MEDICAL GRAND ROUNDS
September 21, 1972

HYPERTENSION and the KIDNEY
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[redacted]

This 40 year old [redacted] man had been normotensive in 1967 when seen at [redacted] for peptic ulcer disease. However, in early 1969, at age 39, he developed progressively more severe, intermittent, pounding headaches. He was admitted in [redacted], 1969, with a 4 day history of weakness, anorexia and vomiting.

BP = 210/130, fundi showed hemorrhages and exudates. The ECG displayed LVH. BUN = 15, creatinine = 0.8. Workup for renal vascular disease was negative with a normal I.V.P. and renal vein renin levels (bioassay) showing:

Vena cava	= 290	ng/100 ml/3 hr
Right renal vein	= 480	"
Left renal vein	= 520	"

Therapy included I.M. hydralyzine initially and oral guanethidine and thiazides chronically. With control of blood pressure, the serum creatinine rose to 2.8.

He was re-admitted 4 months later with BP = 195/125, papilledema, left ventricular failure, microangiopathic hemolytic anemia, BUN = 97 and creatinine = 9.1. Hemodialysis was begun on [redacted] 1970, and on April 27, 1970, bilateral nephrectomy was performed in anticipation of homotransplantation. His blood pressure promptly fell and, despite remaining off anti-hypertensive therapy, severe postural hypotension occurred. However, he did not restrict salt or water and, despite repeated dialyses, fluid overload occurred with BP = 230/135.

On [redacted] 1970, he received one of his sister's kidneys. The transplant seemed to function well and from June through early [redacted] the serum creatinine stayed around 1.2, while he received Imuran, prednisolone, and various other medications. His blood pressure remained between 110/70 to 150/100 and his fundi showed only minimal hypertensive changes. However, complications including various infections and hepatic failure supervened and he died on [redacted] 1970.

This patient portrayed almost the entire spectrum of the relationships between hypertension and the kidney.

HYPERTENSION AND THE KIDNEY

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General References:

1. Symposium on Hypertension: Mechanisms and Management. Amer. J. Med. 52:565-720, May 1972

2. Papper, S. and C. A. Vaamonde: Nephrosclerosis. Chapter 19, p 735-768, in Diseases of the Kidney, ed. M. B. Strauss and L. G. Welt, 2nd Ed., Little, Brown and Company, Boston, 1971.

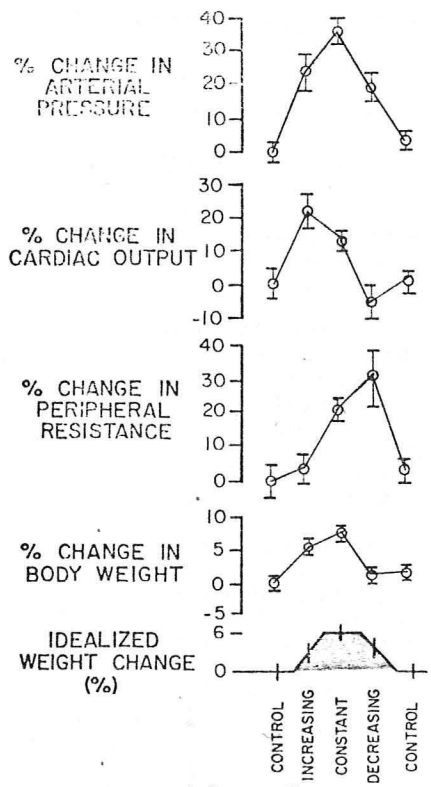
3. Brown, J. J., et al: Hypertension and chronic renal failure. Brit. Med. Bull. 27:128-135, May 1971.

4. Maxwell, M.H., et al: Cooperative study of reno-vascular hypertension. J.A.M.A. 220:1195, May 29, 1972, and J.A.M.A. 221:368, July 24, 1972.

I. Blood pressure in the absence of the kidneys

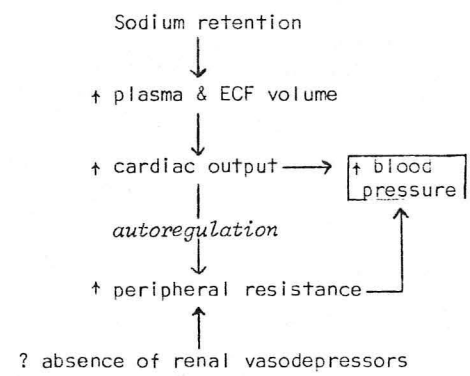
A. Experimental: The classical experiments of Grollman, Muirhead and Vanatta (Amer. J. Physiol. 157:21,1949) suggested that hypertension developed after bilateral nephrectomy in dogs kept alive by hemodialysis or peritoneal dialysis. This "renoprival hypertension" was claimed by others to result from overhydration (Orbison, et al. Arch. Path. 54:185,1952) but Grollman, in turn, showed that the absence of hypertension in the renoprival state was due to under-hydration. As will be discussed later, various renal vasodepressor substances have been identified and the concept of renoprival hypertension remains very much alive.

B. Clinical: When it became possible to keep humans alive and reasonably well in the absence of functioning renal tissue, hypertension was not observed unless overhydration was allowed (Merrill, J.P., et al. Amer. J. Med. 31:931,1961). Dr. Merrill's subsequent experience, however, has indicated that "there is a renoprival hypertension independent of the state of hydration" (Ann. Int. Med. 76:733,1972). From careful studies on 3 anephric patients by Coleman and co-workers the following pathogenetic sequence for hypertension in the anephric state was evolved (Circulation 42:509,1970):



from Coleman, et al.
Circulation 42:509, Sept. 1970

The sequence can be redrawn:



Hypertension in the Anephric State

Except in rare instances (Yu, R., et al. Amer. J. Med. 52:707, May 1972) the renin-angiotensin system is no longer active after bilateral nephrectomy and the control of aldosterone is probably mediated by changes in potassium (Bayard, F., et al. J. Clin. Invest. 50:1585,1971) or ACTH (Mitra, S., et al. New Eng. J. Med. 286:61, Jan 13, 1972).

II. Blood pressure after renal transplantation

A. Acute elevations in blood pressure may be secondary to release of renin (Gunnells, J.C., et al. New Eng. J. Med. 274:543,1966).

