MEDICAL GRAND ROUNDS

September 12, 1968

PLASMA RENIN AND CURABLE HYPERTENSION

I. The control of renin release (1)

A. Location of renin-containing tissue

1. The juxta-glomerular (JG) apparatus

a. Granular cells: differentiated smooth muscle cells in the media of arterioles adjacent to glomerulus.
b. Macula densa: specialized portion of tubule at end of loop of Henle
c. Mesangial cells: interstitial

2. Uterus (probably in endometrium) and chorion
3. Submaxillary glands of mice

B. The mechanism of renin release:

1. Blood flow and hypoxia not involved
2. Baroreceptor: JG granular cells act as stretch receptors, responsive to decrease in mean arterial pressure (2)
3. Marcula densa: Decrease in sodium load or osmolality of fluid in early distal tubule (3)
4. Symphathetic nervous system: Stimulation of renal nerves or infusion of catecholamines (4)
5. Circulating angiotensin exerts a negative feedback effect

II. Variations in Renin Levels (5)

A. Experimental changes in renin release:

1. Increased

a. Decreased renal arterial pressure

1) Clamp on renal artery (Goldblatt hypertension)
2) Systemic hypotension

b. Decreased effective arterial blood volume

1) Hemorrhage
2) Diuretic therapy or low salt intake
3) Upright posture (modulated by sympathetic nervous system)

c. Decreased sodium delivery to distal tubule

1) Hyponatremia
2) Decreased sodium intake

d. Increased intratubular pressure by ureteral occulusion (but not renal venous occulsion)

e. Increased sympathetic activity: hypoglycemia, exercise, upright posture

2. Decreased

a. Increased renal arterial pressure

1) The non-clamped kidney in Goldblatt hypertension
2) DOC + salt hypertension
3) "Essential" hypertension in rats

b. Expanded effective arterial blood volume

c. Increased sodium delivery to distal tubule

1) Hypernatremia
2) Acutely after diuretics

d. Denervation of the kidney (but transplanted kidneys still respond to salt depletion and upright posture)

e. Potassium intake may decrease PRA (6)

1. Vander, A. J. Control of renin release. Phys. Rev. 47:359, July 1967.

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4. Gordon, R. D., et al. Role of the sympathetic nervous system in regulating renin and aldosterone production in man. J. Clin. Invest. 46:599, 1967.

5. Brown, J. J., et al. Renin and angiotensin. Postgrad. Med. J. 42:153, 1966.

6. Veyrat, R., et al. Inhibition of renin by potassium in man. Acta endocr. Suppl. 119:86, 1967 (abstract).

B. Clinical alterations of plasma renin activity (5)

1. Diurnal variation: highest levels between 2 and 8 A.M., lowest levels between noon and 6 P.M. (7)
2. Menstrual cycle and pregnancy (8)

    a. Slightly higher during luteal phase
    b. Elevated during normal pregnancy
    c. Elevated with estrogen therapy (oral contraceptives) (9, 10)
    d. Levels fall toward normal in toxemia of pregnancy (8)

3. Conditions with increased PRA (11)

    a. Decreased effective arterial blood volume

        1) Diuretic therapy or low salt diet
        2) Hemorrhage
        3) Adrenal insufficiency
        4) Cirrhosis with ascites
        5) Nephrotic syndrome

    b. Decreased renal arterial pressure

        1) Renovascular hypertension
        2) Accelerated or malignant hypertension
        3) Coarctation may have normal levels

    c. Miscellaneous

        1) Juxta-glomerular hyperplasia (Bartter's syndrome)
        2) Renin-secreting renal tumor (12)

4. Conditions with decreased PRA (13)

    a. Expanded effective arterial blood volume and/or increased renal arterial pressure

        1) Salt or plasma infusion
        2) Primary aldosteronism
        3) Cushing's syndrome (variable)
        4) Licorice-induced pseudoaldosteronism (14)
        5) Congenital adrenal hyperplasia caused by 17-hydroxylase deficiency (15)

    b. Absence of renal tissue (16, 17)

    c. Decreased activity of the sympathetic nervous system

        1) Autonomic insufficiency with postural hypotension
        2) Ganglionic-blockade (shown in rats)

    d. Essential hypertension (25%) (18)

5. Conditions with normal PRA

    a. Chronic renal parenchymal disease (19)
    b. Chronic congestive heart failure (20)

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18. Helmer, O. M. Renin activity in blood from patients with hypertension. Canad. Med. Assoc. J. 90:221, Jan. 25, 1964.

19. Hickler, R. B., et al. A comparison of unilateral pyelonephritis and renal artery stenosis associated with hypertension. Am. J. Surg. 109:715, June 1965.

20. Kloppenborg, P., et al. Renin and aldosterone in congestive heart failure. Abst. 3rd Int. Endocrin. Congress, Mexico City, June, 1968.

