SECONDARY FORMS OF HYPERTENSION -- RECOGNITION AND MANAGEMENT

Medical Grand Rounds

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SECONDARY FORMS OF HYPERTENSION

It may come about that from the smoke and noise of the battle...the urologist will emerge the hero when he proclaims "Well, I once had a case... and I took one kidney out...and I cured high blood pressure."
It is our task for calculate the probabilities of that happy event.

HOMER SMITH, 1948

Pheochromocytoma -- a great "mimic" among hypertensive disorders.

DeCOURREY, 1952

Features of excess of aldosterone are best described by its former name--mineralocortin.

A great majority of hypertensive patients have so-called "essential" hypertension for which life-long medical therapy is necessary. Only a small percentage have a "secondary" cause for their hypertension. And of these "secondary" forms, surgical cure can be accomplished in some. Since the chances are less than one out of ten that a patient may have secondary hypertension, most physicians justifiably restrict laboratory and other investigations only to those patients who have unusual clinical features or who have not responded to therapy.

The incidence of secondary (not necessarily "curable") forms of hypertension from four studies is shown in Table 1 (1-4). The relatively low incidence of secondary hypertension and the relatively high cost of tests in looking for a secondary cause have attracted much debate and discussion. McNeil et al. have analyzed the data from the Cooperative Study on Renovascular Hypertension (5). The cost of finding a patient with renovascular hypertension was $2,000 and that of a surgical cure $20,000. Mind you that this was in 1975. The cost of some tests used in identifying secondary hypertension are shown in Tables 2 and 3. These costs are based on the November 1981 figures. No doubt adjustments have to be made as times change. Some have suggested that the benefit-risk ratio of medical treatment is high in hypertensive patients (6). Why not, therefore, just lower the blood pressure (BP) and keep it down with medications instead of looking for a correctable cause?

TABLE 1. FREQUENCY OF DIAGNOSES IN HYPERTENSIVE SUBJECTS

	Gifford (Percent)	Iimura (Percent)	Berglund (Percent)	Ferguson (Percent)
Essential Hypertension	88.9	87.3	94.0	89.4
Chronic Renal Disease	5.2	5.7	3.6	2.4
Renovascular Disease	4.4	---	0.6	2.8
Primary Aldosteronism	0.4	(0.9)*	0.1	0.8
Cushing's Syndrome	0.3	---	---	---
Coarctation	0.6	---	0.1	---
Pheochromocytoma	0.2	0.2	---	---
Oral Contraceptives	---	---	---**	4.4
Undetermined	---	2.9	---	---
No. of Patients	4,939	448	689	246

* Unconfirmed
** Men only - B.P.s > 175/115 mm Hg

TABLE 2. APPROXIMATE COSTS OF CERTAIN TESTS (NOVEMBER, 1981)

PLASMA RENIN ACTIVITY	$40 - $50
PLASMA ALDOSTERONE	$78 - $85
PLASMA CATECHOLAMINES	$66 - $72 (Nichols)
SPOT URINE FOR METANEPHRINES	$15 - $18
24 HOUR URINE FOR METANEPHRINES	$16 - $32
24 HOUR URINE FOR VMA	$28 - $34
24 HOUR URINE FOR CATECHOLS	$30 - $45 ($72)
24 HOUR URINE FOR ALDOSTERONE	$78 - $97

TABLE 3. COSTS (APPROXIMATE) FOR SOME RADIOLOGICAL PROCEDURES (NOVEMBER, 1981)

1.	HYPERTENSIVE IVP	$75 - $100+
2.	CT SCAN OF THE ABDOMEN	$300 - $400+
3.	RENAL VEIN RENINS	$250+
4.	RENAL ARTERIOGRAM	$218 - $330+
5.	RENAL SCAN	$230 - $250

For the health planners and social scientists, the above arguments and assumptions seem reasonable to recommend treatment but while minimizing investigations. However, for clinicians involved directly in patient care decisions are not that easy. Although the percentage of patients with secondary hypertension is small (? 5%), their absolute number, however, is by no means small considering the prevalence of hypertension. In our efforts to minimize the cost, should we deny these patients of tests to find a correctable cause? Should we not free this considerable number of patients from the burden of life-long drug therapy?

A study reported from the Mayo Clinic has underscored the low incidence of secondary hypertension (Table 4) (7). However, these low figures may be misleading. Some patients may have been diagnosed but not operated. Interesting is also the fact that repeat visits by the same patient were counted in the estimated total of patients seen. Now I want to present some personal views. Virtually in every form of hypertension, there is an inverse relationship between the duration of hypertension and curability. Therefore, is delaying workup for years considered good medicine? Cost-benefit analysis should not singly form the basis of treating individual patients. We as physicians should consider benefit-risk ratio more than the cost-benefit ratio. If cost-benefit analysis alone were to guide us, then we would deny many patients of chronic dialysis and coronary bypass surgery.

TABLE 4. —**Average Annual Frequency of Operations for Secondary Hypertension at the Mayo Clinic, 1973, 1974, and 1975**

Disorder	No./ year	Hypertensives, expected no.	Hypertensives, per 10,000 No.	Hypertensives, per 10,000 %
Renal artery stenosis	46.7	26,589	18	0.18
Pheochromocytoma removal	10.3	26,589	4	0.04
Aldosterone-producing adenoma excision	2.7	26,589	1	0.01
Total	59.7	26,589	23	0.23

I am not suggesting that we should work up every hypertensive patient for a secondary cause. Instead, I want to make a plea that in our zest to be cost-effective, we should not have the notion that all hypertension is "essential" unless proven otherwise. Except for aortic coarctation and some cases of pheochromocytoma and Cushing's syndrome, many patients with secondary hypertension have no distinguishing symptoms or signs. Failure to respond to medical therapy is not peculiar to secondary hypertension; patients with renovascular hypertension do respond to adequate therapy. Each patient must be considered on an individual basis so that appropriate strategy is outlined which would benefit that patient. Such individualized approach should weigh the one-time cost of finding a secondary hypertension against the expense of life-long drug therapy, quality of life and other costs (frequent tests to monitor drug effects, work absenteeism, etc.). Having discussed some philosophical and scientific views, certain generalities can be made as to the indications for the search for secondary hypertension (Table 5).

TABLE 5. Candidates for Work-up of Secondary Hypertension

1. Age < 30 years or sudden onset of hypertension > 50 years.
2. Severe hypertension, particularly the accelerated-malignant form.
3. Abdominal bruit (systolic & diastolic).
4. History of hematuria, flank pain.
5. Palpable kidney.
6. Unusual lability in blood pressure.
7. Symptomatic hypertensive patients.
8. Unexpected pressor response to certain drugs or anesthesia.
9. Unexplained metabolic problems--weight loss, hypokalemia, hypercalcemia, hyperglycemia, etc.
10. Absent or delayed peripheral pulses.
11. Clinical features of endocrine disorders--hyper- and hypothyroidism, Cushings, acromegaly.
12. Family history of endocrine disorder.
13. Poor response to adequate drug therapy.
14. Non-compliant patients.

INITIAL EVALUATION AND WORK-UP

About 20% of the American adults have hypertension and as discussed above, only a small percentage have a secondary cause. Often the secondary form of hypertension is discovered after several patient visits. However, the initial evaluation and work-up is very important.

Enough time should be devoted on the initial visit in obtaining accurate history in detail, however trivial it may sound to be, and family history should also be explored. A thorough and meticulous physical examination should be performed on every hypertensive individual during the initial evaluation. The basic investigations suggested are listed in Table 6. Special tests like renins, metanephrines, IVP, etc., are reserved for certain patients and will be discussed under specific disease entities. Routine plasma renins are not recommended. Certainly, for most patients a thorough check up and simple outpatient laboratory tests (CBC, SMA, urinalysis, etc.) are all that

will be required. The discovery of secondary causes of hypertension requires knowledge of their pathophysiology, natural course with variations, clinical and biochemical manifestations. Only the important forms of secondary hypertension will be discussed and other causes are mentioned for completeness.

TABLE 6. BASIC INVESTIGATIONS - HYPERTENSION

- CBC
- SMA
- URINALYSIS
- ? CHEST X-RAY
- EKG

Recent reports suggest that laboratory distinction can be made between essential and secondary hypertension by measuring erythrocyte cation fluxes (8, 9) and sodium-lithium countertransport in red cells (10). It was noted that sodium-potassium flux ratio in RBCs was abnormally low in patients with essential hypertension and in their normotensive relatives whereas the cation flux ratio was normal in patients with secondary hypertension (Figure 1). An abnormally low ratio may also be seen in renal failure patients. These studies suggest then that essential hypertension is characterized by possible cellular defect in the sodium transport. However, further studies are needed to confirm the preliminary reports. These studies, however, represent a major advance in the basic mechanism(s) of essential hypertension and (by exclusion) of secondary hypertension and indicate that essential hypertension may indeed be due to an inherited defect in the sodium transport.

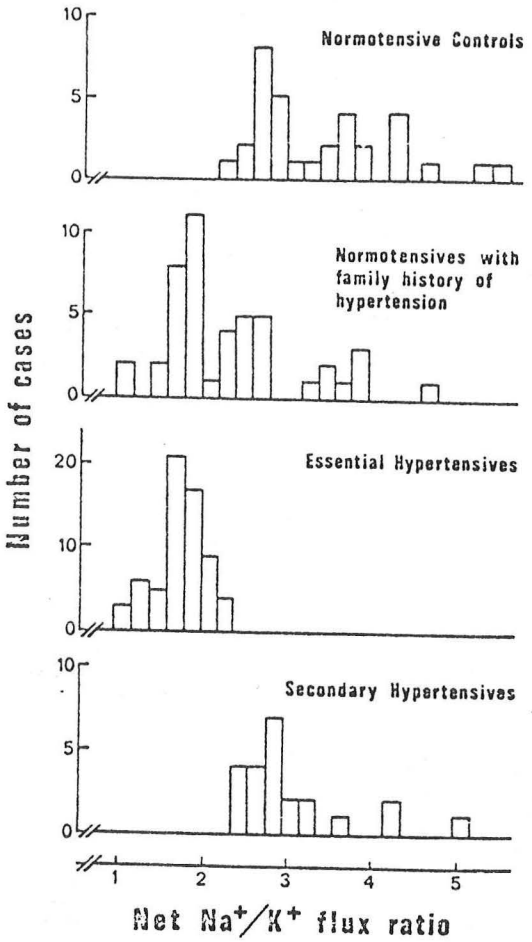


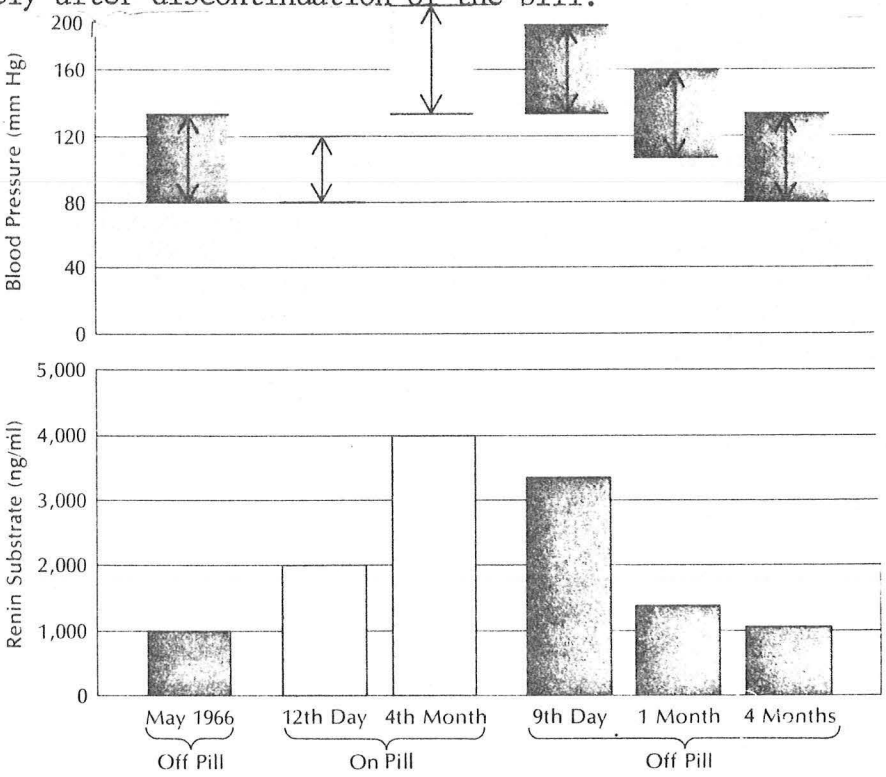
Figure 1. Erythrocyte cation fluxes in essential and secondary hypertension. From Garay RP, Elghozi J, Dagher G, et al.: *N Engl J Med* 302:769, 1980).

HYPERTENSION CAUSED BY ORAL CONTRACEPTIVE AGENTS

The oral contraceptive pills are one of the widely prescribed pharmacological agents and are highly reliable in preventing pregnancy. The changing social values no doubt have contributed to increasing use of oral contraceptive pills (OCP). It is now 21 years since the pill was first marketed, 19 years since the first report of association between OCP and hypertension appeared, 13 years since the first Senate hearings on the issues relating to OCP, and during the last few years OCP has become a principal topic of discussion by many women's and health groups. Since married couples are generally opting for permanent sterilization, it is that large segment of young unmarried women that is increasingly employing temporary method of contraception--OCP. It is thus important for us to recognize the possible unwanted sequelae of OCP use and for today's discussion, I will only address the problem of elevated blood pressure in OCP users.

In 1967, it was reported that hypertension occurring during OCP use can be corrected by the discontinuation of the pills (Figure 2) (11). During the next several years, many workers independently reported strong association

between OCP use and hypertension (12, 13, 14). From reviewing the data, it is evident that it may take months to years for hypertension to manifest in OCP users and it may take several months before hypertension regresses after stopping the pill. However, in some individuals, hypertension may persist indefinitely after discontinuation of the pill.



Hypertensive states linked to the renin/angiotensin/aldosterone system include the blood pressure elevation associated with oral contraceptives; in such cases the principal abnormality is an excess in plasma renin substrate accompanying pill use. As in patient above, substrate levels and blood pressure decline to normal when pill is discontinued. (From Laragh JH, Sealey JE, Ledingham JG, et al.: *JAMA* 201:918, 1967).

INCIDENCE

The exact incidence of hypertension due to OCP is still debated. The incidence figures vary from 0 to 18 percent of women on OCP developing blood pressures of 140/90 or higher. The results of one prospective survey (Kaiser-Permanante Contraceptive Drug Study) are shown in Figure 3. This study compared the blood pressures of 4088 "pill" users with 4661 "non-pill" users and 4609 "past users" over a 2 to 6 year period. Approximately 4% of the pill users developed a blood pressure greater than 140/90 compared with 1.5% in non-users (2.7 fold difference). The observation that "never users" and "past users" had essentially similar incidences underscores the potential reversibility of the hypertensive phenomenon. Another large survey of OCP induced hypertension is that from the British Royal College of General Practitioners in which 5% of 23,000 users developed hypertension over a 5 year period at a rate 2.6 times that of a comparable group of non-users (13). Weir and associates (14) found in a prospective study over a 4 year period that use of

OCP was associated with progressive increase in blood pressure (+ 14.2/8.5 mm Hg, final average) (Figure 4).

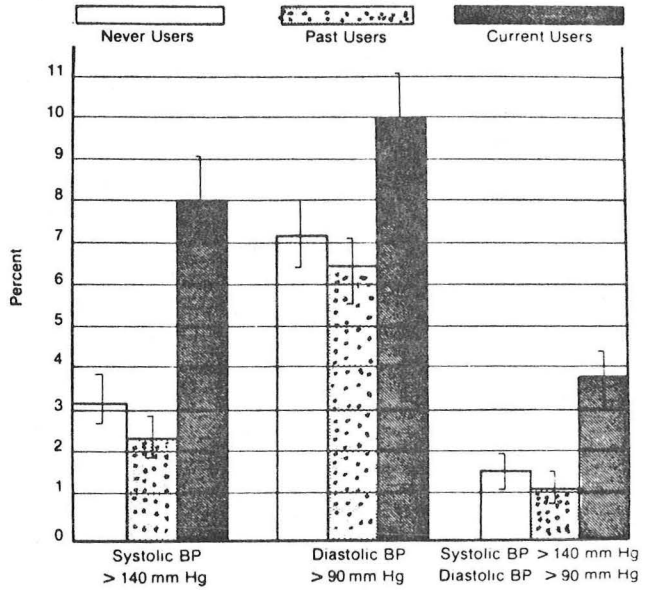


Figure 3. Age-adjusted percentages of women with elevated blood pressure *(BP)* by oral contraceptive use (95% confidence intervals). (From Fisch IR, Frank J: JAMA 237:2499, 1977.

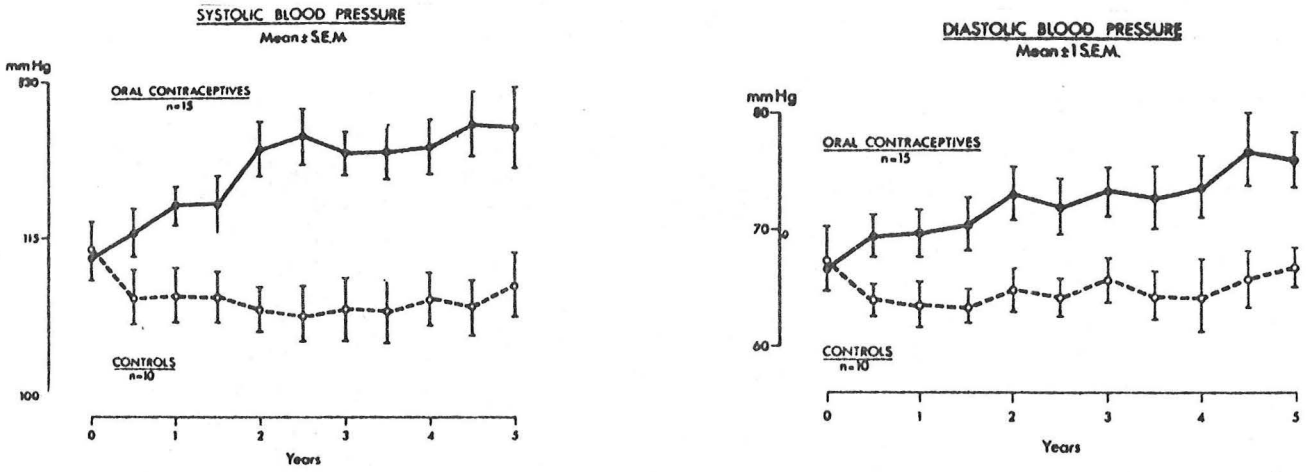


Figure 4. Changes in systolic (*right*) and diastolic (*left*) blood pressure after 5 yr in women taking oral contraceptives and in a control group of women using intrauterine contraceptive devices or cervical diaphragms (From Weir RJ, Briggs E, Mack A, et al: *Br Med J* 1:533, 1974)

There is some evidence that OCP use has no significant effect on mean arterial blood pressure in black women followed for 6-24 months (15). On the other hand, in a separate study it was shown that Mexican-American women have a greater susceptibility to develop OCP induced hypertension (12). The basis for these racial differences is not known at the present. One can only wonder whether the increased prevalences of low-renin status and obesity in blacks and Mexican-Americans respectively are possible factors in the observed differences.

Even in the "normotensive" range, many women using OCP show a definite rise in the blood pressure. And, most demonstrate changes in the renin-angiotensin system independent of blood pressure changes. Thus, there is no doubt that OCP use does induce circulatory and humoral changes, the degree of which varies from one patient to the other. Although the risk is variable, certain risk factors can be identified: older age, past history of hypertension, and family history of hypertension.

INFLUENCE OF THE COMPOSITION OF THE "PILL"

Some studies have shown that progestagen used alone has no deleterious effect on blood pressure (16, 17). The Royal College of General Practitioners study, however, showed a correlation between incidence of hypertension and dose of progestagen. Natural progesterone has aldosterone antagonistic property but synthetic progestational agents do not possess such an effect. The present evidence suggests that synthetic progestational agents have a mineralocorticoid-like effect and therefore cause sodium/fluid retention.

The dose of estrogen may affect the frequency of hypertension (18). It has been suggested that pill containing low dose estrogen (30 μg) had less of an effect on blood pressure than the customary 50 μg estrogen pill. If a patient on OCP develops hypertension, perhaps a low dose estrogen pill can be tried if the oral contraceptive method is to be continued.

MECHANISM OF OCP INDUCED HYPERTENSION

The oral contraceptives have effects on many biochemical mechanisms and it is likely that more than one pathogenetic mechanism may be responsible for the development of hypertension. The renin-angiotensin system appears to be a key mechanism, however. Helmer and Griffith first described increases in the renin substrate with the administration of diethylstilbestrol (19). In 1967, Helmer and Judson reported a markedly elevated renin substrate in pregnancy and in women treated with OCP (20). Subsequently, Cain et al. noted an increase in angiotensin II levels within 5 days of OCP use (21). The increase in angiotensin level would produce hypertension by two effects: direct vasoconstriction and increased aldosterone release resulting in sodium retention (Figure 5). In normal circumstances, high levels of angiotensin II would suppress further release of renin by a negative feedback mechanism. However, in OCP induced hypertension, this inhibitory mechanism is deranged and thus keeping the renin-angiotensin interaction continuously active (Figure 6) (22). Although similar changes in the renin-angiotensin system can be seen in women who do not develop hypertension, angiotensin may still be implicated in OCP hypertension since administration of saralasin, an angiotensin antagonist, has been shown to lower the blood pressure in women with OCP hypertension (23).

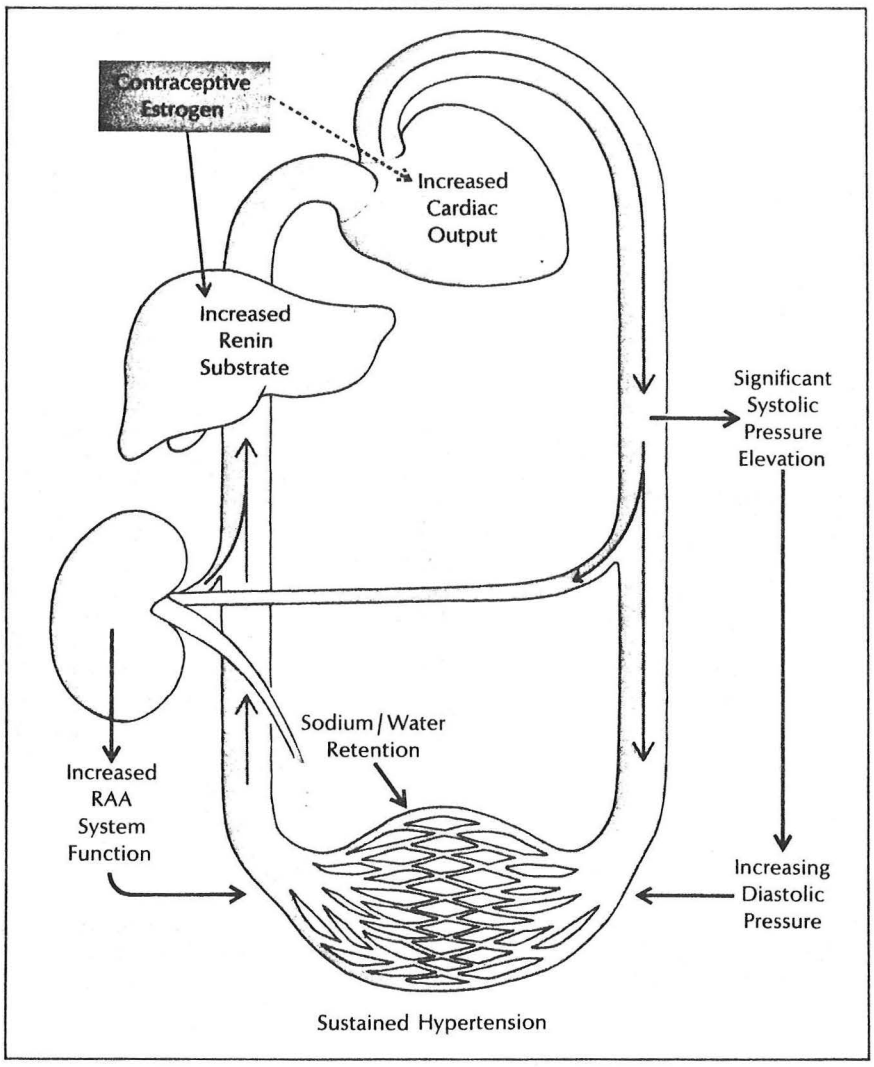


Figure 5. *In contraceptive hypertension, blood pressure rise is thought to begin after increases in renin substrate stimulate renin-angiotensin-aldosterone (RAA) system, leading to sodium retention and volume expansion.*

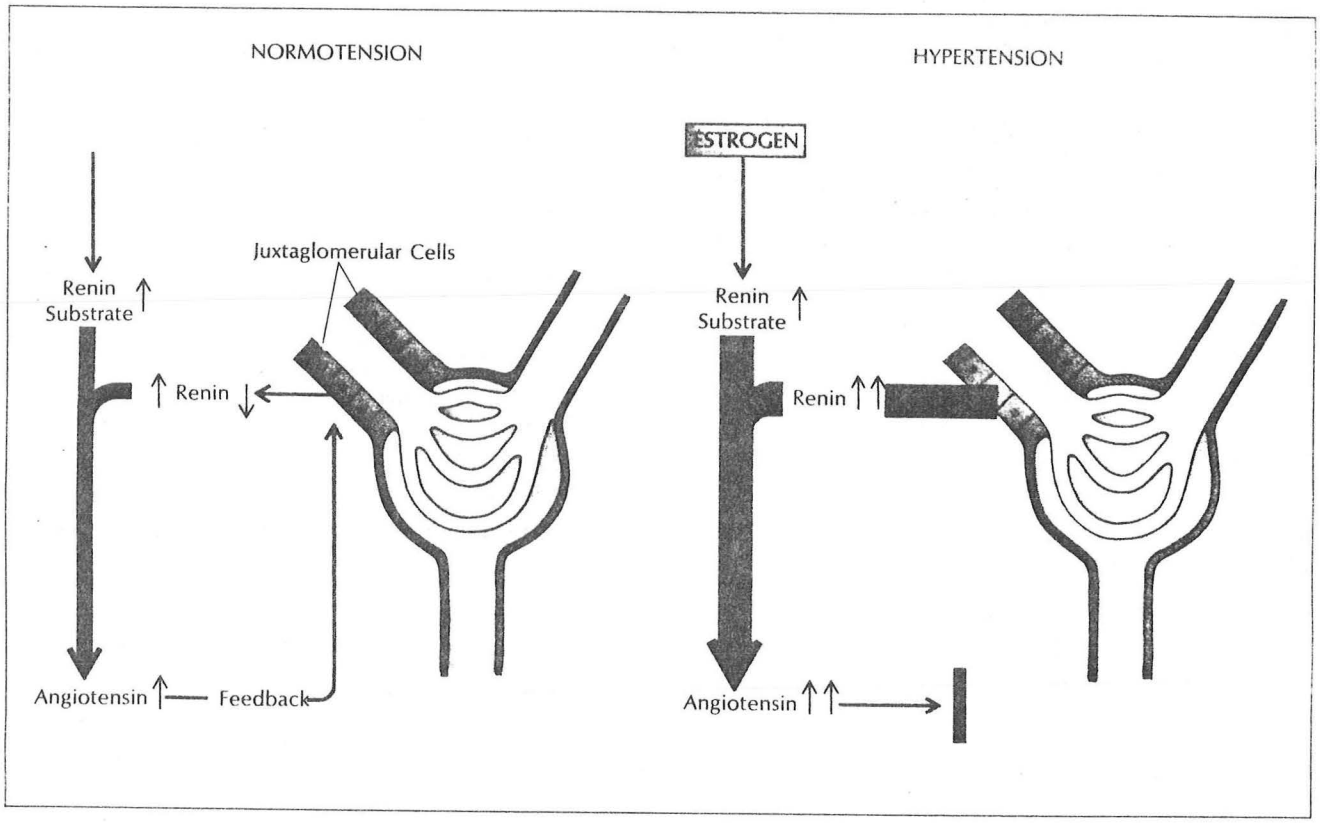


Figure 6. *While estrogen stimulates the renin-angiotensin system through effects on renin substrate, normally excessive activation is prevented via a feedback mechanism, above left, inhibiting renin release from the kidney. A postulated defect in renin suppression that prevents normal feedback in women who become hypertensive on the pill is shown at right.*

It was also shown that women on OCP had an average increase in total exchangeable sodium of 226 mEq (24). This increase in exchangeable sodium could be prevented by administration of spironolactone. It has been reported that in women taking OCP for 2-3 months, cardiac output and plasma volume increased alone with simultaneous rise in the blood pressure (25). These hemodynamic changes then are similar to those found in early pregnancy.