B. More chronic hypertension, post-transplantation, is not always associated with increased renin levels (Blaufox, M.D., et al. New Eng. J. Med. 275:1165, Nov. 24, 1966), though higher levels may occur during rejection when the blood pressure rises (West, T.H. J. Lab. & Clin. Med. 73:564, Apr. 1969). The Denver group find a stronger relation between the dose of prednisone used to prevent rejection and the blood ressure (Popovtzer, M.M., et al, unpublished data). Hypertension, if it occurs, should be vigorously treated since damage to the transplant can rapidly ensue (Parsons, F.M., et al. Brit. Med. J. 1:930, Apr. 6, 1963).

III. Hypertension with chronic renal disease

A. Clinical setting

1. *Hypertension causing renal failure*

a. The end stage of hypertension

Almost 1/3 of the deaths in hypertensive patients are caused by renal failure, as shown in this table from Breckenridge, et al. Quart. J. Med. 39:411,1970. These were patients with hypertension of varying severity, treated between 1960 and 1967.

Causes of Death in 203 Patients with Hypertension

Due to hypertension		88%
Uremia	29%	
Myocardial infarct	27%	
CVA	21%	
Congestive failure	5%	
Aneurysm of aorta	5%	
All other causes		12%

The presence of renal damage is an ominous prognostic sign in hypertension. Note these data on 5 year survival, also from Breckenridge, et al. Quart. J. Med. 39:411,1970:

Fundi:	Grade 1-2		Grade 3		Grade 4	
BUN:	<18	>18	<18	>18	<18	>18
Survival:	90%	81%	84%	57%	64%	23%

b. Acute oliguric renal failure from accelerated-malignant hypertension

The course may be particularly rapid in some patients who have 1) diastolic pressures above 130 mm Hg, 2) advanced hypertensive retinopathy and 3) oliguria or anuria. Our protocol case fits this clinical course, with characteristic weight loss, LVH and micro-angiopathic hemolytic anemia. The diagnosis may not be suspected in the presence of normal or slightly reduced renal size and red blood cells and casts in the sediment, but can be established by renal biopsy.

Conservative management with dialysis and vigorous anti-hypertensive therapy may be successful (Eknoyan, G. J.A.M.A. 215:1122, Feb. 15, 1971; Sevitt, L.H., et al. Quart. J. Med. 40:127, Jan. 1971) but usually will not reverse the course (Mattern, W.D. Amer. J. Med. 52:187, Feb. 1972).

Therefore the more aggressive approach, bilateral nephrectomy, is being advocated, more frequently and sooner:

Wilkinson, R., et al. Quart. J. Med. 39:377, July 1970
Donohue, J.P., et al. J. Urology 106:488, Oct. 1971
Mahony, J.F., et al. Lancet 1:1036, May 13, 1972
Lazarus, J.M., et al. Ann. Int. Med. 76:733, May 1972

The subsequent course of the survivors may be quite good, as shown in these tables from Mahony, et al. Lancet 1:1036, May 13, 1972.

TABLE I—CLINICAL AND LABORATORY DATA ON 9 PATIENTS

Patient no.	Age (yr.)	Sex	Duration of hypertension before nephrectomy (mo.)	Highest blood-pressure (mm. Hg)	Initial serum-creatinine (mg./100 ml.)	Initial Hb (g./100 ml.)	Plasma-renin activity × normal upper limit
1	41	M	36	265/175	4·9	11·6	2·2
2	37	M	30	270/160	16·3	9·5	7·0
3	48	M	12	240/160	13·0	9·9	2·1
4	29	M	1	260/180	5·0	11·8	2·0
5	39	M	2	255/160	16·5	7·0	.
6	32	M	4	250/190	3·6	12·0	..
7	42	F	18	250/150	17·0	10·0	..
8	31	F	48	210/140	15·0	9·9*	10·0
9	35	F	72	290/200	6·8	8·2	..

TABLE II—COURSE AFTER BILATERAL NEPHRECTOMY

Patient no.	Current status of survivors			
	Serum-creatinine (mg./100 ml.)	Blood-pressure (mm. Hg)	Drugs (daily dose)	Time after nephrectomy (mo.
1	0·9	110/80	None	43
2	..	..	..	..
3	..	..	..	..
4	1·2	120/80	250 mg. methyldopa	21
5	..	..	..	..
6	2·0	160/110	0·6 mg. clonidine	14
7	Regular hæmodialysis	125/70	None	13
8	Regular hæmodialysis	130/80	None	10
9	1·1	140/80	None	9

More about the status of nephrectomy for hypertension after mechanisms are considered.

2. *Renal failure causing hypertension*

Much more common than malignant hypertension causing renal failure is chronic renal disease causing hypertension. The hypertension may be variable in severity. Understanding of the mechanism of this

hypertension and its management has improved considerably since dialysis and transplantation have enabled more patients with chronic renal disease to stay alive. Now that the patients are being kept alive, their hypertension has become a more bothersome problem and it has been found to be the major cause of death in patients on regular dialysis (Wilkinson, R. Quart. J. Med. 39:377, July 1970).

Occult primary renal disease may be fairly common among hypertensives (Roland, A.S. Arch. Intern. Med. 113:151, Jan. 1964) but the relationship between such mild renal disease and the hypertension remains in question.

Presuming that the anti-hypertensive function(s) of the kidney arise in the medulla, Muirhead has suggested a role for the renal medullary fibrosis which he frequently found at autopsy in hypertensive patients (Haggitt, R.C., et al. Human Path. 4:587, Dec. 1971).

3. *Hypertension with renal parenchymal disease but without renal insufficiency*

Through the years, hypertension has been described in patients who have neither renal vascular disease nor severe renal insufficiency. Therefore neither the renin mechanism nor excessive fluid retention nor the lack of some anti-hypertensive function would explain their hypertension. Some examples include:

a. Chronic pyelonephritis. Kincaid-Smith postulated that vascular obstruction from pyelonephritic scarring was responsible for the hypertension (Lancet 2:1263, Dec. 17, 1955). Now, we would add that the vascular obstruction leads to excessive renin release, which in turn is responsible for the hypertension. But patients with unilateral pyelonephritis and without demonstrable elevations in renin have hypertension which may occasionally be relieved by unilateral nephrectomy (Hickler, R.B., et al. Amer. J. Surg. 109:715, June 1965).