III. Techniques of renin assay (21)

A. Bioassay: all now use rat preparation for quantitation

1. Methods

a. "Activity": bioassay of angiotensin formed by incubation of plasma after inactivation of angiotensinase (Helmer, Boucher, etc)

b. "Concentration": bioassay of angiotensin formed by incubation with added substrate, using a standard preparation of human renin as a control (Brown, etc)

2. Results

a. Variables of different procedures require establishment of normal values in each laboratory (22)

b. Absolute values of less importance than degree of change with various physiological manuevers

c. Ranges in our laboratory using the technique of Pickens, et al

1) Supine, regular diet: 100 to 500 ng%
2) Upright, regular diet: 300 to 1,000 ng%
3) Upright, low salt diet: an increase of 150 ng% above the supine, regular diet level

B. Radioimmunoassay (23, 24)

1. Methods

a. "Free" angiotensin
b. Renin activity by amount of angiotensin generated after incubation

2. Results

a. Close similarity to bio-assay
b. "Free" angiotensin: 10-50 ng/L

21. Pickens, P. T., et al. Measurement of renin activity in human plasma. Circ. Res. 17:438, 1965.

22. Haas, E., et al. Estimation of endogenous renin in human blood. Lancet 1:657, March 30, 1968.

23. Vallotton, M. B., et al. Radioimmunoassay of angiotensin in human plasma. Nature 215:714, Aug. 12, 1967.

24. Boyd, G. W., et al. Radioimmunoassay for determining plasma-levels of angiotensin II in man. Lancet 2:1002, Nov. 11, 1967.

IV. Renal substances which cause a lowering of blood pressure

A. Renin inhibitors

1. Numerous experimental observations suggest that normal plasma has substances which inhibit renin activity and these substances are lost after nephrectomy.
2. Renal phospholipid "pre-inhibitor" (25)

   a. Inhibits formation of angiotensin by renin in vitro.
   b. Reduces the blood pressure of renal hypertensive rats but has no effect on normotensive rats.

3. Renin inhibitor in plasma of uremic patients (26)

   a. Assayed by rate of angiotensin generation in presence of renin and substrate.
   b. Inhibitor present in plasma of all 5 patients with uremia caused by chronic glomerulonephritis but not in patients with renovascular hypertension or malignant hypertension.

B. Renal anti-hypertensive substances: Grollman's concept of renoprival hypertension due to the absence of a renal anti-hypertensive factor has been supported by the findings of such substances.

1. Renal cortical extract of Grollman, et al (27)

   a. Lowers B.P. of hypertensive animals when administered orally
   b. No effect on B.P. of normotensive animals

2. Neutral renomedullary lipid of Muirhead, et al (28)

   a. Effective orally in lowering B.P. in animals with renoprival or renovascular hypertension
   b. Shares many characteristics with prostaglandins

3. Renomedullary prostaglandins (PGE) (29)

   a. Unsaturated cyclic fatty acids
   b. Exert both vasodepressor and anti-hypertensive effects
   c. Act directly upon kidney to cause vasodilation and increase sodium excretion without effect on GFR (30)

25. Sen, S., et al. Antihypertensive effect of an isolated phospholipid. Am. J. Physiol. 214:337, Feb. 1968.

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30. Vander, A. J. Direct effects of prostaglandin on renal function and renin release in anesthetized dog. Am. J. Physiol. 214:218, Feb. 1968.

V. The angiotensin infusion test

A. Experimental basis

1. Sensitivity to exogenous renin and angiotensin directly related to endogenous plasma level

2. Plasma renin activity and sensitivity to angiotensin in various situations.

a. Low PRA with increased sensitivity

1) Primary aldosteronism
2) Essential hypertension

b. Normal PRA with normal sensitivity

1) Normotensive controls
2) Chronic renal parenchymal disease

c. High PRA with decreased sensitivity

1) Cirrhosis with ascites
2) Malignant hypertension
3) Pregnancy (31)

a) Normal pregnant women required 22 mμg/Kg/min
b) Women with toxemia required 10 mμg/Kg/min
c) These changes in toxemia accompany decreased PRA and aldosterone secretion

B. Clinical results

1. Procedure highly reproducible
2. Considerable variability noted with presumably same technique (See Table)
3. Overall usefulness seems established but with a certain percentage of false positives and, perhaps, false negatives
4. Overall correlation with plasma renin activity quite good (32)

31. Talledo, O. E. Renin-angiotensin system in normal and toxemic pregnancies. Am. J. Ob. & Gyn. 96:141, Sept. 1966.

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Author	Mean Pressor Dose			Per Cent Resistant (Number of patients)	
	Normal	Essential Hypertension	Renovascular Hypertension	Essential Hypertension	Renovascular Hypertension
Kaplan	7.5	3.4	14.2	8 (16/200)	100 (21/21)
Derot	10.2	5.4	13.7	25 (3/12)	100 (6/6)
Hocken	4.5	4.2	13.7	4 (1/24)	100 (7/7)
Simmons	7.4	5.5	15.5	21 (4/19)	100 (7/7)
Morgan	5.0	5.2	24.0	20 (22/112)	85 (11/13)
Silah	-	3.8	9.8	6 (1/16)	100 (11/11)
Guedon	10.3	7.2	12.6	32 (37/117)	94 (15/16)
Roguska	8.3	5.3	19.9	4 (1/24)	100 (11/11)
Catanzaro	7.3	6.0	13.3	6 (2/31)	70 (7/10)
Weidmann	-	4.8	12.2	5 (1/22)	89 (8/9)

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34. Derot, M., et al. Renseignements fournis par le test a l'angiotensine de Kaplan dans l'exploration des hypertensions d'origine renale. J. d'Urologie et de Nephrologie. 70:723, 1964.

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39. Guedon, J. et al. Etude critique du test de perfusion a l'angiotensine. Path.-Biol. 16:559, 1968.

40. Roguska, J., et al. Pressor response to angiotensin II in hypertension. Am. J. Cardio. 41:705, 1968.

41. Catanzaro, F., et al. Angiotensin-infusion test. Arch. Intern. Med. 122:10, 1968.

42. Weidmann, P., et al. Plasma renin activity and angiotensin pressor dose in hypertension: correlation and diagnostic implications. Brit. Med. J. 2:154, July 20, 1968.