In summary, it is likely that there are several inter-related mechanisms by which OCP alters the regulation of blood pressure. There is ample evidence to implicate a key role of the renin-angiotensin system in estrogen induced hypertension and the synthetic progestational agents may have a mineralocorticoid effect and further contribute to increased blood pressure.

CLINICAL PICTURE

The onset of hypertension with OCP use is highly variable. OCP induced hypertension may appear in weeks, months, or years. In one study, the interval from initiation of therapy was one year (26) but in another study hypertension appeared by the 10th week (27). A great majority of patients with OCP induced hypertension only have mild to moderate elevation in blood pressure but few may develop severe accelerated hypertension and renal damage (28). There is no

certain way by which the physician may anticipate which patient will develop hypertension and when. Patients with OCP induced hypertension generally have no unusual physical characteristics.

Plasma renin activity, plasma renin substrate and aldosterone excretion rate are higher in OCP induced hypertension, but these tests need not be routinely performed.

MANAGEMENT

In patients whose blood pressure rises above 140/90, OCP use should be discontinued if possible as soon as some other method of contraception is arranged. Hypertension that is reversible on discontinuation of OCP usually resolves within six months or less. A few patients may respond dramatically within one month but some may take as long as one year. The average interval between OCP discontinuation and resolution of hypertension in one study was 4.4 months. Therefore, it seems wise to follow patients with OCP induced mild hypertension carefully for 4-6 months without any specific treatment or investigations.

Management of patients with significant hypertension (e.g. BP greater than 160/110) and/or with target organ damage requires appropriate clinical judgment. In such situations immediate antihypertensive therapy may be necessary which can be subsequently tapered off if the cardiovascular status remains stable. Most of the patients with OCP induced hypertension respond to diuretics whether or not the pill is discontinued. Although thiazides can be tried, it has been suggested that these patients respond favorably to spironolactone (29). Additional antihypertensive drugs can be given in the conventional way (Table 7).

TABLE 7. MANAGEMENT OF OCP INDUCED HYPERTENSION

1. DISCONTINUE THE OCP IF POSSIBLE
2. IF NOT, TREAT WITH DIURETICS (SPIRONOLACTONE)
3. ADD OTHER AGENTS IN THE USUAL FASHION

Individuals with pre-existing hypertension, strong family history of cardiovascular disease and those with other known cardiovascular risk factors should be discouraged from using OCP. For patients in whom pregnancy may be risky or other contraceptive methods are unacceptable, the pill may be continued along with measures to control hypertension. In such cases, both the patient and physician should recognize the potential risk of continued OCP use. In patients with severe or complicated hypertension induced by OCP, there is no justification for its continued use.

GUIDELINES FOR PREVENTION AND FOLLOW-UP

The incidence and perhaps the complications of OCP use may be reduced by the following approach (Table 8).

TABLE 8. GUIDELINES FOR PREVENTION/FOLLOW-UP OF OCP HYPERTENSION

1.	DISCOURAGE OCP IN OBESE PATIENTS > 35 YEARS WITH PRE-EXISTING VASCULAR DISEASE
2.	IF OCP IS NECESSARY, USE SMALLEST EFFECTIVE DOSE OF ESTROGEN
3.	SWITCH TO "MINI-PILL" (PROGESTAGEN ONLY) IF NECESSARY
4.	SUPPLY ONLY LIMITED QUANTITY OF OCP -- TO LAST FOR 3-4 MONTHS
5.	IF PATIENT DEVELOPS COMPLICATIONS OF HYPERTENSION, STOP THE OCP

1. OCP use must be strongly discouraged in patients with pre-existing hypertension and those who are older than 35 years or obese.

2. If the continued use of OCP is necessary, the smallest effective dose of estrogen should be considered. Even then, the blood pressure must be carefully followed at periodic intervals.

3. If a women develops hypertension with an estrogen-progestagen preparation, perhaps "mini-pill" containing only the progestational component may be tried.

4. Only limited quantities of OCP should be prescribed each time, to last for 3-4 months so that the patient must return for evaluation and blood pressure check.

In the last several years, we have seen emergence of oral contraceptive as the most reliable method of regulating reproduction. In many countries, the use of the pill has led to contraceptive revolution and avoidance of unwanted pregnancies. The benefits of OCP use clearly outlast the possible risks. However, the use of oral contraceptive pills should not be taken casually and periodic surveillance of pill users is warranted to detect and prevent its possible complications.

ILLUSTRATIVE CASES

CASE 1: OCP induced hypertension, initially unrecognized.

R.A.: 28 year old Latin-American female was found to have elevated blood pressures (148/100, 150/100) in 1976-1977. She was placed on antihyper-

tensive drugs and the blood pressure was well controlled. She was seen by me on 11/1/80, her blood pressure was 120/82 on propranolol. Evaluation of her past history revealed that she was taking OCP at the time the diagnosis of hypertension was made 4 years ago. In the mean time (between 1976/1977 and 1980) she stopped OCP but the blood pressure medications were continued without interruption. On 11/24/80 propranolol was discontinued and she was followed monthly. In June, 1981 her blood pressure was 136/76-80 without any therapy.

The above case illustrates the need for proper history taking on the initial visit. If this is not done, the patient may be passed on from one doctor to the other with the assumption of "past history of hypertension" and a reversible cause may be missed.

CASE 2: Prompt resolution of OCP induced hypertension.

J.A.: A 39 year old black female went to see an orthopedist who took her blood pressure and found it to be elevated (170/120 mm Hg) and this was confirmed on repeated measurements. She was seen by me on December 2 and 16, 1980; her BPs were 140-150/94-100. She was taking orthonovum for birth control and this was stopped immediately with her consent. A month later, her BP was 130/84-86.

HYPERTENSION ASSOCIATED WITH RENAL PARENCHYMAL DISEASE

Systemic hypertension can be both a cause and consequence of hypertension. The kidney is a target organ frequently damaged by chronic or uncontrolled hypertension. On the other hand severe hypertension may ensue from renal dysfunction. In some instances it is not possible to decide which came first. In those who end up with renal insufficiency, despite the availability of chronic maintenance dialysis, many patients succumb to cardiovascular disease. Therefore, recognition of hypertension as a major complicating marker should dictate vigorous control of blood pressure in these patients.

TABLE 9. RENAL DISEASES CAUSING HYPERTENSION

1. ACUTE RENAL DISEASE
2. CHRONIC RENAL DISEASE
3. UNILATERAL PARENCHYMAL DISEASE

MECHANISM(S) OF HYPERTENSION

There is no general agreement concerning the mechanism of hypertension in renal disease although certain concepts are well recognized. During the early stages, the hemodynamic abnormality appears to reside in the increased

cardiac output and with time, cardiac output returns toward the normal but the peripheral vascular resistance is elevated (30). Thus the "normal" cardiac output may in effect be inappropriate to the existing peripheral vascular resistance.

Two major mechanisms have been proposed to explain the basis of hypertension in renal disease (31) (Table 10): 1) volume dependent and 2) renin dependent. However, in many patients it is impossible to make a clear cut distinction between these two mechanisms. I will cover this subject very briefly. The controllable form of hypertension is associated with sodium retention, volume expansion and increased cardiac output. Conceivably, the primary fault might not be the increased cardiac output but the failure of renal mechanisms to promote appropriate sodium loss. The reason why sodium is retained in the first place may be an impaired natriuretic response of the kidney to a given level of blood pressure; when normal sodium excretion is no longer possible, the level of blood pressure progressively rises. An increase in plasma volume, extracellular fluid and exchangeable sodium has been demonstrated in uremic hypertensives. Salt and water depletion (by diuretics or by dialysis) has a beneficial effect on hypertension. However, due to differences in methodological techniques, types of renal diseases, stage of renal failure and presence of other factors, some discrepancies exist about the role of "volume" in renal hypertension.

TABLE 10. MECHANISMS OF HYPERTENSION IN RENAL DISEASE

1.	VOLUME
2.	RENIN
3.	ABNORMAL RELATIONSHIP BETWEEN 1 AND 2
4.	? PROSTAGLANDIN DEFICIENCY
5.	? KALLIKREIN SYSTEM

Although the plasma renin activity (PRA) is variable in chronic renal disease, not only the "high" but also "normal" PRA is inappropriate to the level of volume status. Normally, the retention of sodium/volume should exert a negative feedback on renin release but in some forms of renal failure the usual inverse relationship between sodium and renin is distorted and the opposing mechanisms are thrown out of balance. If such is the case, then attempts to control the blood pressure by getting rid of sodium may cause disproportionate activation of renin release. Whatever the primary fault may be, there appears to be an abnormal, disrupted relationship between volume and renin in hypertension associated with renal disease but this concept may be too simplistic.

PROSTAGLANDINS AND KININS

Since the kidney is an important site for the synthesis of "vasodepressor" substances like some prostaglandins, it is possible that a relative or absolute deficiency of these ubiquitous substances may elevate the blood pressure in chronic renal disease. However, since prostaglandins in general serve a local function, conclusions about their role in renal hypertension should be regarded with caution. Moreover, there is variation in response to prostaglandins from one species to the other. Irrespective of which class of prostaglandins are involved, hypertension could result from their deficiency. Since certain PGs synthesized in the vascular smooth muscle relax the resistance vessels and since intrarenal PGs blunt the vasoconstrictor stimuli, the absence of these mechanisms may elevate the blood pressure.

The actions of renal prostaglandins are further complicated by interaction between these substances and other intra- or extrarenal humoral systems, e.g. the kallikrein-kinin system. The kallikrein system has two components--in the plasma and in the kidney, either or both of which may alter the blood pressure by effects on vascular smooth muscle and on sodium transport. Some studies have shown lower kallikrein excretion in renal hypertension (32). Again, considerable caution is necessary in interpreting the kallikrein-kinin data.

In addition to the above, a third set of substances--renomedullary, neutral and polar lipids--may be important in renal hypertension. These substances which are neither diuretic or natriuretic have antihypertensive effects in animals.

CERTAIN SPECIFIC ENTITIES

TABLE CERTAIN SPECIFIC RENAL DISEASES ASSOCIATED WITH HYPERTENSION

1. ACUTE GLOMERULONEPHRITIS
2. ACCELERATED/MALIGNANT HYPERTENSION
3. PYELONEPHRITIS
4. DIABETIC NEPHROPATHY
5. POLYCYSTIC KIDNEY DISEASE
6. SCLERODERMA, ANGIITIS
7. POST-TRANSPLANTATION HYPERTENSION

1. Acute glomerulonephritis: Although the typical syndrome of acute glomerulonephritis has become less common, it still occurs as an important cause of renal disease in the childhood. It is now believed that this entity

can be caused by a variety of agents other than type-specific streptococcus. Usually, in the early phases, hypertension is present in association with edema and oliguria. Because the onset of hypertension is relatively rapid in acute glomerulonephritis, the patients are at risk of developing malignant hypertension and encephalopathy. Therefore, blood pressure should be adequately controlled. Although, for a long time, it has been thought that the elevation of blood pressure in acute glomerulonephritis is due to fluid overload and high cardiac output, some recent observations suggest that peripheral resistance is also increased (33).

The hypertension should be treated by salt and water restriction and, in many cases, with a diuretic sufficient to produce gradual and steady diuresis. However, additional antihypertensive agents such as adrenergic blockers and vasodilators may be necessary. The classical disease is self-limited, but in some patients the disease may progress with inevitable chronic renal insufficiency.

2. Accelerated and malignant hypertension. The accelerated and malignant forms of hypertension are characterized by Grades III and IV Keith-Wagener retinopathy respectively. The major pathophysiological marker of these hypertensive states is rapid vascular damage. The necrotizing arteriolitis accompanying malignant hypertension inevitably leads to irreversible renal damage if the hypertension is not aggressively treated. Although the incidence of malignant hypertension is probably falling, it seems to occur more frequently in patients with prior renal dysfunction than when the kidney is normal. Vigorous control of hypertension permits the damaged arterioles to heal and has been shown to improve the renal function in most patients (34).

3. Hypertension and pyelonephritis. There is no convincing relationship between acute pyelonephritis and hypertension. However, hypertension can be a feature of chronic pyelonephritis. For many years, it has been claimed that the patients with hypertension are susceptible to attacks of pyelonephritis, but this is unproven. The sometimes striking relationship between chronic pyelonephritis and hypertension is probably due to the parenchymal destruction caused by pyelonephritis. Hypertension may be a result of vascular occlusion from scarring and the resultant activation of renin release. High plasma renin activity can be demonstrated in many, but not all, patients with pyelonephritis. Whatever the underlying mechanism may be, the hypertension associated with pyelonephritis should be controlled by appropriate means in order to preserve the renal function.

4. Diabetic nephropathy and hypertension. Hypertension is present in the majority of patients with diabetic nephropathy (35). The hypertension is the result of glomerular disease and also arteriolar disease. Some patients affected by this disorder may have hyporeninemic hypoaldosteronism which may predispose them to develop hyperkalemia and thus potassium supplements or potassium-sparing agents should be used with great caution or not at all. While formulating the antihypertensive regimen, consideration must be given to certain drugs (e.g. guanethidine) that can cause postural hypotension which is unwelcome--particularly in diabetics with autonomic insufficiency. One should also keep in mind that certain diuretics (such as thiazides) may aggravate hyperglycemia, necessitating close attention to the patient and possible adjustment in the insulin dose.

5. Polycystic kidney disease. Hypertension is frequently encountered in the adult form of polycystic kidney disease. Cardiac and cerebrovascular events account for considerable mortality and illustrate the significance of hypertension in this disease. The mechanism of hypertension is not clear, but it could be due to the combination of ischemia caused by the enlarging cysts and loss of vasodepressor (prostaglandins) function from the destruction of renal parenchyma. The hypertension, once detected, should be vigorously controlled.

6. Scleroderma. When scleroderma involves the kidneys, hypertension appears very rapidly and contributes to rapid decline in the renal function; it also heralds an unfavorable prognosis. The renal lesions seen in scleroderma are similar to those seen in malignant hypertension. The fulminating course and the malignant hypertension suggest rapid renal ischemia from narrowing of the interlobular arteries. These patients have high levels of plasma renin activity. The blood pressure should be treated with potent antihypertensive agents and, often, the patient should be hospitalized. The conventional agents are not uniformly effective in controlling the hypertension associated with renal scleroderma. There has been a revival of hope for these patients now by the availability of captopril, an inhibitor of angiotensin formation, supported by encouraging reports of improved survival of patients treated with captopril (36). The specific advantage of captopril in this situation is perhaps a reflection of a toxic role of the renin-angiotensin system in scleroderma kidney, and captopril successfully antagonizes this pressor mechanism.

Treatment of Hypertension in Chronic Renal Disease (patients not yet on dialysis). In this category, the patients who have not yet reached the end-stage renal failure (i.e., the glomerular filtration rate may range between 10 and 30 ml/min) are discussed. The renal insufficiency can be from any cause and effective control of blood pressure may delay or even arrest the progression of renal failure. The therapy of hypertension is important in protecting the failing kidney and the cardiovascular system. With proper control of blood pressure even patients presenting with malignant hypertension survive for long periods of time (37).

TABLE 12. TREATMENT OF HYPERTENSION IN CHRONIC RENAL DISEASE

1. SALT RESTRICTION (MOST BUT NOT ALL PATIENTS)
2. DIURETICS (USUALLY LOOP-DIURETICS)
3. CLONIDINE/METHYLDOPA OR BETA-BLOCKERS PLUS HYDRALAZINE OR MINOXIDIL
4. ? CAPTOPRIL
5. DIALYSIS
6. BILATERAL NEPHRECTOMY

Salt restriction: Patients with impaired renal function are prone to salt and water retention and, therefore, efforts should be made to limit the salt intake. However, a subgroup of patients with chronic renal disease may be "salt losers" and excessive salt restriction in these patients may result in salt and volume deficiency. Therefore, the need for salt restriction should be assessed individually. It is necessary to restrict sodium chloride to 2-4 gms/day in most patients in order to control the blood pressure satisfactorily. Many patients cannot adhere to a salt restricted diet and, therefore, need diuretics for proper regulation of salt and water balance.

Duretics: As with essential hypertension, diuretics are the cornerstone of antihypertensive therapy in patients with renal insufficiency. Thiazide diuretics are not usually used because of their tendency to decrease the glomerular filtration rate and their ineffectiveness when the glomerular filtration rate is reduced below 20 ml/min. A loop diuretic (furosemide or ethacrynic acid) is usually the first agent to be used in the treatment of hypertension complicated by renal insufficiency. The daily dose of furosemide is quite variable and depends on the height of blood pressure and the severity of renal impairment; the therapy may be begun with 40 mg twice a day and the dose adjusted as necessary. Some patients may require doses up to 480-600 mg/day. Potassium-sparing agents, spironolactone and triamterene, should be avoided when azotemia is present because of the risk of hyperkalemia. This risk is particularly present in those with diabetic nephropathy (and hyporeninemic hypoaldosteronism). However, in individuals who develop hypokalemia with diuretics, a potassium-sparing agent may be added with due care. Some patients who are truly refractory to large doses of loop-diuretics may respond after the addition of another diuretic, metolazone (38). But, the combination of these diuretics should be used with great caution and under careful supervision because sometimes a brisk diuresis may ensue with attendant dangers.

Additional therapy: If the blood pressure cannot be successfully controlled with diuretics, additional drugs will be needed. The second drug could be alpha-methyldopa or clonidine. The pharmacological profile and their mechanism of action is similar and both preserve renal blood flow. The starting dose of clonidine is 0.1 mg given twice a day, and the dose should be titrated as necessary and the daily dose should be kept under 1.6 mg/day because of sedation and other side effects with high doses. For alpha-methyldopa, the initial dose should be 250 mg twice a day and can be increased to a maximum daily dose of 3,000 mg. The most common side effects of alpha-methyldopa and clonidine are drowsiness and dry mouth--particularly with high doses--and these effects diminish with continued administration of the drugs. If the blood pressure is not controlled with a diuretic and methyldopa or clonidine, a direct vasodilator such as hydralazine or minoxidil should be used. If methyldopa or clonidine prove ineffective, they should be tapered off when instituting alternate drug therapy. The direct vasodilators produce prompt response and are the most valuable agents for the control of hypertension associated with renal disease. Since the direct vasodilators usually produce reflex tachycardia and activation of the sympathetic nervous system, concomitant administration of an adrenergic blocker is mandatory. The dose of hydralazine is variable and one can initiate the therapy with 25 mg twice a day, increasing it to a maximum of 300-400 mg/day.

An alternative to hydralazine is minoxidil, which is the most potent vasodilator available at the present time. Minoxidil has been found to be extremely useful in the treatment of severe hypertension not responding to conventional agents and hypertension associated with renal impairment. The availability of minoxidil has revolutionized the treatment of hypertension complicated by renal insufficiency. Until a few years ago bilateral nephrectomy was performed in patients not responding to conventional antihypertensive agents, but now the need for such an irreversible procedure has been virtually eliminated by the use of minoxidil (37). There are reports showing significant improvement or stabilization of renal function during chronic therapy with minoxidil. A few patients were removed from hemodialysis after the recovery of renal function by aggressive control of hypertension with minoxidil. The initial dose of minoxidil should be 5 to 10 mg/day, titrated upwards to 60-100 mg/day depending on the response.

The reflex tachycardia accompanying the use of hydralazine and minoxidil can be blocked by the simultaneous administration of a beta-adrenergic blocking agent. The dosage of beta-blocker should be assessed individually--enough to attenuate the sympathetic response to vasodilators. Many patients appear to require upwards of 160 mg/day of propranolol to satisfactorily control the undesirable hemodybanic effects of vasodilators. Another side effect of vasodilators is fluid retention--particularly with minoxidil--and this should always be anticipated and treated with an appropriate dose of a loop-diuretic. Thus, the maximum beneficial therapeutic effect of direct vasodilators can only be achieved with concomitant administration of a diuretic and a beta-blocker. If for some reason a beta-blocker cannot be used or is contraindicated, then one can use alpha-methyldopa or clonidine to block the activation of sympathetic tone. Captopril has been useful in controlling severe renal hypertension (39). Interestingly enough, it has worked even in some patients with renoprival hypertension (40) but has been ineffective in others. The dose and perhaps the frequency of administration of captopril should be reduced in renal insufficiency because it is mainly excreted by the kidney. However, the decision to use captopril in renal hypertension should be made with due consideration of risk versus benefit as the severe complications of this drug (proteinuria, neutropenia) have occurred mostly in patients with prior renal disease.

Beta-blocking drugs alone are not helpful in the management of hypertension complicated by renal dysfunction; but if the renal dysfunction is mild, they may be tried. The role of beta-blockers and their relationship to renal function has been controversial as some isolated reports demonstrated a deterioration in renal function with their use. But, it is not clear whether these observations were due to drug effects or progression of underlying renal disease. It is fair to say that beta-blockers are being used in large numbers of patients with renal disease without evidence of any toxic effect on the kidneys. Although effective blood pressure reduction in patients with chronic renal disease may sometimes be accompanied by rises in the BUN and serum creatinine levels, the physician should not get unduly alarmed by such observations as the renal function will likely stabilize or improve with maintenance of blood pressure control (34).

Treatment of Hypertensive Patients with Chronic Renal Disease (patients on dialysis). These patients have no meaningful excretory function and, therefore, their fluid volume and salt balance are critical in maintaining the hypertension.

In most patients in this stage, hypertension can be controlled by removal of sodium and water by ultrafiltration dialysis and by restriction of salt and fluid intake. If adequate blood pressure control cannot be maintained with regular dialysis and restriction of salt intake, additional antihypertensive measures are instituted similar to the guidelines outlined for patients who are not on dialysis. Appropriate doses of alpha-methyldopa or clonidine should be tried for several weeks and if response is less than optimal, then one should substitute these drugs with the combination of hydralazine or minoxidil with beta-blockers. Although hydralazine is a useful antihypertensive drug in the management of hypertension in chronic renal disease, we are particularly impressed by the therapeutic success with minoxidil. Of course, the accompanying reflex activation of sympathetic tone should be counteracted with a beta-blocker or methyldopa or clonidine.

If the patient's blood pressure cannot be controlled despite ultra-filtration dialysis, dietary restriction of salt and water, and use of antihypertensive drugs in the maximal doses that the patient can tolerate, then consideration should be given to performing bilateral nephrectomy as the vasopressor function of the kidney may be responsible for severe hypertension. It should be reemphasized that, with the availability of minoxidil, the need for bilateral nephrectomy is minimized. It has been suggested that the plasma renin activity may serve as a useful indicator of possible response to bilateral nephrectomy. However, because of overlapping values of plasma renin among patients with end-stage renal disease and since many antihypertensive agents used in this situation affect the renins, it is not possible to recommend plasma renin activity as a predictor of response to bilateral nephrectomy. The decision is made as demanded by patient's clinical condition after all other possible therapeutic modalities have proven ineffective. Bilateral nephrectomy may not only improve the blood pressure drastically, it also results in marked general improvement of the patient.

The choice of antihypertensive drugs and the pharmacological principles for the anephric patient are similar to those patients on maintenance dialysis.

HYPERTENSION IN UNILATERAL RENAL PARENCHYMAL DISEASE

Under this group, heterogenous clinicopathological entities (excluding renovascular hypertension) are included. These entities (Table 13) are grouped together because in some cases nephrectomy relieves the hypertension.

TABLE 13. HYPERTENSION IN UNILATERAL RENAL PARENCHYMAL DISEASES

1. HYDRONEPHROSIS
2. CYSTS/TUMORS
3. CONGENITAL HYPOPLASIA ("ASK-UPMARK KIDNEY")
4. INFECTIONS
5. TRAUMA
6. J.G. CELL TUMORS (PRIMARY RENINISM)

1. Unilateral hydronephrosis. There are numerous case studies showing the association between hydronephrosis and hypertension (41, 42). The renin-angiotensin system is the implicated mechanism in most patients. If the cause cannot be corrected, then perhaps nephrectomy should be considered to alleviate the hypertension, particularly when the renin production by the affected kidney is shown to be high. The "angiotensinogenic" basis of hypertension in hydronephrosis is further substantiated by blood pressure reduction with saralasin.

2. Unilateral cysts and tumors. Although the incidence of hypertension with renal cysts is not strikingly high, significant hypertension may occur from compression of renal vessels by large cysts. Hypertension may be relieved by nephrectomy or simple drainage of the cyst (43, 44).

3. Congenital hypoplasia. This condition predominantly seen in females may be diffuse or segmental. The renal changes could be also due to chronic vesicoureteral reflux. Sometimes, hypertension may be severe with hypoplastic kidney. It is difficult to distinguish congenital hypoplasia (also referred to as the Ask Upmark kidney) from renal artery stenosis clinically, but the renal arteriogram should be helpful. If significant hypertension is present, unilateral nephrectomy must be considered (45).

4. Infections (pyelonephritis, tuberculosis, etc.). The relationship of hypertension to unilateral pyelonephritis and tuberculosis is uncertain. Significant invasion and destruction of the renal tissue may cause obliteration of vessels and activate the renin-angiotensin system or eliminate the vasodepressor system. First, medical treatment of hypertension as well as of primary disease should be undertaken. More aggressive approach (surgical) should be considered only if the hypertension is refractory and that too only if the pathogenetic role of affected kidney is assessed by estimating the renal vein renins. A recent study, however, found frequent false negative renal vein renin tests in patients with unilateral renal disease and some patients benefited from operation despite the lack of lateralizing renal vein renins (46).

5. Renal trauma. Hypertension can be an early or a delayed complication of renal trauma. The cause of hypertension is presumed to be ischemia and activation of the renin-angiotensin system. In 1939 Page in a classic study demonstrated that experimental compression of one or both the kidneys in dogs by cellophane resulted in hypertension (47). In evaluating any hypertensive patient, history of abdominal trauma must be obtained. Observation and medical therapy is indicated initially. However, if the condition is deteriorating, a more aggressive approach will become necessary.

6. Renin producing tumor (primary reninism). Primary reninism (also called Robertson-Kihara syndrome) is a distinct clinicopathological entity due to renin producing juxtaglomerular cell tumor (48, 49). In a few cases, preoperative diagnosis was made and in others it was made post-surgically. This entity which is quite rare is characterized by severe hypertension in young people who show hyperreninemia, secondary hyperaldosteronism in the absence of renal artery stenosis. The tumor has been benign in all reported instances. The size is generally small (2mm to 4cm) and if not suspected, it may be missed by the radiologist and the surgeon. Considering the benignity of tumor, partial nephrectomy is all that will be necessary if the mass is localized preoperatively.

POST-TRANSPLANTATION HYPERTENSION

Hypertension after renal transplantation is unfortunately a fairly common occurrence, the reported incidence varying from 13 to 83% (50, 51) and poses significant diagnostic and management problems. Possible etiologies include steroid therapy, the presence of native kidneys causing high renin hypertension, rejection, recurrent renal lesion, fluid overload and transplant renal artery stenosis.

Hypertension in the transplant recipient is more likely to occur if the patient is known to have hypertension before the transplantation. All the possible etiological factors must be carefully considered so that appropriate control of hypertension is achieved to prevent further renal damage. Although the presence of a bruit over the transplant region suggests renal artery stenosis, such bruits are frequently heard even in patients without hypertension. However, sudden disappearance of a bruit may signify poor renal function. In suspected patients, renal arteriography must be undertaken which may show angiographic findings of immunologic rejection. The clinical significance of angiographically detected stenosis must be confirmed with selective renin determinations from the graft as well as native renal veins if present. If correction is indicated, transluminal angioplasty appears to be the initial choice which minimizes the operative risks. Of course if this fails, revascularization is done. Sometimes in desparate situations, bilateral nephrectomy is done to control the blood pressure.

As far as the medical treatment is concerned, standard antihypertensive therapy discussed previously should be implemented along with measures to adjust the steroid therapy, etc.