Al Shapiro, on the basis of experimental and clinical data, believes that pyelonephritis does not cause hypertension but that hypertensives are more susceptible to renal infection (at a rate of approximately 1% per year) and that the infection may aggravate the pre-existing hypertension (Shapiro, A.P., et al. Ann. Intern. Med. 74:861, June 1971).

b. Unilateral atrophic or hypoplastic kidneys probably cause hypertension via renal ischemia and the renin mechanism. Gifford, et al, found that arterial occlusive disease could explain the unilateral renal atrophy seen in 71% of 75 hypertensive patients. (Mayo Clin. Proceed. 40:834, Nov. 1965).

c. Unilateral hydronephrosis probably causes hypertension by renin release (Belman, A.B., et al. New Eng. J. Med. 278:133, May 23, 1968).

B. Mechanisms and therapy

1. *Volume-dependent*

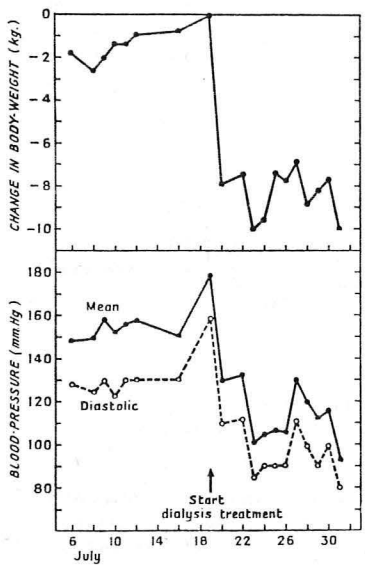
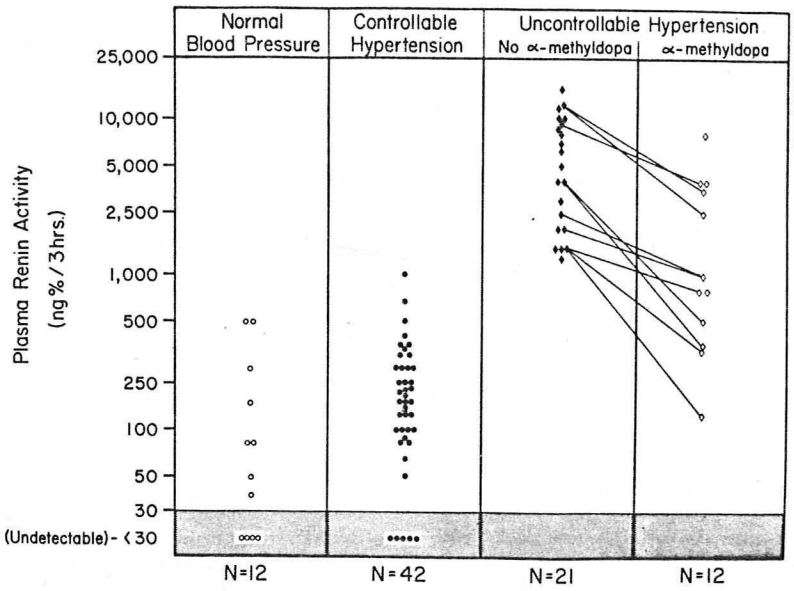


Fig. 7—20-year-old male inpatient in terminal renal failure with malignant hypertension: change in body-weight, and blood-pressure.

from Blumberg, A., et al.
Lancet 2:69, July 8, 1967

As shown rather dramatically in the figure from Scribner's group, the hypertension of most patients with CRD can be controlled by dialysis. The mechanism of the hypertension is almost certainly sodium and water retention, with expansion of plasma and ECF volume. Cardiac output is thereby increased. Total peripheral resistance is normal or only slightly increased. With dialysis therapy, the fall of blood pressure is associated with a decrease in total exchangeable sodium, ECF volume and cardiac output.

The renin-angiotensin system is thought not to be activated in such patients with "controllable hypertension", with plasma levels of both renin activity and angiotensin generally found to be low or normal. The findings in a group of such patients are shown in the following figure, compared to those of a group of CRD patients with normal blood pressure on the left and a group with "uncontrollable hypertension" on the right.

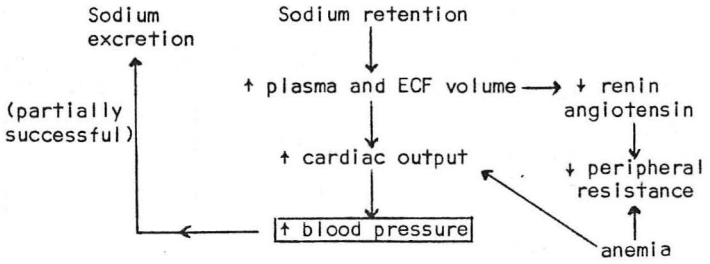


from Weidmann, P., et al.
New Eng J Med 285:757, Sept. 30, 1971

Presumably the relative inactivity of the renin-angiotensin system would be a factor in keeping peripheral resistance at a normal level.

On the other hand, hemodynamic studies of a group of 40 uremic patients reported by Neff, et al, (Circulation 43:876, June 1971) suggest that the cardiac output may be elevated secondary to the anemia that is common to patients with CRD and the peripheral resistance may be relatively decreased by the vasodilation produced by tissue hypoxia. When these patients were transfused, their cardiac outputs fell and peripheral resistance (and blood pressure) rose.