TABLE I: Causes of Curable Hypertension

I. Renal

A. Renovascular disease

B. Renal parenchymal disease

1. Acute glomerulonephritis
2. Unilateral pyelonephritis
3. Unilateral hypoplasia
4. Hydronephrosis
5. Tuberculosis

C. Renoprival state

II. Endocrine

A. Acromegaly

B. Hypothyroidism

C. Adrenal

1. Cushing's syndrome
2. Primary aldosteronism
3. Congenital adrenal hyperplasia
4. Pheochromocytoma

III. Coarctation of aorta

IV. Toxemia of Pregnancy

V. Miscellaneous

A. Polycythemia

B. Burns

C. Lead poisoning

D. Increased intracranial pressure

E. Carcinoid syndrome

VI. Essential hypertension (?)

VI. Renin and Hypertension in Renal Parenchymal Disease

A. The relationship between hypertension and renal parenchymal disease

1. Types of renal parenchymal disease with increased frequency of hypertension (43)

a. Congenital hypoplasia
b. Acute glomerulonephritis
c. Chronic glomerulonephritis
d. Chronic peylonephritis, uliateral or bilateral (44)
e. Tuberculosis (45)
f. Diabetic glomerulosclerosis
g. Polycystic disease
h. Collagen diseases: lupus, periarteritis, scleroderma
i. Hydronephrosis (46)

2. The problem of the atrophic kidney: chronic pyelonephritis, renovascular or hypoplasia (47)

a. Reasons for diagnostic confusion

1) Absence of specific pathological features (48)
2) Failure to recognize renal artery stenosis in patients with "unilateral pyelonephritis"
3) Possible intra-renal vascular stenosis in pyelonephritis (44)

b. Features of probable discriminatory value (47, 49)

1) Hypoplasia: young age, absence of clinical features of pyelonephritis or radiological evidence of vascular stenosis
2) Pyelonephritis: history of urinary tract infection, pyelography demonstrating clubbed calyces and thinned cortex, decreased urine osmolality or increased sodium concentration on split-function studies, normal PRA
3) Renovascular: presence of an abdominal bruit, "ischemic" pattern by pyelography and split-function tests, elevated PRA, stenotic lesion by aortography

c. Removal of a kidney with "unilateral pyelonephritis" by all known criteria may cure hypertension (50)

3. The mechanism of hypertension

a. On basis of J-G histology and PRA assays, the renin-angiotensin mechanism is probably not involved except in tuberculosis and hydronephrosis (51, 52b)
b. Renoprival mechanisms seem unlikely in unilateral disease
c. With bilateral involvement, renoprival mechanisms or volume overload may be factors
d. Ischemia as the mechanism of unilateral atrophy uncovered by arteriography (47) and proven by split function studies (52a) Chance of cure by nephrectomy probably much better with such evidence.

B. The renoprival state

1. Mechanism of hypertension

a. Absence of normal anti-hypertensive function
b. Inability to excrete salt and water with subsequent vascular overload
c. PRA levels probably zero in males, low in females

2. The results of bilateral nephrectomy in man (52)

a. Hypertension does not occur in the absence of vascular expansion.
b. Hypertension may remit by the removal of ischemic tissue producing excess renin
c. Successful transplantation has cured hypertension

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52b. Tu, W. H. Plasma renin activity in acute tubular necrosis and other renal diseases associated with hypertension. Circulation 31:686, May, 1965.

VII. Renal vascular hypertension

A. Experimental studies (52, 53, 54)

1. Changes after renal artery constriction (and contralateral nephrectomy)

a. Blood pressure rises within hours

1) Mainly attributable to increased peripheral resistance
2) Increased cardiac output may be a factor (also reported in human subjects (54a)
3) ECF volume expands transiently

b. Pressure continues to rise until plateau reached by 10-20 days

2. Mechanism of hypertension

a. Activation of the renin-angiotensin system

1) Increased levels acutely probably secondary to fall in intra-arterial pressure
2) Pressure in renal artery distal to construction returns toward normal and renin levels fall so that high levels not demonstrable in "chronic" experimental renovascular hypertension

a) "Normal" levels may be adequate to maintain hypertension in view of progressive pressor response to prolonged infusions (55)
b) Transient high levels may induce permanent hypertension by producing vascular disease (56)
c) Diminished baroreceptor activity (57) or increased arterial wall sodium content may enhance reactivity to angiotensin.
d) When BP is lowered slightly in patients with renovascular hypertension (even with normal PRA) the release of renin is much greater than in normals, suggesting an upward shift in the threshold for renin release (57a).

3) Antibodies to renin or angiotensin relieve hypertension (58, 59)

b. Inhibition of renal anti-hypertensive function

1) Removal of unclamped kidney (with its antihypertensive function) $\longrightarrow$ increase in hypertension; removal of clamped kidney $\longrightarrow$ relief of hypertension (by releasing inhibition on normal kidney)
2) Transplantation of normal kidney $\longrightarrow$ decrease in hypertension
3) Antihypertensive action said to be mediated by high arterial pressure (60) or a humoral substance (61)

c. Other possible mechanisms

1) Other pressor substances (62)
2) After renal artery constriction, hypertension may result from renal compensatory hypertrophy with relative ischemia when blood flow connot increase (63)
3) Potassium depletion said to prevent development of renovascular hypertension (64)

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63. Schlegel, J. U. Renal hypertension. JAMA 183:92, Jan. 12, 1963.