RENOVASCULAR HYPERTENSION

Renovascular hypertension is elevation of blood pressure caused by renal ischemia, which is cured by relief of vascular obstruction. Therefore, mere presence of renal artery stenosis does not denote renovascular hypertension unless the obstruction to renal blood flow is causally linked to hypertension. It is well known that in many individuals the renal artery stenosis may be coincidental and in such patients surgical correction of stenosis will have no effect on the hypertensive process (Table 14). Although only a small percentage of all hypertensives have renovascular hypertension, identification of this entity is important since surgical correction and "cure" of their hypertension is possible. The isolation of patients with renovascular hypertension from that vast number of patients with essential hypertension on clinical grounds is not possible and requires considerable judgment.

TABLE 14. **Incidence of Renal Arterial Lesions in Normotensive and Hypertensive Patients**

	Normotensive		Hypertensive	
Age	Normal	Lesion	Normal	Lesion
31–40	7	3	6	10
41–50	26	8	14	22
51–60	99	35	28	50
Over 60	69	56	15	48

From Eyler WR. et al: *Radiology* 78:879. 1962.

Although the estimates of incidence range from less than 1% to 16% depending on the referral center, diagnostic criteria, etc., my guess is that the actual incidence may be close to 2-4%. The prevalence of renovascular hypertension is likely to be higher in patients with severe hypertension (52) (Table 14A) and in whites than in blacks.

TABLE 14A. RENOVASCULAR HYPERTENSION IN PATIENTS WITH MALIGNANT HYPERTENSION. (From Davis BA, Crook JE, Vestal RE, et al.: *N Engl J Med* 301:1273, 1979).

NO. OF PATIENTS	RENAL ARTERY STENOSIS	RENOVASCULAR HYPERTENSION
123	43 (35%)	28 (23%)

PATHOPHYSIOLOGY

The understanding of renovascular hypertension began in 1934 with the experiment of Goldblatt who demonstrated that bilateral renal artery constriction in the dog resulted in hypertension and relief of this constriction resulted in return to normotension (53). The clinical ramifications of Dr. Goldblatt's experiment were readily apparent and search for curable hypertension began. As early as 1937, relief of hypertension was obtained in a seven year old boy following removal of the diseased kidney (54). In 1956 (55), Homer Smith reviewed the records of 575 patients subjected to surgery for presumed renovascular hypertension and reported that only 20% were cured, whereas the rest had needless surgery. Justifiably, the enthusiasm for surgical treatment of renovascular hypertension faded;with the advent of angiography and the awareness of the role of renin and improvement in surgical therapy, interest has been renewed.

There is overwhelming evidence to suggest that the renovascular hypertension is principally mediated by the activation of the renin-angiotensin system (Figure 7). There is conflicting evidence about a possible relationship between the renin-angiotensin system and vasoactive prostaglandins. Experimental renal ischemia alters the amount of renal vein prostaglandins but the results are not concordant. At the present time, the absolute or a relative role of prostaglandins or their interaction with the renin-angiotensin system is not known.

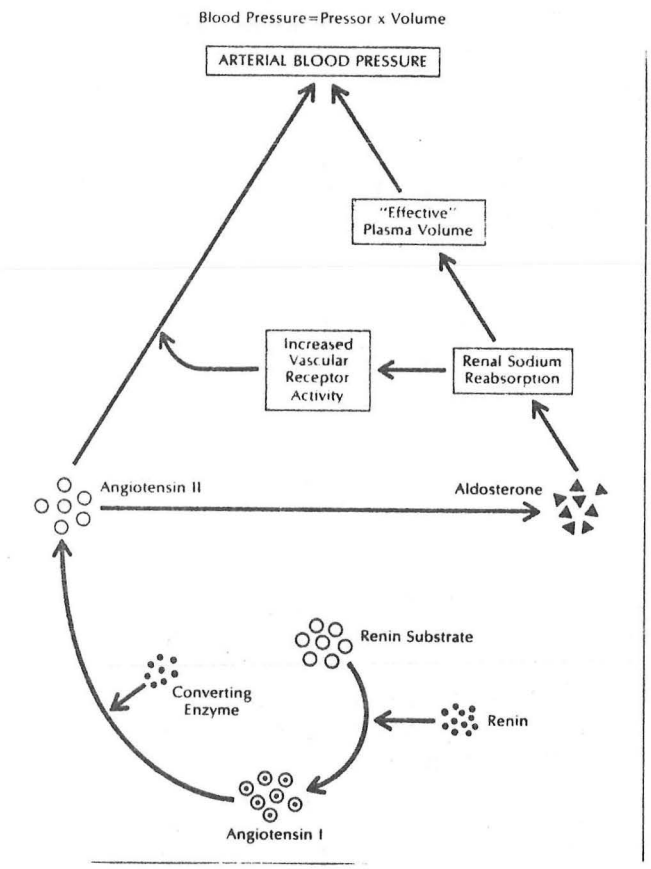


Figure 7. Renal ischemia leading to increased renin production and systemic hypertension.

PATHOLOGY

The advent of angiography has permitted identification of different anatomical entities causing renal artery stenosis. The lesions of the renal artery are divided into categories based upon the pathological or morphological expression of the disease as shown below (Table 15).

1. Atherosclerosis
2. Fibromuscular lesions--subclassified into intimal, medial or adventitial dysplasia
3. Thrombosis and embolism
4. Arteritis
5. Aneurysms or dissections

The most frequently occurring lesion is atherosclerotic which occurs in the fourth through seventh decades and occurs more frequently in men. The lesion is commonly present at the origin on the proximal third of the renal vessel (Figure 8). The atherosclerotic lesions frequently co-exist with extra-renal arterial disease.

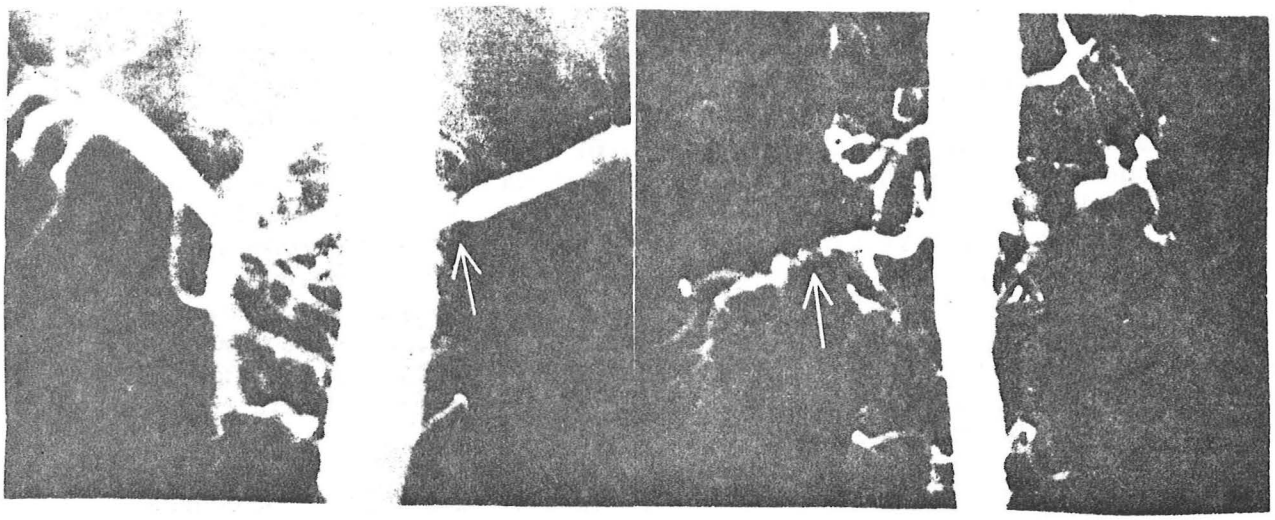


Figure 8. Renal artery stenosis from atherosclerosis (left) and fibromuscular dysplasia (right).

The most common form of fibromuscular dysplasia is the medial hyperplasia, usually of the mid or distal third of one or eventually both renal arteries. It manifests more commonly in women in their second and third decades and is usually found on the right side first. In the Cooperative Study of renovascular hypertension, atherosclerotic lesions accounted for 63% and the arterial dysplasias for 32% (56).

CLINICAL CHARACTERISTICS

There are few distinctive clinical features which strongly suggest the presence of renal artery stenosis and often on clinical grounds alone, it is difficult to isolate this group from that of essential hypertension. Some clinical features of renovascular hypertension contrasted with those of essential hypertension are shown in Table 16. Some clinical clues are worth remembering. Severity of hypertension not responding to conventional therapy may sometimes be seen in patients with renovascular hypertension. Certainly abrupt onset of hypertension after the age of 50 years is strongly suggestive of atherosclerotic renovascular hypertension. Hypertension in the younger age groups (age less than 30) is also a sign of possible secondary etiology such as renovascular obstruction.

Table 16. **Clinical Characteristics of 131 Patients with Proved Renovascular Hypertension Compared to a Matched Group of Patients with Essential Hypertension**

	Essential hypertension (%)	Renovascular hypertension (%)
Duration of hypertension <1 year	12	24
Age of onset after 50	9	15
Family history of hypertension	71	46
Grade 3 or 4 funduscopic changes	7	15
Abdominal bruit	9	46
BUN >20 mg/100 ml	8	15
Serum K <3.4 mEq/liter	8	16
Urinary casts	9	20
Proteinuria	32	46

From Simon N. et al: *JAMA* 220:1209, 1972.

Although some patients with renovascular hypertension may give a family history of hypertension, the absence of such a history warrants consideration of underlying etiology. The presence of an abdominal or flank bruit is of some diagnostic usefulness. The bruit originating from renal vessels is high pitched systolic, or systolic-diastolic high pitched murmur heard over the umbilical area and radiates to the side of stenosis. When a similar bruit is heard in the back at the level of the second-third dorsal vertebrae, it usually signifies severe renovascular obstruction. Although bruits were found to be five times more frequent in renovascular disease, their diagnostic specifity is limited by the not infrequent occurrence of abdominal bruits in patients with essential hypertension. The results of abdominal bruits were correlated with angiograms in 503 patients and it was found that most of the bruits were caused by compression of the celiac artery (57).

Increased incidence of erythrocytosis, diabetes and tachycardia--have been noted in renovascular hypertension but these are of no value in evaluating individual patients. Hypokalemia or borderline potassium levels are seen in about 35 to 45% of patients with renovascular hypertension and the serum sodium also in the low normal range.

DIAGNOSTIC STUDIES

Since clinical characteristics frequently give no clue to the presence of renovascular hypertension, certain non-invasive studies can be performed. If the suspicion is high, invasive procedures are necessary. The aim of the workup is not only to document the renal artery stenosis but also to correlate its role in causing hypertension. Indications for the workup are shown in Table 17.

TABLE 17. INDICATIONS FOR WORK-UP OF RENOVASCULAR HYPERTENSION

1.	AGE < 30 YEARS OR > 50 YEARS (IF HYPERTENSION IS ABRUPT)
2.	SEVERE, ACCELERATED OR MALIGNANT HYPERTENSION
3.	POOR RESPONSE TO MAXIMUM DOSES OF "TRIPLE" DRUG THERAPY (DIURETIC, VASODILATOR AND ADRENERGIC BLOCKER)
4.	INTOLERABLE ADVERSE EFFECTS FROM DRUG THERAPY
5.	ABDOMINAL BRUIT (SYSTOLIC & DIASTOLIC)
6.	RAPID DETERIORATION OF RENAL FUNCTION
7.	NON-COMPLIANT PATIENTS

RAPID SEQUENCE INTRAVENOUS PYELOGRAM (IVP)

This procedure has been widely used as a screening test for renovascular hypertension since its introduction in 1964. The major abnormalities suggestive of renovascular hypertension are disparity in renal size, delayed appearance of the dye and delayed disappearance of the dye. Only rarely is the ureteral notching from the collateral vessels seen on the IVP. A difference of more than 1 cm from pole to pole is considered abnormal. However, the right kidney may appear smaller by 1.0 cm or so normally because of rotation by the liver. This margin must be given while interpreting the findings on the right side.

In the Cooperative Study, the IVP alone gave 11.4% false positives and 17% false negatives. The major advantage with an IVP is that it can be easily accomplished with a complication rate of less than 1%, that too usually mild. Of course, IVPs should be done with caution if at all in diabetics, in some with renal insufficiency and in patients with myeloma, etc.

A positive IVP is seen in 61% of patients with bilateral disease. A negative IVP does not rule out renovascular hypertension and physicians should use clinical judgment in proceeding with additional studies.

TABLE 18. **Diagnostic Accuracy of the Intravenous Pyelogram**

Reference	Patients with essential hypertension		Patients with renovascular hypertension	
	No. of cases	% Abnormal*	No. of cases	% Abnormal*
Cooperative Study: *JAMA* 220:1218, 1972	771	11.4	138	83.0
Maxwell: *New Engl J Med* 270:213, 1964	121	17.0	42	93.0
Wilson: *Arch Intern Med* 112:270, 1963	127	8.0	128	72.0

*Using three variables: differences in renal length, appearance time, and hyperconcentration.
From Bookstein JJ, et al: *JAMA* 220:1218, 1972.

RENOGRAMS AND RENAL SCINTIGRAPHY

The isotope renogram is based on the premise that Hippuran labeled with ^{131}I is taken up and excreted by the kidney. The deviations that can be expected in patients with renovascular obstruction therefore are its decreased uptake and delayed excretion. This procedure too is subject to false positive (20% and false negative (14%) results (58). The Cooperative Study utilized a computerized technique for the analysis of renograms applying multiple variables. However, a simple index of functional asymmetry obtained by comparing the ratio

of amplitudes of the curve at the time of first kidney peak (T max) divided by the ratio of amplitudes at the time of one-half its maximal value (i.e., T 1/2 max) provides good discrimination limiting the false positives. With a critical ratio of 0.8, 90% of patients with renovascular disease showed abnormal studies compared to 10% abnormal studies (false positives) in essential hypertension.

The advantages of renograms are its simplicity and lack of discomfort to the patient. The risk of iodine sensitivity is minimized (but not 100% absent) because of the small quantity of iodine. The disadvantages are that the abnormal scans are obtained in some patients with non-vascular renal diseases and this procedure provides fewer details than an IVP and therefore the latter is preferred.

SPLIT FUNCTION TESTS

These tests are no longer done in most centers for the diagnosis of renovascular hypertension. Split function studies were originally proposed on the principle that with decreased renal blood flow there is increased reabsorption of water and sodium from the glomerular filtrate resulting in decreased urinary volume and sodium with corresponding increase in the concentration of PAH, inulin and creatinine on the affected side (59). The value of this test in predicting surgical cure approaches 75%, much superior to IVP. However, these tests have fallen into general disfavor due to morbidity associated with bilateral ureteral catheterization--infection, ureteral obstruction and sometimes renal shutdown.

PERIPHERAL PLASMA RENIN ACTIVITY

Since true renovascular hypertension is a classical example of so-called "renin-dependent" hypertension, when the PRA became a common laboratory tool, it was quickly assumed that in renovascular hypertension PRA is elevated. Subsequent observations suggested that some patients with essential hypertension also have high PRA. A recent review on this subject reveals that a high PRA was found only in 63% of surgically cured patients (60).

The PRA test should not be ordered and done casually. Many antihypertensive drugs (adrenergic blockers) suppress the PRA and others (diuretics, vasodilators) elevate the PRA. Moreover, PRA is subject to considerable variation by diet, posture, exercise, caffeine, etc. (Figure 9). Therefore, in order to interpret the PRA properly, the test should be done under controlled circumstances when the patient is on a stable diet (100-120 mEq sodium). A collection of simultaneous 24 hour urine for indexing sodium excretion agonist PRA enhances the value of this test (Figure 10). Anyway, a third of patients with renovascular hypertension do not have high PRA. Therefore, PRA should be used as an adjunct and not as a definitive test. Although stimulation of renin secretion may unmask the high-renin state, such a maneuver may not add much to the workup.

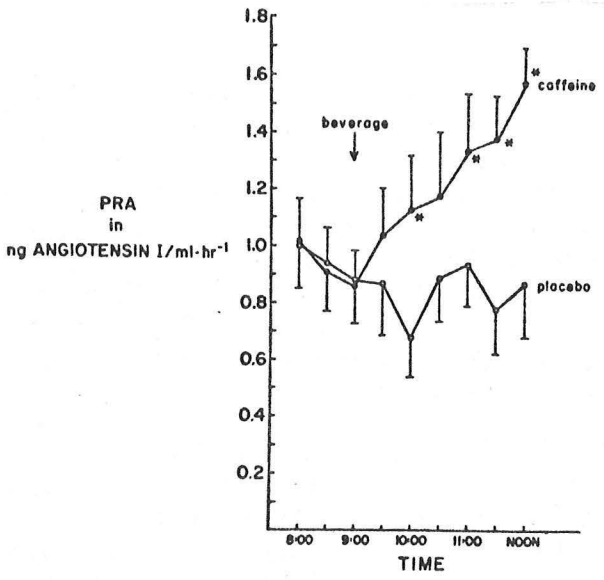


Figure 9. Changes in Plasma Renin Activity (PRA) after Caffeine and Placebo in Seven Subjects on a Diet Containing 150 Meq of Sodium (Mean ± S.E.).
*P<0.05.

(From Robertson D, Frohlich JC, Carr RK, et al.: *N Engl J Med* 298:181, 1978).

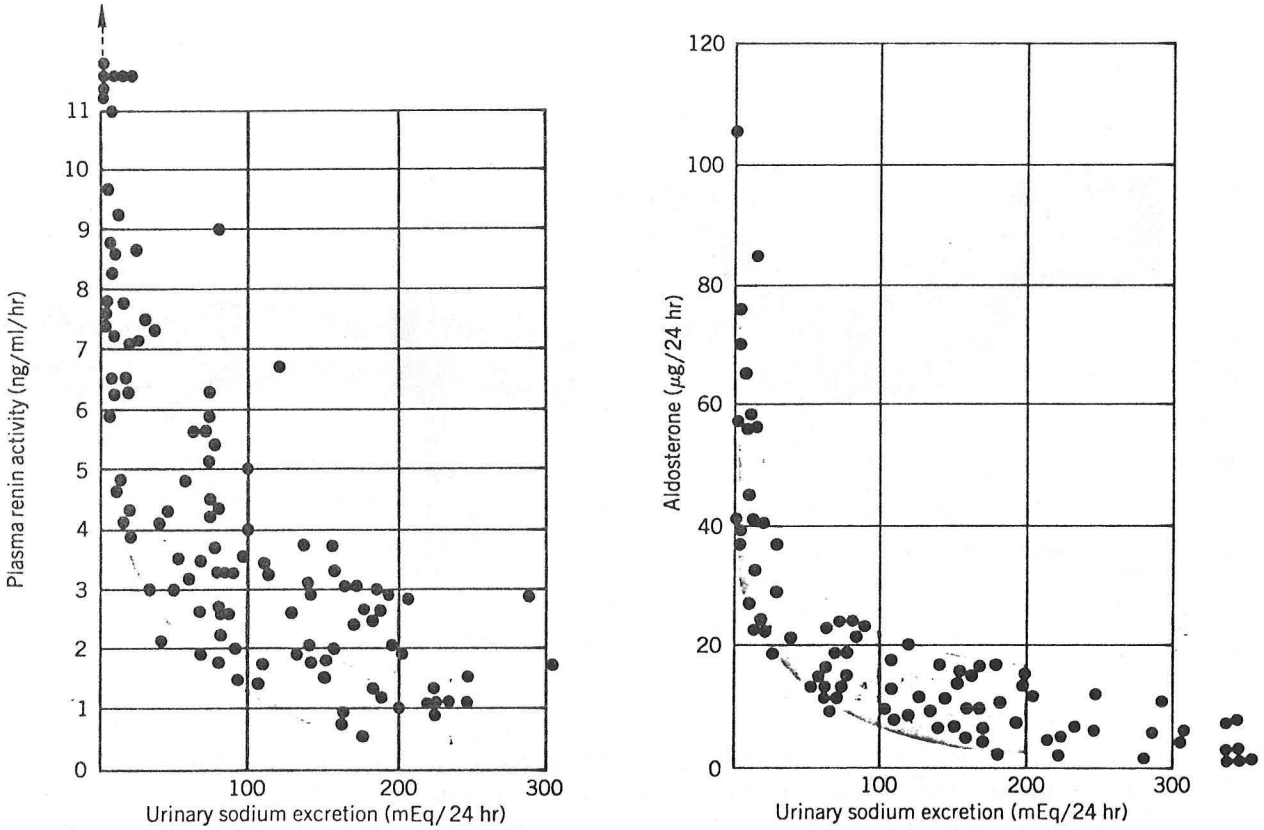


Figure 10: *Relation of noon PRA and corresponding daily aldosterone secretion with concurrent daily sodium excretion rate*

SARALASIN TEST

The angiotensin II antagonist, saralasin, has been proposed as a diagnostic test for detecting renin-mediated hypertension (61-63). Administration of this agent intravenously produces prompt blood pressure reduction in patients with "angiotensinogenic" hypertension by blocking the action of endogenous angiotensin II at the vascular receptor level. In order to enhance its specificity, the test is performed with the subject in a state of mild sodium depletion (net sodium loss of 100-200 mEq Na). This is accomplished by a low salt diet and prior administration of a diuretic, usually furosemide. If this is not done in a volume-replete subject, saralasin may exert an agonistic response resulting in elevated blood pressure.

The initial studies utilizing this procedure for the diagnosis of renovascular hypertension were encouraging. In most studies a "positive" response was defined as a drop in blood pressure by 10/8 mm Hg or more with the infusion of saralasin (Figure 11). This agent can be injected as a bolus or infused at 0.05 to 0.5 to 5.0 µg/kg/min each for 15 to 20 minutes. The wider application of saralasin infusion test has yielded disappointing results. The results of a collaborative study from 13 institutions indicate the test was positive only in 63% with renovascular hypertension (i.e., 37% false negatives) (64). Another study suggested that only 25% of positive saralasin tests will identify renovascular hypertension if its prevalence is 5% (65). The response rate may be improved by infusing saralasin in a seated position.

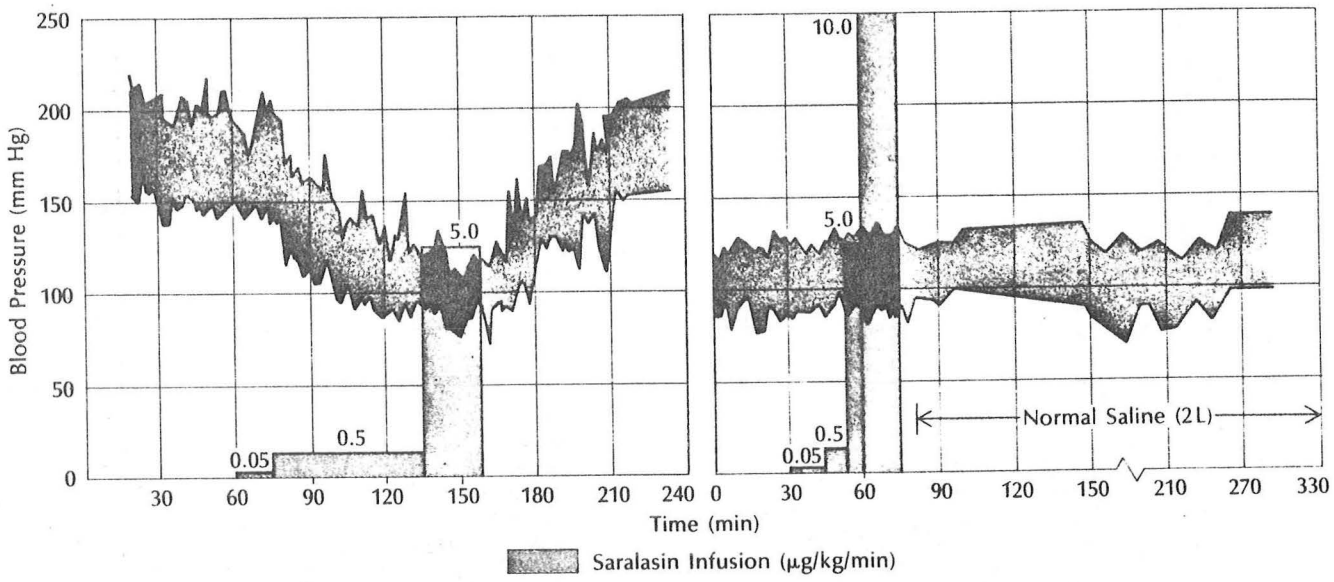


Figure 11. Typical BP response to saralasin infusion in a patient with renovascular hypertension (left), contrasted with lack of response in a patient with normal PRA (right). (Adapted from Streeten et al.)

Other than false responses, discontinuation of saralasin was associated with marked rebound hypertension presumably due to reactive hyperreninism. Hypertensive crisis was reported in a patient with pheochromocytoma (66). It thus appears that a negative saralasin test makes the diagnosis of renovascular hypertension unlikely but a positive response is not conclusive and additional confirmatory tests are needed. As of December 1981, saralasin had not been released by the FDA for general use.

DEFINITIVE STUDIES

TABLE 19A. DIAGNOSTIC STUDIES - RENOVASCULAR HYPERTENSION

1. PERIPHERAL PRA
2. RAPID SEQUENCE IVP
3. RENOGRAM/SCINTIGRAPHY
4. SPLIT FUNCTION TESTS
5. SARALASIN TEST

TABLE 19B. DEFINITIVE STUDIES - RENOVASCULAR HYPERTENSION

1. ARTERIOGRAPHY
2. DIGITAL ANGIOGRAPHY
3. RENAL VEIN RENIN RATIO

Renal arteriogram: The renal arteriogram is obtained after careful consideration of risk versus benefit. It should be emphasized that the definitive studies should be undertaken only if the patient is an operative candidate. There are no absolute guidelines to recommend angiography. The physicians should be guided by severity of hypertension, renal function, presence or absence of abdominal bruit, etc. Usually, the arteriogram is preceded by an IVP or renogram. Percutaneous retrograde transfemoral technique is used to visualize the major as well as small segmental arteries. Standard as well as oblique views with enlargements are necessary so that a small lesion is not missed. In contrast to lumbar aortography, the present day techniques have a low incidence of complications (1-2%).

If the three features in the patient workup--bruit, IVP, renogram--are abnormal, 95% of arteriograms will show functional renal artery lesions (Table 20). Conversely, if all the features are normal, only 16% will be

positive for stenosis. While arteriography is critical in defining the nature and extent of stenosis, bear in mind that it may not be causing the patient's hypertension.

Table 20. **Probability of Essential Hypertension or Renovascular Hypertension on the Basis of Screening Procedures**

	Essential hypertension (%)	Renovascular hypertension (%)
No abnormality	99	1
Abdominal bruit present	61	39
Abnormal IVP	48	52
Abnormal renogram	74	26
Abnormal IVP and renogram	30	70
Abnormal IVP and renogram, and abdominal bruit present	4	96

Digital angiography: This technique is a promising approach to the diagnosis of arterial lesions and in the next few months, its availability is anticipated. With rapid intravenous injection of contrast material utilizing digital video subtraction equipment, main renal arteries can be seen. However, this exciting technique may not visualize small segmental lesions. The test can be performed as an outpatient procedure and the diagnostic yield appears to be as high as 92% (67).

The various investigations we have covered so far generally indicate whether or not a patient has renal artery stenosis, however, it is our task to demonstrate whether or not the observed lesion is in fact causally related to hypertension. At the present, the only way to correlate the morphology of the lesion with functional significance is by obtaining renal vein renins.

