Grand Rounds May 23, 1974

Antihypertensive Drugs, Renin and Angiotensin

William A. Pettinger, M.D.

Grand Rounds May 23, 1974

Antihypertensive Drugs, Renin and Angiotensin

Recent developments in hypertension therapy have included new potent drugs as well as newer concepts of the disease and its relationship to drugs. One recent concept is the attempt to therapeutically classify patients (1) for supposedly more selective and presumably effective therapy. This concept presupposes that drugs are selectively acting on specific hypertensive mechanisms. Since the renin-angiotensin-aldosterone axis is the usual basis for current therapeutic classification, I will address the critical question "are drugs antihypertensive by antirenin-angiotensin mechanisms." Several of these areas are highly controversial at this time, and perspectives are rapidly changing. Thus, I will attempt to review the evidence to date, for and against, these potential sites for antihypertensive drug action.

These potential sites are summarized in Figure 1. The first and probably most controversial site is alteration of renin release. Administration of sodium chloride is a well-known effective mechanism for inhibiting renin release but generally intensifies the hypertension. Therefore, the equating of antihypertensive activity and suppression of renin release is overly simplistic. However, an interesting correlation is noted between the central nervous system site of action of antihypertensive drugs and renin release. Each antihypertensive drug which has a primary central nervous system site of action (see Table I, p. 2) has been shown to lower serum renin activity in hypertensive man (2-4).

A second potential site for drug action is inhibition of the renin enzyme *per se*. Three approaches have been suggested but none are very promising at this time. One is a naturally occurring phospholipid (turn to p. 3)

TABLE I

Correlations of antihypertensive drugs and their site and mechanism of action. Drugs are listed in the anatomic sequence from vascular smooth muscle through the adrenergic receptors, sympathetic neurons etc. to the cardiovascular control center in the brain.

Site of Action	Mode of Action	Pharmacologic Name	Trade Name	Marketed	Unmarketed	Comments
Arteriolar Smooth Muscle	Direct Vaso-dilation	Hydralazine	Apresoline	X		
		Diazoxide	Hyperstat	X		Phosphodiesterase inh. causes diabetes
		Minoxidil			X	Long Acting
		Sodium Nitroprusside			X	i.v. only
Selective Angiotensin Antagonists	Block Angio-tensin Pressor Action	Saralasin (P-113)			X	For i.v. use only
Alpha-Adrenergic Receptor Block-ing Agents		Phentolamine	Regitine	X		
		Phenoxybenzamine	Dibenzyline	X		
Beta-Adrenergic Blockading Drugs	CNS Heart Renin Release	Propranolol	Inderal	Available for Arrhythmias but not for Hypertension		
Sympathetic Neurone Blocking Drugs	Block NE Release	Guanethidine and Other Guanidiniums	Ismelin	X		Long Acting
	Inhibits MAO	Pargyline	Eutonyl	X		Cheese Hypertension
Paravertebral Gangliae	Ganglionic Blockers	Chlorisondamine	Ecolid	X		
		Hexamethonium	-			
		Mecamylamine	Inversine	X		
		Pentolinium	Ansolysen	X		
		Trimethaphan	Arfonad	X		
Central Nervous System	False Neuro-transmitter	Methyldopa	Aldomet	X		
	NE Depletion	Reserpine	Many	X		Subtle and often Severe Depression
	Depress C-V Control Center	Clonidine	Catapres		X	
Kidney	Sodium Excretion Volume Depletion	Thiazide Diuretics	Many	X		
		Furosemide	Lasix			
Distal Tubule of Kidney	Competitive Antagonism of Aldosterone	Spironolactone	Aldactone	X		
	Kaliuretic Action	Triampterene	Diurenium	X		Occasional Hyper-kalemia when combined with KCl

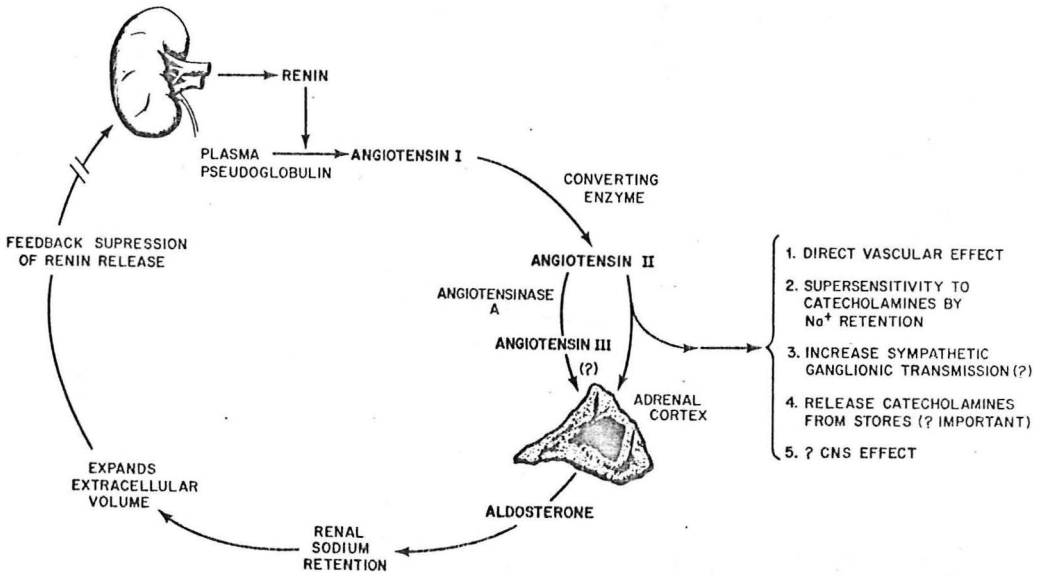

FIGURE 1

Schematic diagram of the renin, angiotensin, aldosterone, sodium and volume axis including vascular and autonomic effects. See ref. #34 for angiotensin III.

(lysophosphotydil ethanolamine) initially obtained from kidney extracts (5,6) pepstatin from bacteria (7) and synthetic analogues of the renin substrate (8).

A third potential site of antihypertensive drug action is inhibition of converting enzyme (9). Naturally occurring peptides originally obtained from snake venoms are effective inhibitors of this enzyme. They are now synthesized using the Merrifield technique of peptide synthesis. They have pharmacologic effects very similar to selective angiotensin antagonists, another potential site for antihypertensive drug action, which will be discussed in more detail later. Drugs

which inhibit aldosterone synthesis will soon be available here at Parkland for clinical investigation.