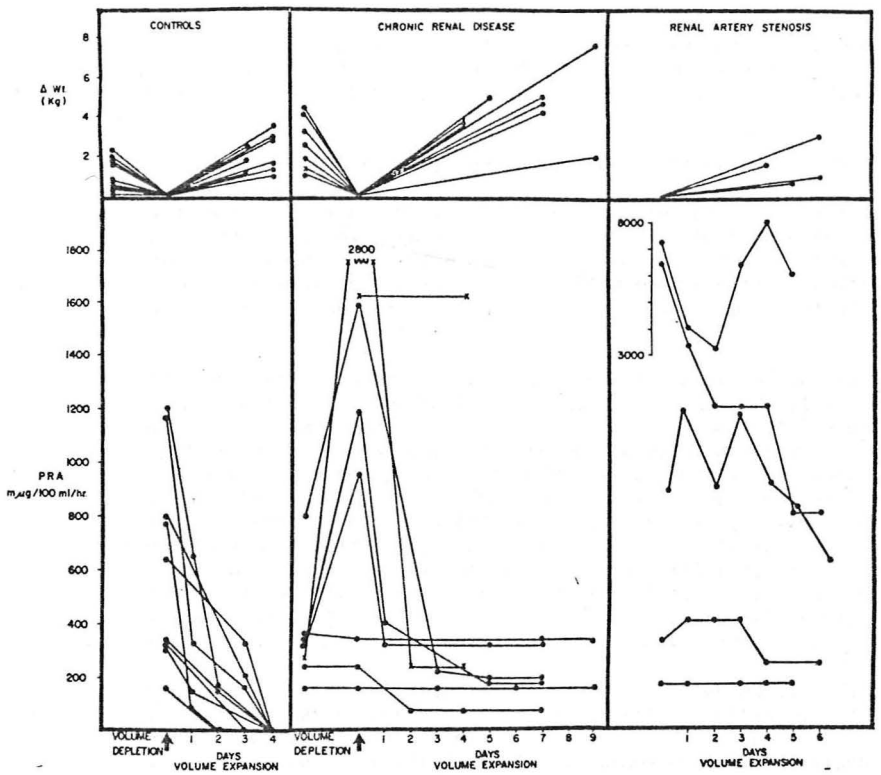
A scheme of these mechanisms is shown below:



Volume-dependent or Controllable Hypertension

Doubts concerning the "inactivity" of the renin mechanism

Despite the fact that plasma and renal venous renin levels are usually normal or even low in CRD patients with controllable hypertension, these "normal" levels may be inappropriately high. The following is taken from a study by D. J. Warren and T. F. Ferris (Lancet 1:159, Jan. 24, 1970). They took 8 CRD patients who had volume-dependent hypertension and first volume depleted them by ultrafiltration during dialysis to the point of postural hypotension. They then gave them extra salt until edema and hypertension developed. The plasma renin (PRA) levels in these patients are shown in the figure, compared to those in controls on the left and in 5 patients with renovascular hypertension on the right. Note the failure of the CRD patients to suppress their renins with volume expansion and the relatively fixed levels in 3 of the 8 CRD patients.



Effect of extracellular depletion and expansion on weight and P.R.A. in controls and in patients with chronic glomerulonephritis and renal-artery stenosis.

Further evidence for a possible role for renin in the volume-dependent group comes from the study by G. Bianchi, et al, (Clin. Sci. 42:27, Jan. 1972). They examined 5 volume-dependent patients before and after 1) hemodialysis and sodium restriction and 2) bilateral nephrectomy. Unlike Gleadle, et al, (Proceed. European Dialysis & Transplant Assoc. 5:131,1969), they observed a fall in BP after nephrectomy in these patients, without change in body fluid volume or sodium content. They interpret this as support for the findings of Onesti, et al, (Transact. Amer. Soc. Artificial Intern. Organs 14:361,1968) that BP is higher for a given concentration of exchangeable sodium before nephrectomy than after, suggesting a hypertensive role for renin in these patients. This corresponds to

our finding that the pressor effect of a given amount of angiotensin by infusion was greater after salt loading and lesser after salt deprivation (Kaplan, N.M. and J.G. Silah. J. Clin. Invest. 43:659, 1964).

Therapy of volume-dependent or controllable hypertension in CRD

1) Sodium restriction. Many CRD patients waste salt if on a rigidly restricted intake. Practically, few will follow such a restricted diet. Therefore, a 2 to 4 gram (30 to 60 mEq) low salt diet would seem reasonable for most. A nice review of the entire spectrum of dietary management in renal failure by D. S. David, et al, is in Lancet 1:34, July 1, 1972.

   The question, "how strict salt restriction should be" was examined in a recent paper from Scribner's group (Ulvila, J.M. et al. J.A.M.A. 220:233, April 10, 1972). They conclude that "hypertension in chronic renal failure develops because many patients must have elevated blood pressure in order to excrete the amounts of sodium usually ingested." Their data show a wide spectrum of salt excretion, those patients excreting the least having the greatest difficulty with hypertension. They state that "control of blood pressure in patients with CRD is difficult, if not impossible without dietary sodium restriction." However, since their attempts to lower blood pressure by dietary salt restriction were often intolerable to the patients, they turned to diuretics.

2) Diuretics. Thiazides have been the usually accepted diuretic but furosemide (Lasix) seems to be gaining wider acceptance, particularly in patients with significant renal insufficiency. The doses may have to be large, up to 2.0 grams per day, (Allison, M. and A. C. Kennedy. Clin. Sci. 41:171, 1971); side effects of abdominal pain, nausea and diarrhea are uncommon and serious toxicity very rare. The efficacy of furosemide in a severely hypertensive patient not previously controlled on aldomet + guanethidine is shown in this table from Ulvila, et al (J.A.M.A. 220:233, April 10, 1972).

Table 3.—Data on Patient 3

Day	Average Daily Blood Pressure (mm Hg)	Sodium Intake (mEq/day)	Average Sodium Excretion (mEq/day)	Average Weight (kg)	Average Serum Creatinine Level (mg/100 ml)	F* (mg/day)	A* (gm/day)	G* (mg/day)
1-21	145/95	20	23	46.2	4.8	0	1.0	0
22-27	148/98	20	26	46.5	4.9	0	1.0	10
28	150/90	40	33	46.5	4.9	0	1.0	10
29-64	165/130	40	37	47.7	5.6	0	1.0	10
65	160/120	20	33	47.6	7.0	80	1.25	5
66	165/116	20	61	46.9	7.0	80	1.25	5
67	150/106	20	50	46.6	...	80	1.25	5
68	...	20	45	...	...	160	1.25	5
69-73	140/90	20	30	46.4	...	240	1.25	5
74	132/94	20	20	46.0	8.0	240	0.75	5
75	130/90	ad lib	4.5	45.5	...	0	0.75	5
76-99	130/86	20	24	46.3	6.7	120	0.75	5
100-110	124/86	40	38	45.5	6.8	120	0	5
110-190	130/88	40	41	45.6	6.7	120	0	0

*F=furosemide; A=aldomet; G=guanethidine sulfate.