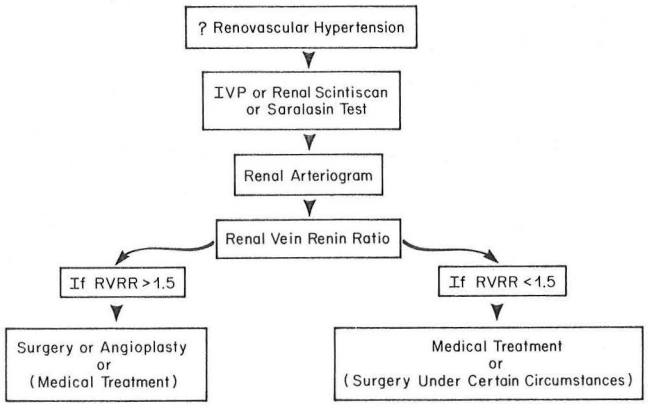
Renal vein renin activity: The concept of direct sampling of renal venous blood in hypertensive patients was established in the mid-60s by Judson and Helmer (68). Several other investigators found that the renin secretion from the stenotic kidney is increased if the lesion is functionally significant. When the renal vein concentration from the involved kidney is more than 1.5 times the value of the contralateral side, it constitutes good evidence of significant secretion of renin. It has been further suggested that not only the hypersecretion of renin from the stenotic side but also demonstration of suppressed renin release from the contralateral side is indicative of surgically curable hypertension. There is some disagreement in the literature about the predictive value of renal vein renin ratio but for the most part it provides a reasonable estimate of possible surgical success.

In addition to renal venous and venacaval renin ratios, absolute values of renin from the affected kidney or in the peripheral blood have been found to be of value in predicting the operability. However, for practical purposes, a simple renin vein ratio of 1.5 or more is suggestive of renovascular hypertension and more complicated formulas are unnecessary. Although lateralization of renin is helpful in predicting surgical success, many patients who do not show lateralization also benefit from surgery. For example, it was found that

out of 66 patients with renovascular hypertension, approximately a third were benefited by operation although renins did not lateralize (69). Some inaccuracies of renal vein renin sampling may result from technical errors such as catheter misplacement, etc. False negative results are also seen if the patient has been on drugs that inhibit the renin release, like methyldopa, clonidine and beta-blockers. Therefore, an important prerequisite for renin vein renin sampling is that the patient should not have received such drugs for 1-2 weeks prior to the procedure. Although ideal, this is frequently not possible because of severity of hypertension, etc. Vaughan et al. (70) proposed a renin scoring system to predict operative response which takes into consideration not only the renal vein renin ratio, but applies the following: 1) ipsilateral hypersecretion of renin compared to peripheral PRA; 2) contralateral suppression compared to peripheral PRA; 3) absolute peripheral PRA. If all the three criteria are met, the chances of surgical success are excellent.

It has been suggested that inaccuracies may result from non-simultaneous catheterization of renal veins because of episodic nature of renin release. However, a recent carefully done prospective study demonstrated no significant difference between simultaneous and non-simultaneous renal vein sampling (71). Similarly injection of contrast material had no significant effect on renal vein renins. Maneuvers like salt restriction, administration of vasodilators, converting enzyme inhibitors and diuretics (particularly, furosemide) have been recommended to stimulate renin release, thereby accentuating the renal vein renin ratio. But, a recent study (72) refutes the need for renin stimulation by furosemide--it was noted that furosemide did not increase predictive value of renal vein renins and in fact resulted in high percentage of false positives and negatives. However, it should be reemphasized that the greater the renal vein renin ratio, the greater will be the likelihood of operative success. Since some patients with non-lateralizing renins (7%) may benefit from operation, results of renin determinations alone should not deny a patient of surgical treatment. The decision should be individualized taking into consideration such factors as severity of hypertension, age of the patient, response to medical treatment, etc.

FLOW DIAGRAM FOR THE WORK-UP OF RENOVASCULAR HYPERTENSION



MANAGEMENT OF RENOVASCULAR HYPERTENSION

Many factors must be considered in deciding about the medical or surgical treatment of renovascular hypertension. One should consider the age of the patient, severity of hypertension itself and response to drug therapy, type and location of the renal artery stenosis, state of renal function and presence of extrarenal vascular disease. In general, younger patients and those with fibromuscular dysplasia respond more favorably. Older patients with advanced atherosclerosis may not tolerate the surgery very well and initially, conservative treatment must be attempted.

TABLE 21. MANAGEMENT OF RENOVASCULAR HYPERTENSION

1. DRUG THERAPY
2. SURGICAL - VEIN GRAFT, DACRON GRAFT, NEPHRECTOMY, ETC.
3. PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY

Medical treatment: Although increasing numbers of patients with renovascular hypertension are being benefited by surgery, medical management is indicated if the patient is unwilling or unable to undergo operative procedures. If the patient is not a surgical candidate, then there is no rationale in doing a workup in the first place. The medical treatment of renovascular hypertension is similar to that of essential hypertension. The choice of drugs, however, may be more specifically directed at inhibiting the renin-angiotensin-aldosterone axis at various levels. In this respect, one may choose beta-blockers or angiotensin converting enzyme inhibitors in particular. Regarding the choice of a diuretic, it depends on the renal function and spironolactone may be advantageous for patients with secondary hyperaldosteronism. However, in many instances, multiple drug regimen is necessary to permit effective control of hypertension.

In general, it appears that patients treated surgically seem to do better than those treated medically in the long run (73). For patients treated medically, close follow-up is necessary to assess the quality of blood pressure control and renal status. Even in medically treated patients, surgery should be considered if the renal function or blood pressure control or both are deteriorating.

SURGICAL MANAGEMENT

The surgical approach to the renovascular hypertension is aimed at removing the obstruction to renal blood flow, thus curing the symptom complex. With proper selection of patients and appropriate operative repair, excellent results can be expected with cure or improvement in about 90% of patients with negligible

morbidity and mortality (74). The key to operative success resides in proper selection of patients for vascular repair. Among other things, preoperative duration of hypertension is an important factor in determining the surgical outcome as the highest surgical benefit is likely to occur in patients with short duration of hypertension (75). However, this factor is only one of the determinants of surgical outcome, and in many patients the exact duration of hypertension is not known. Concrete data are not available in helping the physician in deciding whether operative or medical therapy is best for a particular patient. Decisions are not easy, careful evaluation is necessary and each patient must be considered individually. Let us take a look at one prospective study by Hunt and colleagues at the Mayo Clinic (73). Out of 214 patients with renovascular hypertension, 100 underwent surgery and the remaining were treated medially. After 7-16 years follow-up, 16% in the surgical group died compared to 40% in the medically treated group. The authors concluded "Any decision for medical management of a patient with a potentially correctable renal artery lesion requires close continued observation as to blood pressure control and function of the individual kidneys. According to our experience, however, most physicians do not give adequate attention to the former and seldom or rarely consider the latter until renal insufficiency or failure has developed."

I will not discuss the details of operative techniques. A number of procedures have been used--aortorenal bypass, splenorenal shunt, endarterectomy, autogenous arterial grafts, renal autotransplantation, ex-vivo renal surgery and nephrectomy. In many centers including here in Dallas, aotorenal bypass using autogenous saphenous vein is the procedure of choice. Due to differential flow characteristics, an end-to-end anastomosis is superior to an end-to-side procedure. This allows the graft to lie easily without causing tension. Although long-term follow-up studies are favorable with this approach, about a fifth fail during the first year for various reasons.

Surgical Results: The operative results vary from one center to the other and must be interpreted carefully. Aggregating patients from different centers may be misleading due to differences in patient selection, surgical techniques and renin estimations. Bearing this in mind, certain generalities can be made. Cure or improvement (meaning fewer drugs to control the blood pressure) can be expected in more than 90% of patients, particularly in the young and in those with dysplasia.

Renal vein renin ratio if high is an excellent predictor of surgical cure (Figure 12). But some patients with non-lateralizing renins also respond to surgery. For this reason, surgical selection must be based on the total evaluation--clinical features, angiographic findings and renin data. Patients with generalized atherosclerosis obviously present with diffuse vascular disease and a less successful result is expected. Because of co-existing coronary/cerebrovascular disease, some morbidity and mortality is unavoidable in this group but the complications can be minimized by close medical-surgical care.

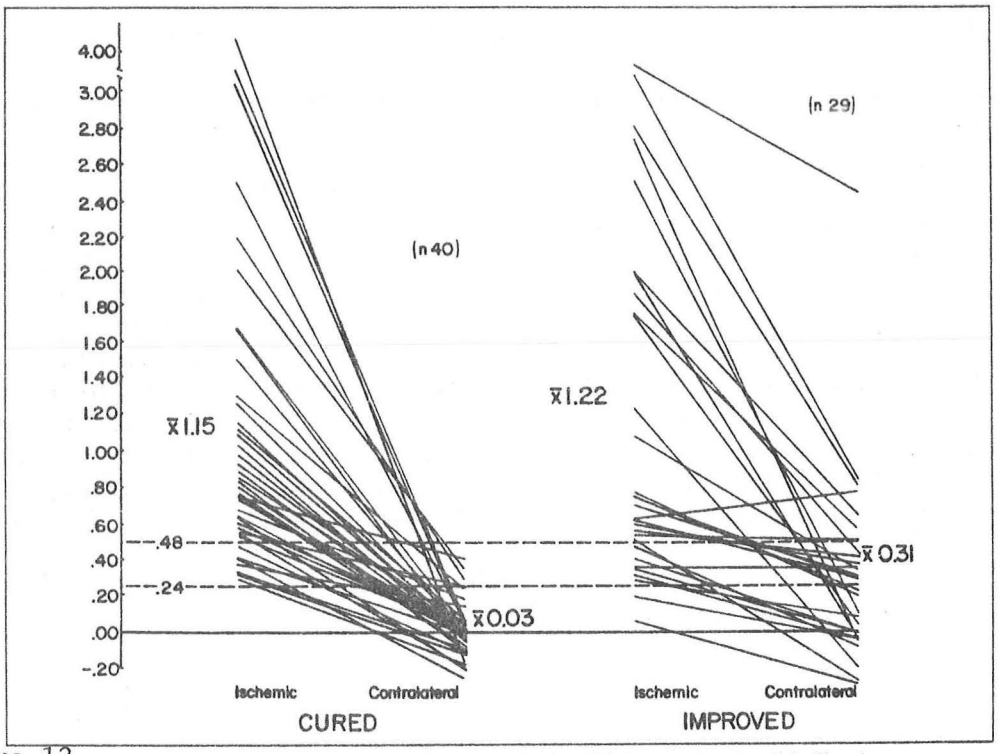


Figure 12. Renal:systemic renin indices comparing individual renal renin activity to systemic renin activity. Mean ischemic kidney hypersecretion in cured vs improved groups (1.15 and 1.22. respectively) did not prove to be statistically different. Contralateral suppression of renin activity was obvious in cured (0.03) group and nonexistent in improved (0.31) group. Differences in degree of suppression proved significant ($P < .01$).

(From Stanley JC, Fry WJ: *Arch Surg* 112:1291, 1977)

PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY (PTA)

Percutaneous transluminal angioplasty is an important advance in the management of renovascular hypertension. PTA was originally intended for the treatment of atherosclerotic peripheral vascular disease and the development of salt, flexible Gruntzig balloon catheter has allowed the procedure to be applied to the renal arteries. This technique has been utilized successfully to dilate the renal artery stenosis from atherosclerosis as well as fibromuscular dysplasia (76-78). The use of PTA is spreading rapidly. Angiographers are making up for lost time with vengeance. In the first half of 1981, one manufacturer sold 10,000 dilation catheters!

PRINCIPLE INVOLVED IN PTA

Originally, it was proposed that PTA worked by "squeezing-out" the atheromatous materials from the stenosis (I wonder what happens to the "squeezed-out" material?). It is difficult to accept such a simple expalanation. It is hard to imagine how a long segment can be squeezed, molded and redistributed leaving a patent lumen! PTA probably works by "controlled injury" to the stenosis-periatheromatous longitudinal and circumferential ruptures are produced between the intima and the media. Then, the expandable media and adventitia are separated from the intima and are dilated while the atheromatous material is compressed with the expanded wall. The healing must presumably occur in the dilated state

to keep the lumen patent. In the fibromuscular dysplasias, the mode of action of PTA presumably is shearing, stretching and rupturing the fibrous components of the lesion.

COMPLICATIONS

It should be emphasized that although PTA is relatively a safe procedure, certain complications can occur (79) (Table 21); PTA is not risk-free. This procedure should not be undertaken unless there is a backup by expert vascular surgical team. Most of the complications, however, are mild and permanent vascular/renal damage is extremely rare. Since PTA causes disruption of the intima, prevention of thrombosis is important. Although some have used heparin and/or warfarin, a more simple regimen would consist of aspirin and dypyridimole during the post-PTA period. How long should the patient take these medicines is not determined--?? 6 to 12 weeks/months?

TABLE 21. COMPLICATIONS OF PTA

Complications of PTA	Incidence (%)
Puncture site	
Thrombosis	1-3
Hematoma	2
Pseudoaneurysm	1-5
Distant	
Embolization	5
Thrombosis	5
Dissection	1
Perforation	0-3
Spasm	0-5
Occlusion or rupture (by overinflated or burst balloon)	0-1

PTA IN PERSPECTIVE

Several hundred renal PTA Procedures have been performed in the past 2-3 years with the initial success rate of 75-90% and complication rate of 3%. An important question concerns the duration of success beyond 2 years. Better results can be expected with dysplastic lesions than atherosclerotic disease. Especially, the medial dysplasia responds readily even to gentle inflation of the balloon.

PTA offers the potential for simple, relatively safe and inexpensive approach in the management of renovascular hypertension. There is very little morbidity and in my experience, patients are ambulatory within a day after PTA. The technique should be attempted only in hospitals with expertise in angiography and vascular surgery.

Before PTA is routinely advised, its efficacy with regard to duration of vascular patency must be evaluated and compared against established surgical techniques. Clearly, PTA offers a distinct advantage over surgery for certain patients. The enthusiasm for performing PTA must be tempered by the knowledge that certain complications may require emergency surgery, the results of which may be less favorable than an elective procedure.

In summary, PTA is a promising approach to the management of renovascular hypertension. Its long term efficacy and comparison with surgical results must be ascertained by carefully planned and conducted randomized controlled studies.

SPECIAL CONSIDERATIONS IN RENOVASCULAR HYPERTENSION

TABLE 22. RENOVASCULAR HYPERTENSION - SPECIAL SITUATIONS

1. PEDIATRIC PATIENTS
2. BILATERAL RENAL ARTERY STENOSES
3. RENAL INSUFFICIENCY
4. SEGMENTAL RENAL ARTERY STENOSIS

Renovascular hypertension in the pediatric patient: Renovascular hypertension in children is a potentially curable form of hypertension. The blood pressure elevation may be quite severe and refractory to medical therapy. Fibromuscular dysplasia is the most common cause. With careful but aggressive and precise surgical techniques, the operative results are excellent (80).

Bilateral renal artery lesion: About a third of patients with renovascular hypertension have bilateral lesions and are prone to develop renal insufficiency. Split renal vein renins are helpful in deciding the side for initial vascular repair. In some cases, if both the sides are "functional", a two-stage procedure may be necessary.

Patients with renal insufficiency: Several authors have reported restoration or improvement in renal function following bypass procedures in patients with renal artery stenosis and renal insufficiency (81, 82). Even in patients with no meaningful renal function, renovascularization of renal vessels has yielded good results (Figure 13). Therefore in hypertensive patients, if renal insufficiency appears or is getting worse, a thorough search for a correctable cause such as renal artery stenosis must be undertaken irrespective of the degree of functional impairment.

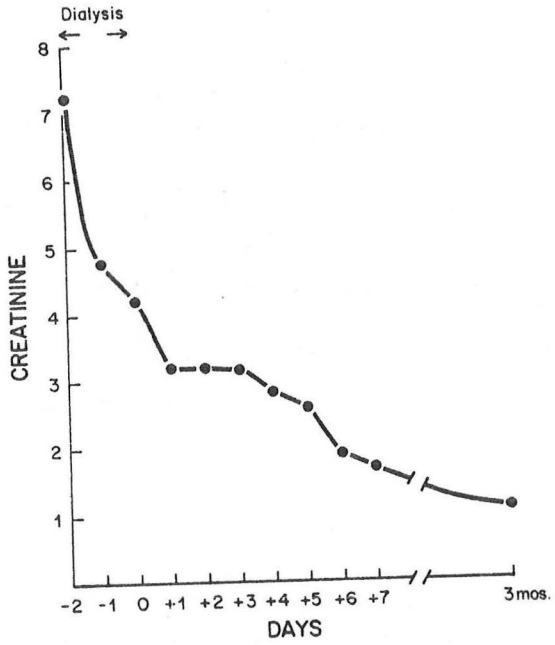


Figure 13. Marked improvement in the renal function of a patient operated upon for renovascular hypertension (Fry RE and Fry WJ: Renovascular hypertension in the patient with severe atherosclerosis, in press).

Segmental renal artery stenosis: Segmental renal artery stenosis can occur sometimes especially in the pediatric age group. The functional significance of these branch lesions should be ascertained by selective segmental renal vein renin sampling (83). Although nephrectomy used to be done for such lesions, in some centers successful revascularization is accomplished obviating the need for more radical procedures.

Post-transplant renovascular hypertension: A small number of patients with post-renal-transplant hypertension have stenosis of transplant renal artery. Using meticulous techniques, post-transplant renal artery stenosis can be successfully corrected (84).

Rare causes of renovascular hypertension: The following causes of renovascular hypertension are very rare.

TABLE 23. INTRINSIC LESIONS

1. Aneurysm (Cummings: J Urol 102:144, 1973)
2. Emboli (Arakawa: Arch Intern Med 129:958, 1973)
3. Arteritis
   Polyarteritis nodosa (Dornfield: JAMA 215:1950, 1971)
   Takayasu's (Kirshbaum: Am Heart J 80:811, 1970)
4. Arteriovenous fistula (Oxman: Mayo Clin Proc 48:207, 1973)
5. Angioma (Ferreras-Valenti: Am J Med 39:355, 1965)
6. Neurofibromatosis (Schurch: CMAJ 113:879, 1975)
7. Tumor thrombus (Jennings: Br Med J 2:1053, 1964)
8. Rejection of renal transplant (Gunnels: N Engl J Med 274:543, 1966)

TABLE 23, continued

9. Thrombosis after umbilical artery catheterization (Plumber: J Pediatr 89:802, 1976)
10. Surgical ligation of renal artery (McCormack: Arch Surg 198:220, 1974)
11. Traumatic occlusion (Knorring: Lancet 1:934, 1976)
12. Radiation (Staab: Am J Roentgenol 126:634, 1976)
13. Intrarenal cyst (Babka: N Engl J Med 291:343, 1974)
14. Congenital unilateral renal hypoplasia (Ask-Upmark kidney) (Rosenfeld: Br Med J 2:217, 1973)
15. Unilateral renal infection (Marks: J Urol 109:149, 1973)

TABLE 24. EXTRINSIC LESIONS

1. Pheochromocytoma (Raghavaiah: J Urol 116:243, 1976)
2. Congenital fibrous band (Silver: Ann Surg 183:161, 1976)
3. Pressure from diaphragmatic crus (Martin: Am J Surg 121:351, 1971)
4. Metastatic tumors (Weidmann: Am J Med 47:528, 1969)
5. Subcapsular or perirenal hematoma (Spark: Arch Intern Med 136:1097, 1976)
6. Retroperitoneal fibrosis (Castle: JAMA 225:1085, 1973)
7. Ptosis (Derrick: Am J Surg 106:673, 1963; Zeeuw: Lancet 1:213, 1977)
8. Ureteral obstruction (Nemoy: JAMA 225:512, 1973)

ILLUSTRATIVE CASES

CASE 1: Renovascular hypertension in a patient with severe hypertension.

J.M.: A 46 year old white female was admitted to a local hospital because of chronic hypertension which has not been responding to incremental doses of antihypertensive drugs. Patient's BP was 210/140 mm Hg on hydralazine (200 mg/day), metoprolol (200 mg/day) and furosemide (80 mg/day). As the doses were gradually doubled, BP stabilized at 170/106 mm Hg.

The possibility of renovascular hypertension was considered based on the above clinical course plus the presence of high pitched systolic, diastolic, abdominal bruit and work-up revealed bilateral atherosclerotic renal artery stenosis. Renal vein renins were 85 ng/ml/hr (left) and 18 ng/ml/hr (right), venacaval PRA was 20 ng/ml/hr. The renal vein renin ratio--left:right was 4.7:1 and surgery was recommended. The night before surgery her BP remained at 200/110. A few days after surgery, her BP stabilized close to 130/90 (off treatment). Subsequent follow-up in the office revealed BPs 140-150/90 but her home BPs were much lower--130/80.

This case underscores the need to consider renovascular hypertension in a patient not responding to potent antihypertensive drugs, especially if the patient is white (in blacks, the prevalence of renovascular hypertension is probably quite low).

CASE 2: Renovascular hypertension cured by unilateral nephrectomy.

D.M.: A 51 year old male was evaluated because of severe hypertension (BP 210/140 on multiple drugs). The BP responded fairly well to minoxidil, beta-blockers and diuretics but patient developed congestive heart failure posing considerable therapeutic problems. Patient had undergone repair for right renal artery stenosis many years ago.

A re-evaluation for renovascular hypertension revealed near total occlusion of right renal artery. Renal vein renins were 41 ng/ml/hr (right), 10 ng/ml/hr (left) and peripheral PRA was 31 ng/ml/hr. Therefore, this patient had contralateral suppression of renal vein renin (ratio 4:1), further indicating the pathogenetic role of the right kidney. Surgery was recommended due to problems with medical control. Due to technical difficulties, bypass was impossible and a right nephrectomy was done. Following this the patient's course was uneventful with normalization of BP without drug therapy. The last time I saw him (a few months ago), he was doing very well without any drug therapy, BP was 130/88.

This case illustrates the importance of surgical skill in deciding the type of operative approach in a patient with renal artery lesion that cannot be bypassed. Without proper judgment, unnecessary nephrectomies may result and on the same token in some patients like DM, anything short of nephrectomy would not have helped the patient.

CASE 3: Renovascular hypertension in a patient with intolerable side effects to simple antihypertensive drugs.

G.D.: A 53 year old female was seen by me because she was "unable" to take blood pressure medications, as they were causing unbearable side effects like sedation, dizziness, palpitations, etc. Her BP was 210/120 but I was not sure if she was taking the medication (? nadolol) because she did not like it. A previous IVP was "abnormal".

Close observation confirmed patient's inability to tolerate the drug therapy. A renal arteriogram revealed bilateral fibromuscular dysplasia and renal vein renin ratio was 1·5:1 (L:R). Preoperative BP was 170/100 on beta-blockers. Right renal revascularization was done. She was discharged on no therapy and follow-up BPs were normal (130-132/90).

This case illustrates the need to consider work-up in patients with demonstrated intolerable adverse effects to antihypertensive drugs.

CASE 4: Percutaneous transluminal angioplasty (PTA) and cure of severe renovascular hypertension.

T.F.: A 58 year old female with chronic hypertension and diabetes presented without symptoms and a BP of 250/120 on hydralazine (200 mg/day), propranolol (320 mg/day) and a diuretic. Work-up revelaed significant right renal artery stenosis and slight stenosis on the left with severe atherosclerosis of the aorta. The right to left renal vein renin ratio was 4·7:1. On July 15, 1981, PTA was done on the right side.

Patient's BP became easily controllable after the procedure--it was 130/90 on propranolol alone. This drug was tapered off gradually. Her last BP (on November 6) was 140/88 without any antihypertensive drugs.

The above case shows the role of PTA in the treatment of renovascular hypertension. This patient has to be followed periodically to monitor the stability of BP response.

CASE 5: PTA may not have lasting effect in some patients.

M.C.: A 74 year old female was referred by her family physician because of increasing BP despite good therapy. Her BP was 200/108-110 on hydralazine (200 mg/day), propranolol (160 mg/day) and HCTZ (50 mg/day). She had a loud high-pitched abdominal bruit. IVP was normal but in view of severe hypertension, an arteriogram was done which revealed right renal artery stenosis. The renal vein renin ratio was nearly 2:1 (right to left). PTA was performed which improved the BP to 150/80 (on therapy) in the hospital. Follow-up for the next 6 months demonstrated progressive rise in BP to pre-PTA levels despite drug therapy.

The above case illustrates the need for careful follow-up of patients undergoing balloon dilatation.

CASE 6: Failure of surgery to correct hypertension in a patient with non-lateralizing renin secretion.

H.T.: A 57 year old female with a history of hypertension (unknown duration) was evaluated because of a mild stroke from hypertension. The BPs ranged close to 170/100 on therapy. Sequential investigations showed right renal artery stenosis (FMH). The renin vein renins were 5.8 and 4.6 ng/ml/hr in the right and left respectively. A few months later surgery was performed to correct the stenosis. The BP did not fall and 6 weeks later it was 170/100 (on medication). A few months afterwards the BP remained high requiring multiple drugs. The above case illustrates that surgical results are in general not so good if the stenotic kidney does not demonstrate hypersecretion of renin. However, there may be isolated exceptions.

PHEOCHROMOCYTOMA

"A great mimic" among hypertensive disorders--DeCourey, 1952.

There are few clinical conditions that can simulate as many other syndromes as can pheochromocytoma. The diagnosis of pheochromocytoma can be easy as well as extremely difficult. It has always attracted much attention because of its spectacular features and the dramatic cure following the removal of the tumor. In several patients, pheochromocytoma behaves like a "volcano". It remains quiescent for varying periods then suddenly and without obvious reason erupts with such violent activity which may pose a threat to the patient's life.

Pheochromocytomas are tumors originating from chromaffin cells which contain catecholamines; the latter turn brown when exposed to chromium salts. Although pheochromocytoma is an unusual cause of hypertension, its detection is important because surgical removal ameliorates the syndrome, which is otherwise potentially lethal. Frenkel in 1886 (85) was probably the first to demonstrate the presence of adrenal tumor and elevation of blood pressure. However, it was Dr. Charles Mayo who in 1927 reported successful removal of pheochromocytoma (86).

Incidence

The exact incidence of pheochromocytoma is probably unknown and the estimates vary tenfold--from 0.1 to 1% of hypertensive population. The latter figure probably represents an exaggereated incidence. However, using a conservative estimate (0.1%) in 18 million people with sustained hypertension, perhaps at least 36,000 persons in the US harbor a pheochromocytoma (87). The incidence will be likely higher if patients with paroxysmal spells are included.

Pathophysiology

The distinctive clinical features of pheochromocytoma are related to excessive production of catecholamines which produce characteristic (and lethal) effects on the cardiovascular system. Catecholamines are so named because they are the amine derivates of catechol nucleus. Three catecholamines are found in the human tissue--epinephrine, norepinephrine and dopamine. Chromaffin cells synthesize catecholamines from the dietary amino acid, tyrosine. The formation of dopamine from tyrosine is the rate limiting step in the biosynthesis of catecholamines. Norepinephrine is the end-product of this biosynthesis except in the adrenal medulla where about 75% of the catecholamine content is converted to epinephrine due to the presence of the enzyme, phenenthanolamine-N-methyl-transferase. Epinephrine and norepinephrines are largely metabolized to metanephrine and normetanephrine respectively. By monamine oxidation of these metabolites, vanillylmandelic acid is formed (Figure 14). The direct effects of catecholamines on the cardiovascular system are reflected by the clinical manifestations of pheochromocytoma and estimation of their metabolites therefore is biochemical basis for the diagnosis of pheochromocytoma.

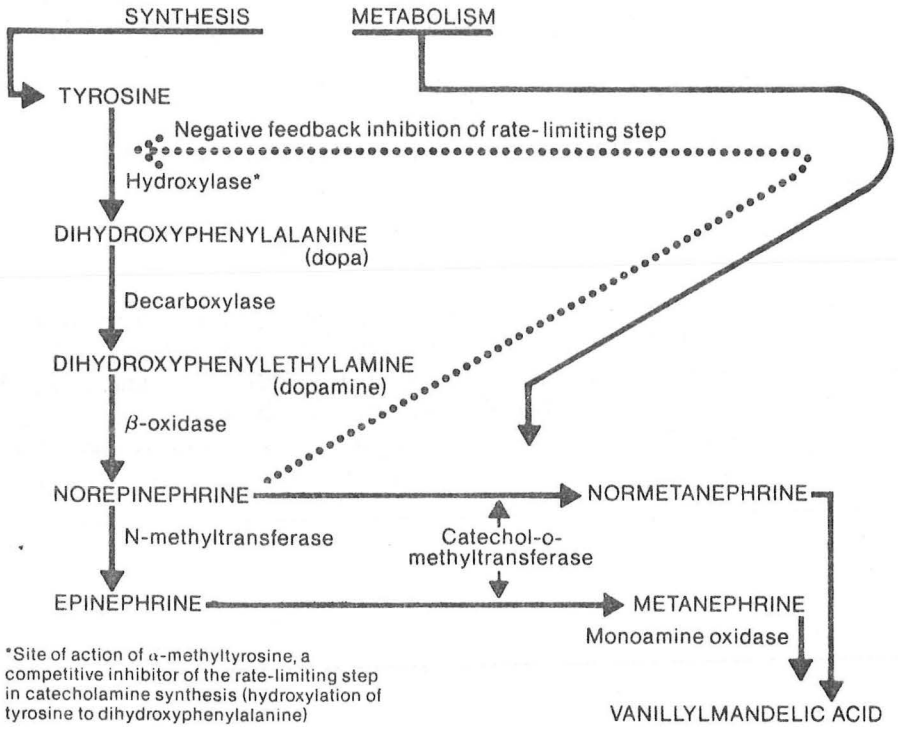


Figure 14. *Site of action of α-methyltyrosine, a competitive inhibitor of the rate-limiting step in catecholamine synthesis (hydroxylation of tyrosine to dihydroxyphenylalanine). Synthesis and metabolism of the adrenal catecholamines.