Antagonism of aldosterone's sodium retaining effect at the renal tubular level is an important site of antihypertensive drug action in this axis. The loop is complete with the well-known intrarenal volume-dependent feedback suppression mechanism which is the physiologic mechanism for inhibiting renin release. This feedback suppression loop fails in some patients with malignant hypertension (10-12) and/or renal failure (13), renal artery stenosis and patients with lesser degrees of renal disease (14), probably acute glomerulonephritis and in preeclampsia. It also occurs late in the course of hypertension of rats whose hypertension occurs spontaneously and is genetically determined (15).

Now let's discuss each of these potential sites for antihypertensive drug action in more detail in the reverse sequence. First, there are selective and non-selective antagonists of aldosterone. The selective aldosterone antagonists are analogues (spironolactones) of this steroid and are particularly effective in several types of hypertension. These hypertensive types are characterized by an excess of aldosterone secretion relative to renin and include patients with primary aldosteronism (16) and the frequently encountered "low-renin" essential hypertension (17-19).

The site of pharmacologic action of spironolactone drugs is in the distal nephron and they simply antagonize aldosterone, having no natriuretic action *per se*. Diuretic agents such as hydrochlorothiazide and furosemide are also antagonists of aldosterone in that they induce the opposite effect, i.e., sodium excretion. Interestingly, these diuretic drugs are essentially as effective as specific aldosterone antagonists in most patients with relative aldosterone excess, i.e., low renin hypertension (19) and primary aldosteronism.

In common with all drugs which interfere with the renin-angiotensin-aldosterone cycle, administration of the aldosterone antagonists results in compensatory increments in the preceding components of the axis. Thus, serum renin activity as an indicator of renin release can be significantly elevated with administration of aldosterone antagonist or diuretic agents. In face of the elevated serum renin activity and aldosterone secretion, blood pressure tends to fall. Thus, the state of sodium and water balance, i.e., volume expansion, is a more critical determinant of blood pressure than absolute levels of serum renin activity and aldosterone in most hypertensive patients using diuretic agents.

The second major role of diuretic agents in combination with any other anti-hypertensive drug is to prevent the phenomenon of pseudotolerance (Figure 2).

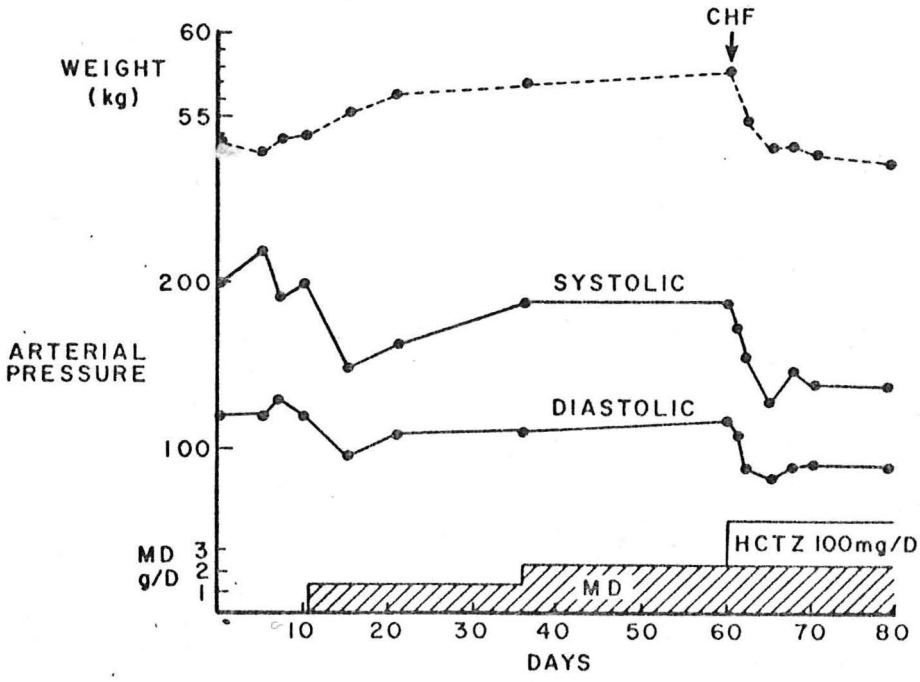

FIGURE 2

Example of pseudotolerance in a WF age 53 with intermediate hypertension. Note the initial decline in blood pressure with methyldopa, the gradual loss of effect with increasing weight gain and no effect from increasing dose of methyldopa. Congestive heart failure occurred which responded well to thiazides along with the fall in blood pressure.

Pseudotolerance is the gradual loss of antihypertensive drug activity associated with fluid retention and cannot be overcome by increasing doses of the primary agent. It can be prevented or reversed by simultaneous administration of diuretic agents. This drug-related volume expansion has been described under a number of circumstances (20-26). Factors predisposing to this fluid retention are related to the severity of hypertensive disease. Thus, patients with renal disease or diminished cardiac reserve tend to accumulate salt and water to a greater extent than patients in the early stages of hypertension. Simultaneous to preventing pseudotolerance the diuretic agents potentiate the hypotensive activity of all other drugs, even in patients in which diuretics have minimal antihypertensive effects *per se*.

Like aldosterone antagonists the angiotensin antagonists are of two types, selective and non-specific. All vasodilating antihypertensive agents are non-specific antagonists of angiotensin (27) (Figure 3). That is, they antagonize

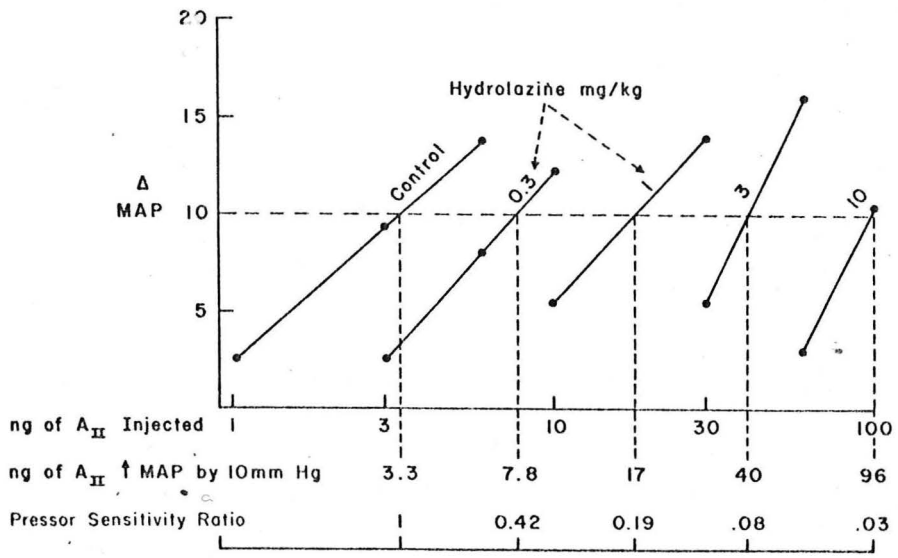

FIGURE 3

Angiotensin antagonism by the vasodilating drug hydralazine in the rat. This result is quite reproducible if compensatory cardiovascular reflexes are blocked by prior administration of a ganglionic blocking drug such as chlorisondamine (27).

