evidence that renin comes from the J-G cells:

13. Tobian, L., Janecek, J. and Tomboulian, A.: Correlation between granulation of juxtaglomerular cells and extractable renin in rats with experimental hypertension. Proc. Soc. Exp. Biol. Med. 100:94, 1959.
These studies correlated J-G granularity with renin content.

14. Cook, W. F. and Pickering, G. W.: Location of renin within kidney. J. Physiol. 143:78, 1958.
Microdissection studies showing that renin is found only in the area occupied by the J-G cells. (Similar studies were done by Bing. Acta. path. et microbiol. Scandinav. 44:138, 1958.)

15. Edelman, R. and Hartroft, P. M.: Localization of renin in juxtaglomerular cells of rabbit and dog through the use of flourescent-antibody technique. Circulation Res. 9:1069, 1961.

E. The mechanism by which renin-angiotensin control aldosterone secretion

Even before aldosterone was known to come from the zona glomerulosa, renin was found to cause a selective enlargement of this zone.

16. Deane, H. W. and Masson, G. M. C.: Adrenal cortical changes in rats with various types of experimental hypertension. J. Clin. Endocrinol. 11:193, 1951.

Renin has long been known to be the enzyme responsible for the release of angiotensin from a renin-substrate in the circulation (Figure 1). This information as well as most of our knowledge about the chemistry and pharmacology of renin-angiotensin has come from Page, et al. in Cleveland and Houssay's group in Argentina.

17. Page, I. H. and Bumpus, F. M.: Angiotensin. Phys. Rev. 41:331, 1961.

18. Braun-Mendez, E.: Pharmacology of renin and hypertension. Pharmacol. Rev. 8:25, 1956.

Angiotensin was then shown to have a striking effect on aldosterone secretion, first by Genest's group, then by Laragh, Davis, Bartter, etc.

19. Biron, P., Koiw, E., Nowaczynski, W., Brouillet, J. and Genest, J.: The effects of intravenous infusions of valine-5 angiotensin II and other pressor agents on urinary electrolytes and corticosteroids, including aldosterone. J. Clin. Invest. 40:338, 1960.

The effect of renin on aldosterone secretion is almost certainly exerted by its enzymatic action on angiotensin, since renin alone did not stimulate aldosterone biosynthesis, in vitro.

20. Kaplan, N. M. and Bartter, F. C.: The effect of ACTH, renin, angiotensin II and various precursors on biosynthesis of aldosterone by adrenal slices. J. Clin. Invest. 41:715, 1962.

With the knowledge of the effect of renin on angiotensin and of angiotensin on aldosterone, a unifying concept has been formulated (Figure 2). But years ago, such a mechanism was suggested.

21. Kohlstaedt, K. G. and Page, I. H.: The liberation of renin by perfusion of kidneys following reduction of pulse pressure. J. Exp. Med. 72:201, 1940.
Reduction of pulse pressure in the dog's kidney led to release of a substance into the renal vein which reacted with purified renin substrate to produce a substance thought to be angiotensin.

Gross first suggested that renin via angiotensin increases aldosterone secretion with a negative feedback control.

22. Gross, F.: Renin and hypertensin, physiologische oder pathologische Wirkstoffe Klin. wochschr. 36:693, 1958.

Tobian showed that the release of renin was controlled by the degree of stretch of the renal afferent arterioles.

23. Tobian, L., Tomboulian, A. and Janecek, J.: The effect of high perfusion pressures on the granulation of juxtaglomerular cells in an isolated kidney. J. Clin. Invest. 38:605, 1959.
When the stretch within the renal arterial bed is increased, there is a reduction in J-G granularity, signifying a slowing of renin secretion; when stretch is decreased, granularity increases, indicating hypersecretion.

Tobian's work and an extensive review of the entire subject are given in Tobian, L.: Interrelationship of electrolytes, juxtaglomerular cells and hypertension. Phys. Rev. 40: 280, 1960. Less extensive and more available is the paper by Tobian in Ann. Int. Med. 52: 595, 1960.

The extensive studies of Davis, et al. showed in a direct way that the kidney was the receptor site for the mechanism controlling aldosterone secretion and that renin was almost certainly the "aldosterone stimulating hormone." These studies, published in 1960, '61 and early '62 in the J.C.I., are summarized in:

24. Davis, J. O.: The control of aldosterone secretion. The Physiologist 5: 65, 1962.
Others have confirmed these results: Mulrow and Ganong, J.C.I. 41:505, 1962; Bartter, et al. Metabolism 10:1006, 1961.

