MEDICAL GRAND ROUNDS

Parkland Memorial Hospital

November 11, 1965

HYPERTENSION: ESSENTIAL, RENAL AND ALDOSTERONE

[redacted]

This 54-year old [redacted] woman was found to have hypertension in 1962 but was asymptomatic other than for occasional headaches and nocturia until just before her first [redacted] admission. After a spontaneous nose-bleed, she developed weakness, dizziness, blurred vision and then nausea.

The blood pressure was 210/120. The fundi revealed A/V nicking, hemorrhages and exudates, but no papilledema. The heart was enlarged and had a Grade III holosystolic apical murmur. A bruit was heard at the left CVA area and over both femoral arteries. The posterior tibial and dorsalis pedis pulses were symmetrically weak.

The laboratory workup showed a normal CBC, trace albuminuria, BUN of 14, creatinine of 1.9, serum sodium of 123, potassium 2.9 mEq/L. A 24-hour urine of questionable completeness had 12 mEq of potassium and 28 mEq of sodium. The aldosterone content was only 3.9 µg per day (normal = 5-20 µg). The IVP showed poor visualization of the right kidney and none of the left kidney. Retrogrades revealed a small left kidney. Aortagraphy showed occlusior of the left renal artery, an aneurysm of the lower abdominal aorta, occlusions of the left iliac and both superficial femoral arteries. No pressor substance was found in blood from either renal vein, but the catheters may not have been properly placed. The angiotensin infusion test revealed resistance, with a 20 mm Hg rise in the diastolic BP occurring with 12 mµg/Kg/min.

A left nephrectomy and aortic-femoral bypass were performed with return of good pulsations to the legs but only temporary lowering of the blood pressure to 180/90. Seven months later an aneurysm developed at the site of anastomosis to the right femoral artery. Despite insertion of a new graft, the right leg became gangrenous and was amputated. The patient died suddenly on the 13th post-operative day.

At autopsy, the left ventricle was massively hypertrophied and severe generalized atherosclerosis was noted. There was extensive coronary arteriosclerosis with old and recent thromboses. The vessels in the right kidney showed only slight nephrosclerosis. A 14 mm cortical adenoma was found in the right adrenal.

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I. The Pathophysiology of Essential Hypertension.

A. Increased sodium excretion in hypertensives after infusion of saline, glucose or mannitol or ingestion of water or beer.

(1) Thompson, J. E., et al. The effect of acute salt loads on the urinary sodium output of normotensive and hypertensive patients before and after surgery. Circulation 10:912, 1954.

1. This effect may be related to an excessive increase in cardiac output, which in turn may be secondary to a deficient ability of capacity vessels to dilate in response to sudden increments in plasma volume.

(2) Ulrych, M., et al. Cardiac and renal hyperresponsiveness to acute plasma volume expansion in hypertension. Am. Heart J. 68:193, August, 1964.

2. Moreover, emotional stress or infusion of pressor amines or angiotensin also provokes exaggerated natruresis. Under these circumstances, a greater degree of vasoconstriction could produce a relatively expanded plasma volume relative to the size of the vascular space.

3. Not all procedures which expand plasma volume will produce natruresis (e.g. dextran or plasma).

(3) Eisinger, R. P. Failure of expanded plasma volume to induce exaggerated natruresis in hypertensive man. Am. J. Med. Sci. 249:216, February, 1965.

4. The exaggerated sodium diuresis will occur in normal people made hypertensive, as well as in other forms of hypertensive disease, so it may be a direct consequence of the hypertension per se.

(4) Vaamonde, C. A., et al. Augmented natruretic response to acute sodium infusion after blood pressure elevation with metaraminol in normotensive subjects. J. Clin. Invest. 40:496, 1964.

5. Possible mechanisms for this exaggerated response to fluid loading have been suggested. It does not appear to involve changes in GFR or aldosterone excretion, but may involve changes in renal perfusion pressure.

(5) Tobian, L., et al. The effect of renal perfusion pressure on the net transport of sodium out of distal tubular urine as studies with the stopflow technique. J. Clin. Invest. 40:118, January, 1964.