the pressor action of angiotensin, norepinephrine and vasopressin equally, a quantity which has proven useful for expressing and characterizing this component of antihypertensive drug action (27). That this site of action in the renin-angiotensin-aldosterone axis is important is suggested by recent studies of Parker et al. (28). In those studies seven high renin hypertensive dialysis patients were refractory to conventional agents including propranolol. Angiotensin dependence was confirmed by blood pressure lowering in several of the patients using the selective angiotensin antagonist, saralasin (P-113). The nonselective angiotensin antagonist minoxidil was effective in controlling high blood pressure in each of the patients. Thus, the hypertensive effects of high angiotensin levels appear to have been neutralized by minoxidil.

We have noted blood pressure control in most high renin hypertensives with minoxidil. However, there have been two patients with extremely high renin without renal failure in which the diastolic pressures remained near 110 mm Hg while using minoxidil-propranolol. That angiotensin vasoconstriction may have overridden the vasodilating effect of minoxidil and thus limiting antihypertensive drug action is suggested by the marked hypotensive effect of saralasin infusion (30) (Figure 4). These interrelationships are not surprising in view of the dynamic physiologic antagonism of angiotensin and vasodilating agents (Figure 3) (27).

Saralasin, 1-sar-8-ala angiotensin II, is a selective antagonist of angiotensin's vasoconstrictor action (31) which is in the investigative stage of development. When given as a bolus dose or as an infusion, blood pressure lowering occurs in most high renin hypertensive patients (30,32). There is, in fact, from preliminary studies of 130 patients some promise for using saralasin injections as a screening test for patients having hypertension due to renal artery stenosis (33). Because of metabolism after oral administration and short duration

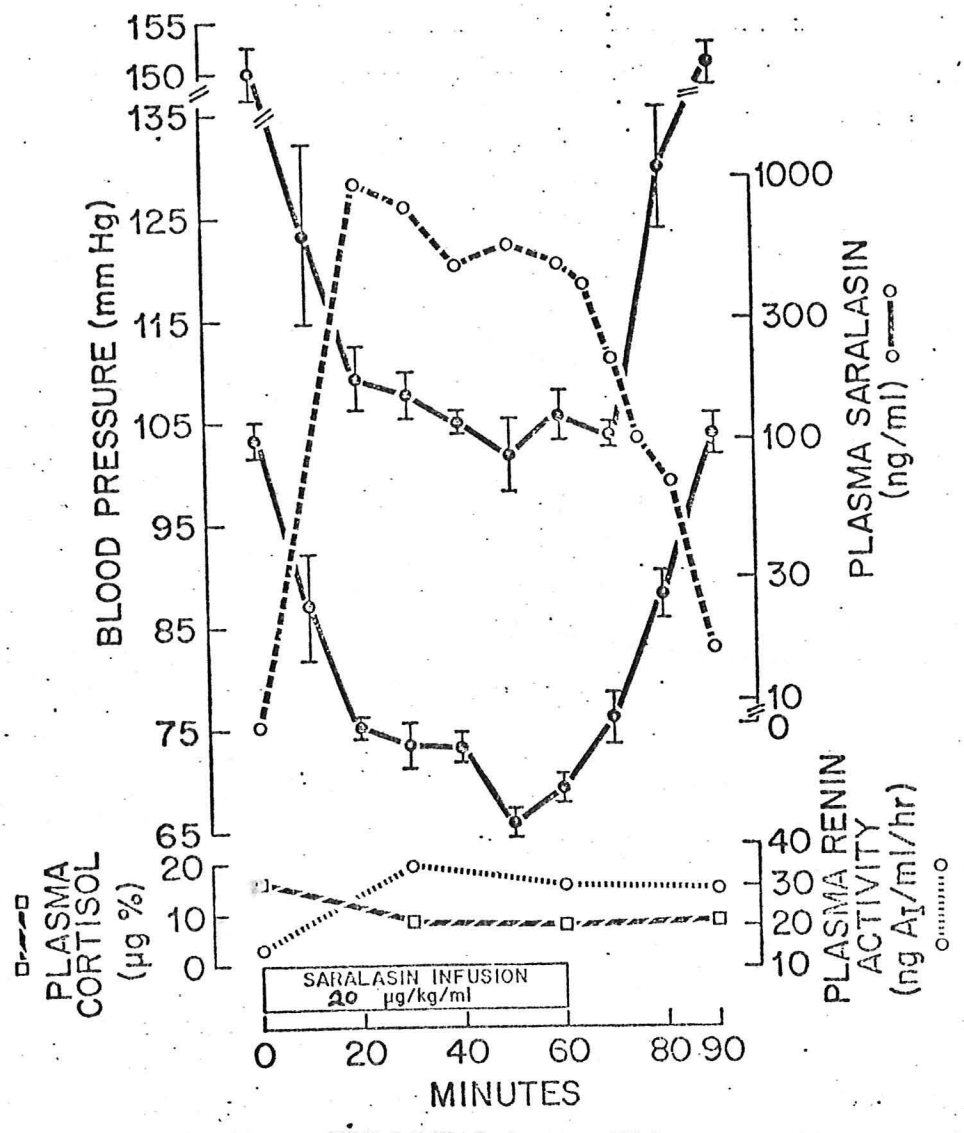

FIGURE 4

Saralasin (P-113) induced hypotensive activity in minoxidil-propranolol treated patient. Saralasin plasma concentration was measured by radioimmunoassay (30). Blood pressure response was reciprocally and chronologically related to saralasin concentration.

of action with the parenteral route, intravenous infusion is required for sustained action of this peptide. These factors will thus limit therapeutic use of saralasin to relatively acute problems in which undesired effects of other drugs preclude their use. Saralasin inhibits angiotensin mediated aldosterone release in rats whether increased angiotensin blood levels result from exogenous

administration (34) or endogenous formation of angiotensin (35). However, saralasin does not lower normal levels of aldosterone in rats (34) or in hypertensive man (30).