The fascinating clinical observation of J-G cell hyperplasia as a cause of hyperaldosteronism was first noted by Bartter, et al.

25. Bartter, F. C., Casper, A. G. T., Delea, C. S. and Slater, J. D. H.: On the role of the kidney in control of adrenal steroid production. Metabolism 10:1006, 1961.

F. Possible direct role of renin-angiotensin

The effects of aldosterone on sodium reabsorption are not immediate. However changes in intrinsic renal hemodynamics are associated with rapid changes in sodium reabsorption. These acute changes may be mediated by a direct effect of renin-angiotensin upon the renal tubule. The J-G cells are contiguous with the macula densa cells of the distal convoluted tubule. A recent abstract presented by Laragh, et al. revealed evidence for such a direct effect of angiotensin upon blocking tubular reabosrption of sodium.

26. Laragh, J. H., Cannon, P. J., Ames, R. P., Sicinski, A. M., Bentzel, C. J. and Meltzer, J. I.: Angiotensin II and renal sodium transport: Natriuresis and diuresis in patients with cirrhosis and ascites. J. Clin. Invest. 41:1375, 1962 (abstract).

An attractive hypothesis, but still to be proven. We have observed a fall in aldosterone secretion with angiotensin infusions to patients with hyperaldosteronism, similar to the fall with other vasopressor agents reported by Laragh. Thus the "direct" effect of angiotensin may be secondary to a paradoxical depression of aldosterone secretion when hyperaldosteronism is present. Moreover, angiotensin causes a diuresis with increased sodium excretion in patients with severe hypertension who may have had hyperaldosteronism.

27. Peart, W. S. and Brown, J. J.: Effect of angiotensin on urine flow and electrolyte excretion in hypertensive patients. Lancet I:28, 1961.

28. del Greco, F.: Effects of valine-5 angiotensin II on excretion of water and salt in primary and secondary hypertension. Proc. Soc. Exp. Biol. Med. 107:973, 1961.

Peart attributes this to a lowered sensitivity to the vaso constrictor action of angiotensin in the hypertensive, so that the fall in G.F.R. and R.P.F. seen in normals does not occur.

G. Other stimuli

ACTH will increase aldosterone secretion, but, under physiologic conditions, ACTH is supportive rather than initiative in the regulation of aldosterone secretion. Changes in serum sodium and potassium concentration are followed by changes in aldosterone secretion. The sodium changes are almost certainly exerted through variations in plasma volume, via the renin-angiotensin mechanism. Potassium changes, on the other hand, act directly on the adrenal.

29. Laragh, J. H. and Stoerk, H. C.: A study of the mechanism of secretion of the sodium-retaining hormone (aldosterone). J. Clin. Invest. 36:383, 1957.

30. Blair-West, J. R., Coghlan, J. P., Denton, D. A., Goding, J. R., Munro, J. A., Peterson, R. E. and Wintour, M.: Humoral stimulation of adrenal cortical secretion. J. Clin. Invest. 41:1606, 1962.

Other factors may play a role, but too little is known about them at present to be sure.

31. Orti, E., Ralli, E.P., Laken, B. and Dumm, M. E.: Presence of an aldosterone stimulating substance in the urine of rats deprived of salt. Am. J. Physiol. 191: 323, 1957.

32. Peterson, R. E. and Muller, J.: Aldosterone-stimulating material in urine. Endocrinology 71:174, 1962.

## The Relation of Renin, Angiotensin and Aldosterone to Hypertension

### A. Experimental hypertension

As early as 1898, kidney extracts were shown to induce hypertension and the material responsible was called renin. After the studies of Goldblatt showed that renal ischemia induced hypertension, Houssay's group (see reference 18) and the Cleveland group showed that renin was released under these circumstances.

33. Goldblatt, H.: The renal origin of hypertension. Springfield, Ill., Thomas, 1948.

34. Corcoran, A. C. and Page, I. H.: Renal blood flow in experimental hypertension due to constriction of the renal artery. Am. J. Phys. 133:249P, 1941.