Spironolactone (Aldactone) and triamterene (Dyrenium) are to be avoided in most patients with severe CRD since hyperkalemia may be induced. However, the combination of either with a thiazide may be useful in those with milder renal disease in whom hypokalemia may be a problem with a thiazide or furosemide alone.

3) Anti-hypertensive drugs.

a. Chronic therapy: Aldomet has been particularly favored since it may maintain renal blood flow better than other anti-hypertensives. Part of its efficacy relates to its being excreted through the kidneys, resulting in a longer duration of action and lower dosage requirement in patients with CRD.

Patients with more severe hypertension may do better with the combination of hydralazine (Apresoline) plus propranolol (Inderal). The side effects (tachycardia, headache) of large amounts of the peripheral vasodilator are prevented by the beta-sympathetic blocker. (Zacest, R., et al. New Eng. J. Med. 286:617, March 1972). The pharmaco-dynamics of propranolol do not seem to be significantly altered in renal failure (Brit. Med. J. 1:434, May 20, 1972). Dr. Pettinger has been using another vasodilator, Minoxidil, in patients with moderate renal insufficiency and has found it even more effective, as reported by Gottlieb, et al, (Circulation 45: 571, March 1972).

b. Acute therapy: When the blood pressure is dangerously high, I.M. hydralizine is probably the best anti-hypertensive but others prefer I.M. reserpine or I.V. aldomet. Perhaps the best agent, Diazoxide, is still unavailable in the U.S. Glowing reports of its efficacy have appeared, as demonstrated in these figures from Pohl, J.E.F. and H. Thurston, Brit. Med. J. 2:142, Oct. 16, 1971.

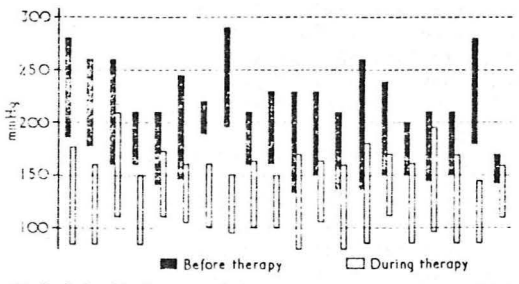


FIG. 2—Lying blood pressure before diazoxide therapy and mean lying blood pressure for each patient during diazoxide treatment.

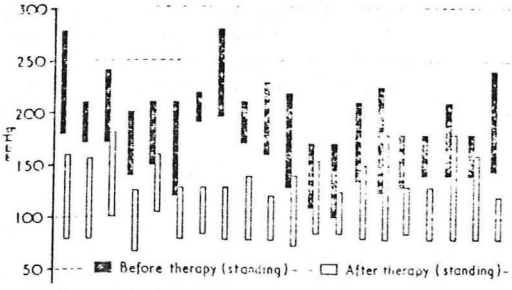


FIG. 3—Standing blood pressure before diazoxide therapy and mean standing blood pressure for each patient during diazoxide therapy.

The aggressive therapy of hypertension with repeated doses of I.V. diazoxide to keep the diastolic blood pressure below 110 mm Hg plus oral furosemide to keep urinary output over 1 liter/day has been said to provide better control of severe hypertension in patients with azotemia, most of whom showed improvement in renal function with continued anti-hypertensive therapy (Mroczek, W.J., et al. Circulation 40:893, Dec. 1969).

The following tables were included in "A practical guide to drug usage in adult patients with impaired renal function" by W. M. Bennett, et al. J.A.M.A. 214:1468, Nov. 23, 1970.

Drug	Maintenance Dose Intervals				Significant Dialysis of Drug (H, Hemodialysis; P, Peritoneal Dialysis)	Route of Excretion Normal Half-Life	Toxic Effects *Remarks
	Normal	Renal Failure					
		Mild	Moderate	Severe			
Antihypertensive Agents							
(a) Methyldopa	Q6h	Q6h	Q8-12h* (x1.5-2)	Q12-18h* (x2-3)	Yes (H)	Renal Hepatic	Prolonged hypotension *Blood pressure best guide to dose intervals
(b) Guanethidine	Q24h	unchanged	unchanged	unchanged	?	?Nonrenal	...
(c) Hydralazine	Q8h	unchanged	unchanged	unchanged	No (HP)	?Nonrenal	...
(d) Reserpine	Q24h	unchanged	unchanged	unchanged	No (HP)	Nonrenal	GI bleeding
Diuretics							
(a) Ethacrynic acid	Q6h As needed for diuresis	Q6h	Q6h	Avoid*	?	Hepatic Renal	Ototoxic; volume depletion *Use alternate if possible
(b) Furosemide	Q6h As needed for diuresis	unchanged*	unchanged*	unchanged*	?	Hepatic	Rare ototoxicity; volume depletion *May use large doses to achieve effect with relative safety
(c) Mercurials	Q24h	Q24h	Avoid	Avoid	?	Renal	Systemic mercury accumulation Nephrotoxic
(d) Thiazides*	Q12h	Q12h	Q12h	Avoid**	?	Renal	Hyperuricemia; volume depletion *Prototype; chlorthiazide **Ineffective
(e) Spironolactone	Q6h	Q6h	Avoid	Avoid	?	Hepatic	Hyperkalemia
(f) Triamterene	Q12h	Q12h	Avoid	Avoid	?	Hepatic	Hyperkalemia

4) Dialysis: The indications for and techniques of dialysis were covered by Dr. Hull and are best left to such experts in this field. As indicated, repeated dialyses may be excellent therapy for volume-related hypertension in CRD (Thomson, E.D., et al. Arch. Intern. Med. 120:153, Aug. 1967).