The antihypertensive role of propranolol inhibition of renin release is one of the most controversial subjects discussed here. This subject should be considered in two categories. One is propranolol inhibition of renin release *per se* as an antihypertensive mechanism. The second is under active investigation in several centers and is characterization of the antihypertensive role of propranolol inhibition of vasodilatory drug-induced renin release. The first systematic study in the former area was published by McAllister et al. in 1971 (36). Renin release was characterized in a small group of high-renin hypertensives. The pattern of change of this abnormality was followed as a function of blood pressure control using guanethidine or methyldopa combined with diuretic agents. The high-renin state gradually reverted to normal over periods of time up to 5 months. This reduction of renin release was accomplished by drugs which have relatively little effect on renin release. Thus, it would appear that the abnormally high renin release may result from the hypertension *per se*. Similar results have been reported by Buhler et al. (1) who have interpreted the correlation of lower blood pressure and renin activity as sufficient evidence for a cause and effect relationship. Obviously, this is an unjustified assumption, even though the conclusion may in the long run turn out to be correct.

Michelakis et al. (4) have demonstrated a dissociation between suppression of renin release and antihypertensive action of propranolol. Suppression of renin release was demonstrated with plasma propranolol concentrations in the range required for inhibition of other β-receptors, that is 30-50 ng/ml. Antihypertensive activity did not occur suggesting a lack of cause and effect

relationships (one defect in that study was the short duration of observation period of 4 hours. It should be repeated with a 2-3 day observation period with precise plasma propranolol concentrations sustained by administration at ½ × ½-life intervals.). Additionally, the doses of propranolol required for antihypertensive activity (39,40) are frequently in the range of 5 mg/kg which is well above those required for inhibition of renin release (4,38).

We have treated a small group of high renin dialysis patients with propranolol and have noted reduction of renin activity but the remainder was still extremely high (15 ng A_I/ml/hr) even in the volume expanded state (normal <0.5 ng/ml/hr) and blood pressure control was not established (28) using propranolol alone. Thus, the facts are 1) that high renin states may be reverted to or toward normal by blood pressure control, 2) that propranolol can suppress at least part of the high renin activity and 3) that propranolol has a central nervous system site of antihypertensive drug action (41) and thus is not necessarily dependent on suppressed renin release for lowering of blood pressure. Thus, there is <u>insufficient evidence</u> at this time to conclude that propranolol controls hypertension by inhibiting endogenous renin release *per se*.

The evidence for cause and effect relationships of antihypertensive activity and inhibition of renin release by other drugs such as methyldopa, reserpine and clonidine is even less developed than for propranolol.

A closely related phenomenon is the mechanism of interaction between propranolol and vasodilating antihypertensive drugs. Vasodilating or beta adrenergic receptor blocking drugs alone each have modest blood pressure lowering activities (Figure 5). However, when combined, they are remarkably effective (42-46). An attractive hypothesis is that by inhibiting vasodilating drug-induced renin release, propranolol permits the vasodilatory action to occur free of angiotensin vasoconstriction. This hypothesis has been supported by studies

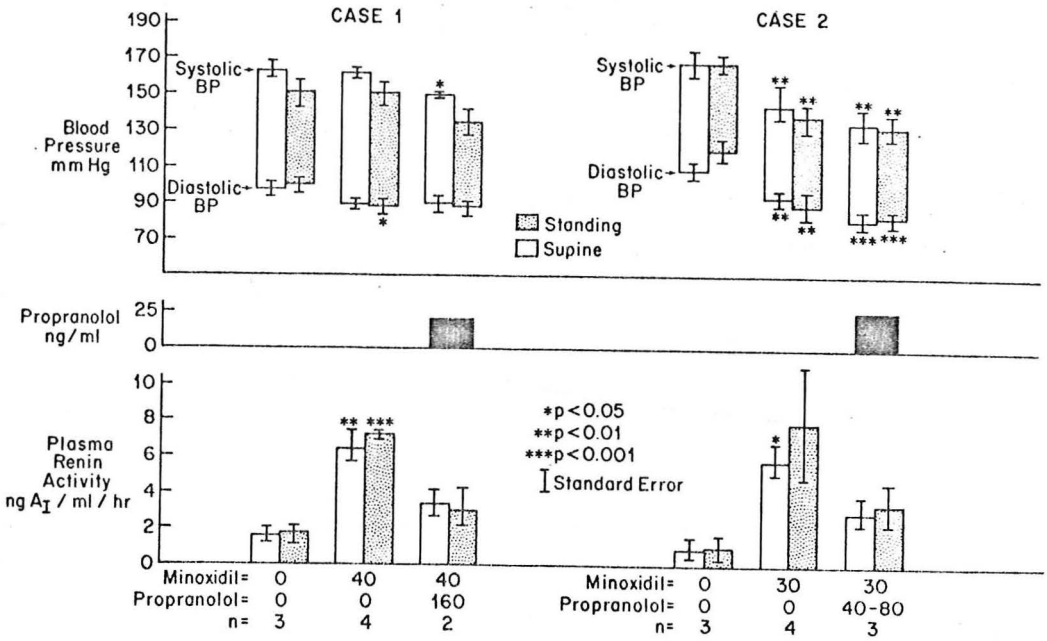

FIGURE 5

Minoxidil-propranolol effects or blood pressure and plasma renin activity in two moderately hypertensive patients. Minoxidil induced significant renin release in each subject, both in upright and supine positions. Propranolol impaired renin release in both patients, as previously reported for animals (38,45), and further lowered blood pressure.

in conscious normotensive rats (45) but needs confirmation in hypertensive man. Interestingly, this may be one of the few important beneficial drug interactions.

This concludes the section "are drugs antihypertensive by antirenin-angiotensin mechanisms." In keeping with tradition, I would like to make several comments that may be additionally helpful in the routine clinical use of antihypertensive drugs. The usual hypertensive patient of moderate or intermediate severity, after a routine initial workup, should first be treated with diuretics. I have a slight preference for thiazide diuretics because of

the intrinsic difference from furosemide in dose responses (47). The dose response to furosemide is continuous over a wide range while thiazides induce their maximal effect usually before excess natriuresis occurs. Antihypertensive action of diuretics during the first 1-2 months of therapy may be remarkable but addition of other drugs such as guanethidine, methyldopa or hydralazine-propranolol combination is frequently necessary later. Interestingly, a daily dose of 50 mg of hydrochlorothiazide is frequently sufficient to prevent pseudotolerance yet below the doses which intensify diabetes mellitus or gouty arthritis.

The basis for deciding on the second drug is rather difficult and in flux at this time. The hydralazine-propranolol combination has recently become popular because of its effectiveness and minimal drug-related side effects. Propranolol has not been approved for use as an antihypertensive agent. However, it has been approved for controlling tachyarrhythmias. These arrhythmias can be precipitated by hydralazine hypotension through reflex activation of cardiac sympathetic nerves (Figure 6). Thus, an approved indication can be implicated in a prophylactic sense for use of propranolol in this drug conformation. Incidentally, some of the premature ventricular contractions (PVC) are propranolol resistant and occasionally made worse by this drug (Figure 7). However, these arrhythmias have been responsive to quinidine.