Along with the increased renin content of the kidney, aldosterone secretion is elevated in dogs with malignant renal hypertension.

35. Carpenter, C. C. J., Davis, J. O. and Ayers, C. R.: Relation of renin, angiotensin II, and experimental renal hypertension to aldosterone secretion. J. Clin. Invest. 40:2026, 1961.

Since tachyphylaxis to renin develops, the hypertensive effect presumably results from the angiotensin released. Angiotensin is the most potent vasopressor known. In addition, the increased amount of aldosterone secreted may also have a hypertensive effect which is independent of excess salt intake.

36. Kumar, D., Hall, A. E. D., Nakashima, R. and Gornall, A. G.: Hypertension as a cumulative effect of aldosterone administration. Canad. J. Biochem. 35:113, 1957.

Single injections of renin, in the presence of aldosterone and salt, will produce a syndrome in rats similar to malignant hypertension.

37. Masson, G. M. C., Mikasa, A. and Yasuda, H.: Experimental vascular disease elicited by aldosterone and renin. Endocrinology 71:505, 1962.

This may explain why renin content may not remain elevated in experimental renal hypertension, but the hypertensive process persists (Haynes and Dexter, Am. J. Physiol. 150:190, 1947).

### B. Renin and angiotensin levels in human hypertension

The entire picture is clouded by the inability to measure either substance accurately. Thus, sharply conflicting reports have appeared.

Angiotensin:

38. Kahn, J. R., Skeggs, L. T., Jr., Shumway, N. P. and Wisenbaugh, P. E.: The assay of hypertensin from the arterial blood of normotensive and hypertensive human beings. J. Exp. Med. 94:523, 1952.

Increased angiotensin levels were found in humans with malignant hypertension and dogs with experimental renal hypertension. The levels in essential hypertension overlap those in normotensive patients.

39. Genest, J., Biron, P., Chretien, M., Boucher, R. and Koiw, E.: Blood angiotensin levels in normal subjects and hypertensive patients. J. Clin. Invest. 41:1360, 1962 (abstract).

Some patients with all types of hypertension had high levels; most were normal.

40. Morris, R. E., Jr., Ransom, P. A. and Howard, J. E.: Studies on the relationship of angiotensin to hypertension of renal origin. J. Clin. Invest. 41:1386, 1962 (abstract).
Angiotensin was detected in the blood (peripheral arterial and renal venous) of all 13 patients with renal hypertension, but not in patients with essential or malignant hypertension.

Renin:

41. Helmer, O. M.: Presence of renin in plasma of patients with arterial hypertension. Circulation 25:169, 1962.
The highest renin levels were found in accelerated hypertension and renal vascular occlusive disease. Variable results were found in essential hypertension.

42. Peart, W. S.: Hypertension and the kidney. Brit. Med. J. 2:1383 and 1421, 1959.
Renin couldn't be detected in human malignant or experimental renal hypertension. He argues that renin and angiotensin are not responsible for the hypertension seen with renal ischemia.

Another less direct, but perhaps more exact approach has been made by Mendlowitz, et al. They find that the turnover of labelled angiotensin is slower in patients with essential hypertension and that the total body exchangeable pool is much increased in malignant hypertension.

43. Mendlowitz, M., Wolf, R. L., Gitlow, S. E. and Naftchi, N. E.: Angiotensin II studies in hypertension. Circulation 25:231, 1962.

This may explain the increased sensitivity to angiotensin noted in patients with essential hypertension.

44. Doyle, A. E. and Black, H.: Reactivity to pressor agents in hypertension. Circulation 12:974, 1955.

Wood has found that the hypertensive patient is not able to neutralize the vasoconstrictor activity of angiotensin with his peripheral blood in vitro as rapidly as the normotensive person.

45. Wood, J. E.: Genetic control of neutralization of angiotensin and its relationship to essential hypertension. Circulation 25:225, 1962.

We have attempted to demonstrate an increased level of angiotensin in patients with malignant hypertension in yet another, indirect way.

C. Aldosterone secretion in human hypertension

The levels of aldosterone excretion and secretion have been found to be elevated in malignant hypertension, but are probably normal in uncomplicated essential hypertension. The hyperaldosteronism with malignant hypertension is thought to be secondary to the renal ischemia resulting from the vascular damage consistently found in this syndrome.