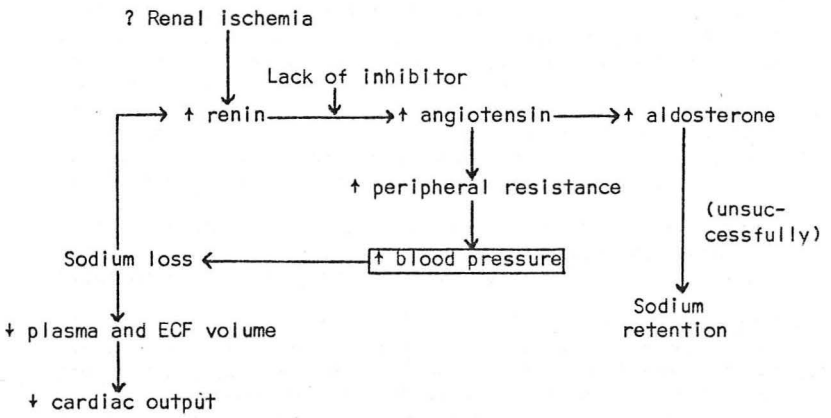
2. *Renin-dependent*

A smaller group of patients with CRD, perhaps 10 to 20%, have hypertension which is not controllable by maintenance of normal fluid volume. The attempt to do so by dialysis may, in fact, cause them to suffer from incapacitating postural hypotension. They tend to have greatly elevated blood pressures when supine and great

sensitivity to even small changes in ECF volume.

These patients with "uncontrollable hypertension" usually have decreased plasma and ECF volume, exchangeable sodium and cardiac output but increased peripheral resistance. And their renin-angiotensin levels are elevated, as shown on the right of the figure on page 8, from Wiedemann, et al. T. A. Kotchen, et al, (J. Clin. Endocrinol. 34:928, June 1972) has shown that the rate of angiotensin generation is strikingly increased in plasma of uremic patients, so that more angiotensin would be produced for any given level of renin. They interpret this enhanced renin reactivity as due to a deficiency of a renin inhibitor that is present in normal plasma. Similarly, enhanced renin reactivity was noted in plasma from patients with renovascular hypertension. The endogenous action of renin may involve other activators or inhibitors (Rieger, D., et al. J. Lab. & Clin. Med. 80:342, Sept. 1972).

A hypothetical scheme for this type of hypertension is shown below:



Uncontrollable or Renin-Dependent Hypertension

Therapy of renin-dependent hypertension

1) Conservative: The hallmark of this hypertension is its resistance to the modalities listed on page 11. The pressure may be worsened by volume depletion, presumably by further activation of renin release.

A glitter of hope has come from John Laragh's group at Columbia-Presbyterian. They presented an abstract (Bühler, F.R., et al. J. Clin. Invest. 51:17a, June 1972) in Atlantic City claiming excellent control of high-renin hypertension by propranolol in doses of 40 to 540 mg a day. Though a few of these patients had malignant hypertension, they did not appear to have marked renal insufficiency so it may be improper to apply their limited experience to the larger number of CRD patients with high renins. Their data should soon be published.

2) Surgical. As previously discussed, bilateral nephrectomies have been performed on a fairly sizable number of these patients with usually excellent control of blood pressure and, if transplantation is feasible, a chance for survival (see Table, page 5). As first documented by Kolff, et al, (Circulation 29-30 Supplement II:23, August 1964), the blood pressure usually decreases to normal within 2 weeks and thereafter remains relatively easy to control by dialysis. . If salt and water intake is excessive, the hypertension can recur but it's now a "volume-dependent" type. As of today, nephrectomies are being done more frequently and earlier to control hypertension in CRD.

In their review of this literature, Brown, et al (Brit. Med. Bull. 27:128, May 1971) make the following comments about hypertension in CRF (chronic renal failure):

"In making the distinction between controllable and uncontrollable hypertension, we have concentrated on the two extremes of what is probably a wide spectrum of response. It is not implied that all cases of hypertension with CRF will be either completely controllable or completely uncontrollable. Criteria of "uncontrollable" hypertension will vary from one centre to another as different dialysis techniques are used. Furthermore, it is likely that some hypertensive patients with CRF are subjected to bilateral nephrectomy partly because their blood pressure is increased and partly because renal function has deteriorated to a point where elective bilateral nephrectomy is justified in preparation for renal transplantation. The fact that a hypertensive patient has had both kidneys removed does not, therefore, imply that hypertension was uncontrollable. For this reason the data relating to nephrectomy are likely to over-estimate the prevalence of the uncontrollable hypertensive state."

3. *Lack of anti-hypertensive mechanism(s)*

In addition to the volume and renin mechanisms, hypertension may supervene from a lack of normal renal vasodepressor mechanisms. The following are possibly involved:

a. Prostaglandin A_1. This is the most likely of the prostaglandins to be anti-hypertensive. (Lee, J.B., et al. Ann. Intern. Med. 74:703, 1971.) It works in humans with essential hypertension but it must be infused intravenously and is only active transiently. Renal vasodilatation and natriuresis are induced by the drug so that as renal perfusion decreases from the lowered arterial pressure, the patient is left normotensive, with a normal renal blood flow and normal sodium excretion. Upjohn is banking heavily on the promise that these agents will find a place in clinical medicine. A general review on the prostaglandins appeared in the Amer. J. Med. 53:92, July 1972, by C. B. Higgins and E. Braunwald.

b. Renomedullary (papillary) interstitial cells secrete a neutral lipid which E. E. Muirhead has shown protects against malignant hypertension in the rabbit (Muirhead, E.E., et al. J. Clin. Invest. 51:181, Jan. 1972). L. Tobian believes these interstitial cells secrete prostaglandins and has presented data on their granularity and content (Amer. J. Med. 52:595, May 1972).

c. Kallikrein is an enzyme which acts on a plasma globulin to produce the precursor of the very potent vasodilator, bradykinin. H. S. Margolius, et al, (Lancet 2:1063, Nov. 13, 1971) have shown a decreased level of urinary kallikrein in patients with essential hypertension.

IV. Hypertension with renovascular disease

A. Experimental: Hypersecretion of renin, in turn causing increased peripheral resistance, had been widely accepted as the mechanism of hypertension after clamping of the renal artery. However, both the role of renin and the mechanism of hypertension have recently been questioned.