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B. Clinical course

1. Incidence: In view of frequency of functionally-insignificant renovascular disease, only those patients whose hypertension is cured (relieved) by removal of a stenotic lesion can be accepted. Most references include "hypertensive subjects with renovascular disease of questionable significance"

   a. Frequency of renovascular disease

      1) Some degree of stenosis found in 32% of 304 normotensive patients and in 67% of 193 hypertensives by aortography (65)
      2) In 295 unselected autopsies, 53% had renal artery stenosis - 49% of normotensive patients and 77% of hypertensives (66).
      3) Of 60 patients with marked stenosis, 50% had hypertension (67)
      4) Of 20 patients with severe stenosis, 6 had normal split-function studies (68)
      5) Anomalies of the renal arteries (mainly the presence of multiple arteries) may be present in as many as 2/3 of all hypertensives (69). Their significance is unknown.

   b. Frequency of renovascular hypertension

      1) Much lower among Negro hypertensives (73). May be higher among diabetics (74).
      2) Some studies based on aortography alone, many on I.V.P. ± split-function, almost none on surgical cure

         a) Without obvious selection of patients, incidence found to be 0/50 (70) and 27/750 or 3.6% (71)
         b) Many series have obviously selected patients with incidence of 9% (72) and 21% (73).

2. Clinical features (75)

   a. Abdominal bruit of some value but may be heard in as few as 25% of patients with and as many as 20% of patients without the disease. The majority of hypertensives with a bruit do not have renovascular disease (76).
   b. Higher frequency in either young (below 30) or old (over 50) who suddenly develop rapidly progressive hypertension.
   c. Evidence of secondary aldosteronism rarely noted.
   d. The nephrotic syndrome has been described in 3 patients with renal-artery stenosis (77).
   e. Polycythemia has been reported in 2 patients (78) and erythropoietin assays were above normal in a group of patients with renovascular disease and high renin levels (79).

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C. Pathology (80)

1. Types

a. Intrinsic

1) Atherosclerotic plaque, usually in proximal 1 cm; most common in older men
2) Fibromuscular hyperplasia or fibroplasia-intimal, medial, subadventitial, often with aneurysmal dilatations - more common in younger women
3) Aneurysm (81)
4) Embolism (82) and infarction with collateral vessels (98)
5) Arteritis (83)
6) A-V fistula (84) and angioma (85)
7) Tumor thrombus (86)
8) Neurofibromatosis (87)
9) Rejection of renal transplant (88)

b. Extrinsic

1) Pheochromocytoma (89)
2) Congenital fibrous band (90)
3) Metastatic tumors (90)

2. Mechanisms

a. Atherosclerosis (80)
b. Maternal rubella may cause renal artery stenosis (91)
c. Marked ptosis may cause renal ischemia as a result of stretching or kinking of the renal artery (92, 93)

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D. Diagnostic tests (52, 53, 54, 71, 72, 73, 75, 94)

1. Rapid sequence intravenous pyelography

a. Positive criteria

1) Greater than 1.0 cm difference in renal length
2) Delay in appearance or hypoconcentration on one side in early films
3) Hyperconcentration on one side in late films
4) Defects in renal silhouette in nephrogram phase suggestive of segmental infarction
5) Ureteral notching

b. Usefulness (See Table)

1) Each of above criteria abnormal in about 2/3 of patients with renovascular hypertension
2) Using all criteria, about 15% false negative and 10% false positive
3) Most useful "screening" test in view of wide availability, safety, ease of performance and interpretation. In the experience of Morgan (72), the I.V.P. gave fewer false positives and negatives than the renogram or the angiotensin infusion test:

	False +	False -
I.V.P.	30%	13%
Renogram	20%	33%
AIT	29%	20%

2. Radioisotope Renogram

a. No specific differences from unilateral parenchymal disease
b. Usefulness (See Table)

1) False negative - 14% (48/348)
2) False positive - 20% (73/357)

c. Despite safety and ease of performance, difficulties in technique and interpretation diminish usefulness as screening test

VALUE OF INTRAVENOUS UROGRAPHY IN INDICATING RENAL ARTERIAL DISEASE WHEN MULTIPLE CRITERIA ARE USED

REFERENCE	YEAR	NUMBER OF SUBJECTS	POSITIVE		NEGATIVE		CRITERIA
			Number	Per Cent	Number	Per Cent	
Stewart and Haynie	1962	49	42	86	7	14	Size, pyelocalyceal concentration, contour, ureteral notching, 3-minute appearance time
Halikiopoulos, Ballou, and McDonald	1962	23	21	91	2	9	Size, pyelocalyceal concentration, early nephrogram
Wilson et al.	1963	128	92	72	36	28	Size and pyelocalyceal concentration
Quinn	1963	41	33	80	8	20	Size, pyelocalyceal concentration, nonfunction, contour
Brannan, Birchall, and Kittredge	1963	11	11	100	0	0	Size, pyelocalyceal concentration, rapid-sequence pyelogram
Martin, Deyton, and Glenn	1963	14	13	93	1	7	Size, pyelocalyceal concentration, early nephrogram, rapid-sequence urogram
Maxwell et al.	1964	42	39	93	3	7	Size, pyelocalyceal concentration, early nephrogram

From: Renal Hypertension, ed. Page and McCubbin, Year Book Publishers, 1968.