B. The possible role of this response in the pathogenesis of hypertension.

1. The cardiac output is normal in the great majority of patients with established hypertension, though a few cases have been described in which a relatively mild hypertension

is attributable primarily to raised cardiac output.

(6) Werko, L. and H. Lagerlof. Studies on the circulation in man IV. Cardiac output and blood pressure in the right auricle, right ventricle and pulmonary artery in patients with hypertensive cardiovascular disease. Acta Medica Scandinavica 133:427, 1949.

2. Experimental renal hypertension has been shown to involve a transient increase in cardiac output.

(7) Ledingham, J. M. and R. D. Cohen. The role of the heart in the pathogenesis of renal hypertension. Lancet 2:979, November 9, 1963.

3. The mechanism for the increased cardiac output may be a transient expansion of ECF and plasma volume, although other factors, including changes in capacity-vessel tone, may play a part.

(8) Ledingham, J. M. and R. D. Cohen. Changes in the extracellular fluid volume and cardiac output during the development of experimental renal hypertension. Canad. Med. Assoc. J. 90:292, 1964

(9) Floyer, M. A. and P. C. Richardson. Mechanism of arterial hypertension. Lancet 1:253, February 4, 1961.

4. The manner in which these early changes may eventuate in the increased peripheral resistance and the normal cardiac output typical of established hypertension has been postulated.

(10) Borst, J.G.G. and A. Borst - deGeus. Hypertension explained by Starling's theory of circulatory homeostasis. Lancet 1:677, March 30, 1963.

The postulated sequence:

DEFICIENT SODIUM EXCRETION ⟶
INCREASED ECF AND BLOOD VOLUME ⟶
INCREASED CENTRAL VENOUS PRESSURE ⟶
INCREASED CARDIAC OUTPUT ⟶
RISE IN ARTERIAL PRESSURE ⟶

(Here, the autoregulation of tissue circulation comes into play, maintaining blood flow in relation to metabolic demands. The mechanism may be purely myogenic in response to the raised intravascular pressure, and presumably then raises arterial pressure further and maintains the increased peripheral resistance. In turn the vascular bed is now "overloaded" setting off the following sequence:

INCREASED RENAL EXCRETION OF ECF ⟶
RETURN OF ECF AND PLASMA VOLUME TO NORMAL ⟶
FALL OF VENOUS PRESSURE TO NORMAL ⟶
RETURN OF CARDIAC OUTPUT TO NORMAL ⟶

5. This scheme can explain renal vascular hypertension and the hypertension of aldosterone or DOC excess, but its role in essential hypertension remains unknown.

(11) Peters, G. Letter to the editor. Lancet 1:1270, June 8, 1963.

C. Other evidence suggests a primary role of sodium excess.

1. Dietary salt intake may be related.

(12) Dahl, L. K. Possible role of salt intake in the development of essential hypertension. Essential Hypertension: An International Symposium, ed. by F. C. Reubi. Springer-Verlag, Berlin, p. 53, 1960.

2. The blood vessel walls contain excess sodium.

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

3. Salt restriction on diuresis will lower blood pressure.

(14) Grollman, A. Therapeutic aspects of salt restriction. Essential Hypertension: An International Symposium, ed. by F. C. Reubi. Springer-Verlag, Berlin, p. 168, 1960.

D. The role of the renin-angiotensin system in "essential" hypertension.

1. As will be described below, it is unlikely that this system plays a role in benign, essential hypertension.

2. However, as the hypertensive process becomes "accelerated" or malignant, it does come into play, perhaps to aggravate the hypertensive process and, frequently, to produce secondary aldosteronism.

(15) Laragh, J. H., et al. Aldosterone secretion and primary and malignant hypertension. J. Clin. Invest. 39:1091, 1960.

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

(17) Kaplan, N. M. and J. G. Silah. The angiotensin infusion test: A new approach to the differential diagnosis of renovascular hypertension. New Eng. J. Med. 271:536, 1964.

II. The Mechanism of Hypertension in Renal Parenchymal Disease.

A. Three mechanisms have been supported:

1. The elaboration of a pressor substance (pressor hypertension).

2. The failure to produce some humoral substance (renoprival hypertension).

3. The abnormal retention of salt and water.

(18) Peart, W. S. Hypertension and the kidney. Brit. Med. J. 2:1421, 1959.