46. Laragh, J. H., Ulick, S., Januszewicz, V., Deming, Q. B., Kelly, W. G. and Lieberman, S.: Aldosterone secretion and primary and malignant hypertension. J. Clin. Invest. 39:1091, 1960.

47. Genest, J., Koiw, E., Nowaczynski, W. and Sandor, T.: Study of a large steroid spectrum in normal subjects and hypertensive patients. Acta. endocrinologica 35: 413, 1960.

48. Venning, E. H., Dyrenfurth, I., Dossetor, J. B. and Beck, J. C.: Essential hypertension and aldosterone. Circulation 23:168, 1961.

The biochemical effects (hypokalemic alkalosis) of this hyperaldosteronism were noted even before the aldosterone measurements were made.

49. de Wesselow, O. L. V. S. and Thomson, W. A. R.: A study of some serum electrolytes in hypertension. Quart. J. Med. 8:361, 1939.

50. Wrong, O.: Incidence of hypokalemia in severe hypertension. Brit. Med. J. 2:419, 1961.

With hypertension secondary to renal ischemia, hyperaldosteronism may appear even with only "benign" hypertension.

51. Gowenlock, A. H. and Wrong, O.: Hyperaldosteronism secondary to renal ischemia. Quart. J. Med. 31:323, 1962.

The authors note that the finding of hypokalemia in a hypertensive patient will more often be secondary to renal ischemia than primary aldosteronism.

But since hypokalemia is found in about 50% of all patients with malignant hypertension (due to neither renal ischemia nor primary aldosteronism), this finding should not be used as evidence for anything more than hyperaldosteronism and other procedures will be necessary for the differential diagnosis.

The problem is even more difficult since "congenital" primary aldosteronism with bilateral adrenal hyperplasia is usually accompanied by malignant hypertension.

52. Conn, J. W.: Aldosteronism and hypertension. Arch. Int. Med. 107:813, 1961.

The relationships of renin, angiotensin and aldosterone to essential hypertension are much less apparent. The levels of all 3 are usually normal and the manifestations of their presence in excess are usually absent.

53. Hollander, W., Chobanian, A. V. and Burrows, B. A.: Body fluid and electrolyte composition in arterial hypertension. I. Studies in essential, renal and malignant hypertension. J. Clin. Invest. 40:408, 1961.

ECF volume, total body exchangeable sodium and potassium are normal in essential hypertension. In malignant hypertension, as in primary aldosteronism, ECF volume and sodium content are high, potassium content low.

There is the possibility that increases in renin, angiotensin and aldosterone may occur in essential hypertension, play a role in its pathogenesis but yet be undetectable by present techniques. If so, this might explain the increase in the content of sodium within the arteriole wall which Tobian, et al. have observed and feel to be an important cause for increased peripheral resistance.

54. Tobian, L., Jr. and Binion, J. T.: Tissue cations and water in arterial hypertension. Circulation 5:754, 1952.

55. Tobian, L., Janecek, J., Tomboulian, A. and Ferreira, D.: Sodium and potassium in the walls of arterioles in experimental renal hypertension. J. Clin. Invest. 40: 1922, 1961.

## CASE REPORTS

1. Primary aldosteronism with malignant hypertension

Forty-one year old white male with hypertension for 3 years with recent levels around 200/130 and papilledema. After taking Diuril, he had become paralyzed and was found to be hypokalemic. Serum sodium - 142-150, serum potassium - 2.9 - 3.4, urine potassium - 90 meq/day. Aldosterone excretion - 33 µg/day, secretion rate - 428 µg/day.

A solitary 5 Gm. adenoma was removed in June, 1962. Since then the blood pressure and aldosterone excretion have fallen, the serum potassium has returned to normal and the papilledema has receded.

2. Malignant hypertension with secondary hyperaldosteronism

Forty year old white male with hypertension for seven years, with frequent headaches, obligatory nocturia and occasional epistaxis, despite anti-hypertensive therapy. B.P. - 230/170 with papilledema. Serum sodium - 125-140, serum potassium - 2.0 - 3.4, urine potassium - 82 meq/day, aldosterone excretion - 80 µg/day, secretion rate - 1,040 µg/day.

The hypertensive symptoms persisted and progressive renal insufficiency supervened. At post-mortem, bilateral adrenal cortical hyperplasia was noted.