EXPERIENCE WITH RADIOISOTOPE RENOGRAPHY IN PATIENTS WITH ESSENTIAL HYPERTENSION AND RENAL ARTERY STENOSIS

REFERENCE	YEAR	METHOD OF ANALYSIS		ESSENTIAL HYPERTENSION			RENAL ARTERY STENOSIS				
				Group Total	False Positive		Group Total	Positive		Negative	
		Qual.	Quant.		No.	%		No.	%	No.	%
Morgan et al.	1962	+					12	12	100	0	0
Stewart and Haynie	1962		+	44	11	27	20	15	75	5	25
Doig et al.	1963	+		9	3	33	9	8	89	1	11
Burbank et al.	1963		+	44	3	7	37	36	97	1	3
Pircher, Carr, and Patno	1963		+				13	7	54	6	46
Quinn	1963		+	10	0	0	41	38	93	3	7
Friis and Krogsgaard	1964		+	21	4	19	5	5	100	0	0
Wax and McDonald	1964		+	51	12	24	27	25	93	2	7
Burrows and Farmelant	1965		+	41	1	2	58	53	91	5	9
Wedeen et al.	1965		+	33	4	12	20	14	70	6	30
Sandler and Richards	1966		+	15	5	33	11	9	82	2	18
Maxwell and Kaufman	Unpublished	+		89	30	34	95	78	82	17	18
TOTAL				357	73	20	348	300	86	48	14

From: Renal Hypertension, ed. Page and McCubbin, Year Book Publishers, 1968.

3. Split-function tests

   a. On the ischemic side, urinary volume and sodium concentration decreased; concentration of non-reabsorbed solutes (creatinine, inulin and PAH) increased
   b. Usefulness (See Table)

      1) Large majority of patients with significant unilateral main renal artery stenosis have abnormal tests by any technique
      2) Limited value in bilateral or segmental lesions
      3) Technical difficulties and need for ureteral catherization limit usefulness
      4) Not always predictive of surgical cure

4. Renal biopsy (95)

   a. Presence of J-G hyperplasia of some diagnostic value
   b. Presence of severe ischemic tubular atrophy and interstitial scarring may indicate need for nephrectomy
   c. Contralateral vascular disease may indicate poor prognosis (or contraindication) of surgery

5. Renal arteriography (96)

   a. Techniques

      1) Translumbar
      2) Transfemoral

         a) Better visulization which may uncover segmental disease in over 10% of patients (97, 98)
         b) Permits evaluation of intrarenal vessels (99)
         c) Safer (100)
         d) Permits upright arteriography to demonstrate ptosis (93)

   b. Problems

      1) The need for careful technique to demonstrate segmental lesions in supernumerary arteries (101)
      2) The question of the significance of multiple arteries (69,101, 102)
      3) Artifactitious contractions (103) which may induce transient functional stenosis (104)
      4) Renal injury: functional impairment, emboli, infarction (105)
      5) Inability to demonstrate lesions located at ostium or primarily in anterior or posterior wall (106)

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6. Assays of renin angiotensin activity

   a. Indirect

      1) J-G cell count and granularity

         a) Good correlation with surgical cure rate (107)
         b) Requires open biopsy and special technique

      2) Angiotensin infusion test

   b. Direct

      1) Peripheral blood plasma renin activity (108)

         a) Comparisons are of questionable validity because of variability in patient selection, assay technique and control of factors which may affect renin activity
         b) Normal "supine, regular diet" PRA found with functionally significant renovascular hypertension
         c) Upright posture (2-4 hours) may elevate PRA to abnormally high levels (112)

Peripheral PRA in Non-accelerated Renovascular Hypertension

Author	Ref Reference	Number	PRA Incr.	Diagnostic Criteria Aortogram	Split-function	Surgery
1. Fitz	109	10	9	+	-	+
2. Tremblay	110	10	10	+	-	+
3. Brown	111	19	7	+	+	-
4. Cohen	112	9	5	+	+(5)	+
5. Kirkendall	113	12	6	+	+(9)	+
6. Gunnells	114	11	11	+	+	+(5)
7. Del Greco	115	7	4	+	+	+
8. Kaneko	116	10	7	+	+(8)	+(5)
9. Winer	117	6	5	+	-	+
10. Meyer	118	23	6	+	-	+

2) Renal venous PRA

a) Relatively simple procedure but does require femoral vein catheterization
b) Excellent correlation with surgical success

(1) With unilateral disease, differences between normal and abnormal side usually greater than 1.5 (119, 120)
(2) No such differences may be noted with bilateral vascular disease
(3) Actual PRA level of lesser discriminatory value; much higher during anesthesia
(4) Only rarely have differences been found in essential hypertensives or patients with parenchymal disease

c) Renin release may be inhibited by the high arterial pressure or by a higher threshold of the J-G receptor mechanism. Lowering of the pressure by I.V. hydralazine (20 mg) or nitroprusside (0.1 mg/min) has been shown to increase markedly the renin release from the involved but not from the normal kidney. This may be a useful manuever during renal vein catheter studies (57a, 116)
d) A simple assay for pressor activity in renal venous blood performed by Dr. Grollman, has given excellent correlation with other evidences of functional significance and surgical curability (32, 121)

Renal Vein PRA in Renovascular Hypertension

Author	Surgical Success		Surgical Failure	
	No.	Abnormal	No.	Abnormal
Kirkendall (113)	6	6	2	0
Del Greco (115)	3	2	2	0
Kaneko (116)	4	2		
Winer (117)	9	9	4	0
Meyer (118)	11	10 (?)	6	0
Michelakis (119)	18	17	3	1
Fitz (120)	9	8	6	0
Tremblay (110)	4	3	2	2