B. The role of a pressor mechanism.

1. Although almost certainly involved with the hypertension of renal ischemia, the renin-angiotensin system is almost certainly not involved with the hypertension of chronic parenchymal disease.

(19) Goorno, W. E. and N. M. Kaplan. Renal pressor material in various hypertensive diseases. Ann. Int. Med. In press, November, 1965.

C. Recent work has substantiated the concept proposed by Grollman that the kidney is necessary to maintain normal pressure and that hypertension results from destruction of renal tissue.

(20) Grollman, A. A unitary concept of experimental and clinical hypertensive cardiovascular disease. Perspect. in Biol. & Med. 2:208, 1959.
(21) Hickler, R. B., et al. Vasodepressor lipid from the renal medulla. Canad. Med. Assoc. J. 90:280, January 25, 1964.
(22) Muirhead, E. E., et al. Renomedullary vasodepressive and antihypertensive function. Arch. Path. 80:43, July, 1965.

D. Abnormal retention of salt and water is probably the mechanism for hypertension in acute glomerulonephritis.

(23) DeFazio, V., et al. Circulatory changes in acute glomerulonephritis. Circulation 20:190, 1959.

III. The Relationship of Primary Aldosteronism and Essential Hypertension.

A. The direct evidence: Using the criteria of increased aldosterone excretion and suppressed plasma renin activity, Conn has found "primary aldosteronism" in five of thirty-three patients with "essential hypertension" who had normal serum potassium levels.

(24) Conn, J. W., E. C. Cohen and D. R. Rovner. Suppression of plasma renin activity in primary aldosteronism. J.A.M.A. 190:213, October 19, 1964.
(25) Conn, J. W., E. C. Cohen and D. R. Rovner. Normokalemic primary aldosteronism. J.A.M.A. 193:200, July 19, 1965.
(26) Conn, J. W., D. R. Rovner and E. C. Cohen. Normokalemic primary aldosteronism. A frequent cause of curable "essential" hypertension. J. Lab. & Clin. Med. November, 1965. Abstract.

B. The indirect evidence: Conn believes "at least 20% of patients with "essential" hypertension harbor a small aldosterone-secreting adrenal cortical tumor as its cause".

1. Adrenal cortical adenomas, identical to those seen with primary aldosteronism, found in 20% of hypertensives.

(27) Shamma, A. H., J. W. Goddard and S. C. Sommers. Study of adrenal status in hypertension. J. Chronic Dis. 8:587, 1958.

2. Increased aldosterone excretion in 25% of patients with "essential" hypertension.

(28) Garst, J. B., et al. Aldosterone excretion in essential hypertension. J. Clin. Endocrinol. 20:1351, 1960.

3. Subnormal plasma renin activity in 21% of forty-eight hypertensives.

(29) Brown, J. J., et al. Variations in plasma renin concentration in several physiological and pathological states. Canad. Med. Assoc. J. 90:201, 1964.

4. About 25% of hypertensives treated with thiazides develop hypokalemia.

Reference 25.

C. Further inspection of the indirect evidence.

1. Adrenal adenomas in normotensive and hypertensive patients.

a. Incidence;

TABLE I Adrenal Gland Morphology

Author	Date	Normotensive		Hypertensive	
		No.	Percent Adenomas	No.	Percent Adenomas
Dempsey	1942	50	8	19	16
Dawson	1956	45	9	45	16
Commons	1948	1155	2.5	198	5
Russi	1945	7746	0.4	1254	7.4
Shamma	1958	220	1.8	220	20

b. Functional significance:

(30) Kaplan, N. M. The incidence of primary aldosteronism in patients with "essential" hypertension. J. Lab. & Clin. Med. November, 1965. Abstract.