The mechanism which triggers a massive discharge of catecholamines remains obscure. In contrast to the adrenal medulla, there is no evidence for nervous innervation of pheochromocytomas. Although catecholamines can be released spontaneously in patients with pheochromocytoma, the release may also occur in response to such stimuli as hypoxia, hypovolemia, hypoglycemia, asphyxia and severe muscular exercise. Clinical features may sometimes indicate the predominant hormone secreted by the tumor. Patients with tumors that mainly secrete epinephrine (almost always an adrenal tumor) have disproportionate systolic hypertension (due to increased cardiac output), tachycardia, sweating and flushing. Those with tumors secreting both epinephrine and norepinephrine tend to have systolic and diastolic hypertension and fewer paroxysms of hypertension.

Defined rigidly, the term pheochromocytoma is applied only to tumors of the adrenal medulla. Tumors of similar biochemical and clinical potential originating from the extra-adrenal sites are referred to as paragangliomas. The difference in terminology is purely an anatomical one. Only a small percentage of tumors arise from the extra-adrenal sites. These extra-adrenal sites include abdominal para-aortic ganglia, sympathetic ganglion in the urinary bladder, posterior mediastinal ganglia and ganglia at the bifurcation of the common carotid artery and the embryonal sympathetic tissue found in association with the intracranial branches of the vagus nerve. A site from which these tumors may arise is from a collection of para-aortic paraganglion cells around the origin of inferior mesenteric artery--the organ of Zuckerkandl.

Pheochromocytoma has been described to occur in all age groups but is more commonly diagnosed between the 3rd and 5th decades. Of course, the age at which the diagnosis is made is not necessarily synonymous with the age of occurrence, as patients may experience symptoms for many years before the diagnosis is established. There appears to be no sex predilection. For unknown reasons, tumors occur more commonly in the right adrenal than in the left.

Familial incidence, about 10%, is intriguing and is transmitted by autosomal dominant mode of inheritance. Familial pheochromocytomas are most often in the adrenals and are prone to be bilateral. Most pheochromocytomas weigh less than 70 g but the weight is variable--from microscopic size to very large ones. Approximately 10% of tumors are malignant. However, it is not possible to determine whether a tumor is benign or malignant on histology alone. Only the presence of metastasis establishes the malignant nature of the tumor.

Clinical Features

The clinical features encountered in patients with pheochromocytoma consist of a large variety of symptoms and signs (88) (Tables 25 and 26). Although the diagnosis is relatively easy in a few who present with "typical" features, the pleomorphic nature of the disease may pose considerable difficulties. The most important feature, however, is hypertension in the majority of patients. Only in about 50% of the cases is the hypertensive truly paroxysmal, the others may have sustained elevation of blood pressure. "Typical" pheochromocytoma paroxysm consists of severe headache, profuse sweating, pallor (flushing, very rare), nausea and vague discomfort in the chest or abdomen, in association with marked elevation of blood pressure. Frequently, systolic blood pressure during a paroxysm may rise up to 300 mm Hg. Often, these paroxysms occur spontaneously but, occasionally, an attack is brought on by stress, severe exercise, change in posture, abdominal palpation, certain drugs and anesthetics. Some episodes are accompanied by paresthesias. After resolution of paroxysm, patients experience profound fatigue. Rarely, patients may experience a premonition that an attack is about to occur. Symptomatic intervals vary from once every few months to several times a day and may last in duration anywhere from less than a minute to several days. With passage of time, the "attacks" become more frequent, if not severe. Occasionally, a patient with pheochromocytoma may present with rapidly progressive accelerated hypertension with relentless symptoms. Most patients describe recurrent pattern of "attacks" and features may be stereotyped. Some can identify a particular physical activity as a precipitating factor--such as bending, twisting, intercourse, sweating, or micturition.

Symptoms

Headaches when present are usually paroxysmal and throbbing with generalized distribution. Often along with headaches, patients also complain of *nausea* and *vomiting*. Excessive *sweating* is a symptom identified with pheochromocytoma but this symptom is prominent only in some patients. Profuse sweating, however, appears in the patients with paroxysmal attacks. The intensity of sweating may not be synchronous with severity of blood pressure elevation. In fact, severe sweating occurs as the attack is resolving. The mechanism of

diaphoresis is not known in pheochromocytoma. It is surprising that catecholamine excess should cause profuse sweating since this is mainly a function of cholinergic activity. Nevertheless, it is possible that catecholamines (especially epinephrine) can cause sweating either directly or through interaction with parasympathetic innervation or even possibly by activating CNS mechanisms of heat loss.

Palpitations (and tachycardia) are very common in patients with pheochromocytomas with sustained or paroxysmal hypertension. Occasionally, reflex bradycardia may occur from increased blood pressure. *Anxiety, tremors, dizziness* and *nausea* are reported by many patients. Chest and *abdominal pain/discomfort* may occur in some patients. Although the exact cause may not be recognized, these symptoms may signify ischemia to heart and abdominal organs. The physician should also consider the possibility of *cholelithiasis* which is quite common in pheochromocytoma patients. Severe and protracted pain may occur as a result of hemorrhage into the tumor.

Fatigue and *weakness* occur towards the end of a paroxysm and may persist after its termination. *Weight loss* is reported by most patients and may be a helpful clue in the diagnosis of pheochromocytomas. Weight change, however, is not usually seen in patients with infrequent episodes. It is uncommon to encounter a "fat pheo". *Dyspnea* may be due to transient left ventricular dysfunction resulting from severe hypertension and patient may develop acute pulmonary edema. Development of so-called catecholamine *cardiomyopathy* may result in congestive heart failure. *Visual problems* occur in some patients with persistently functioning tumors, usually due to hypertensive retinopathy. Pain in the extremities or paresthesias undoubtedly occur in some patients with pheochromocytomas, especially if the tumor is functioning paroxysmally. Rarely, intense prolonged vasoconstriction may lead to cyanosis and tissue necrosis (89). Neuromusculear excitatory phenomenon including grand mal *seizures* have occurred in patients with pheochromocytomas.

TABLE 25. SYMPTOMS OF PHEOCHROMOCYTOMA

1. HEADACHES
2. SWEATING
3. PALPITATIONS
4. ANXIETY, TREMULOUSNESS
5. NAUSEA, ABDOMINAL OR CHEST PAIN
6. WEAKNESS, PROSTRATION
7. WEIGHT LOSS
8. PARESTHESIAS

TABLE 26. SYMPTOMS ASSOCIATED WITH PHEOCHROMOCYTOMA IN 76 PATIENTS (Gifford RW, Kvale WF, Maher FT, et al.: Mayo Clin Proc 39:281, 1964).

SYMPTOMS	PAROXYSMAL FUNCTION (37 PATIENTS) NO. OF PATIENTS	(%)	PERSISTENT FUNCTION (39 PATIENTS) NO. OF PATIENTS	(%)
Headache	34	91.9	28	71.8
Excessive perspiration	24	64.9	27	69.2
Palpitation with or without tachycardia	27	73.0	20	51.3
Pallor, usually of face	22	59.5	11	28.2
Nervousness or anxiety	22	59.5	11	28.2
Tremor	19	51.4	10	25.6
Nausea with or without vomiting	16	43.2	10	25.6
Weakness, exhaustion, or fatigue	14	37.8	6	15.4
Chest pain	12	32.4	5	12.8
Abdominal pain	6	16.2	6	15.4
Visual disturbance	1	2.7	8	20.5
Marked loss of weight	5	13.5	6	15.4
Raynaud's phenomenon	3	8.1	1	2.6
Dyspnea	4	10.8	7	17.9
Marked constipation	0	–	5	12.8
Grand mal	2	5.4	1	2.6
Warmth or flushing or both	4	10.8	3	7.7
Bradycardia (noted by patient)	3	8.1	1	2.6
Intolerance to heat	1	2.7	3	7.7
Dizziness or faintness	4	10.8	1	2.6
Paresthesia or pain in arms	4	10.8	0	–
Miscellaneous	*		†	

*Mentioned only once: low back pain, cold hands, leg pains, perioral numbness, itching of scalp, gagging, hunger and pounding in epigastrium.
†Mentioned only once: tightness of throat and elevated temperature.

Signs

TABLE 27. SIGNS OF PHEOCHROMOCYTOMA

1. HYPERTENSION, SUSTAINED/PAROXYSMAL
2. TACHYCARDIA (RARELY, BRADYCARDIA)
3. ORTHOSTATIC HYPOTENSION
4. PARADOXICAL BLOOD PRESSURE RESPONSE TO DRUGS, ANESTHESIA, ETC.
5. DIAPHORESIS
6. PALLOR (RARELY, FLUSHING)
7. WEIGHT LOSS
8. TREMORS
9. ASSOCIATED CONDITIONS - NEUROFIBROMATOSIS, THYROID SWELLING, ETC.

Despite the protean ways in which pheochromocytoma may present, *hypertension* is the most important clinical lead. As discussed above, about 50% of patients may have *sustained* hypertension whereas the remaining may present with *intermittent* hypertension and only very rarely are these attacks associated with hypotension.

In some patients, paroxysmal elevation of blood pressure is very striking whereas in a few others blood pressure may be unimpressive. It should be emphasized that pheochromocytoma should be suspected in a patient with hypertensive spells who also complains of severe headache. On the other hand, *paroxysmal hypotension* can occur in patients with predominantly epinephrine secreting tumors. Hypertension associated with pheochromocytoma does not respond readily to conventional antihypertensive drugs which sometime may have a paradoxical effect. Sometimes a "shock" like picture can occur during a paroxysm; this is due to intense vasoconstriction making blood pressure unobtainable with a sphygmomanometer. The erroneous peripheral blood pressure in such instances can be quickly ascertained by the palpation of bounding axillary or carotid arteries. It is of importance to assess whether any physical maneuver produces the features experienced by the patient during a spontaneous attack. However, such maneuvers should be undertaken with caution and appropriate measures to reverse the attack must be available.

Whereas hypertension is a well recognized feature of pheochromocytoma, *orthostatic hypotension*, although very common, is less well appreciated. Orthostatic hypotension in a hypertensive patient should bring to the mind the possibility of pheochromocytoma if other causes are not present, such as drug therapy, etc. If looked carefully, this phenomenon may be seen in 70% of patients. The exact mechanism of this hypotensive response is not known but it may be due to autonomic desensitization by excessive circulating catecholamines (90). It has been earlier suggested that orthostatic hypotension may be due to hypovolemia but subsequent studies have revealed normal blood volume in most patients with pheochromocytomas. Postural hypotension is seen primarily in patients with pheochromocytomas who have sustained hypotension, thereby reflecting the possible role of persisting high circulatory catecholamines (87). The presence of postural hypotension is best evaluated by recording the blood pressure after 3 minutes of standing.

As mentioned earlier, sweating is a useful sign in the diagnosis of pheochromocytoma. The occurrence of spontaneous *diaphoresis* in a hypertensive patient who is at rest suggests the possibility of this diagnosis.

Sinus *tachycardia* can be a feature of pheochromocytoma particularly in those with other paroxysmal features. Rarely, reflex bradycardia may be present. Cardiac *arrhythmias* can occur in patients with pheochromocytoma. Skin manifestations such as *pallor* (rarely, flushing or cyanosis) occur mainly in patients with paroxysmal hypertension. Lacrimation and mydriasis are sometimes observed but only during paroxysmal hypertensive spells along with retinal arteriolar spasm; these abnormalities resolve as the paroxysm is controlled. Retinopathy (including grades III and IV) can be seen in pheochromocytoma patients and is perhaps no different from the general hypertensive retinopathy. *Fever* may be a manifestation of pheochromocytoma but is usually slight. However, at least in one series, it was present in 76% of the patients (91). Most likely, fever is due to a catabolic state caused by catecholamines. Rarely, a large tumor can be palpated during abdominal examination. In most patients pheochromocytomas are deeply situated and cannot be felt. If the

diagnosis of pheochromocytoma appears certain, vigorous palpation of the abdomen should be avoided.

SPECIAL FEATURES

One of the early observations in the patients with pheochromocytoma was hypermetabolism and history of *weight loss* (Table 28). In many patients, basal metabolic rates of +30 to 40% have been observed. Rarely, the tumor may occur in the absence of weight loss. *Hyperglycemia* is yet another finding of interest in many pheochromocytomas. However, usually it is not severe enough to warrant specific treatment. Importantly, the glucose abnormalities are usually reversed by the removal of the tumor. Catecholamines not only promote glycogenolysis but alpha-adrenergic stimulation may suppress the insulin release--thus causing hyperglycemia. On the other hand, less appreciated is the occurrence of severe *hypoglycemia* in a few patients with pheochromocytoma. This can occur spontaneously but has been commonly noted following the removal of the tumor. It is speculated that some tumors elaborate a substance with non-suppressible insulin-like activity (NSILA) (92).

TABLE 28. SPECIAL FEATURES OF PHEOCHROMOCYTOMA

1. HYPERMETABOLISM
2. HYPERGLYCEMIA
3. HYPOGLYCEMIA
4. ORTHOSTATIC HYPOTENSION
5. SEVERE CONSTIPATION
6. CHOLELITHIASIS
7. POLYCYTHEMIA
8. RENAL ARTERY OBSTRUCTION

Orthostatic hypotension is common in patients with pheochromocytoma (see above). *Myocardial infarction* can occur in pheochromocytoma even in the absence of coronary artery disease--perhaps related to pressor crises in which the myocardial work load becomes excessive in relation to the circulation. An important and serious myocardial complication of pheochromocytoma is the so-called "catecholamine cardiomyopathy". The occurrence of this complication in some patients without evidence of severe hypertension lends credence to the hypothesis that it is secondary to excessive catecholamines. Focal myocarditis is a common post-mortem finding in patients with pheochromocytoma. Cardiac function should be carefully evaluated in all patients suspected of pheochromocytoma.

In some patients, *gastrointestinal complaints* such as constipation, abdominal discomfort may be prominent. Cholelithiasis (even in young men!) occurs frequently in association with pheochromocytoma. The incidence of gallstones in pheochromocytoma patients may be up to 30% (87). While catecholamines can significantly influence bile formation and secretion, the exact mechanism of gallstone formation in this condition has not been studied nor is their composition carefully analyzed. Rarely pheochromocytomas have been reported in association with Cushing's syndrome, Addison's disease, and acromegaly.

Polycythemia is noted in some with pheochromocytoma. *Renovascular hypertension* has been observed in some patients with pheochromocytomas. It may be due to extrinsic compression of the renal vasculature or can occur independently. One wonders whether high levels of circulating catecholamines can cause vascular proliferation and vascular obstruction.

FAMILIAL SYNDROMES

Knowledge of the family history is important in the evaluation of pheochromocytoma (Table 29).

TABLE 29. PHEOCHROMOCYTOMA SYNDROMES

1. SIMPLE FAMILIAL
2. VON RECKLINGHAUSEN'S DISEASE
3. VON HIPPEL-LINDAU DISEASE
4. MEN

Often, the diagnosis of pheochromocytoma can be made in younger age groups if there is a family history of this disorder.

SIMPLE FAMILIAL

Simple familial pheochromocytomas comprise about 60% of all inherited forms of the disease. Simpler familial cases often show multiple tumors. The simple familial pheochromocytoma gene is inherited with virtually 100% penetrance.

PHEOCHROMOCYTOMA WITH NEUROFIBROMATOSIS

The co-existence of pheochromocytoma and neurofibromatosis has been known for nearly half a century (93). Neurofibromatosis (i.e. von Recklinghausen's disease) occurs in 5% of patients with pheochromocytoma. However, the incidence of pheochromocytoma in von Recklinghausen's disease is considerably less (1%). Neurofibromatosis is diagnosed clinically by the subcutaneous nodules and cafe-au-lait spots. It should be kept in mind that neurofibromatosis can also cause renovascular hypertension (renal artery stenosis or compression, renal artery aneurysm).

PHEOCHROMOCYTOMA AND VON HIPPEL-LINDAU DISEASE

Pheochromocytoma has been noted with von Hippel-Lindau disease (cerebellar hemangioblastoma, retinal angiomatosis, etc.) (94).

PHEOCHROMOCYTOMA AND MULTIPLE ENDOCRINE NEOPLASIA (MEN)

Genetic association of pheochromocytoma with other endocrine tumors was reported by Sipple in 1961 (95). It was clearly established that in certain kindreds, bilateral adrenal pheochromocytomas, medullary carcinoma of thyroid and hyperparathyroids were inherited by autosomal dominance with high degree of penetrance. It appears that in MEN IIA, pheochromocytoma and thyroid cancer represent inherited features and hyperparathyroidism is a consequence of the medullary carcinoma of thyroid. The latter arises from the "C" cells in the thyroid tissue following their embryological migration from cells which have in common with sympathetic chain an ectodermal origin. These cells are capable of synthesizing precursors or hormones in the hydroxy indole series (catecholamines and calcitonin--the so-called APUD cells, amine precursor uptake and decarboxylation).

MEN IIA comprises 30% of familial pheochromocytomas (Table 30). Most of the pheochromocytomas are bilateral and in some "tumor" may not be evident (adrenomedullary hyperplasia). The hypertension usually is paroxysmal reflecting the epinephrine-producing adrenal pheochromocytomas. Recently, it has been reported that the enzyme, neuron specific enolase is uniformly elevated in neuroendocrine tumors including pheochromocytomas (96). The mechanism of hyperparathyroidism in this disorder is not known--parathyroids may demonstrate either hyperplasia or adenomas. Serum calcitonin is widely used in the detection of medullary carcinomas of thyroid and the reader should consult reference textbooks for evaluating medullary cancer of thyroid.

TABLE 30. **Multiple endocrine neoplasia: Classification**

Type 1
Pituitary disease*
Parathyroid disease†
Pancreatic disease
Zollinger-Ellison syndrome
Insulinoma
Syndrome of watery diarrhea, hypokalemia, and achlorhydria
Type 2
Medullary cancer of the thyroid††
Pheochromocytoma
Parathyroid disease†
Type 3
Medullary cancer of the thyroid††
Pheochromocytoma
Mucocutaneous syndrome
Multiple neuromas
Marfanid habitus
Hypertrophied corneal nerves

*Usually chromophobe adenoma
†Chief-cell hyperplasia, hypercalcemia and high parathormone level
††Calcitonin assay, calcifications on flat plate of the neck

MEN TYPE IIB (formerly Type III)

If the originally described Sipple's Syndrome (Type IIA) occurs in conjunction with mucosal neuromas, hypertrophied corneal nerves, gastrointestinal neuromas and skeletal defects--the syndrome is called MEN Type IIB. A notable finding, however, is the absence of parathyroid disorder in this group. Mucosal neuromas constitute a valuable marker and may indeed antedate pheochromocytoma and thyroid cancer. Involvement of alimentary tract is common and patients may present with megacolon as the initial manifestation.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of pheochromocytoma includes a long list of possibilities. Few other tumors are capable of causing such varied, diversified manifestations as pheochromocytomas. Often pheochromocytoma has been referred to as the "great mimic". The extra-ordinary overlap of clinical features listed in Table 31 is fascinating (or frustrating). However, many conditions can be excluded by careful clinical evaluation and simple laboratory tests. It should be emphasized that other diagnoses be excluded first before pursuing work-up for pheochromocytoma.

The physicians should have high index of suspicion in evaluating for pheochromocytomas. This fact is emphasized by a fifty year experience at Mayo Clinic: out of 54 pheochromocytomas found at autopsy, only 13 were diagnosed antemortem (97).

TABLE 31. DIFFERENTIAL DIAGNOSIS

1. Anxiety, psychosis
2. Hyperthyroidism
3. Paroxysmal cardiac arrhythmias
4. Hyperdynamic circulatory states
5. Migraine, cluster headaches
6. Coronary artery disease, heart failure
7. Diabetes
8. Hypertension induced by drugs or drug/food interactions
9. Carcinoid
10. Hypoglycemia
11. Autonomic insufficiency
12. Hypertension from sudden drug withdrawal
13. Neuroblastoma
14. Eclampsia
15. Porphyria
16. Lead intoxication
17. Autonomic hyperreflexia-quadriplegia
18. Labile "essential" hypertension

Since the clinical diagnosis of pheochromocytoma is not always an easy one, no physician can be criticized for obtaining tests to "rule out pheo" nor can he be criticized for omitting such tests in asymptomatic hypertensives.

ESTABLISHING THE DIAGNOSIS FOR PHEOCHROMOCYTOMA

The potential danger of undiagnosed pheochromocytoma should underscore the need for accurate diagnosis. As mentioned previously, one must have strong index of suspicion in order not to miss the diagnosis. Keep in mind the clinical features we have discussed and any patient presenting with history of hypertension and one or more of the clinical and inherited features, should be screened for pheochromocytoma. It is worthwhile recalling the "pearls" illustrated in Table 32.

TABLE 32

- 5 H's - Hypertension, Headache, Hypermetabolism, Hyperhydrosis, Hyperglycemia
- 95% will have headache, hyperhydrosis, palpitations
- "Rule of 10" - 10% familial, 10% bilateral, 10% malignant, 10% occur in children
- Additional clues - postural hypotension, weight loss, skin lesions, gallstones, hypertensive crisis induced by operative procedures and drugs

PHARMACOLOGICAL TESTS:

The pharmacological tests to diagnose pheochromocytomas are rarely used these days but I will cover them purely for historical interest and completeness. Prior to the availability of assays for catecholamines and their metabolites, these tests were widely employed. The pharmacological tests are based on either a hypertensive response to certain provocative drugs or a hypotensive response to adrenergic blocking drugs. The provocative tests (using histamine, glucagon or tyramine) produce both false positive and negative results. Although these tests are discarded in most centers, sometimes a provocative test can be employed in patients suspected of having a familial or intermittently active tumor. The diagnostic value of these tests is enhanced by measuring plasma catecholamines before and after injecting the drug; phentolamine must be readily available to abort a potential hypertensive crisis.

The other group of pharmacological tests measure the reduction in blood pressure and/or catecholamines in response to an anti-adrenergic agent. The phentolamine test is limited by lack of specificity. Although the phentolamine test (I.V. injection of 1-5 mg) is not recommended for the diagnosis of pheochromocytomas, it can be used in the treatment of pheochromocytoma hypertensive crisis.

Two suppression tests in the diagnosis of pheochromocytoma have been described recently. In one study, it was found that IV injection of ganglion blocking agent, pentolinium, suppressed the plasma catecholamines in patients without a tumor but did not do so in patients with pheochromocytoma (98). The other test, a more practical one, uses the effect of sympathetic inhibitor, clonidine on plasma catecholamines which were measured before and 3 hours after 0.3 mg oral dose. Plasma catecholamines in pheochromocytoma patients were unchanged whereas they fell in those without tumor (99) (Figure 15).

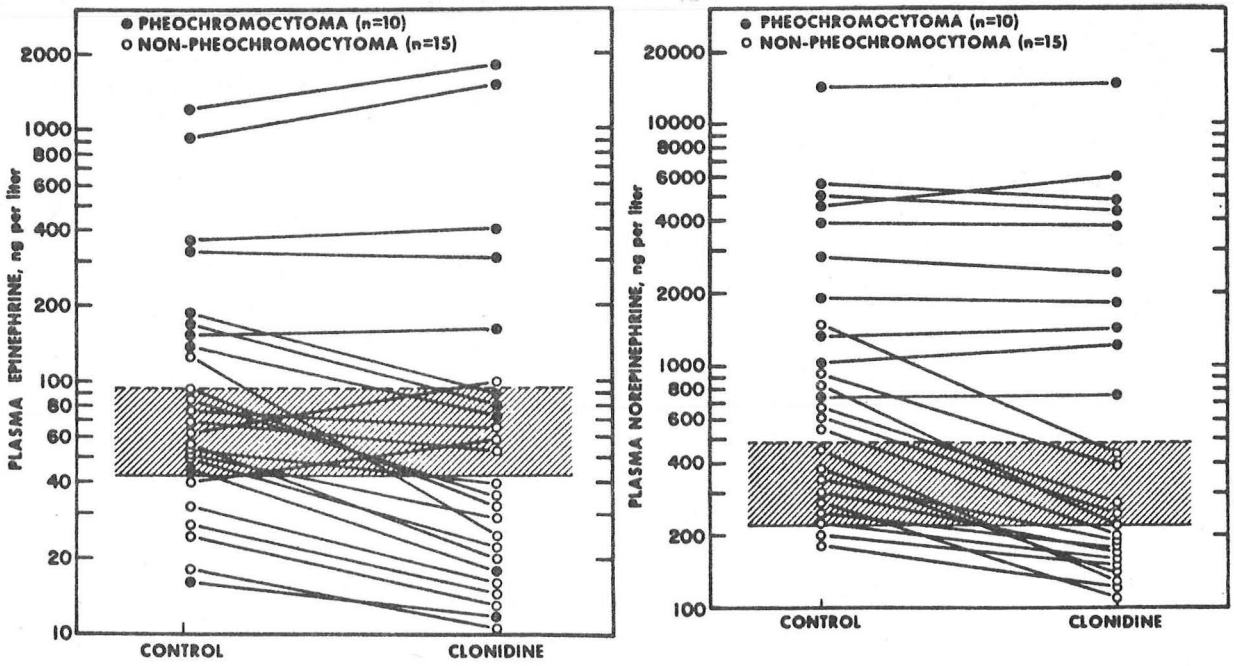


Figure 15. Plasma catecholamines before and three hours after a single dose of clonidine (0.3 mg). The hatched area represents values in healthy volunteers (Bravo EL, Tarazi RC, Fouad FM, et al.: *N Engl J Med* 305:190, 1977).

BIOCHEMICAL TESTS

The only way to diagnose pheochromocytoma preoperatively is by demonstrating high levels of catecholamines or their metabolites in the urine or in the blood. Surgery should not be undertaken without biochemical confirmation of pheochromocytoma. Tests used for demonstration of excessive catecholamines or their metabolites--metanephrine and normetanephrine (together "metanephrines") and vanillylmandic acid (VMA) have proved invaluable in the diagnosis of pheochromocytoma.

URINE TESTS -- METANEPHRINES

The measurement of urinary metanephrines offers a simple and rapid way of screening for pheochromocytoma. Metanephrines are often elevated in pheochromocytomas and most believe that it is the best screening test. The upper

limit of metanephrine excretion is 1.3 mg/24 hours using the Pisano method. The experience at NIH with 64 patients with pheochromocytomas showed excellent correlation between metanephrines, VMA and free catecholamines (Figure 16). The diagnostic accuracy and reliability of all the biochemical tests is clearly enhanced when the specimens are collected during a hypertensive spell. Norman Kaplan et al. noted good correlation between 24 hour urine and single voided urine for metanephrines in patients with pheochromocytomas the values were significantly higher than in those with essential hypertension (100) (Figure 17). My feeling is that if a patient is truly suspected of having pheochromocytomas, the negative results on a spot urine should not be relied upon and one should get a 24-hour urine collection.