Renal Vein PRA - Parkland Series

Diagnosis	Patient	Renal Vein Right	Renal Vein Left	Vena Cava Above	Vena Cava Below
Essential Hypertension					
	N.T.	223	228	208	200
	B.H.	270	321	270	-
	S.P.	980	1,137	660	-
	D.F.	637	663	618	470
	M.K.	484	482	420	425
	R.C.	659	561	-	621
	O.F.	371	342	-	237
	E.G.	566	613	640	-
Essential hypertension with renal vascular disease					
	J.A.	1) 310	380	-	-
		2) 138	75	-	59
Accelerated hypertension					
	S.A.	3,403	3,433	3,366	2,900
	H.T.	3,015	2,496	2,335	1,640
Renovascular hypertension, unilateral					
	R.M.	6,618	1,700	2,444	2,045
	J.T.	1,780	900	1,480	-
	E.F.	21,100	14,660	-	14,660
	M.L.	8,130	2,560	-	-
	E.I.	435	1,140	745	-
	M.C.	4,620	1,040	1,665	-
	J.M.	3,333	1,385	-	-
Renovascular hypertension, bilateral					
	N.A.	,3900	1,630	-	-
	E.S.	3,690	3,718	-	2,333
	J.S.	2,150	2,300	-	1,660

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E. Treatment

1. Surgical (See Table)

a. The reported results (122, 123)

1) Variations which preclude valid comparison between series

a) Diagnostic criteria: some only require aortographic demonstration of an occlusive lesion; no large series reported based upon renal venous PRA
b) Surgical procedures: nephrectomy, various re-vascularization techniques
c) Follow-up procedures and criteria of success
d) Failure to document re-vascularization or presence of contralateral disease in "failures"

2) Generalizations which seem valid:

a) Nephrectomy may be more successful
b) Repair of fibrous lesions more successful than atherosclerotic lesions
c) Presence of significant arteriolar nephrosclerosis may prevent cure
d) Other than (hopefully) renal venous PRA, no good predictive test is readily available.

b. More than the control of hypertension, preservation of renal function may be the indication for surgery

1) Improvement more closely related to preoperative functional status than with cure of hypertension (124)
2) At least temporary relief of renal insufficiency may follow revascularization with bilateral involvement (125, 126)
3) Similar improvement has been noted in patients with only one kidney (127)

c. Prolonged improvement usual but survival and improvement of blood pressure significantly less after 5 years (128).

1) After 1 year: 87% survival, 81% improved
2) After 5 years: 68% survival, 44% improved

2. Medical (129, 130)

a. No controlled or matched comparisons between medical and surgical treatment are available
b. Despite relatively poor condition of patients given medical therapy, results are surprisingly good:

	No.	Duration	Good B.P. control	Worsening of renal function	Deaths
Sheps (129)	54	2/3 to 3 1/3 yr	39	3	5
Dustan (130)	23	1 to 8 yrs	15	7	0

Value of the Howard Test in Predicting Arterial Pressure Responses to Surgical Treatment

Reference		Number of Patients	Arterial Pressure Responses: Normal or Decreased, Pos. Test	Normal or Decreased, Neg. Test	Unchanged, Pos. Test	Unchanged, Neg. Test
Unilateral Main Renal Arterial Stenosis						
Perloff et al.	1961	8	6	1	0	1
Maxwell	1962	10	5	3	1	1
Dustan et al.	1963	20	13	2	3	2
Stewart et al.	1965	23	14	1	4	4
Richardson et al.	1965	4	3	1	0	0
Group Totals		65	41	8	8	8
Bilateral Main Renal Arterial Stenosis						
Perloff et al.	1961	6	2	1	1	2
Maxwell	1962	1	0	1	0	0
Dustan et al.	1963	6	2	2	1	1
Group Totals		13	4	4	2	3
Arterial Branch Lesions (Unilateral or Bilateral)						
Perloff et al.	1961	8	3	4	1	0
Maxwell	1962	3	0	3	0	0
Dustan et al.	1963	9	0	7	0	2
Stewart et al.	1965	5	0	4	0	1
Richardson et al.	1965	4	0	4	0	0
Group Totals		29	3	22	1	3

From: Renal Hypertension, ed. Page and McCubbin, Year Book Publishers, 1968.

Effects of Surgical Treatment on Hypertension Associated with Renal Arterial Stenosis