1. The role of renin

a. Against

1) Renin levels are only high transiently (Bianchi, G., et al. Clin. Sci. 42:651,1972)

2) Levels of renin-angiotensin may not change after unclipping of the renal artery and relief of hypertension (Funder, J.W., et al. Circ. Res. 27:249, Aug. 1970)

3) Immunization against angiotensin does not protect against the development of experimental renovascular hypertension or reverse the disease once induced (Louis, W.J., et al. Lancet 1:333, Feb. 14, 1970)

b. For

1) Renin levels in the chronic hypertensive state, though below the initially high values, are still relatively increased for the state of the blood pressure and body fluids (Bianchi, G., et al. Clin. Sci. 42:651,1972)

2) Increased pressor sensitivity to angiotensin could explain persistence of hypertension with decreasing levels of renin (Dickinson, C.J. and J.R. Lawrence, Lancet 1:1354,1963)

3) Removal of the clipped kidney as long as 16 months after induction of hypertension in the dog relieves the hypertension (Lupu, A.N., et al. Circ. Res. 30:567, May 1972)

4) Immunization against angiotensin does protect against hypertension (Christlieb, A.R., et al. J. Clin, Invest. 48:1506, 1969)

2. The hemodynamic mechanisms of renovascular hypertension: The studies of Ledingham (Circ. Res. 20-21 Supplement II:187, July 1967) have been amplified by those from Guyton's lab (Fourcade, J.C., et al. Nephron 8:1,1971) and J. D. Swales, et al, (Lancet 2:1181, Nov. 27, 1971). The latter paper is particularly good in putting all of the confusing experimental data into a sensible framework. They show that most of the confusion arises because 2 different rat models have been used, one with the other kidney intact, the other with the other kidney removed.

L. Tobian was the first to demonstrate a difference in the body sodium content in rats with the two types of Goldblatt hypertension (Amer. J. Physiol. 217:458, Aug. 1969). Those animals with the other kidney removed had a 10% increase in total exchangeable sodium. He concludes that "the extra sodium in the one-kidney hypertensive rats can explain the paradox wherein the ischemic kidney in the one-kidney rat secretes a 'normal' amount of renin while the ischemic kidney of the two-kidney rats has a heightened renin secretion."

The work of Swales, et al, (Lancet 2:1181, Nov. 27, 1971) further clarifies the issue. As shown on the left, rats with only one clamped kidney retain sodium, those with the other kidney intact usually lose sodium. (An effect which Guyton's lab believes is secondary to the heightened blood pressure.) As shown on the right, when salt is removed, the blood pressure falls in the clipped-other

kidney removed (and the bilaterally nephrectomized) animals, whereas it goes up in those animals with the other kidney intact (presumably by further stimulating renin release).

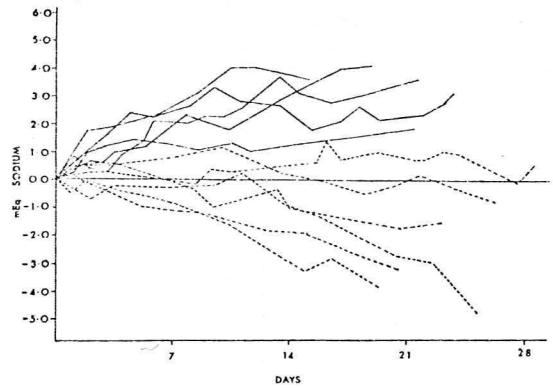


Fig. 1—Cumulative sodium balance in rats with unilateral renal-artery constriction with (——) and without (- - - -) contralateral nephrectomy.

Mean blood-pressure of contralateral-nephrectomy group rose from 95 mm. Hg preoperatively to 140 mm. Hg at the end of first week, rising to 160 mm. Hg. Clip-only animals remained normotensive for 1–2 weeks and then blood-pressure rose to a mean value of 176 mm. Hg over the next 3 weeks.

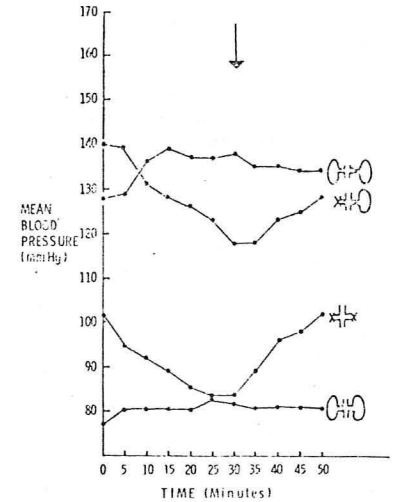
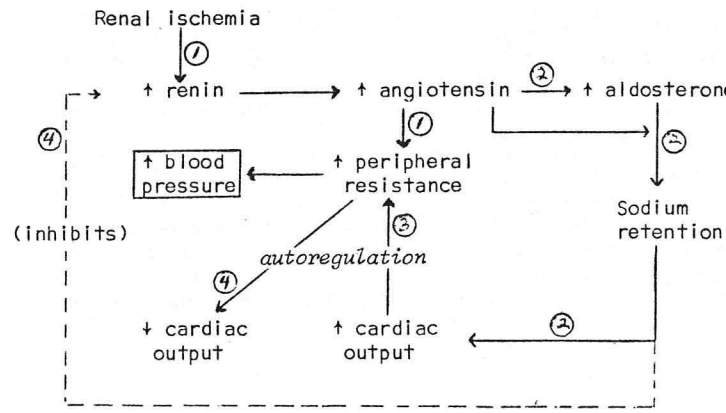


Fig. 3—Blood-pressure changes after removal of 1-2 meq. of sodium from rats by peritoneal dialysis.

An approximately equal amount of saline was reinfused after 45 minutes (arrow). Animals had previously undergone unilateral renal artery constriction without or with contralateral nephrectomy, bilateral nephrectomy with saline loading, or sham bilateral nephrectomy.

Putting it all together, the following step-wise scheme for the hemodynamic mechanism of renovascular hypertension seems valid:



3. Diagnosis of RVH (Renovascular Hypertension)

a. General characteristics: Publications from a large cooperative study of renovascular hypertension (J.A.M.A. 220:1195, May 29, 1972; J.A.M.A. 221:368, July 24, 1972) have mainly confirmed our prior knowledge of the clinical, pathological and radiological aspects of the disease. The care taken in collecting and analyzing the data make this a useful collection. They found these variables to be significantly different between 131 patients with R.V.H. cured by surgery and a group of patients with essential hypertension matched by age, sex, race and blood pressure.