Physicians have had difficulty when first using methyldopa because clinical pharmacokinetics of the drug have not been well promulgated. Characteristics described herein are the result of personal experience with the drug during introduction into man and studies of the mechanism of action and continued clinical use (48-51). Appropriate kinetics are summarized in Figures 8 and 9. There is a delay of 3-4 hours after oral or i.v. administration before onset of antihypertensive action. Peak effect occurs in six hours which gradually dissipates within 24 hours. Metabolism from oral administration is variable between 30 and

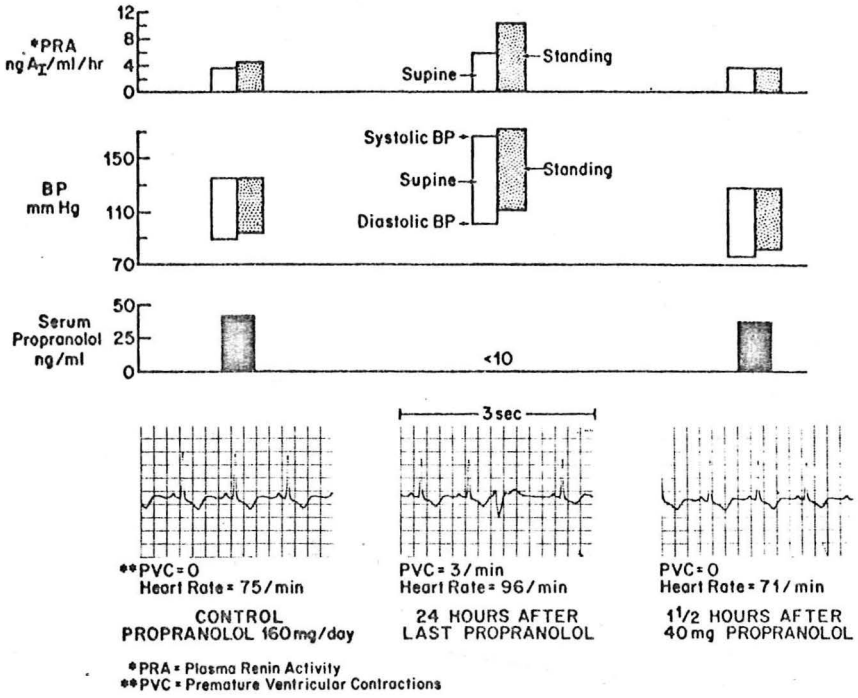

FIGURE 6

Propranolol responsive premature ventricular contractions resulting from minoxidil administration.

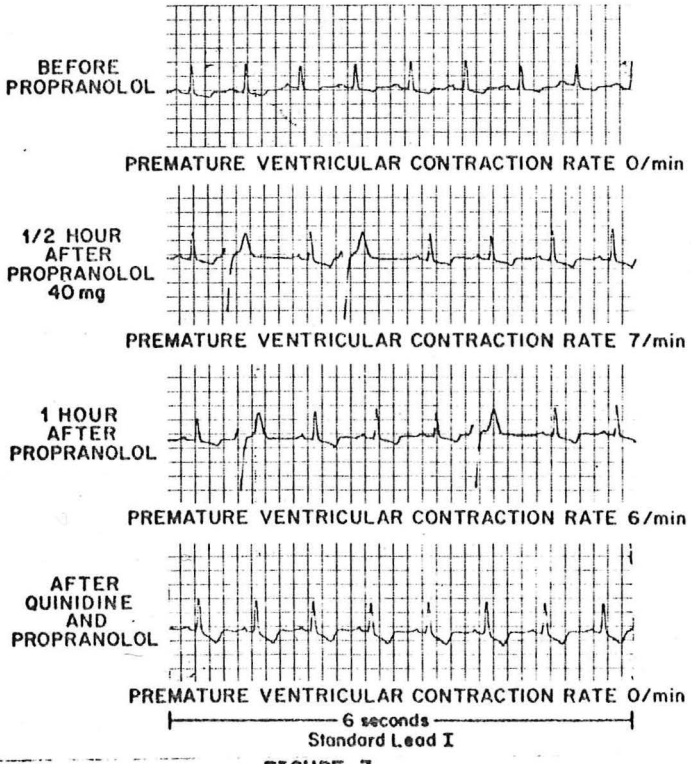

FIGURE 7

Propranolol resistant premature ventricular contractions actually precipitated with propranolol. These PVC's were responsive to Quinaglute 300 mg twice daily.

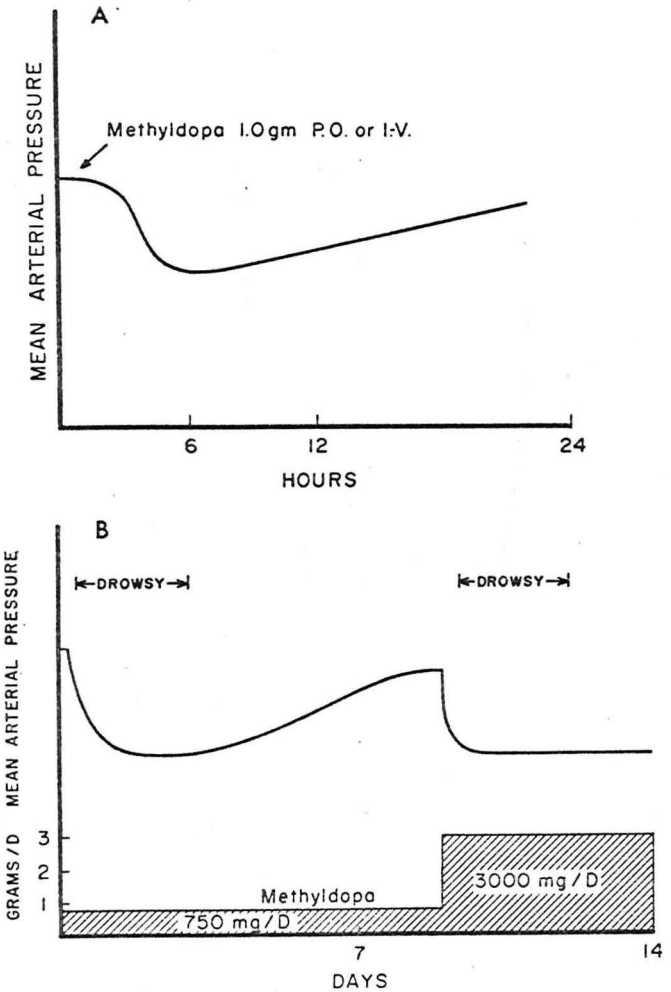

FIGURE 8

Schematic of kinetics for methyldopa-induced blood pressure lowering in the majority of patients. A. Response to a single dose. Antihypertensive activity is ∿ 2-fold greater after i.v. than after oral administration, particularly if given over thirty minutes i.v. B. Subacute kinetics for methyldopa showing initial tolerance that develops in the majority of patients.