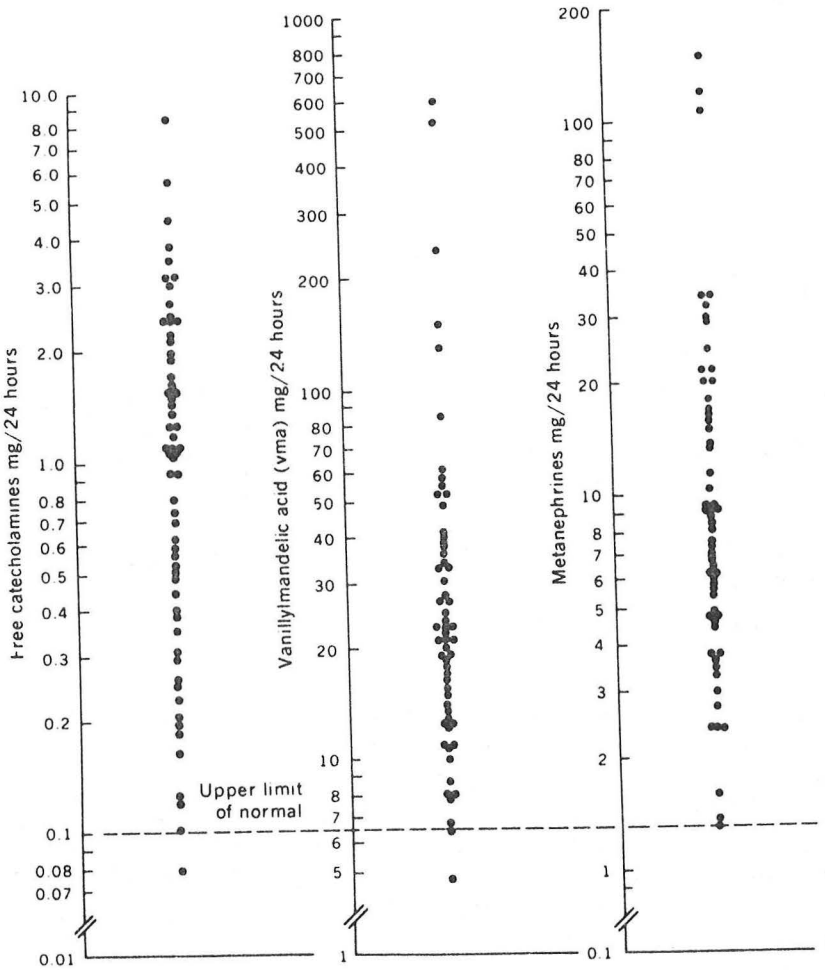


Figure 16. Results of urine assays for free catecholamines, VMA and metanephrines in 64 patients with proved pheochromocytoma. The upper limits of normal per 24-hour urine are: free catecholamines, 0.1 mg; VMA, 6.5 mg; metanephrines, 1.3 mg. (From Sjöerdsma A, Engelman K, Waldman TA, et al.: *Ann Intern Med 65:*1302, 1966.)

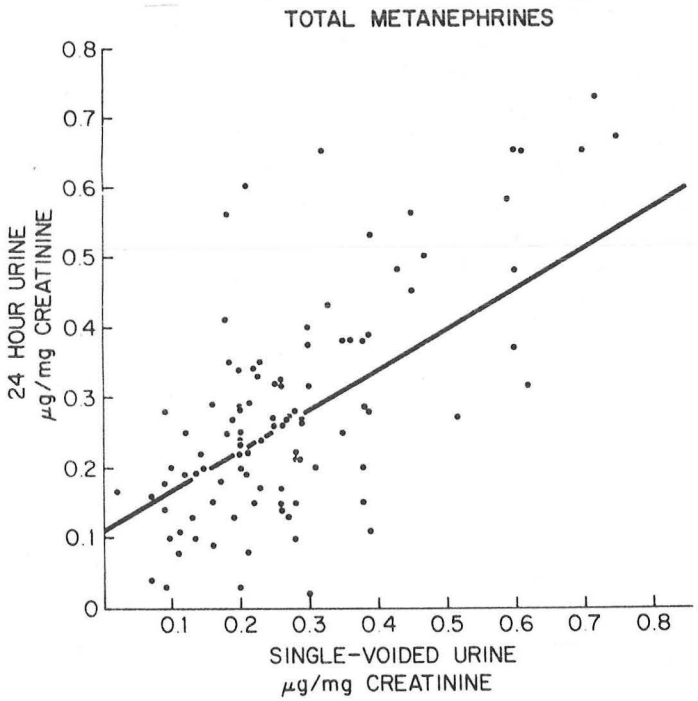


Figure 17. Relationship between total metanephrines in 24-hour urines and single-voided urine specimens in 100 patients with essential hypertension. (From Kaplan NM, Kramer NJ, Holland OB, et al.: *Arch Intern Med* 137:190, 1977. Copyright © 1977, American Medical Association.)

Metanephrines are spuriously increased by chlorpromazine, MAO inhibitors and ? methyldopa. Metanephrines are spuriously decreased by x-ray contrast media containing methylglucamine (e.g. Conray, Hypaque, Renografin, etc.)--wait for about 3-4 days after the contrast study to order metanephrines.

Metanephrine assay is highly specific, sensitive, reliable and is subject to very few false results.

VMA

In general, metanephrine values parallel with those of VMA. If there is divergence, the possibility of an interfering substance must be entertained. Fluorometric determination of VMA is subject to considerable errors because of interference by various food stuffs containing vanillyn. Such crude and antiquated methods should be avoided. VMA measurement by spectrophotometry is a valid procedure and is quite accurate. Normal excretion of VMA should not exceed 7 mg/24 hours. Any laboratory reporting higher normal values is relying on outdated techniques.

Using valid procedures, VMA is spuriously increased by

1)nalidixic acid
2)anileridine
3)levodopa
4)lithium slight
5)nitroglycerine

VMA is spuriously decreased by

1)clofibrate
2)? methyldopa
3)MAO inhibitors
4)?? ethanol

URINARY FREE CATECHOLAMINES

If the excretion of metanephrines and VMA are high, next free catecholamines are determined in the urine using modification of trihydroxy indole method of Lund. This procedure is sensitive but more difficult to do more than the metabolites. Therefore, it should not be used for routine screening.

Free catecholamines are increased by:

1)tetracycline
2)quinidine, quinine
3)chloral hydrate
4)methyldopa, L-dopa
5)isoproterenol
6)prochlorperazine
7)hypoglycemia, severe stress and muscular exercise

Free catecholamines are decreased by

1)clonidine
2)fenfluramine

It is better to collect the specimens preferably when the patient is not taking any drugs. But if this cannot be avoided, a note should be made to that effect. The values may be normal during the attack-free interval in patients with paroxysmal hypertension. In such patients, urine collections in close proximity to a hypertensive period or spell would be helpful.

PLASMA CATECHOLAMINES

Considerable advances have been made in developing highly sensitive and accurate isotopic or radioenzymatic techniques for the measurement of plasma catecholamines. Liquid chromatography technique holds considerable promise.

Recent studies have confirmed the usefulness of plasma catecholamines in the diagnosis of pheochromocytoma (101) (Figure 18). However, plasma concentration of catecholamines is influenced by activity, posture, pain, coffee, nicotine, many drugs, and other factors and the blood should be drawn under strictly controlled situations so that errors in interpretation can be avoided. The effect of ingestion of 250 mg caffeine (= 2 1/2 cups of coffee) on plasma catechols is shown in Figure 19 (102).

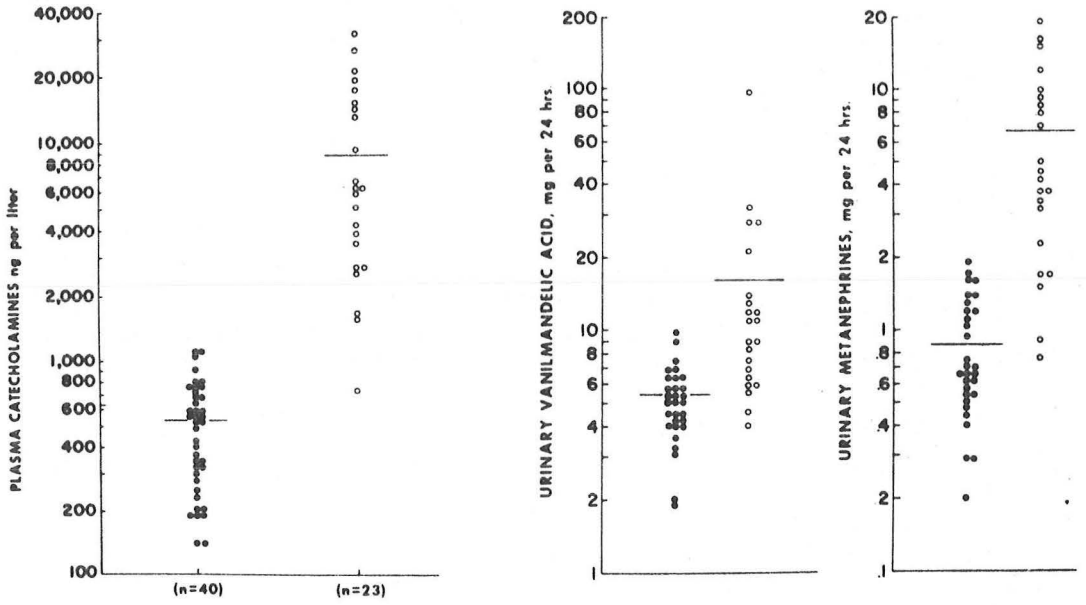


Figure 18. Circulating catecholamines and urinary metabolites in patients with pheochromocytoma (Bravo EL, et al.: *N Engl J Med* 301:682, 1979).

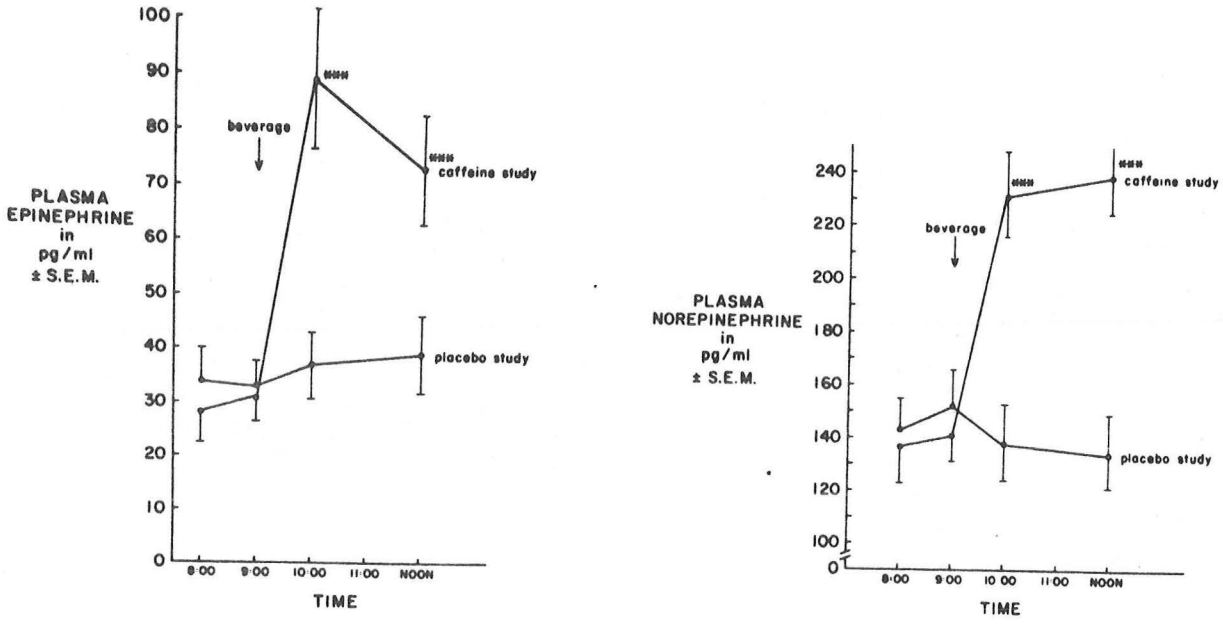


Figure 19: Effects of caffeine on plasma catecholamines (Robertson D, Frohlich JC, Carr RK, et al.: *N Engl J Med* 298:181, 1978).

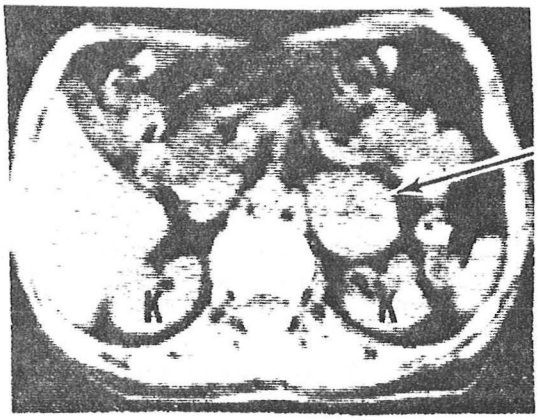
Plasma catecholamine assay is convenient if done properly. Of course, the diagnostic value is enhanced if the blood is drawn during a "spell" but in pheochromocytoma patients, even when the blood pressure is "normal", the levels may be elevated. A recent study, however, demonstrated that urine tests are more reliable than the plasma catecholamines (103).

PRE-OPERATIVE LOCALIZATION OF THE TUMOR

In adults 98% of pheochromocytomas occur in the abdomen, especially in the adrenals. In children, there is high incidence of multicentric and extra-adrenal tumors.

TABLE 33. LOCALIZATION OF PHEOCHROMOCYTOMA

1. CT SCAN
2. ULTRASOUND
3. ARTERIOGRAPHY
4. VENACAVAL SAMPLING FOR CATECHOLAMINES
5. SCINTIGRAPHY USING ^{131}I-MIBG



CT findings in a patient with left adrenal pheochromocytoma

IVP combined with nephrotomograms can localize the tumor in many (? 70%) but not all patients. Computed tomography (CT) has revolutionized the pre-operative localization of pheochromocytoma (105). CT scan is recommended as the initial radiographic procedure in the evaluation of patients with biochemical abnormalities suggestive of pheochromocytoma. One caution--propantheline instead of glucagon must be used for bowel paralysis when CT examinations are done with early generation scanners (i.e. 18 sec or slower scan times), since glucagon may evoke a hypertensive response.

Arteriography can accurately demonstrate adrenal and extra-adrenal tumors. This procedure is not necessary if the CT scan is positive. When arteriography is planned, its risk is minimized by pre-treating the patients with adrenergic blockers for 5-7 days (see below). Gray Scale ultrasonography may demonstrate adrenal tumors but is not good enough for extra-adrenal sites. If the tumor cannot be localized by any of the above techniques, then serial venous sampling from the inferior venacava, adrenal and other veins can localize the tumor (106) but this procedure is too tedious and can only be accomplished in a few centers.

Recently the University of Michigan group has developed and applied a scintigraphic technique to localize pheochromocytomas (107, 108). This exciting technique utilizes Iodine-131-metaiodobenzylguanidine (^{131}I-MIBG) for scintigraphic portrayal. ^{131}I-MIBG, an analogue of guanethidine, enters adrenergic tissue by the same mechanism as that of neurotransmitters. The initial results are encouraging and further experience is awaited.

Rarely, a tumor may be present in the neck or in the posterior mediastinum. The latter can be picked up by a chest x-ray (oblique views).

PHEOCHROMOCYTOMA OF THE URINARY BLADDER

Bladder pheochromocytoma is very rare. It is more common in females than in males and in patients between 10-20 years of age. Patients may present the paroxysms occurring during micturition, or during defecation. Painless hematuria is a common finding (109). In about 80%, tumors can be seen on cystoscopy.

PHEOCHROMOCYTOMA IN PREGNANCY

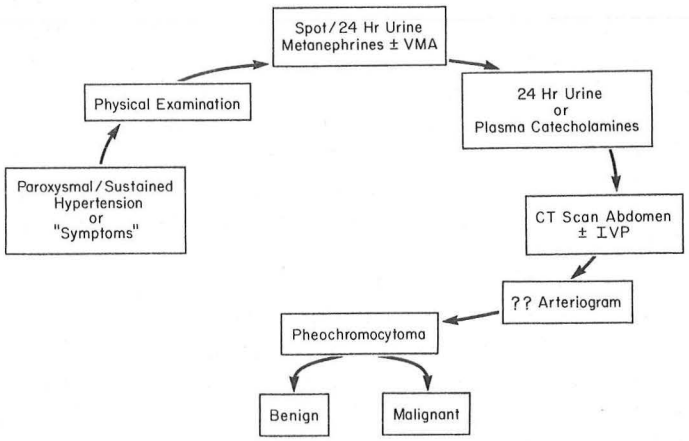
In women, pheochromocytoma is unmasked by pregnancy perhaps due to compression of the tumor by uterus and suspicion is aroused by frequent blood pressure measurements during the pregnancy. Pheochromocytoma in pregnancy can have a lethal effect on the mother and the fetus if the diagnosis is missed.

Many patients experience typical features of pheochromocytomas. Some may develop severe hypertension and fulminant toxemia. The diagnosis can be made by biochemical means and, except for sonography, other localizing procedures are not performed because of radiation risk.

MALIGNANT PHEOCHROMOCYTOMA

It is not possible to distinguish benign from malignant pheochromocytoma on histological grounds. Malignancy implies that pheochromocytoma is present in tissues which do not have chromaffin cells. The usual locales of malignancy are the liver, bone marrow, lung and lymph nodes. Generally malignant pheochromocytoma grows slowly and is resistant to chemotherapy and irradiation. The prognosis of these patients largely rests on adequate pharmacological therapy and has little bearing on "malignancy" itself. As long as the effects of catecholamines are controlled, these patients do well.

FLOW DIAGRAM FOR THE WORK-UP OF PHEOCHROMOCYTOMA



MANAGEMENT

Once the diagnosis of pheochromocytoma is established, the only curative therapy available is surgical removal of the tumor. Perhaps in no other form of secondary hypertension is such a dramatic relief of hypertension witnessed as in pheochromocytoma when the tumor is removed. However, all patients should be treated medically in the beginning irrespective of other plans.

TABLE 34. PHEOCHROMOCYTOMA - MANAGEMENT

1. PHEOCHROMOCYTOMA CRISIS - PHENTOLAMINE NITROPRUSSIDE
2. PRE-OPERATIVE/CHRONIC MEDICAL THERAPY
-- α-BLOCKERS, ± β-BLOCKERS, α-METHYL-PARA-TYROSINE
3. SURGERY
4. PROGNOSIS

MEDICAL THERAPY

The therapeutic objective is to prevent the pathophysiological and metabolic consequences of excessive catecholamines. In cases of malignancy or where surgery is otherwise contraindicated, medical therapy can be successfully accomplished. Even in patients who are to be operated, adequate preoperative medical treatment is invaluable in minimizing the operative risk. However, in some centers (e.g. Cleveland Clinic) routine pre-operative medical treatment is not implemented.

TREATMENT OF PHEOCHROMOCYTOMA CRISIS

Pheochromocytoma crisis is a medical emergency manifesting with constellation of signs and symptoms discussed earlier. As soon as the diagnosis appears certain, under cardiac monitoring, phentolamine 2-5 mg is given intravenously every 5-10 minutes until the blood pressure improves. If the patient has tachycardia or tachyarrhythmias, propranolol (1-2 mg IV) can be given as necessary. If the patient truly has pheochromocytoma, the response to these maneuvers is dramatic. Keep in mind that very rarely, hemorrhage and infarction of tumor with subsequent hypotension can occur with phentolamine (110). Treatment of pheochromocytoma crisis can also be accomplished with nitroprusside.

ADRENERGIC BLOCKERS

Adrenergic blocking drugs form the cornerstone of medical treatment of pheochromocytoma. Phenoxybenzamine given orally is an excellent agent for chronic medical therapy as well as for pre-operative care of the patient. It blocks the effects of catecholamines and thus relieves the hypertension and other symptoms. It has a smooth and prolonged action-permitting only one or

two doses daily. The starting dose is 10-20 mg/day which can be increased as necessary. For the majority of patients 40-60 mg/day will suffice but a few may require up to 200 mg/day. Common side effects of this drug are nasal stuffiness, orthostatic hypotension and inhibition of ejaculation and tachycardia.

Prazosin, another alpha-adrenergic blocker, has been reported to control symptoms of pheochromocytoma (111). If it works, then it may be better tolerated by patients.

Beta-blockers will be necessary in some (not all) who have tachycardia, etc. However, beta-blockers should be given only after alpha-blockers are started so that paradoxical rise in blood pressure can be avoided. One should be careful not to give beta-blockers routinely as some patients may have heart failure/cardiomyopathy. Labetalol, a combined alpha-& beta-blocker, has been successfully used abroad in the treatment of pheochromocytoma but the experience is limited.

INHIBITION OF CATECHOLAMINE SYNTHESIS

α-methyl-para-tyrosive (α-MPT) is an orally active inhibitor of catecholamine synthesis. α-MPT blocks the rate limiting step, conversion of tyrosine to dopa, and in sufficient dose can inhibit catecholamine synthesis by 80% (112). The drug can be used (in place of alpha and beta-blockers) in the preoperative care as well as for chronic therapy but side effects such as sedation, tremors, diarrhea and crystalluria may limit its long term usefulness (113). α-MPT represents a rational approach to the medical treatment of pheochromocytoma. The initial dose is 250 mg q.i.d. which can be increased daily to a maximum of 4 gm/day; sufficient oral fluid intake must be advised to minimize the risk of crystalluria.

SURGERY

Once the patient is stabilized with medical treatment, surgery is recommended. The key to successful outcome is close team-work and integrated approach by the physicians caring for the patient.

Previously the choice of anesthetic agent was felt to be critical, various centers preferring one or more agents (112). Although enflurane is thought to be a good choice, selection of an anesthetic agent is not of primary importance as long as the blood pressure elevations and cardiac arrhythmias are well controlled. In the operating room, sufficient quantities of phentolamine, propranolol, nitroprusside, norepinephrine, and lidocaine should be available. Depending on the operative team's preference either phentolamine (drip or bolus) or nitroprusside can be used to treat significant hypertensive episodes.

Since almost all the pheochromocytomas are located in the abdomen, most surgeons prefer a transverse abdominal incision that will permit through exploration of both adrenals, entire para-aortic sympathetic chain and the urinary bladder. Not only the obvious, but all potential sites of the tumor should be explored. In familial cases, multiple tumors are common. Sudden rise in blood pressure during palpation is an invaluable clue to locate small tumors.

If a single tumor is found, the entire adrenal must be taken out. If there are bilateral tumors, sufficient adrenocortical tissue may be left in place in the hope of preventing dependence on steroids. Some believe that total bilateral adrenalectomy should be performed in patients with MEN syndrome.

When the pheochromocytoma is removed, blood pressure may fall drastically. A contributing factor to this phenomenon is the shrunken blood volume which is no longer supported by intense vasoconstriction. This can be treated by appropriate IV fluids.

POST-OPERATIVE CARE

Severe hypoglycemia has been reported after removal of pheochromocytomas (114, 115) presumably due to brisk insulin secretion and diminished glycogenolysis following sudden decrease in catecholamines. Therefore, blood sugar must be monitored during immediate post-operative period.

Return or persistence of hypertension in the post-operative period may be due to fluid overload, incomplete removal of pheochromocytoma, or rarely due to accidental ligation of a renal artery--each of the possibilities deserves careful assessment and therapy. As far as the question of persistent pheochromocytoma is concerned, the biochemical tests should be done only after 6-7 days when the patient is relieved of stress.

PHEOCHROMOCYTOMA IN PREGNANCY

Early in term, some recommend surgical removal of the tumor because of (unknown) complications of medical treatment on the fetus (87). However, if the diagnosis is made late in the pregnancy--last trimester, alpha-adrenergic blockade with phenoxybenzamine is recommended (116, 117). When the fetus is mature, it must be delivered by cesarean section and with coordinated efforts, the surgeon should remove the pheochromocytoma at the same time if the tumor is readily identified.

PROGNOSIS

The prognosis of benign pheochromocytoma is excellent with a 5 year survival rate of 96%! For malignant pheochromocytomas, the prognosis is less impressive but still reasonably good with at least half the patients surviving longer than 5 years. In these patients, medical therapy should be continued indefinitely.

A repeat urine metanephrine should be done 1 week after surgery and thereafter at periodic intervals (2-5 years) since the disease may reappear occasionally. Patients with familial syndromes should be followed throughout their lifetime.

Pheochromocytoma with its multiple facets and sometimes, striking clinical features represents a truly curable form of hypertension. Less subtle cases, however, pose a diagnostic challenge which can only be met by an index of suspicion and careful (and prolonged) observation and follow-up. The improved

management of patients with this potentially lethal condition is no doubt the result of better understanding of biochemical pharmacology and physiology and is also due to well planned and executed pre-operative, surgical and post-operative care.

ILLUSTRATIVE CASES

CASE 1: Pheochromocytoma uncovered by evaluation of inappropriate hypertension.

K.M.: An 18 year old black female was admitted to the hospital because of increased BP in pregnancy. Hysterotomy was performed because of possible toxemia. During and in the first few hours following surgery patient's BP increased further ranging between 140/90 and 190/120 mm Hg. Metanephrines were 2.57 mg/24 hours (normal < 1.3), and urine catecholamines were 0.58 mg/24 hours (normal < 0.1 mg). Patient was operated and a tumor from the organ of Zuckerkandl was removed. This patient's tumor was malignant and post-surgically she is maintained on chronic alpha-blockade.

Unexplained and inappropriate elevation of BP particularly in the young with no previous history of hypertension should make us think of a secondary cause such as a pheochromocytoma illustrated by this patient.

CASE 2: "Typical" pheochromocytoma.

W.D.: A 40 year old white female presented with a four year history of hypertension. She had discontinued the treatment (? diuretics) because often the medicines caused her BP to get worse. Her past history was remarkable for many spontaneous spells of "nervousness", palpitations, tingling and sweating. She was admitted to the hospital because of metromenorrhagia and hysterectomy was performed. With the induction of anesthesia, her BP shot up to 190/120 from 160/90 mm Hg. The post-op course was highlighted by wide fluctuations in the BP (from 110/60 to 170/100 to 205/130) and tremulousness, etc. Spot and 24 hour urine metanephrines were 3.5 to 10.5 µg/mg creatinine and 4.5 to 14.1 mg respectively. Plasma norepinephrine and epinephrine were 1532 and 586 pg/ml (markedly elevated). CT scan showed bilateral adrenal pheos which were removed with uneventful post-operative course and resolution of "spells" and she has remained normotensive.

The above case illustrates the presentation and features of "typical" pheochromocytoma.

CASE 3: Accidentally discovered pheochromocytoma.

F.D.: A 29 year old black male was admitted to the hospital for the evaluation of gross hematuria. His past history was only notable for deafness. A sonogram revealed right renal mass which was confirmed

by angiography. The patient was taken to the operating room, and a tumor involving both the kidney and the adrenal gland was removed. The histopathological diagnosis--pheochromocytoma and (unrelated) intrarenal infections process. This patient had no demonstrable symptoms or signs of pheochromocytoma, although his hearing defect may have obscured obtaining proper history. His BP dropped somewhat after the operation but it was not high to begin with.

The above case signifies the protean behavior of pheochromocytoma and, sometimes, patients are asymptomatic only to be discovered accidentally.

PRIMARY ALDOSTERONISM

Primary aldosteronism is an uncommon cause of hypertension in unselected populations. The exact prevalence is probably unknown although the generally accepted figure is less than 0.5% of all hypertensives (119). The initial overenthusiastic assumption that primary aldosteronism accounts for a fifth of patients with hypertension has been now firmly disproven. It is possible that the recognition of this syndrome may be underestimated by the implementation of low-salt diet which may mask subtle biochemical abnormalities accompanying primary aldosteronism.

Primary aldosteronism is characterized by excessive aldosterone production from adrenocortical pathological state whereas in secondary aldosteronism hypersecretion of aldosterone occurs in the absence of adrenal pathology (Figure 20). It is extremely important to distinguish these entities because the diagnostic and therapeutic approaches are quite different.