TABLE II Steroid Content of Adrenal Tissue

	NO.	ALDOSTERONE	CORTICOSTERONE	CORTISOL
		micrograms / gram tissue		
Aldosterone adenomas	6	10.8	21.3	11.1
Hypertensive adenomas	8	0.4	3.9	8.3
Normotensive tissue	5	0.3	2.8	10.1

2. Aldosterone excretion in essential hypertension

a. Reported results:

TABLE III Aldosterone Levels in Hypertension

Author	Date	Technique	Normal µg/day	Essential Hypertension		
				No.	Mean µg/day	Percent Increased
Genest	1956-1960	Physico-chemical	4.3	46	10.6	41
Garst	1960	Physico-chemical	9.1	38	13.3	25
Murakami	1962	Physico-chemical	6.5	32	8.0	(22)
Venning	1961	Physico-chemical	5.1	22	8.8	(12)
Gerasimova	1964	Physico-chemical	5.3	20	5.8	0
Yamauchi	1961	DIDA	3-15	6	6.5	0
Laragh	1960	ASR by DIDA	150-330	8	264	0
Cope	1962	ASR by DIDA	143	7	107	0
Kaplan	1965	DIDA	5-20	43	13.9	0

b. Relationship to stage of hypertension:

Reference 15.

(31) Gerasimova, E. N. Aldosterone (in) hypertensive disease and symptomatic renal hypertension in Aldosterone. E. E. Baulieu and P. Robel, editors, F. A. Davis Co., Philadelphia, 1964.

1) Stage I - 20 patients = 5.8 ± 0.7 µg/day
2) Stage 2A - 26 patients = 8.4 ± 0.8 µg/day
3) Stage 2B - 37 patients = 11.6 ± 0.6 µg/day
4) Stage 3 - 19 patients = 15.8 ± 1.2 µg/day
5) Malignant- 15 patients = 22.7 ± 1.8 µg/day

(Normal = 5.3 ± 0.5 µg)

3. Renin activity in hypertension

a. The finding of low values:

(32) Helmer, O. M. Renin activity in blood from patients with hypertension. Canad. Med. Assoc. J. 90:221, 1964.

b. The meaning of low values:

(33) Brown, Et al. and J. W. Conn. Letters to the Journal. J.A.M.A. 191:867, March 8, 1965.

(34) Brown, J. J., et al. Plasma renin concentration in human hypertension I: Relationship between renin, sodium and potassium. Brit. Med. J. 2:144, July 17, 1965.

1) Renin levels increase with increased diastolic pressures.
2) Renin levels inversely related to serum sodium concentration.

(35) Brown, J. J., et al. Plasma concentration of renin in a patient with Conn's syndrome with fibrinoid lesions of the renal arterioles: The effect of treatment with spironolactone. J. Endocrinol. 33:279, October, 1965

4. Hypokalemia in hypertensives treated with thiazides.

a. Incidence: 5 - 10%

(36) V.A. Cooperative study on antihypertensive agents III. Chlorothiazide alone and in combination with other agents. Arch. Int. Med. 110:230, August, 1962.

(37) Grieble, H. G., et al. Treatment of arterial hypertensive disease with diuretics. Arch. Int. Med. 110:34, July, 1962.

b. Significance:

(38) Kaplan, N. M. Primary aldosteronism with malignant hypertension. New Eng. J. Med. 269:1282, 1963.

Reference 30.

5. Other evidence.

a. Plasma volume, exchangeable Na+ and K+.

1) Normal in essential hypertension.

(39) Hollander, W. et al. Body fluid and electrolyte composition in arterial hypertension. J. Clin. Invest. 40:408, February, 1961.

2) Abnormal in primary aldosteronism.

(40) Slaton, P. E. and E. G. Biglieri. Hypertension and hyperaldosteronism of renal and adrenal origin. Am. J. Med. 38:324, March, 1965.

b. Serum sodium concentration.

1) Hypernatremia usual in primary aldosteronism (Mean = 146)

(41) Conn, J. W. Aldosteronism and hypertension. Arch. Int. Med. 107:813, June, 1961.

2) Normal serum sodium in essential hypertension

Reference 34.

c. Effects of aldosterone administration in man.

(42) August, J. T., D. H. Nelson and G. W. Thorn. Response of normal subjects to large amounts of aldosterone. J. Clin. Invest. 37:1549, November, 1958.

d. Non-specific results of therapy.

(43) Volini, I. F. and N. Flaxman. The effect of non-specific operations on essential hypertension. J.A.M.A. 112:2126, May 27, 1939.

(44) Smith, H. W. Unilateral nephrectomy in hypertensive disease. J. Urol. 76: 685, December, 1965.