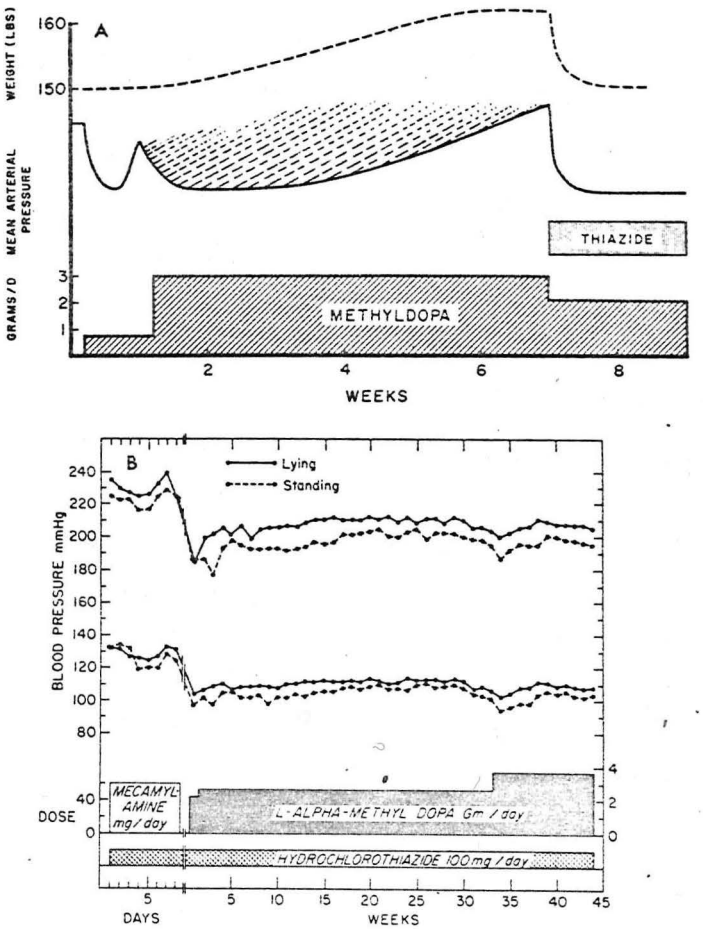

FIGURE 9

A. Kinetics of methyldopa pseudotolerance and reversal with hydrochlorothiazide and potentiation of methyldopa antihypertensive activity. B. Continued control of blood pressure, once established in a severely hypertensive patient, over extended periods of time using methyldopa and a diuretic agent.

70 per cent. Thus, the i.v. dose is about ½ the oral dose. Interestingly, the time interval required for dissipation of antihypertensive activity is 18-20 hours independent of dosage (Figure 8). Thus, 20-24 hours is a sufficient drug-free interval prior to anesthesia, if even this is necessary. Knowledge of these kinetics are particularly important in the management of severe hypertension. An oral dose of 750-1000 mg can be given followed in six hours by 500 mg depending on the blood pressure. If blood pressure becomes normal or even low-normal, do not discontinue medication but take advantage of the kinetics in Figures 8 and 9. During the first 2-4 days of therapy blood pressure lowering can be maintained in most patients with low doses (500-750 mg daily) even if blood pressure is initially high. However, tolerance occurs in the majority of patients in 4-7 days and doubling or tripling of the dose may be required. If the patient has a volume expanded state, blood pressure lowering with methyldopa, as with all non-diuretic antihypertensive agents, is limited. Thus, diuretic agents are required in most patients to reduce or prevent volume expansion as occurs with pseudotolerance which is schematically illustrated in Figure 9.

Drowsiness is pronounced during the first several days of initiating therapy or increasing the dose of methyldopa. Patients should be warned of this effect and certain tasks such as automobile driving avoided. Hypothyroid patients have a continued antihypertensive response to low doses of methyldopa along with marked sedation. Also patients with advanced cerebral vascular disease tend to have continued drowsiness with this drug.

Once blood pressure control is established in a given patient with methyldopa combined with a diuretic agent, normotension can be successfully maintained indefinitely as shown in Figure 9.

The decision whether to use methyldopa or guanethidine is an important and sometimes difficult one. Some of the important kinetic differences between the two drugs are shown in Figure 10. The dose response of guanethidine hypotension

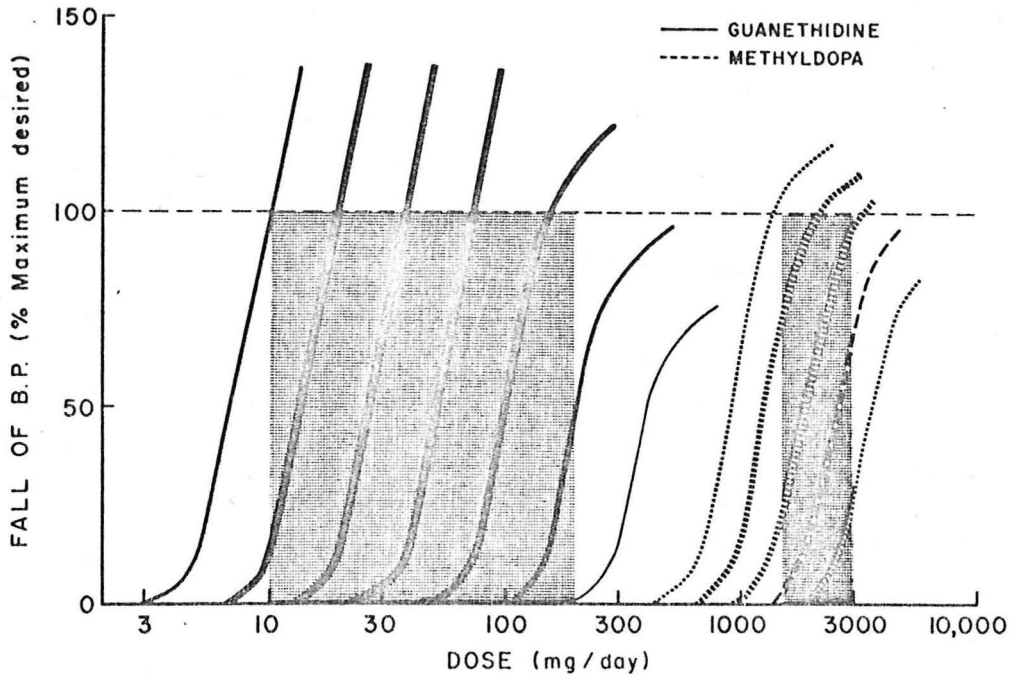

FIGURE 10

Schematic contrasts in dose-response curves between methyldopa and guanethidine. Wider curves indicate larger population density in corresponding dose ranges.