Reference*	Date	Total Patients Treated	Operative Mortality No. (%)	Follow-Up: Duration (Months)	Follow-Up: No. of Patients†	Arterial Pressure Response: Normal No. (%)‡	Arterial Pressure Response: Improved No. (%)	Arterial Pressure Response: Unchanged No. (%)
Perloff et al. (1-a)	1961	38	7 (18)	1–84	31	14 (45)	11 (36)	6 (19)
Wylie, Perloff, and Wellington (1-b)	1962	24	0	3–40	24	13 (54)	8 (33)	3 (13)
Spencer et al.	1961	27	1 (4)	4–36	24	12 (50)	10 (42)	2 (8)
Stewart et al.	1962	32	2 (6)	2–24	30	15 (50)	9 (30)	6 (20)
Baker, Page, and Leadbetter	1962	25	2 (8)	6–37	21	9 (42)	6 (29)	6 (29)
Dustan et al. (2-a)	1963	99	10 (10)	12–72	76	44 (58)	15 (20)	17 (22)
Gifford and Poutasse (2-b)	1963	28	0	3–34	25	4 (16)	15 (60)	6 (24)
Gifford, McCormack, and Poutasse (2-c)	1965	45	2 (4)	6–105	37	15 (41)	19 (51)	3 (8)
Gifford et al. (2-d)	1967	80	6 (8)	2–105	73	19 (26)	34 (47)	20 (27)
Kaufman and Maxwell	1964	67	3 (5)	12–72	64	25 (39)	30 (47)	9 (14)
Thompson, Austin, and Wheeler	1964	28	1 (4)	1–47	27	8 (30)	17 (63)	2 (7)
Hunt et al. (3-a)	1965	34	0	N.S.	34	22 (64)	6 (18)	6 (18)
Sheps and Bernatz (3-b)	1966	138	0	6+	138	68 (49)	42 (31)	28 (20)
Genest et al.	1966b	37	0	N.S.	34	22 (64)	6 (18)	6 (18)
Morris, De Bakey, and Zanger	1966							
Before 5/1/64		432	30 (7)	12–120	394	161 (41)	158 (40)	75 (19)
Since 5/1/64		195	8 (4)	<18	187	107 (57)	54 (29)	26 (14)

* References grouped primarily chronologically, but when two or more papers were from one institution, they were grouped together, because there is considerable overlap within patient groups.

1. University of California Medical Center, San Francisco
   (1-a) both atherosclerotic and fibrosing lesions.
   (1-b) fibrous stenoses, "fibromuscular hyperplasia."
2. Cleveland Clinic:
   (2-a) lesions of both types.
   (2-b) patients over 55 years of age.
   (2-c) patients with severe "ischemic" atrophy.
   (2-d) atherosclerotic lesions in patients of all ages.
3. Mayo Clinic:
   (3-a) fibrous stenoses only.
   (3-b) both atherosclerotic and fibrous stenoses.

† Number of patients followed for assessment of antihypertensive effects of operations; excludes those patients who died postoperatively and patients not traced.

‡ Percentages refer to the patients followed, and not the total group.

From: Renal Hypertension, ed. Page and McCubbin, Year Book Publishers, 1968.

3. Recommendations for diagnosis and therapy (131)

   a. All hypertensives should have a basic workup for the etiology and the effects of their disease

      1) History and physical exam
      2) Urine analysis, BUN, creatinine, serum electrolytes
      3) E.C.G., chest x-ray
      4) Rapid-sequence I.V.P.

   b. If the I.V.P. is abnormal or the clinical situation indicative (recent onset of progressive hypertension in young or old, significant bruit, renal impairment) proceed with:

      1) Peripheral blood PRA (regular diet, upright) or
      2) Angiotensin infusion test
      3) Retrograde selective aortogram
      4) Renal vein catheterization for PRA

   c. If a functionally significant lesion is found, surgery indicated
   d. If the blood pressure is relatively mild, the patient old or complications exist which make surgery more dangerous, effective antihypertensive therapy should be given

      1) Medical therapy may be given without specific workup listed under b.
      2) If pressure not controllable or renal function deteriorates, proceed with remainder of work-up or surgery

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VIII. Primary aldosteronism and essential hypertension

A. Normokalemic primary aldosteronism

1. Conn has reported on 14 such patients out of 184 studied at Ann Arbor, an incidence of 7.6%
2. Three additional cases have been reported and all 3 were recognized after they became hypokalemic after thiazide administration (133-135)

   a. As Conn points out, some patients with hypokalemic disease were known to be normokalemic while already hypertensive (32)
   b. In 50 patients, Brown et al found 27 to be persistently hypokalemic but 22 had some normal serum potassiums and 1 had persistent normokalemia (135)

3. In the best prospective study of minimally selected patients, 3 of 90 normokalemic patients had high aldosterone excretion and low PRA. However in the 2 of the 3 operated upon, no adrenal pathology was found (136).

B. The present state of Conn's postulates in favor of a 20 to 25% incidence

1. Adrenal adenomas were found in only 1.4% of patients at necropsy with an equal incidence among those who had been normotensive or hypertensive (137)
2. Aldosterone hypersecretion is noted in about 5% of essential hypertensives and in most of these it appears to be secondary (138)
3. Plasma renin is suppressed in about one-fourth of all hypertensives, but these patients do not have other evidence (such as elevated aldosterone excretion or secretion) or primary aldosteronism (138-143)
4. Hypokalemia appears in about 10% of hypertensives treated with thiazides but there were no cases with primary aldosteronism among 75 such patients studied (144).

C. The use of PRA assays in the diagnosis of primary aldosteronism

1. Suppressed PRA has been noted in every patient but one of some 100 reported (135). This includes a pregnant woman in whom PRA would have been markedly elevated (145)
2. With enough volume depletion or spironolactone therapy, the PRA will rise in primary aldosteronism (146)
3. Since 25% of essential hypertensives have suppressed PRA, this can be used used to substantiate, but not to establish the diagnosis. High aldosterone levels must be found to make the diagnosis.
4. Techniques used to test for PRA suppression (143)

   a. 500 mg low salt diet, for 3 days followed by 2 to 4 hours upright posture
   b. I.V. chlorothiazide
   c. Oral furosemide

D. Other diagnostic tests

1. Failure to suppress aldosterone excretion by saline loading (147)
2. Failure to suppress aldosterone excretion by DOC (148)
3. Relief of hypertension by large doses (400 mg/day or more) of spironolactone (Aldactone) for 3 to 5 weeks (149)
4. Percutaneous adrenal vein catheterization for steroid analysis and angiography (150). At Ann Arbor, this technique has been found to be harmful and of little value (151)