3. Unilateral renal disease with possible secondary hyperaldosteronism

Seventeen year old white female (referred to Dr. Norman Carter by Dr. Rush Pierce) with hypertension (180/120) for 18 months and Grade II fundi. I.V.P. revealed a small left kidney which was slow in excreting dye. Serum sodium - 140, serum potassium - 3.1. Aldosterone measurements are being performed.

## THE PROBLEM

1. An increased secretion of aldosterone is found in these varieties of hypertension:

   a) Primary aldosteronism with adrenal adenoma
   b) Congenital aldosteronism with adrenal hyperplasia
   c) Malignant hypertension
   d) Unilateral renal disease
   e) ? Essential hypertension - probably not early, but perhaps with complications

2. The proper differential diagnosis of these causes of hyperaldosteronism is vital.

   a) Curable hypertension may become incurable if allowed to persist
   b) Improper diagnostic evaluation has lead to improper surgery with significant mortality
   c) Bilateral adrenalectomy may be needed for the cure of primary aldosteronism

3. The differentiation of these various diseases may be impossible by usual clinical or laboratory means.

## THE SOLUTION

1. Clinical guides: These are based on the prolonged presence of hyperaldosteronism causing potassium wastage but usually only mild hypertension in primary aldosteronism but the rapid progression of hypertension with secondary aldosteronism. The differences may be in part due to the different levels of renin-angiotensin in these two conditions.

| | | 1° aldo | Renal Ischemia | Malignant H.T. |
|---|---|---|---|---|
| 1. | Nature of H.T. | usually benign | frequently accelerated | accelerated |
| 2. | S/S of aldosteronism | prominent | variable | infrequent |
| 3. | Serum sodium | usually high | usually low-normal | usually low-normal |
| 4. | Serum potassium | always low | variable | 50% low |

2. If hypokalemia is noted in any hypertensive who has not taken diuretics in the recent past, urinary potassium excretion while on a normal sodium intake should be measured. If elevated (above 20 meq per day), aldosterone excretion or secretion should be measured.

3. The possibility of unilateral renal ischemia should be especially considered in:

a) all hypertensives under 35 in whom no cause for the hypertension can be found.
b) where malignant hypertension develops in a patient over 55.
c) in non-familial hypertension of recent origin with rapid progression of disease.
d) where an episode of pain in the renal area is followed by increasing hypertension.
e) when a bruit is heard over the renal areas.
f) when the I.V.P. reveals a disparity in size or function of the two kidneys.
g) if the hypertension secondary to renal ischemia is due to the release of a circulating pressor substance (? renin) which also significantly stimulates aldosterone secretion, the easiest way to prove that renal ischemia is the cause of hypertension may be to find hyperaldosteronism. The problem of differentiating unilateral renal ischemia from bilateral ischemia (e.g. malignant hypertension) would remain, however.

4. Since endogenous angiotensin levels are elevated in secondary aldosteronism, but presumably depressed in primary aldosteronism, there may be a difference in the responsiveness to exogenous angiotensin in these states. Our initial studies are in keeping with this view. This simple procedure may prove to be a valuable method for differentiating these diseases.

FIGURE 1: THE FORMATION OF ANGIOTENSIN II

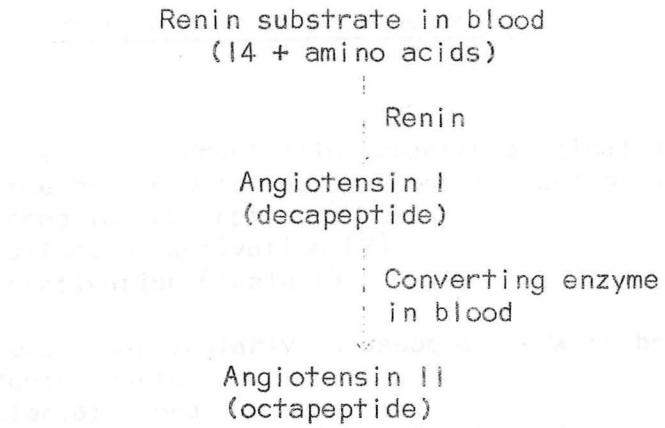


FIGURE 2: THE CONTROL OF ALDOSTERONE SECRETION