is highly individualized and tends to be linear through and beyond the optimal effect. Also the daily dose range within the hypertensive population covers 1½ orders of magnitude from 10-400 mg. Thus, for optimal blood pressure control in any one individual the process of titration may be time consuming and nearly impossible to achieve. Methyldopa, on the other hand, has a relatively narrow dose range (<½ order of magnitude) and the dose response curve tends to flatten

as blood pressure reaches normal levels. One additional important difference is the potential for methyldopa to lower blood pressure in both the supine and standing position as shown in Figure 10 (52). Alternatively, guanethidine induces greater orthostatic and exercise hypotension. Guanethidine also tends to induce more muscle weakness and diarrhea than methyldopa.

Alternatively, the advantages to be weighed in favor of guanethidine are the extremely low incidence of toxicity in contrast to the 1-4% of methyldopa-treated patients who develop either a flu-like syndrome and/or abnormal liver function tests (42). The former appears to be allergic in origin and the latter a dose-dependent effect. A positive direct Coombs test due to IGG coating of red blood cells (53,54) occurs in >30% of patients treated with methyldopa for more than six months; however, no detrimental hematologic effects have been correlated with this observation. Lactation due to high prolactin levels occurs in approximately 1/3 of women taking fairly high doses of methyldopa (49).

In summary, we are at that point in medical history in which the complications of hypertension can be prevented or markedly delayed by appropriate use of available therapeutic agents. We are also at or near the time when this can be achieved with minimal drug-related side effects. In contrast to recent publicity, the evidence for specificity toward disease mechanisms in our drug therapy is probably limited to aldosterone and angiotensin antagonists. Until the basic mechanism of essential hypertension is more clearly understood and definitively selective agents developed, the empiric approach to therapy will predominate.

References

1. Buhler, F.R., Laragh, J.H., Baer, L., Vaughn, E.D., Jr. and Brunner, H.R.: Propranolol inhibition of renin secretion: A specific approach to diagnosis and treatment of renin-dependent hypertensive disease. New Engl. J. Med. 287:1209, 1972.

2. Mohammed, S., Dasola, A.F., Privitera, P.J., Lipicky, R.J., Martz, B.L. and Gaffney, T.E.: Effect of methyldopa on plasma renin activity in man. Circ. Res. 25:543-548, 1969.

3. Onesti, G., Schwartz, A.B., Kim, K.E., Paz-Martinez, V. and Swartz, C.: Antihypertensive Effect of Clonidine. Circ. Res. Suppl. II: vol. 28 and 29:53, 1971.

4. Michelakis, A.M. and McAllister, R.G.: The effect of chronic adrenergic receptor blockade on plasma renin activity in man. J. Clin. Endocr. 34: 386, 1972.

5. Sen, S., Smeby, R.R. and Bumpus, F.M.: Isolation of a phospholipid renin inhibitor from kidney. Biochemistry 6:1572, 1972.

6. Tinker, D.O., Osmond, D.H., Schwartz, H-J. and Ross, L.J.: Dog kidney phospholipids and the question of renin inhibition. Can. J. Biochem. 51: 863, 1973.

7. Gross, F., Logan, J. and Orth, H.: Inhibition of the renin angiotensin reaction by pepstatin. Sci. 175:656, 1972.

8. Haber, E., personal communication.

9. Gutmann, F.D., Tagawa, H., Haber, E. and Barger, A.C.: Renal arterial pressure, renin secretion and blood pressure control in trained dogs. Am. J. Physiol. 224:66, 1973.

10. Gill, J.R., Jr., George, J. M., Solomon, A. and Bartter, F.C.: Hyperaldosteronism and renal sodium loss reversed by drug treatment for malignant hypertension. New Engl. J. Med. 270:1088, 1964.

11. Sambhi, M.P., Beck, J.C. and Venning, E.H.: Malignant hypertension and aldosterone secretion. Influence of reversal and progression of the syndrome in two cases. Amer. J. Med. 35:251, 1963.

12. McAllister, R.G., Van Way, S.W., Dayani, K., Anderson, W.J., Temple, E., Michelakis, A.M., Coppage, W.S. and Oates, J.A.: Malignant hypertension: Effect of therapy on renin and aldosterone. Circ. Res. Suppl. II: vol. 28 and 29:160, 1971.

13. Parker, T.F., Long, D.L., Prati, R.C., Hull, A.R. and Pettinger, W.A.: Refractory high renin and hypertension in patients with end-stage kidney disease: Vasodilation and beta-blockade. Submitted for publication.

14. Warren, D.J. and Ferris, T.F.: Renin secretion in renal hypertension. Lancet 1:159, 1970.

15. Czyzewski, L. and Pettinger, W.A.: Failure of feedback suppression of renin release in the spontaneously hypertensive rat. Am. J. Physiol. 225:234, 1973.

16. Conn, J.W., Rovner, D.R., Cohen, E.L. and Nesbit, R.M.: Normokalemic Primary Aldosteronism. J.A.M.A. 195:21-26, 1966.

17. Woods, J.W. et al.: Effect of an adrenal inhibitor in hypertensive patients with suppressed renin. Arch. Intern. Med. 123:366, 1969.

18. Crane, M.G. and Harris, J.J.: Effect of spironolactone in hypertensive patients. Am. J. Med. Sci. 260:311, 1970.

19. Douglas, J.G., Hollifield, J.W. and Liddle, G.W.: Treatment of low-renin essential hypertension. J.A.M.A. 227:518, 1974.

20. Muelheims, G.H. and Bround, G.O., Jr.: Effect of guanethidine therapy on total blood volume in patients with essential hypertension. Proc. Soc. Exp. Biol. Med. 109:613, 1962.

21. Rønnov-Jensen, V.: Blood-volume during treatment of hypertension with guanethidine. Acta Med. Scand. 174:307, 1963.

22. Gill, J.R., Mason, D.T. and Bartter, F.C.: Adrenergic nervous system in sodium metabolism: Effects of guanethidine and sodium retaining steroids in normal man. J. Clin. Invest. 43:177, 1964.