Table 2.—Clinical Characteristics of Essential Hypertension and Renovascular Hypertension Cured by Surgery*

	Essential Hypertension, %	Renovascular Hypertension, %
Duration of hypertension		
< 1 yr	12	24
>10 yr	15	6
Age of onset (>50 yr)	9	15
Family history of hypertension	71	46
Fundi (grade 3 or 4)	7	15
Bruit		
Abdomen	9	45
Flank	1	12
Abdomen or flank	9	48
BUN (>20 mg/100 ml)	8	15
Serum K (<3.4 mEq/liter)	8	16
Serum CO_2 (>30 mEq/liter)	5	17
Urinary casts	9	20
Proteinuria (trace or more)	32	46

b. Renin assays (PRA)

1) Peripheral blood: Some continue to find peripheral blood assays to be useful and adequate (Dixon, S.H., et al. Arch. Surg. 103:615, Nov. 1971). Most, however, find a high frequency of normal peripheral PRA values in patients with curable R.V.H. (Bianchi, G., et al. Clin. Sci. 39:559,1970). In the series reported by J. R. Stockigt, et al, (Lancet 1:1194, June 3, 1972), peripheral PRA would have correctly predicted the response to surgery in only 20 of 37 patients.

2) Renal vein PRA: On the other hand, everyone seems to find this procedure to be valid for diagnosis and prognosis, particularly if evidence of suppression of renin release from the normal side is also observed as shown on the left. The ratio seems to also predict surgical response for lesions other than renal artery stenosis, as shown on the right. (Both taken from Stockigt, J.R., et al. Lancet 1:1194, June 3, 1972.)

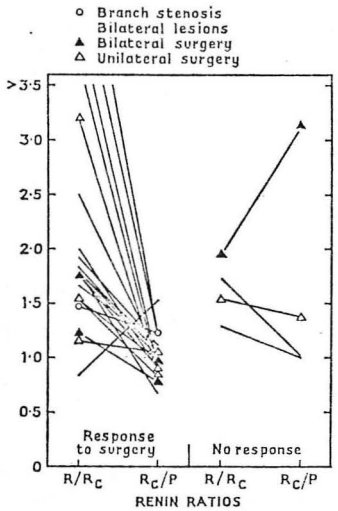


Fig. 2—Relation between the renal-vein-renin ratio (R/Rc) and Rc/P in 25 patients with unilateral or bilateral renal-artery stenosis, classified according to response to surgery.

Rc/P is the ratio between renal-vein P.R.A. from the less involved side and the peripheral level. Unilateral main renal-artery stenosis is shown without symbol.

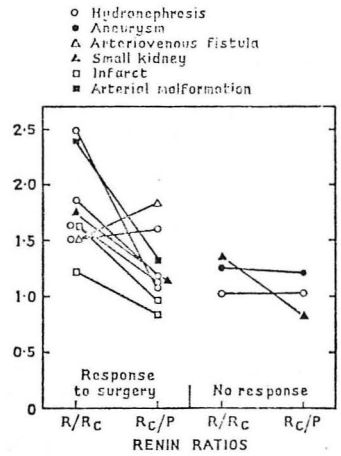


Fig. 3—Relation between the renal-vein-renin ratio (R/Rc) and the ratio of contralateral renal vein to peripheral P.R.A. (Rc/P) in 12 patients with lesions other than renal-artery stenosis, classified according to response to surgery.

Part of this difference may reflect a faster rate of angiotensin generation in assay of the blood from the ischemic kidney (Sambhi, M.P., and C.E. Wiedeman, J. Clin. Invest. 51:22, Jan. 1972).

The ratio also turns out to usually be abnormal, i.e, a difference of more than 1.5, in most patients with bilateral R.V.H. (Klatte, E.C., et al. Radiology 101:301, Nov. 1971). However, an occasional biological quirk may occur, as the patient with malignant hypertension in whom blood from the non-stenotic kidney had a much higher PRA. (McAllister, R.G., et al. J.A.M.A. 221:865, Aug. 21, 1972) This is analagous to the Floyer rat model wherein the stenotic kidney is protected while the non-stenotic kidney is ravaged by necrotizing arteriolitis and hypersecretes renin.

C. Therapy: As more experience is gained, less enthusiasm for surgery has been noted. The following table is taken from a paper based on the experience at the Cleveland Clinic (Stewart, B.H., et al. J. Urology 104:231, Aug. 1970):

Type	Frequency	Age/Sex	Indication for Surgery
Atherosclerosis	60%	60/Men	Good risk, unilateral, recent onset
Intimal fibroplasia	5%	20/	All patients
Medial fibroplasia	30%	30/Women	Few patients
Subadventitial fibroplasia	5%	20/Women	Most patients

A somewhat different view about the management of the 30 to 40% of R.V.H. patients with fibrous or fibromuscular stenoses comes from the Mayo Clinic (Sheps, S.S., et al. Amer. J. Cardiol. 30:55, July 11, 1972). They found progression of the process in 12 of 40 patients with the fibromuscular form and conclude that "Diminishing renal function in the presence of stenotic lesions amenable to revascularization procedures should be considered an indication for surgical intervention, because, although an improvement in hemodynamic function is uncommon, a relentlessly downhill course to irreversible ischemic fibrosis of the renal parenchyma can be arrested."

If the excellent results reported by Bühler, et al, with propranolol therapy of high-renin hypertension holds up, a better approach to the control of R.V.H. may soon be available.

V. Renin-secreting tumors

There have now been about 8 of these reported. It may be that the relatively common association of hypertension with Wilm's tumor (nephroblastoma) involves hyper-secretion of renin (Mitchell, J.D., et al. Arch. Dis. Child. 45:376, 1970).

The case reported by Dick Eddy and S. A. Sanchez from Scott and White Clinic (Ann. Intern. Med. 75:725, Nov. 1971) seems typical with these features:

1) Severe hypertension in relatively young patients

2) Secondary aldosteronism, manifested by hypokalemia

3) Very high renin levels from the kidney harboring the tumor. The renin levels may respond to physiologic stimuli such as posture

4) The tumor is usually recognizable by angiography

5) High renin levels are found in the tumor, which is morphologically a hemangiopericytoma arising from the J-G apparatus