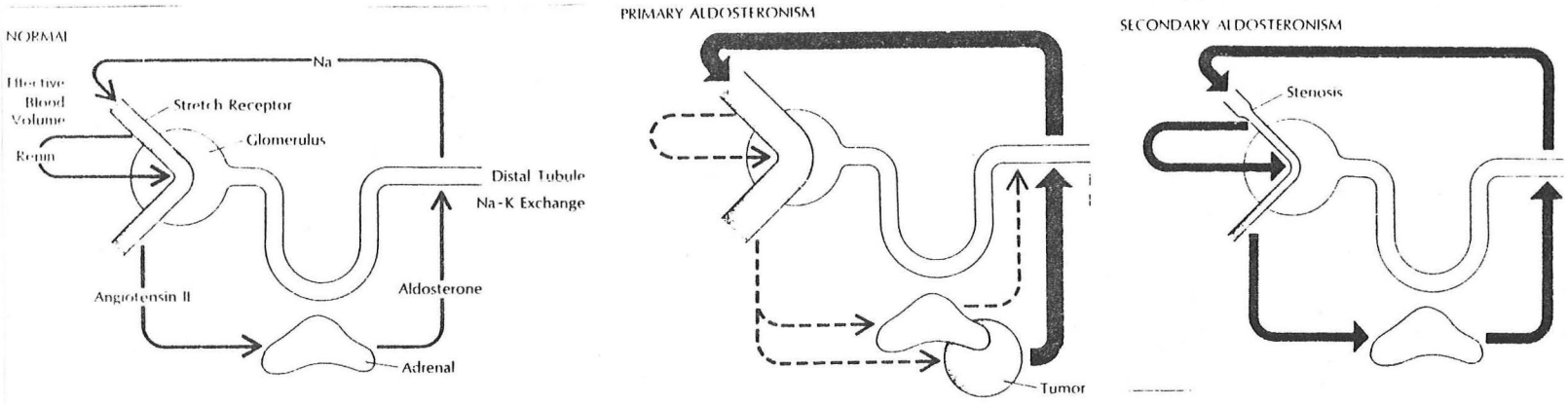


Figure 20. The renin-angiotensin-aldosterone axis in normals and in aldosteronism.

PATHOPHYSIOLOGY

Aldosterone, a potent natural mineralocorticoid is secreted by the zona glomerulosa of the adrenal cortex. Aldosterone secretion is mainly governed by the renin-angiotensin system, ACTH and plasma potassium level, and possibly by plasma sodium concentration (Figure 21). The primary action of aldosterone is to increase sodium reabsorption and potassium excretion by the distal renal tubule (Figure 22).

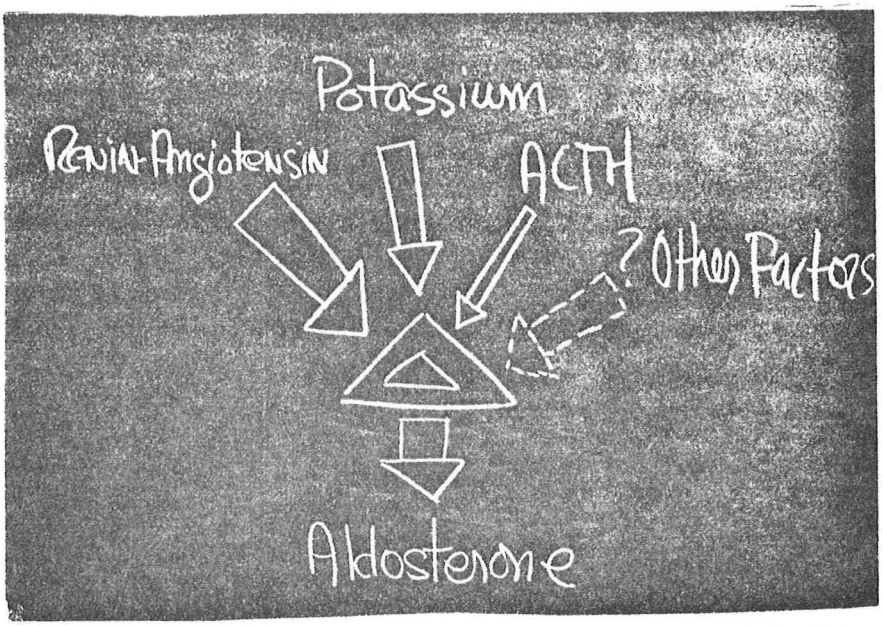


Figure 21. The factors governing aldosterone release.

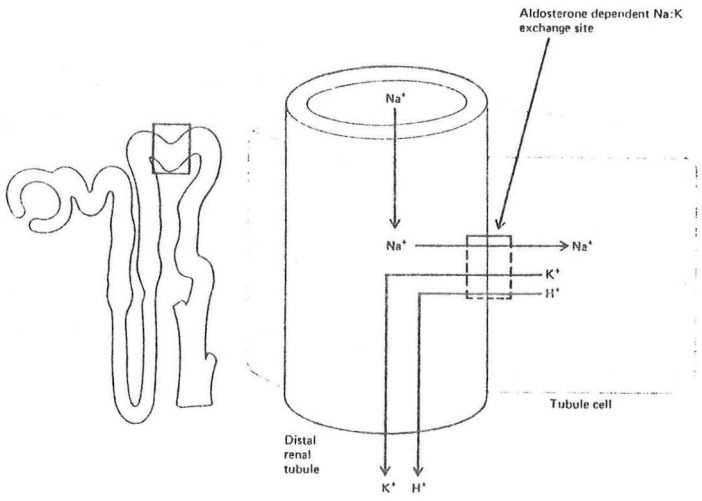


Figure 22. The site of action of aldosterone in the kidney.

The major regulator of aldosterone appears to be the renin-angiotensin system. In primary aldosteronism, the production of aldosterone is autonomous. Single adenomas account for most cases of primary aldosteronism and bilateral hyperplasia is present in the remainder; several variants have been rarely documented. Circulating aldosterone is a free moiety and is metabolized in the liver and excreted mainly as tetrahydroaldosterone. A small portion is metabolized in the kidney and excreted as 18-glucoronide. Aldosterone exerts its main sodium retaining action on the distal convoluted renal tubule. The ensuing excretion of potassium and hydrogen ions is probably secondary to sodium absorption. As sodium ions with the positive charges are reabsorbed, the cellular lumen becomes electro-negative while the interstitial fluid becomes electro-positive. This electrical gradient favors continued loss of potassium (and hydrogen ions).

In the presence of excessive aldosterone, increased extracellular fluid leads to hypervolemia. The expansion of plasma volume results in decreased sodium absorption by the proximal tubule. A new steady state is thus achieved but with relative hypervolemia. The serum sodium concentration is often in the high normal range but the net total body sodium content is increased. Because of the expanded plasma volume, renin secretion is suppressed.

The mechanism of hypertension in primary aldosteronism is not fully understood. Previously, it was believed that primary aldosteronism represented a classical example of volume-dependent hypertension. However, recent studies (121) do not support this simplistic view and suggest that, like in essential hypertension, the persistent elevation of blood pressure in primary aldosteronism is due to increased peripheral vascular resistance.

CLINICAL FEATURES

The clinical features of primary aldosteronism in general are indistinguishable from those of essential hypertension. The diagnosis is suspected in a hypertensive patient who has spontaneous hypokalemia. Some patients with this disorder manifest hypokalemia only when treated with a diuretic or when exposed to a high salt intake. Many patients complain of headache, and prolonged hypokalemia may lead to muscular weakness but tetany and periodic paralysis are rare (Table 35).

TABLE 35. Signs and symptoms of primary aldosteronism

- Hypertension
- Potassium depletion
  - Symptoms
    - Weakness, loss of stamina
    - Paresthesias
    - Flaccid paralysis
    - Polyuria, polydipsia, nocturia
  - Findings
    - Urinary potassium loss
    - Hypokalemia
    - Alkalosis
    - Urinary concentration defect
- Sodium retention
  - Hypernatremia
  - Decreased hematocrit; increased plasma volume
- Autonomic dysfunction
  - Postural hypotension; bradycardia

Chronic hypokalemia may alter the structural integrity of the distal convoluted tubule resulting in nephrogenic diabetes insipidus and some patients may present with polyuria or polydipsia.

Hypertension is present in the majority of patients with primary aldosteronism and "normotensive" primary hyperaldosteronism is very rare (122). The common belief is that hypertension in primary aldosteronism is mild but many patients with severe degrees of hypertension have been reported (123, 124). Patients with bilateral hyperplasia are likely to have milder forms of hypertension because the aldosterone excess in these patients is moderate compared to those with adenoma.

DIAGNOSTIC AIDS IN PRIMARY ALDOSTERONISM

The best single clue to the suspicion of primary aldosteronism is the presence of unprovoked hypokalemia in a hypertensive patient (Table 36). The diagnosis of primary aldosteronism should be pursued only when other causes of hypokalemia and secondary hyperaldosteronism are carefully considered and excluded (Table 37 a & b). Once it appears certain that hypokalemia is truly spontaneous, the diagnosis of primary aldosteronism can then be established by the demonstration of inappropriate kaliuresis, low plasma renin activity and high levels of aldosterone in the urine or in the blood.

TABLE 36 . FEATURES OF PRIMARY ALDOSTERONISM

1. UNPROVOKED HYPOKALEMIA
2. INAPPROPRIATE KALIURESIS
3. SUPPRESSED PRA - CANNOT BE STIMULATED
4. ELEVATED ALDOSTERONE LEVELS (URINE/PLASMA) - CANNOT BE SUPPRESSED
5. ALDOSTERONE: PLASMA RENIN ACTIVITY RATIO (> 400)

TABLE 37A. Characteristics of Some Disorders Involving Excess Aldosterone

Disorder	Blood pressure	Edema	Serum Na^+	Serum K^+	Plasma renin activity	Aldosterone
Primary aldosteronism	↑	0	↑, N	↓	↓ ↓	↑
Secondary aldosteronism:						
Accelerated hypertension	↑ ↑	0	↓, N	↓	↑ ↑	↑ ↑
Edema disorders	N, ↓	+	↓, N	N, ↓	↑	↑

TABLE 37B. **Plasma Renin Activity (PRA) and the Renal-Adrenal Axis in Hypertensive States**

LOW PRA	NORMAL PRA	HIGH PRA
Without Aldosteronism	*Without Aldosteronism*	*With Secondary Aldosteronism*
Low-renin essential hypertension	Normal-renin essential hypertension	Malignant or severe hypertension
Parenchymal renal disease	Unilateral renal disease	Unilateral renal disease with severe hypertension
Liddle's syndrome	Bilateral renal vascular or parenchymal disease	Bilateral renal vascular or parenchymal disease
Iatrogenic: mineralocorticoid or licorice ingestion	Cushing's syndrome	High-renin essential hypertension
With Aldosteronism	Coarctation of the aorta	Renin-secreting kidney tumors
Primary	Pheochromocytoma	Iatrogenic: oral contraceptive use
Pseudoprimary		
Tertiary (?)		Note: Plasma renin activity may be high in potassium-depleted patients with the disorders named above but without secondary aldosteronism.
Glucocorticoid suppressible		
With Mineralocorticoidism		
11-β-hydroxylase deficiency		
17-α-hydroxylase deficiency		
Adrenal carcinoma		
Ectopic ACTH-secreting tumors		
Excess 18-OH deoxycorticosterone		

HYPOKALEMIA

Almost all the patients with primary aldosteronism have hypokalemia at one time or the other. True that a fraction of patients with this disorder become hypokalemic only when taking a diuretic. Even in these patients, the severity and persistence of hypokalemia and difficulties encountered in restoring normokalemia should alert one to suspect primary aldosteronism. A few patients have been recognized with "normokalemic primary aldosteronism". Even in these patients, the serum potassium usually does not exceed 4 mEq/1. If the patient has been on a diuretic, serum potassium should be checked 2-3 weeks after its discontinuation. One should always take sufficient precautions to prevent spurious elevation of serum potassium levels by vigorous muscular exercise (or tight tourniquet) and hemolysis. Also, recall that the plasma level of potassium is normally 0.5 mEq/1 less than that of serum. Vigorous salt restriction may prevent the hypokalemia and it is advisable to recheck the serum potassium level when the patient is on an unrestricted salt intake (at least 7-10 gm sodium intake daily for 4-5 days).

If the patient has borderline serum potassium levels (3.2 to 3.5 mEq/1) or becomes hypokalemic only with modest doses of a diuretic, the dilemma is whether or not to proceed with further workup. If primary aldosteronism is present, such patients usually turn out to have bilateral hyperplasia which cannot be cured surgically and therefore the physician is certainly faultless if it is elected to treat such patients medically without proceeding with further workup. The decision, however, should be individualized.

URINARY POTASSIUM

After the finding of hypokalemia, the next step in the diagnosis of primary aldosteronism is to measure 24 hour excretion of potassium. Patients with this disorder continue to loose excess potassium in the urine despite hypokalemia. Patients with primary aldosteronism excrete greater than 30 mEq potassium per day. In the presence of hypokalemia, if the 24 hour urine potassium is less than 30mEq, the diagnosis of primary aldosteronism is unlikely the additional evaluation is not necessary (Figure 23) (119). To ensure adequate sodium/-potassium exchange in the renal tubules, the collection of urine should be performed when the patient is not on rigid salt restriction. We would like to see at least 100 mEq sodium in the urine in order to interpret the potassium losses. If hypokalemia and inappropriate kaliuresis are present, then the following tests should be performed.

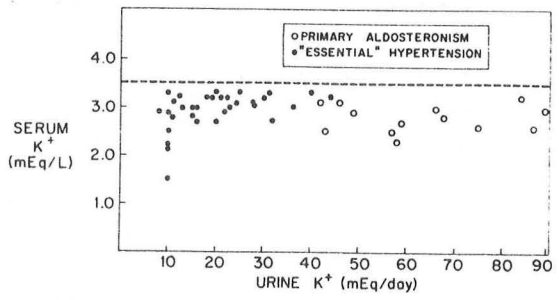


Figure 23. Urinary potassium excretion in patients with primary aldosteronism was uniformly above 30 mEq/day, whereas most patients with essential hypertension and comparable hypokalemia (mostly secondary to prior thiazide therapy) had less than 30 mEq of potassium in the 24-hour urine specimen. (Kaplan NM: *Ann Intern Med* 66:1079, 1967.)

PLASMA RENIN ACTIVITY (PRA)

Hyporeninism is an important and useful diagnostic feature of primary aldosteronism. This is in contrast to secondary aldosteronism which is characterized by high PRA. In primary aldosteronism, PRA is usually subnormal due to negative feedback of aldosterone excess on the renin release mechanism. Although PRA is low in primary aldosteronism, this finding is also seen in patients with low-renin "essential" hypertension. The suppressed PRA in primary aldosteronism is of further significance in light of the known stimulatory effects of hypokalemia on renin release. The PRA which is low to begin with in primary aldosteronism fails to respond to maneuvers employed to stimulate the renin release (Figure 24). Not only the baseline PRA but a stimulated PRA must also be obtained after employing maneuvers such as a low salt diet (500 mg) for three days or administration of oral or intravenous furosemide combined with upright posture. After the demonstration of persistently suppressed PRA, then an excess of aldosterone (in the plasma or urine) must be demonstrated.

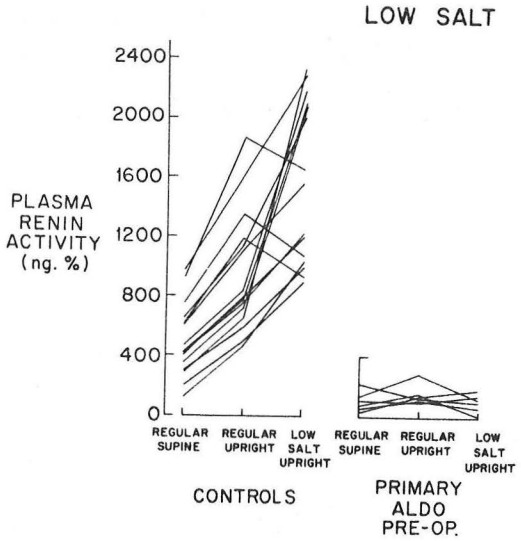


Figure 24. PRA by bioassay in control subjects and patients with primary aldosteronism while on a regular diet, supine and upright, and after 3 days on a 500-mg low salt diet plus 4 hours of upright posture. (From Jose A, Kaplan NM: *Arch Intern Med 123*:141, 1969.

ALDOSTERONE MEASUREMENTS

Demonstration of excessive aldosterone that cannot be suppressed clinches the diagnosis of primary aldosteronism. Since hypokalemia has the potential of inhibiting aldosterone secretion, it should be measured only after replenishing the body potassium stores. This can be achieved by giving potassium chloride or triamterene for 3-4 weeks; in some, longer periods of potassium supplementation may be necessary. Since spironolactone can interfere with aldosterone measurements it is not recommended at this stage. After the serum

potassium level is normalized, stop the supplementation for three days before measuring the aldosterone, since excess potassium itself stimulates aldosterone secretion.

Aldosterone can be measured either in plasma or in the 24 hour urine. The former is more convenient but the latter represents cumulative excretion of aldosterone metabolites over a fairly long period. Considerable caution is advised in interpreting single plasma aldosterone values because of dynamic changes in its secretion and clearance. It is better to obtain 2-3 plasma aldosterones in a 24 hour period. If this is not possible, a single 24 hour urine for aldosterone is quite satisfactory.

After the demonstration of aldosterone excess, the next step is to show that it cannot be suppressed. This is of critical importance because the aldosterone excess in conditions other than primary aldosteronism can be suppressed. Of various suppression tests, the most convenient approach is to measure plasma aldosterone before and after the infusion of 2 liters of normal saline over 4 hours. Patients with primary aldosteronism have high basal levels of plasma aldosterone but more importantly saline infusion fails to lower these values (Figure 25) (125). The other suppression tests employ synthetic mineralocorticoids or a high salt intake. A few patients with a normal urinary aldosterone but elevated tetrahydroaldosterone levels have been described (126).

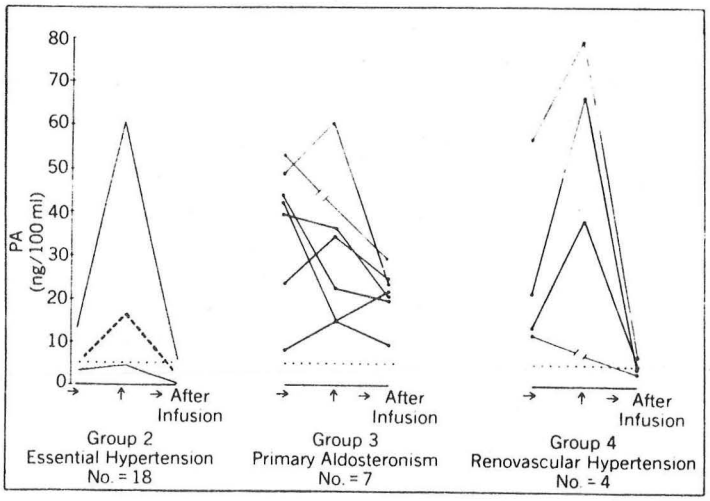


Figure 25. Plasma aldosterone (PA), by radioimmunoassay, in 18 patients with essential hypertension, 7 with primary aldosteronism and 4 with renovascular hypertension. The *initial horizontal arrow* represents 8 hours of recumbency; the *middle upright arrow,* 2 hours of upright posture; the *horizontal arrow on the right,* the end of a 4-hour infusion of 2 liters of normal saline. (From Kem DC, Weinberger MH, Mayes DM, et al.: *Arch Intern Med 128*:380, 1971. Copyright © 1971, American Medical Association.)

In a recent study, serum aldosterone-PRA ratio was calculated and it was noted that only patients with aldosterone producing adenoma had aldosterone-PRA ratio > 400 whereas in essential hypertension this ratio was considerably lower (127) (Figure 26).

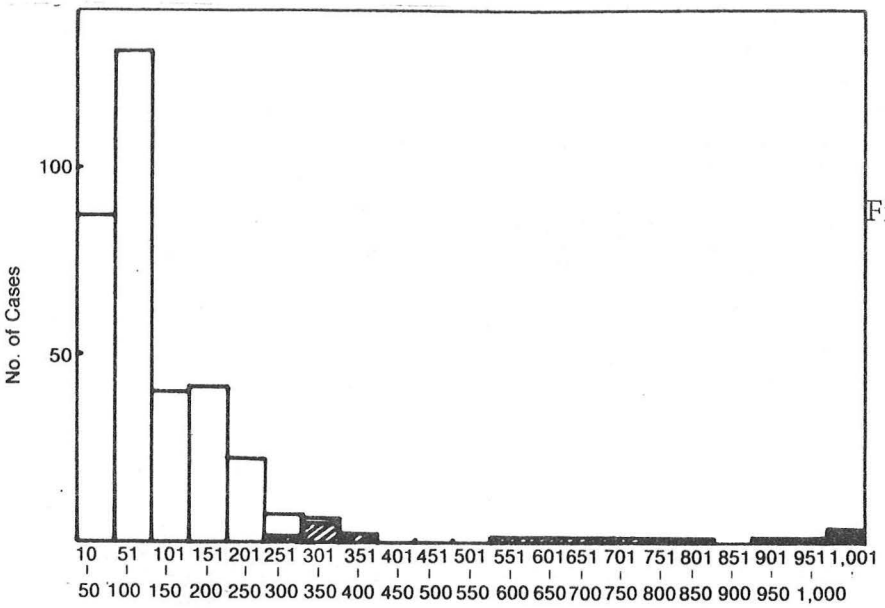


Figure 26.—Aldosterone–plasma renin activity (PRA) ratio in 348 patients with hypertension. Black area indicates patients with aldosterone-producing adenoma; shaded area, patients with moderately high aldosterone-PRA ratio. (Hiramatsu K, et al.: *Arch Intern Med* 141:1589, 1981).

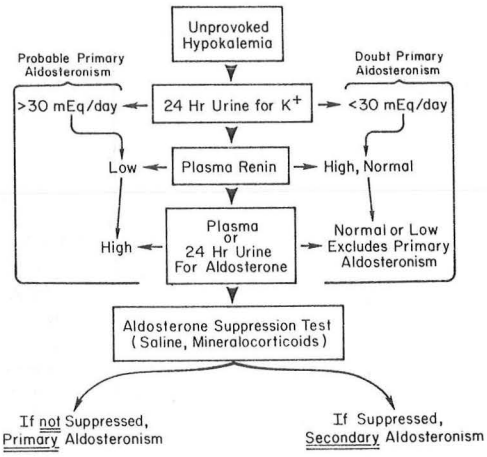
MISCELLANEOUS TESTS IN THE DIAGNOSIS OF PRIMARY ALDOSTERONISM

Response to spironolactone: Spironolactone, a competitive inhibitor of aldosterone, is useful in the medical treatment of primary aldosteronism. It has been proposed that therapeutic response to a course of spironolactone is indicative of primary aldosteronism (128). This diagnostic test is not reliable because of false negative responses and also false positive responses seen in patients with low-renin essential hypertension.

Measurements of electrical gradient across the rectal epithelium: This interesting test proposed by the British never gained any support! (129). The idea was that the potential difference between the patient's skin and rectal mucosa (normal -35 to -50 mv) is enhanced in primary aldosteronism because of increased absorption of positively charged sodium ions from the lumen into the blood. I would hasten to say that this test is prone to false results and therefore is not applied at least here in the United States.

To recaptulate, the diagnosis of primary aldosteronism should be suspected in a hypertensive patient with spontaneous hypokalemia and inappropriate kaliuresis. And it is confirmed by the demonstration of low PRA which cannot be stimulated and of high aldosterone which cannot be suppressed.

FLOW DIAGRAM FOR THE WORK-UP OF PRIMARY ALDOSTERONISM



DIFFERENTIAL PATHOLOGICAL DIAGNOSIS OF PRIMARY ALDOSTERONISM AND LOCALIZING PROCEDURES

Having made the diagnosis of primary aldosteronism, it is necessary to know the probable pathological state--adenoma or hyperplasia. The distinction is not just academic but of crucial importance in planning the therapy--surgery is beneficial only in the former whereas bilateral hyperplasia is treated medically. The following points are useful in predicting whether the patient has adenoma or hyperplasia (130, 131, 132).

1. The various features of primary aldosteronism are more severe in a patient with adenoma than in one with hyperplasia. The metabolic consequences such as hypokalemia and hyporeninism are likely to be severe with adenoma (Table 38).

TABLE 38. *Primary aldosteronism—classification and features*

	Aldosterone-Producing Adenoma	Idiopathic Hyperaldosteronism	Indeterminate Hyperaldosteronism	Glucocorticoid Remediable Hyperaldosteronism
Incidence	80–90 per cent of all cases	10–15 per cent	Rare	Only few cases reported
Laterality	Unilat.	Bilat.	Bilat.	Bilat.
Hypertension	++	+++	+	+
Metabolic abnormalities	+++	++	+	+
Plasma renin activity	Lowest, often non-detectable, cannot be stimulated	Low, can be minimally stimulated	Low but can be stimulated by orthostatism	Low
Plasma aldosterone concentration	+++, decreases with upright posture	++, increases with upright posture	+, increases with upright posture	+, postural stimulation not studied
Suppression of plasma aldosterone concentration with fludrocortisone	No	No	Yes	Yes
Suppression of diurnal changes in plasma aldosterone concentration with dexamethasone	Yes	No	?	Suppresses plasma aldosterone concentration below normal limits and corrects metabolic abnormalities
Plasma 18-hydroxycorticosterone	+++	+	Not studied	Normal
Treatment	Surgery/spironolactone	Antihypertensive agents/spironolactone	Spironolactone	Glucocorticoids

In general, the plasma concentrations of aldosterone tend to be higher in adenoma than in hyperplasia. Although the mean values for each group are significantly different, there is considerable overlap between individual values and hence, the diagnostic specificity of absolute levels is low.

2. The PRA in hyperplasia is amenable to some degree of stimulation but in adenoma it is uniformly suppressed.

3. The circadian rhythm of aldosterone production is preserved in hyperplasia, it is disrupted in adenoma.

4. An anomalous fall in plasma aldosterone concentration from supine value after four hours of upright posture favors the diagnosis of adenoma, an increase occurs in hyperplasia (Figure 27).

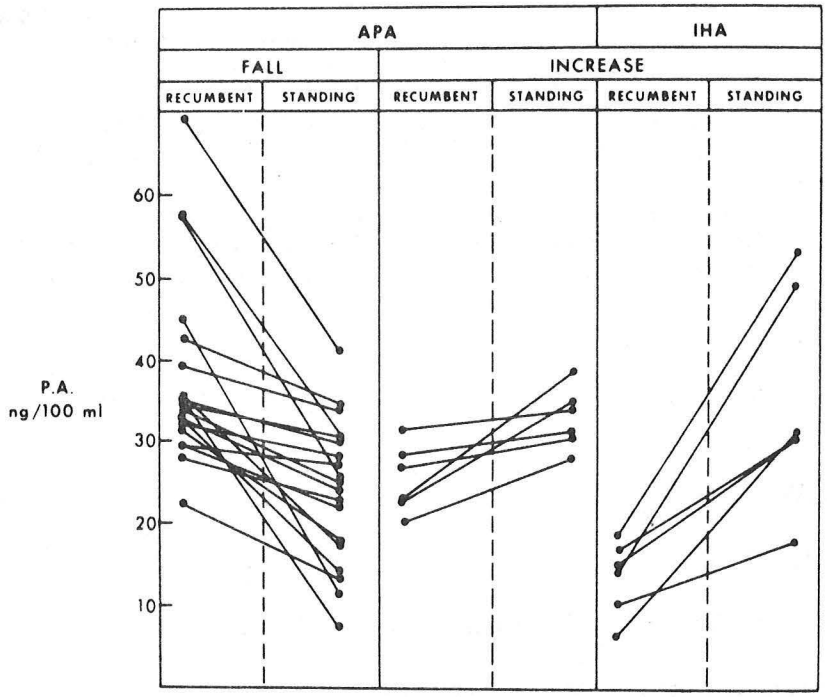


Figure 27. . Response of plasma aldosterone (PA) concentration to postural change in surgically proved cases of aldosterone-producing adenoma (APA) and idiopathic hyperaldosteronism (IHA), the latter group having bilateral hyperplasia. Most of the adenoma cases had a fall in PA upon standing, whereas most of the hyperplasia cases had a rise. (From Biglieri EG, Schambelan M, Brust N, et al.: *Circ Res 34 and 35 (suppl I):*I-83, 1974. By permission of the American Heart Association, Inc.)

5. Plasma 18-hydroxycorticosterone levels are higher in patients with adenomas than in patients with hyperplasia.

6. Aldosterone is suppressed by the administration of cyproheptadine in patients with hyperplasia but not in those with adenoma. This observation raises the possibility that aldosterone production in patients with hyperplasia is mediated by serotonin-regulated release of an unknown secretagogue (Figure 28) (133).