23. Dollery, C.T. and Harington, M.: Methyldopa in hypertension. Clinical and pharmacological studies. Lancet 1:759, 1962.

24. Rønnov-Jensen, V. and Hansen, J.: Blood volume and exchangeable sodium during treatment of hypertension with guanethidine and hydrochlorothiazide. Acta Med. Scand. 186:255, 1969.

25. Gaffney, T.E., Bryant, W.M. and Braunwald, E.: Effects of reserpine and guanethidine on venous reflexes. Circ. Res. 11:889, 1962.

26. Finnerty, F.A.: Relationship of extracellular fluid volume to the development of drug resistance in the hypertensive patient. Am. Heart J. 81: 563, 1971.

27. Pettinger, W.A., Sheppard, H., Palkoski, Z. and Renyi, E.: Angiotensin antagonism and antihypertensive activity of phosphodiesterase inhibiting agents. Life Sci. 12:49, 1973.

28. Parker, T.F., Long, D.L., Prati, R.C., Hull, A.R. and Pettinger, W.A.: Refractory high renin and hypertension in patients with end-stage kidney disease: Vasodilation and beta-blockade. Submitted for publication.

29. Pettinger, W.A., Long, D.L. and Parker, T.F.: High dose propranolol in refractory high renin patients: Plasma drug concentrations versus renin release. In Preparation.

30. Pettinger, W.A., Keeton, K. and Tanaka, K.: The radioimmunoassay and pharmacokinetics of saralasin (1-Sar-8-Ala-Angiotensin II) in the rat and hypertensive man. Submitted for publication.

31. Pals, D.T., Masucci, F.D., Sipos, F. and Denning, G.S., Jr.: A specific competitive antagonist of the vascular action of angiotensin II. Circ. Res. 29:664, 1971.

32. Brunner, H.R., Gavras, H. and Laragh, J.H.: Angiotensin-II blockade in man by Sar-1-8-Ala-Angiotensin II for understanding and treatment of high blood pressure. Lancet :1045, 1973.

33. Streeter, David, personal communication.

34. Campbell, W.B., Brooks, S.N. and Pettinger, W.A.: Angiotensin II- and angiotensin III-induced aldosterone release in vivo in the rat. Science, in press.

35. Campbell, W.B., Brooks, S.N., Keeton, K. and Pettinger, W.A.: Vasodilating antihypertensive drug-induced aldosterone release--A study of endogenous angiotensin-mediated aldosterone release in the rat. In preparation.

36. McAllister, R.G., Van Way, S.W., Dayani, K., Anderson, W.J., Temple, E., Michelakis, A.M., Coppage, W.S. and Oates, J.A.: Malignant hypertension: Effect of therapy on renin and aldosterone. Circ. Res. Suppl. II: vol. 28 and 29:160, 1971.

37. Michelakis, A.M. and McAllister, R.G.: The effect of chronic adrenergic receptor blockade on plasma renin activity in man. J. Clin. Endocr. 34: 386, 1972.

38. Pettinger, W.A., Campbell, W.B. and Keeton, K.: Adrenergic component of renin release induced by vasodilating antihypertensive drugs in the rat. Circ. Res. 33:82, 1973.

39. Buhler, F.R., Laragh, J.H., Vaughan, E.D., Brunner, H.R., Govras, H. and Baer, L.: Antihypertensive action of propranolol. Specific antirenin response in high and normal renin forms of essential, renal, renovascular, and malignant hypertension. Am. J. of Cardiology 32:511, 1973.

40. Prikhard, B.N.C. and Gillam, P.M.S.: Treatment of hypertension with propranolol. Brit. Med. J. 1:7, 1969.

41. Dollery, C.T., Lewis, P.J., Myers, M.G. and Reid, J.L.: Central hypotensive effect of propranolol in the rabbit. Brit. J. of Pharmacology 48:343, 1973.

42. Gilmore, E., Weil, J. and Chidsey, C.A.: Treatment of essential hypertension with a new vasodilator in combination with beta-adrenergic blockade. New Engl. J. Med. 282:521, 1970.

43. Pettinger, W.A. and Mitchell, H.C.: Minoxidil: An alternative to nephrectomy for refractory hypertension. New Engl. J. Med. 289:167, 1973.

44. Zacest, R., Gilmore, E. and Koch-Weser, J.: Treatment of essential hypertension with combined vasodilation and beta-adrenergic blockade. New Engl. J. Med. 286:617, 1972.

45. Pettinger, W.A. and Keeton, K.: Altered renin release and propranolol potentiation of vasodilatory drug hypotension. Submitted for publication.

46. Gottlieb, T.B., Katz, F.H. and Chidsey, C.A.: Combined therapy with vasodilator drugs and beta-adrenergic blockade in hypertension: a comparative study of minoxidil and hydralazine. Circ. 45:571, 1972.

47. Controlled comparison of furosemide and hydrochlorothiazide: Dose ranging in ambulatory subjects. Exact reference not available at time of this writing.

48. Pettinger, W.A., Horwitz, D., Spector, S. and Sjoerdsma, A.: Enhancement by methyldopa of tyramine sensitivity in man. Nature 200:1107, 1963.

49. Pettinger, W.A., Horwitz, D. and Sjoerdsma, A.: Lactation due to methyldopa. Brit. Med. J. 1:1460, 1963.

50. Pettinger, W.A., Spector, S., Horwitz, D. and Sjoerdsma, A.: Restoration of tyramine pressor responses in reserpine-treated animals by methyldopa and its amine metabolites. Proc. Soc. Exp. Biol. Med. 118:988, 1965.

51. Horwitz, D., Pettinger, W.A., Orvis, J.A., Thomas, R.E. and Sjoerdsma, A.: Effects of methyldopa on fifty hypertensive patients. Clin. Pharmacol. Ther. 8:224, 1967.

52. Oates, J.A., Seligmann, A.W., Clark, M.A., Rousseau, P. and Lee, R.E.: The relative efficacy of guanethidine, methyldopa and pargyline as antihypertensive agents. New Engl. J. Med. 273:729, 1965.

53. Breckenridge, A., Dollery, C.T., Worlledge, S.M., Holborow, E.J. and Johnson, G.D.: Positive direct Coombs tests and antinuclear factor in patients treated with methyldopa. Lancet #7529:1265, 1967.

54. MacDougall, A.I., Addis, G.J., MacKay, N., Dymock, I.W., Turpies, A.G.G., Ballingall, D.L.K., MacLennan, W.J., Whiting, B. and MacArthur, J.G.: Treatment of hypertension with clonidine. Brit. Med. J. 3:440, 1970.