E. Variants of the disease

1. Aberrant adrenal adenoma (152)
2. Bilateral adrenal hyperplasia

   a. Frequency varies from 0 to 40 per cent in various series (153-156)
   b. Some said to respond to dexamethasone with relief of hypertension and correction of increased aldosterone and low PRA (157)
   c. However, adrenal adenomas may also respond to dexamathasone suppression (158) or ACTH stimulation (159)

3. Malignant hypertension has been reported in 4 or so patients (160-161)
4. Aldosterone excretion may be "normal" in presence of hypokalemia (144, 162)

F. Treatment

1. Surgery is the treatment of choice for most patients, but should not proceed to total adrenalectomy (163)
2. Medical therapy may be quite effective

   a. Chronic, moderate-dose spironolactone (164)
   b. Heparin or heparinoid-drugs (165)
   c. Steroid inhibitors (166)

G. The problem with birth-control pills

1. Estrogens will markedly increase PRA and have a modest stimulatory effect on aldosterone (167)
2. Estrogens will uncover or aggravate (and cause ?) hypertension in probably a significant number of women (168-169)

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CASE REPORT

This effect of oral contraceptives on renin, aldosterone and hypertension was well demonstrated in Mrs. J. T., a 29 year old woman seen here in August, 1967. At that time, the effects on PRA were known but the aggravation of hypertension had not yet been recognized.

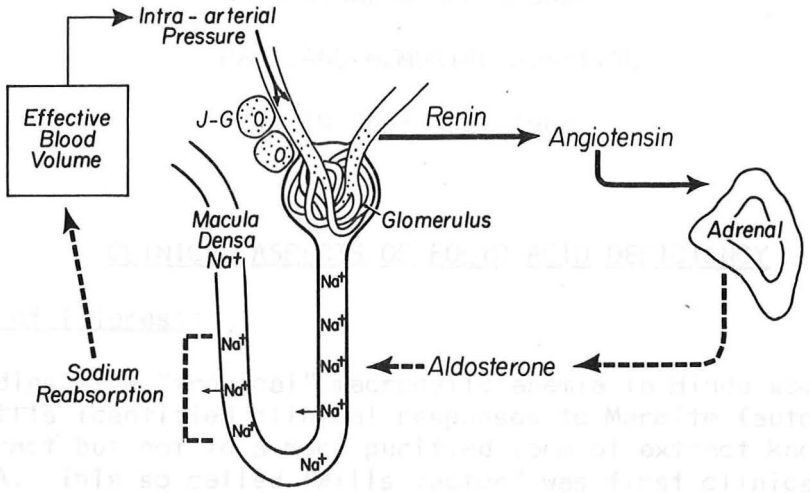
Mrs. T. had become hypertensive toward the end of her second pregnancy, in 1964. The blood pressure returned to normal until October, 1966 when it was found to be in the 150/100 range. She was given reserpine and a thiazide and was started on birth control pills. In February, 1967, she developed severe headaches and the blood pressure was recorded as 220/140. Workup revealed a normal I.V.P., renogram and renal arteriogram. She was hypokalemic (2.9 mEq/L) but the urine contained only 20 mEq of potassium per 24 hours.

She was referred to PMH to rule out primary aldosteronism. Her serum K+ was 3.0 mEq/L, the urine had 61 mEq of K+ and 305 mEq of Na+ per 24 hours, with aldosterone level of 23.0 µg/24 hours (normal = 5 to 20 µg). PRA results were:

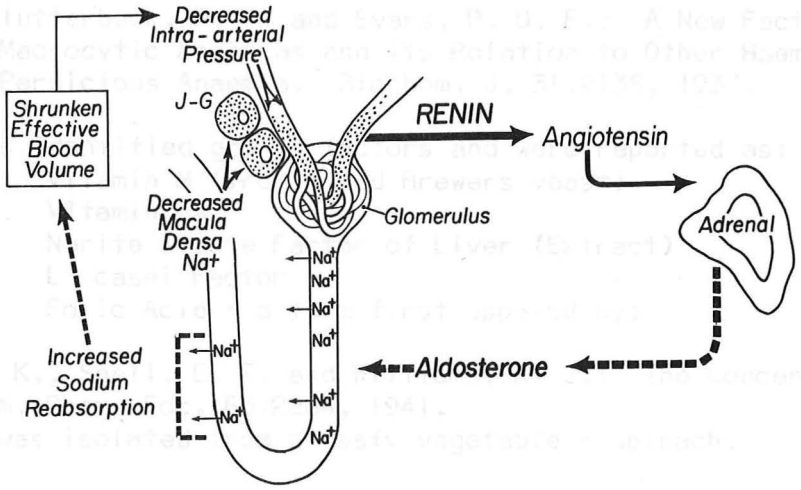
Regular, supine	- 520 ng%
Regular, upright	- 1,160 ng%
Low salt, upright	- 1,700 ng%

In view of these results and the known effects of estrogens on PRA, she was asked to discontinue the pills in August, 1967. Her blood pressure (on Ismelin - 10 mg and Hygroton - 50 mg daily) was 120/88 in October, 1967. She then discontinued the anti-hypertensive medications and in April, 1968 her blood pressure was 120/90. She had an intra-uterine loop inserted in October, 1967.

Normal



Plasma Volume Depletion



Primary Aldosteronism