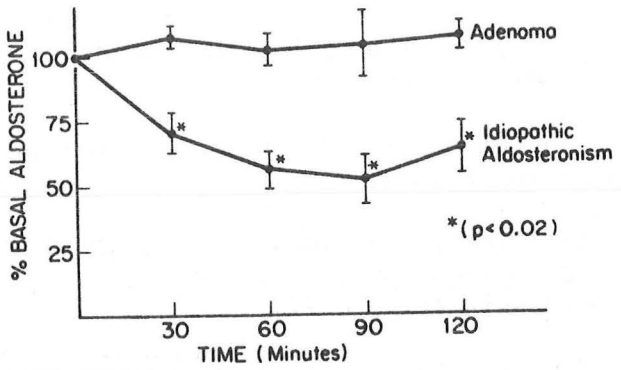


Figure 28. Comparison between Responses of Serum Aldosterone to Cyproheptadine in Patients with Idiopathic Aldosteronism and Patients with Adrenal Adenoma. Results are calculated as percentage of basal aldosterone and expressed as mean ±S.E.

Despite the above observations, the only definite way of distinguishing hyperplasia from adenomas in most centers is by one or more of the following procedures:

TABLE 39. PROCEDURES TO LOCALIZE AND LATERALIZE PRIMARY ALDOSTERONISM

1. CT SCAN ABDOMEN
2. ? ULTRASOUND
3. ADRENAL VENOGRAPHY AND SAMPLING
4. SCINTIGRAPHY USING NM-145 OR NP-59

1. Computed Tomography (CT): This non-invasive technique is helpful in localizing the adenoma, especially if it is more than 1 cm in diameter (134). However, smaller tumors are missed by the CT scan. Bilateral hyperplasia is diagnosed by bilateral enlargement or normally appearing adrenals. With further improvement in the resolution from CT scanners, no doubt much smaller tumors will be diagnosed by this technique. If the patient has biochemical features of primary aldosteronism and the CT scan shows an adrenal mass, the most likely diagnosis is an adenoma--no further work-up is indicated.

TABLE 39. Abnormalites Among Patients With a Positive CT Adrenal Scan

Tumor	Type	Percent
Stromal	Cyst	5
	Lipoma, myelolipoma	3
Medullary	Ganglioneuroblastoma, neuroblastoma	5
	Pheochromocytoma	22
Cortical	Carcinoma	8
	Adenoma	26
	Nonfunctioning 40%	
	Aldosteronism 40%	
	Cushing syndrome 20%	
	Hyperplasia	14
Metastatic		17

2. Adrenal Vein Catheterization for Aldosterone and Venography: In experienced hands, adrenal venography is successful in identifying an adenoma in the majority of patients (135). However, technical difficulties have limited its wide-scale use. Because the right adrenal vein drains directly into the vena cava, it is difficult to locate this vein. Fortunately, adenomas occur more commonly on the left side (Figure 29).

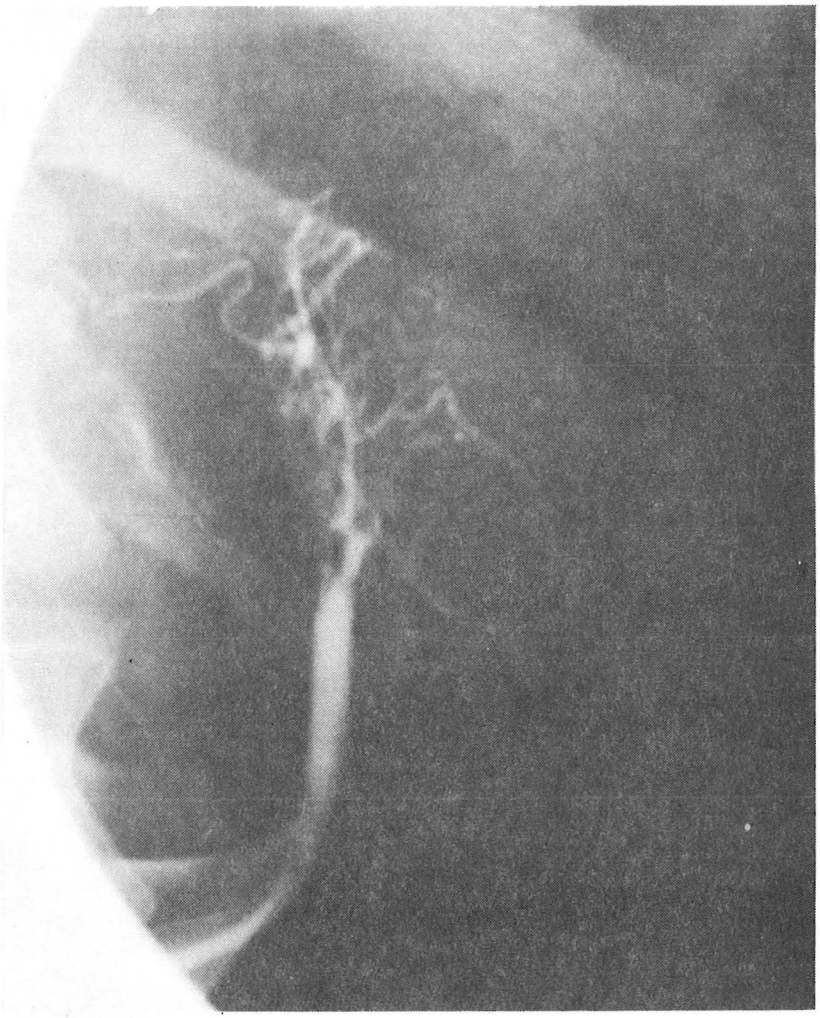


Figure 29. Adrenal venogram showing an adenoma.

Bilateral adrenal vein catheterization for the assay of aldosterone is usually combined with venography. To assure the proper location of the catheters, at least two samples of blood must be obtained from each side if possible, and cortisol also should be analyzed in the same sample to be certain about the origin of the effluent. This procedure can distinguish adenoma from hyperplasia in more than 90% of cases. In bilateral hyperplasia, aldosterone levels will be elevated in both the sides whereas in adenoma a high value is seen only in the ipsilateral vein. Even when the right adrenal vein is not accessible, determination of aldosterone values in the left adrenal venous blood and in the caval blood should provide sufficient information about the location of an adenoma but bilateral hyperplasia cannot be accurately predicted. In one recent series utilizing the aldosterone/cortisol ratio, an adenoma was correctly lateralized in all patients (136). In patients with adenomas, the aldosterone/cortisol ratio was high on the affected side whereas it was suppressed on the contralateral side. In bilateral hyperplasia, the ratio from both sides is high relative to that in the vena cava.

Adrenal vein catheterization should be done when the patient is not on spironolactone therapy as this drug can potentially stimulate aldosterone production by the unaffected gland. To prevent fluctuations in aldosterone secretion, ACTH has been used but this may not be necessary if multiple samples are obtained. The risk of adrenal hemorrhage with venography is 10%.

3. Adrenal Scintigraphy: The development of adrenal scintigraphic techniques by Beierwaltes and colleagues has provided a major advance in the differential diagnosis of primary aldosteronism. Utilizing ^{131}I-19-iodocholesterol (NM-145) as the imaging agent, presence of adenoma is demonstrable in 90% of the cases (137). The results are improved with dexamethasone suppression prior to imaging which provides further distinction between adenoma and hyperplasia. This procedure may take 2-7 days and the patient is exposed to a moderate degree of radiation.

Another closely related isotope, 6β-^{131}I-iodomethyl-19-norcholesterol (NP-59), achieves greater adrenal uptake and the study can be completed with less time delay (138). Preliminary experience suggests that NP-59 is superior to NM-145. Since there is an overlap in visualization times for adenomas and hyperplasia with NP-59, confirmation of the scan patterns on two separate occasions is beneficial. With either agent, small adenomas (less than 7mm) remain difficult to detect. The scintigraphic techniques and counting equipment are available only in very few centers at the present time.

Besides the biochemical differences, in most institutions including here in Dallas, the distinction between an adenoma and hyperplasia is made by CT scan and/or adrenal vein catheterization with venography.

MANAGEMENT OF PRIMARY ALDOSTERONISM

After making the distinction between adenoma and hyperplasia, specific therapy must be planned. Surgical removal is the treatment of choice for the former whereas chronic medical therapy is indicated for the latter since the hypertension associated with this condition is not relieved by operation.

TABLE 40. MANAGEMENT OF PRIMARY ALDOSTERONISM

1. SURGICAL - ADENOMA
2. MEDICAL → HYPERPLASIA, SOME CASES OF ADENOMA
   - A. SALT RESTRICTION
   - B. SPIRONOLACTONE, TRIAMTERENE, AMILORIDE
   - C. THIAZIDES
   - D. ADDITIONAL DRUGS AS NECESSARY

SURGICAL TREATMENT

Prior to the operation, a 3-4 week course of therapy with aldosterone antagonist, spironolactone, should be given to improve the patient's blood pressure and metabolic status. It may be necessary to give as much as 300-400 mg/day initially to accomplish this goal but the dosage can then be reduced. Preoperative preparation of the patient with spironolactone also restores the renin responsiveness which may be protective in the postoperative period.

A trans-abdominal incision is advisable to permit thorough examination of both adrenal glands. Many surgeons excise the entire adenomatous gland but some will resect the adenomatous portion only. Both the glands should be inspected so that rare multiple adenomata are not missed. If the tumor is not found, the left adrenal gland is sectioned looking for small adenoma. If an adenoma is not found, the practice has been to remove the right adrenal gland. With the improved techniques that permit preoperative distinction between adenoma or hyperplasia, it is hoped that needless surgery can be avoided. In any case, sufficient adrenal tissue must be left in place.

Patients should be watched carefully in the post-operative period for possible hypoaldosteronism. While this occurrence is not common, adequate salt intake must be permitted. Potassium therapy is not indicated unless hypokalemia reappears.

After the operation, metabolic abnormalities correct quickly but the effect on blood pressure is slow. It may take weeks, months or rarely years for normalization of blood pressure. It is worth repeating that in hyperplasia, even bilateral adrenalectomy has no effect on hypertension.

MEDICAL TREATMENT

Chronic medical therapy aimed at correcting the metabolic abnormalities and hypertension is recommended for patients with hyperplasia and for those with

adenoma who are unable to undergo surgery. Therapy with spironolactone is a rational approach since this drug antagonizes the effects of aldosterone excess (139). Although high doses (300-400 mg/day) are needed in the initial weeks, subsequently lower doses (50-100 mg/day) are sufficient especially when a thiazide diuretic is also added. If this combination therapy does not lower the blood pressure, additional antihypertensive agents may be sequentially added. Chronic spironolactone therapy may cause some side effects--gynecomastia (painful at times), Raynaud's phenomenon, sexual disturbances, pigmentation and gastrointestinal irritation. Aspirin antagonizes the effects of spironolactone and this interaction must be avoided.

For those patients who do not tolerate spironolactone, a low salt diet combined with potassium-sparing agent such as triamterene (140) or the newly released drug amiloride (141) are effective alternative choices.

UNCOMMON FORMS OF PRIMARY ALDOSTERONISM

Two other variants of primary aldosteronism have been described--indeterminate hyperaldosteronism and glucocorticoid-suppressible hyperaldosteronism (142).

The glucocorticoid-suppressible hyperaldosteronism is rare and unlike the other forms of hypertension, this condition is usually familial, suggesting a heritable disorder, probably by autosomal dominant type of transmission (143). This disorder is characterized by dramatic normalization of blood pressure, aldosterone levels and PRA with glucocorticoid therapy; this response is seen quickly within 7-10 days. This variant is seen in younger patients and the paradoxical postural decline in plasma aldosterone that is observed in patients with adenoma is also seen in glucocorticoid-suppressible hyperaldosteronism (144). The exact abnormality responsible for this disorder is unclear and likely complex. Patients with primary aldosteronism in whom radioisotopic or CT scanning fail to locate unilateral lesion, a therapeutic trial of dexamethasone (1-2 mg/day) should be undertaken before adrenal vein catheterization. Glucocorticoid-suppressible hyperaldosteronism should be suspected in young patients with primary hyperaldosteronism.

ILLUSTRATIVE CASES

CASE 1: Bilateral adrenal hyperplasia.

A.J.: A 60 year old male known to have chronic hypertension was noted to have frequent hypokalemia. His only complaint was numbness in the legs. The first SMA on him (off therapy) showed sodium 146 mEq/l and potassium 2.3 mEq/l. Subsequent serum electrolytes revealed serum K+ between 2 and 3 mEq/l. He was worked up for primary aldosteronism. The pertinent finding was a high plasma aldosterone level (30.4 ng %). Adrenal venography did not reveal a tumor and bilateral adrenal vein sampling showed aldosterone concentration of 914 and 898 ng % in the right and left adrenal veins. Patient's BP and hypokalemia responded readily to spironolactone and he is on chronic medical therapy without any problems.

CASE 2: Adenoma.

A.M.: A 53 year old white male was evaluated for primary aldosteronism on the basis of severe and recurrent hypokalemia often induced by diuretics. This patient developed such a degree of hypokalemia that he has muscular weakness and was hospitalized on one occasion for IV potassium therapy. His hypertension has been chronic, quite severe and was not responding to therapy. The plasma K+ varied between 2.7 and 3.1 mEq/l (off diuretics). The BP was very high (200/120) and eventually required minoxidil therapy after he failed to respond to captopril. The work-up revealed persistent hypokalemia, urine K+ 90 mEq/day, plasma aldosterone levels were 18 and 30 ng % (normal 2-9). Pre-saline infusion aldo level was 47 and post-saline was 38 ng %. PRAs were 0.5 and 0.3 ng/ml/hr, supine and standing respectively. CT scan was reported as " normal" initially. Adrenal venogram revealed a fairly large (3 1/2 - 4 cm) left adrenal adenoma which was removed. Immediately post-op his K+ improved, eliminating the need of spironolactone which he was taking previously. There was also striking improvement in the BP and all the medicines were discontinued.

The above case represents a classical aldosterone-producing adenoma which was diagnosed by step-wise investigations. The initial clinical clue was severe hypokalemia with and without the use of diuretics.

MISCELLANEOUS FORMS OF SECONDARY HYPERTENSION

So far we have discussed major forms of secondary hypertension and in this final section, let us quickly consider rare forms (Table 41). Due to constraints on the time and space, the discussion of these rare causes will be very brief. In some rare forms of secondary hypertension, the cause and effect relationship is not established convincingly. Thus it is possible that entities like hypothyroidism and hyperparathyroidism may simply co-exist with essential hypertension and the treatment of primary disease therefore may not always alleviate hypertension.

TABLE 41. MISCELLANEOUS CAUSES OF SECONDARY HYPERTENSION

1. CHEMICAL/DRUG INDUCED HYPERTENSION
2. COARCTATION OF THE AORTA
3. CUSHING'S SYNDROME
4. HYPERPARATHYROIDISM
5. HYPER- AND HYPOTHYROIDISM
6. ACROMEGALY
7. INCREASED INTRACRNIAL PRESSURE
8. SPINAL CORD TRANSECTION
9. BODY BURNS
10. ACUTE PANCREATITIS
11. POST-OPERATIVE HYPERTENSION (ESPECIALLY CABG)

CHEMICAL AND DRUG-INDUCED HYPERTENSION

Various chemicals, drugs, and drug interactions are capable of activating vasopressor mechanisms or inhibiting the vasodepressor systems--such that hypertension may ensue (145). Therefore, we have to be very careful in history taking, especially in the medical, health and allied personnel. Drug-induced hypertension can sometimes be so severe that any catastrophic complication may occur. Prompt discontinuation of identified drug(s) usually results in rapid normalization of blood pressure.

TABLE 42. Pathogenetic Mechanisms of Chemically Induced Hypertension

Predominant Mechanism	Chemical Agent
Expansion of extracellular fluid volume	Sodium Antacids Glycyrrhiza and derivatives Mineralocorticoids Anabolic or androgenic steroids Oral contraceptives Nonsteroidal anti-inflammatory drugs
Affecting autonomic nervous system	Direct or indirect sympathomimetics Tricyclic antidepressants Monoamine-oxidase inhibitors (in combination) Levodopa Anesthetics or narcotics Ergot alkaloids
Mixed or unknown mechanism	Poisons Metals Organic and inorganic compounds Spider bites and scorpion stings Various diagnostic and therapeutic agents
Paradoxical response to antihypertensive agents (catecholamine excess?)	β-Adrenergic receptor blockers Labetalol Saralasin acetate Postganglionic blocking agents Clonidine hydrochloride, methyldopa
Rebound hypertension (catecholamine excess?)	Clonidine hydrochloride, methyldopa Propranolol hydrochloride Postganglionic blocking drugs

There is a homeopathic doctrine which says that any drug capable of producing morbid symptoms will remove similar symptoms occurring as an expression of disease. This doctrine applies to some antihypertensive medications. For example, paradoxical increase in blood pressure has been reported with beta-blockers in pheochromocytoma and in some cases of low-renin hypertension. Drugs like clonidine when given in high doses can actually elevate the blood pressure by producing peripheral vasoconstriction via alpha-adrenergic receptor stimulation (146). Sometimes marked elevation of blood pressure may occur following sudden discontinuation of certain antihypertensive agents, especially clonidine (147).

Mineralocorticoids/anabolic steroids: These agents are capable of causing hypertension by volume expansion. In fact, mineralocorticoids are commonly used to produce experimental hypertension in animals. Even topical administration of these potent agents can elevate the blood pressure (148).

Licorice and carbenoxolone: Licorice contains a substance, glycyrrhizic acid, which has aldosterone-like effects and its excessive use may cause volume expansion and hypertension. A related compound, carbenoxolone, used in some

countries for the treatment of gastric ulcer, exerts similar biochemical and blood pressure effects.

Non-steroidal anti-inflammatory drugs: These agents (aspirin, indomethacin, phenylbutazone, etc.) can cause mineralocorticoid-like effects as well as inhibition of prostaglandin synthesis; either of these mechanisms may result in increased vasculator reactivity--further elevating the blood pressure.

Sympathomimetics: Drugs like amphetamines and their derivatives, phenylphrine, phencyclidine, etc., can cause hypertension presumably by stimulating the post-ganglionic alpha-receptors. All these agents or related compounds are in common use taken orally or applied topically (149). The diagnosis, therefore, rests entirely on proper history taking. Clinical signs like dilated pupils, damaged nasal mucosa, etc., are helpful clues.

Tricyclic antidepressants: These agents cause slight postural hypotension in therapeutic doses but high doses may stimulate alpha-receptors and cause increased blood pressure. Hypertensive reactions to tricyclics have occurred in combination with sympathomimetics, in pheochromocytoma, and when given along with MAO inhibitors. Tricyclics antagonize the effects of guanethidine, clonidine and methyldopa resulting in loss of blood pressure control.

Ergot alkaloids: These derivatives cause peripheral vasoconstriction and may elevate the blood pressure. Severe pressor reactions with their use have been reported (150).

MAO inhibitors and tyramine interaction: This interaction is not commonly encountered these days but before the availability of newer drugs, MAO inhibitors were commonly used in psychiatric medicine. Severe hypertension has been associated with interaction between MAO inhibitors and foods with high tyramine content (yeast, yogurt, old cheeses, red wines, certain beers, chicken liver, etc.) (151). Normally, the tyramine contained in the food stuffs is degraded in the bowel (and liver) by MAO. However, in the presence of an inhibitor of MAO, the tyramine "escapes" into the circulation and elevates the blood pressure either directly or by potentiating the effects of catechols. This hypertensive reaction is characterized by signs and symptoms of enhanced adrenergic tone and mimics pheochromocytoma crisis or drug withdrawal hypertension. The diagnosis is established clinically by the history of psychiatric depression and ingestion of tyramine-containing food.

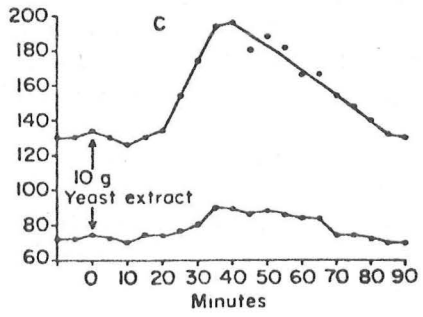


Figure 30. Rise in BP following ingestion of yeast by a patient on MAO inhibitor.

Toxins: Lead and cadmium are indeed rare causes of hypertension. Although cadmium can elevate the blood pressure experimentally, studies in humans are conflicting. It has been suggested that chronic low level exposure to cadmium causes hypertension but acute intoxication with high concentrations does not. Although lead intoxication is associated with hypertension, it is not clear whether the effects are direct or mediated by renal damage, central nervous system, etc.

Certain pesticides (especially, parathion) have been linked to hypertension. A few studies have linked hypertension to alcohol intake but this association is far from proven.

Other causes: Hypertension has been reported to occur following spider bites and scorpion stings. Hypertension has also been linked with the use of certain anesthetics (ketamine HCL, cyclopropane), naloxone, innovar, indigo carmine, pentagastrin, lithium, ginseng use, etc.

A large number of drugs, chemical and toxins can cause hypertension and usually the blood pressure elevation and sometimes severe hypertension with complications can occur. The key to the recognition of iatrogenic hypertension is proper history taking and careful initial evaluation of every hypertensive individual. If we do not suspect the cause, the diagnosis is easily missed and the patient may be inadvertently included in that large group of people with essential hypertension.

AORTIC COARCTATION

Coarctation of the aorta is a developmental malformation and accounts for 4 to 8.5% of all congenital heart diseases (152). The coractation may occur anywhere in the aorta but commonly near the left subclavian artery and ligamentum arteriosum. Coarctation may be detected in four ways. Absent femoral pulses in infants; hypertension in young individuals leading to detection of absent or delayed femoral pulses; rib-notching on routine chest x-ray; and detection of collateral vessels. Infantile coarctation usually occurs with other cardiac anomalies.

Coarctation if undetected can cause considerable morbidity and mortality from heart failure, aortic dissection, bacterial endocarditis and intracranial hemorrhage. The mechanism of hypertension in coarctation is not clear. It may be on a mechanical basis or due to a humoral component (renin, catecholamines). Anyway, hypertension is the hallmark, and the diagnosis should be suspected on the basis of physical findings--delayed, absent femoral pulses, low systolic and pulse pressures in the legs. The arterial flow, however, is normal in resting condition. The definitive diagnosis is established by aortography.

Mortality is very high in infantile coarctation associated with other cardiac anomalies. Therefore, early surgical repair is recommended although surgical intervention is also risky. The longer the duration of aortic coarctation, the lesser are the chances of surgical success. Surgery should be attempted before age 15 to prevent progression of vascular disease. Operative mortality in 112 cases from the Columbus Children's Hospital was reduced from 75 to 30% in the recent years by a combination of early surgery,

better patient selection and intensive peri-operative care (153).

CUSHING'S SYNDROME

Hypertension is common in Cushing's syndrome irrespective of underlying pathology; it may be present in up to 90% of the patients. The diagnosis of Cushing's syndrome suspected on clinical grounds is confirmed by hormonal measurements with and without dexamethasone. I will not discuss this aspect.

Historically speaking, this condition was the first adrenocortical disorder to be associated with hypertension. The hypertension is probably due to activated renin-angiotensin system resulting from increased synthesis of the renin substrate by glucocorticoids (154). This concept is supported by a fall in blood pressure with saralasin in a few patients with Cushing's syndrome. Some additional mechanisms--direct effects of glucocorticoids or enhanced vasopressor reactivity may be operative. Hypertension may be severe in some patients and it may not always resolve despite treatment of the primary disease.

HYPERPARATHYROIDISM

There is an increased prevalence of hypertension in patients with primary hyperparathyroidism and vice versa (155). The causal relationship is not clear. With the widespread use of automated SMA tests, many patients with hypercalcemia are being detected, thus the diagnosis of primary hyperparathyroidism is being increasingly made. In the absence of renal damage, the relationship of hypercalcemia to the development of hypertension is not understood.

Calcium may alter the renin-angiotensin system or have direct effect on vascular smooth muscle. In some instances surgical correction of hyperparathyroidism will result in significant reduction in blood pressure. It is not possible to predict preoperatively whose blood pressure will or will not respond to parathyroidectomy. In most of the hypertensives, the cause of hypercalcemia is the use of thiazides and work-up for hyperparathyroidism should be postponed until 2-3 months after discontinuing the thiazides.

HYPERTHYROIDISM

Systolic and perhaps mild diastolic hypertension is often seen in patients with hyperthyroidism. Undoubtedly, increased adrenergic activity and enhanced cardiac output contribute to the elevation of blood pressure. After the thyroid function is restored, the blood pressure and the hyperdynamic circulatory state may become normal.

HYPOTHYROIDISM

An extraordinarily high incidence of hypertension in hypothyroid patients was reported 50 years ago (156). Others also have suggested that about half of untreated hypothyroid patients have blood pressures greater than 150/90 (157). However, the relationship between these entities is subject to criticism because most of the early reports did not compare an age-matched control group and follow-up of the blood pressure after restoration of thyroid function

was not available. A recent study found no increase in the incidence of hypertension in hypothyroid patients compared to age-matched control subjects (158).

Acromegaly: Perhaps a third of patients with acromegaly have hypertension due to sodium and water retention effects of growth hormone.

Quadriplegia: Patients with transverse lesions of cervical spinal cord sometimes develop severe hypertension because of reflex sympathetic stimulation (159). The spells may resemble those of pheochromocytoma; these hypertensive reactions can be minimized by preventing bladder and bowel distension and by avoiding unnecessary stimulation of involved dermatomes.

Bulbar neuropathies may be associated with severe hypertension. It is not certain whether the blood pressure response is due to central nervous system damage or secondary to anoxia and stress.

Body burns: Hypertension is common and sometimes a serious complication of thermal injury. Limited data suggest that the renin-angiotensin-aldosterone system is directly stimulated as a part of the neuroendocrine response to trauma (160).

Acute pancreatitis: This condition may sometimes cause hypertension. This may be due to activation of the renin-angiotensin system from the initial volume contraction.

Post-operative hypertension: Hypertension may occur as a result of carotid artery surgery, perhaps from derangement of baroreceptor mechanisms. Usually this type of hypertensive response is transient but may require treatment. Post-surgical hypertension could also be due to excessive infusion of IV fluids and withdrawal of antihypertensive drugs.

In recent years, significant hypertension is becoming increasingly recognized in patients following coronary artery bypass graft surgery. Certainly, pre-existing hypertension is a risk factor. The pathogenesis of this phenomenon has been studied at the Cleveland Clinic and Cornell University and it appears that renin-angiotensin and the sympathetic nervous system may play a role (161, 162). Appropriate therapy is indicated to preserve cardiac function.

SUMMARY/CONCLUDING REMARKS

After discussing some aspects of secondary hypertension, these concluding remarks do not differ very much from the introductory comments. Secondary forms of hypertension constitute only a small percentage of all patients with hypertension. Often the manifestations of these entities are so subtle that their detection is missed in the shadow of "essential" hypertension. Since all of us see "essential" hypertension time and again, day after day, the few patients with secondary hypertension may slip by. The key to the recognition of secondary hypertension is a high index of suspicion and careful initial evaluation followed by periodic observation.

The idea of finding a curable hypertension is attractive to the physicians and patients alike. However, to find a few, indiscriminate work-up and shotgun

approach should be avoided. The challenge therefore lies in our ability to separate the "needle from the haystack" and this requires clinical judgement together with proper utilization of the laboratory. Exhaustive work-up is not indicated for patients who are unsuitable for surgery. With the inevitable advances in the biochemical and radiological techniques, no doubt our skills to uncover secondary hypertension will improve and hopefully, more patients can be offered the prospect of "cure". The cost-effective use of resources is integral to controlling an epidemic disorder such as hypertension. However, both this approach and the individual patient's potential benefit from consideration for secondary hypertension---- can co-exist.

ERRATA

1. Page 19, para 2, line 6 - to read "hemodynamic" effects
2. Page 35, para 2, line 4 - to read "aorto-renal"
3. Page 36, para 1, line 4 - "soft", not salt
4. Page 38, last para, line 4 - to read "revascularization"
5. Page 41, Case 3, para 2 - R:L instead of L:R
6. Page 81, line 3 - "had" instead of has
7. Page 82, item 7 - to read "intracranial" pressure
8. Page 85, para 4, line 2 - to read blood pressure elevation is mild but.....

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