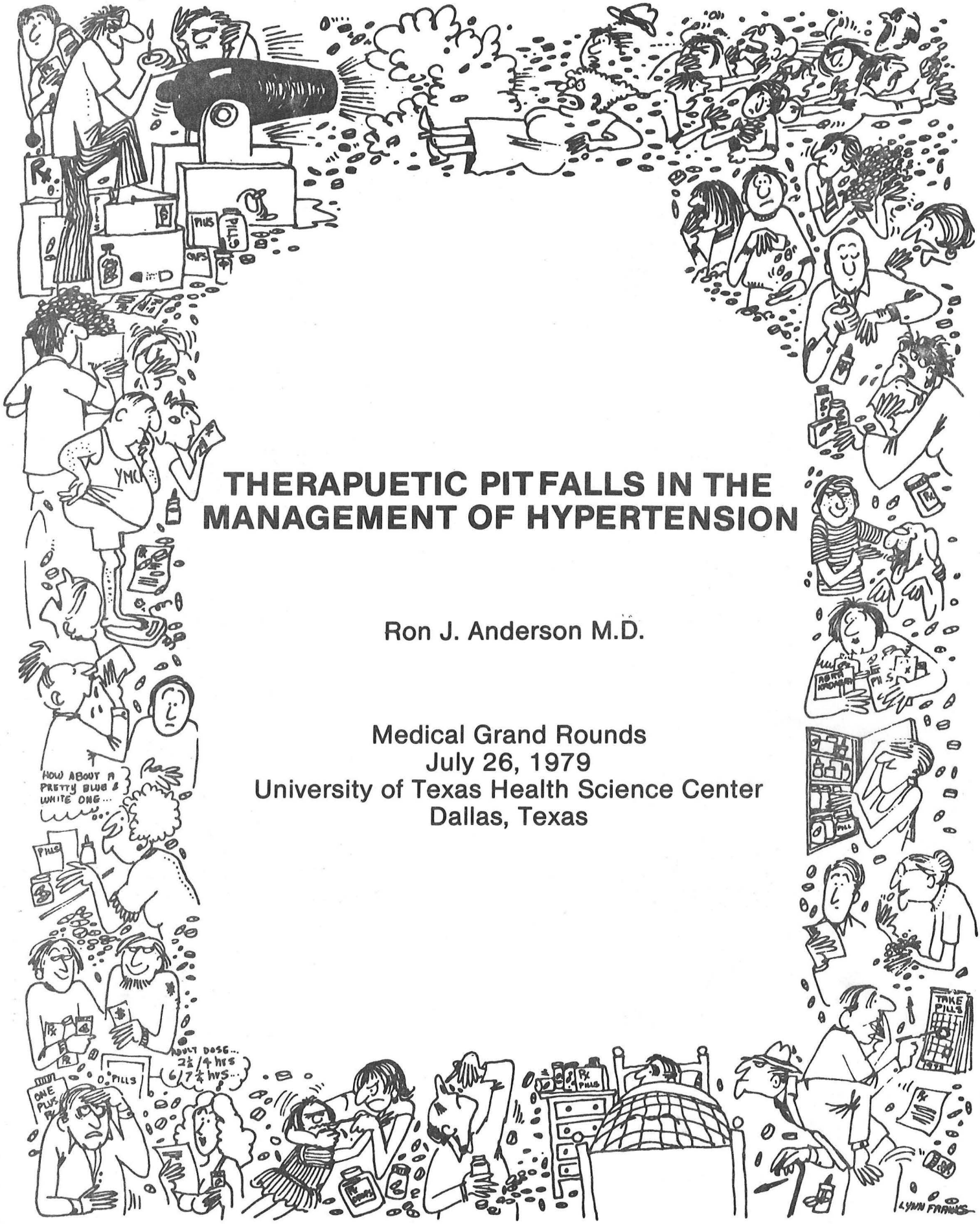

THERAPUETIC PITFALLS IN THE MANAGEMENT OF HYPERTENSION

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Medical Grand Rounds
July 26, 1979
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Dallas, Texas

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OF HYPERTENSION

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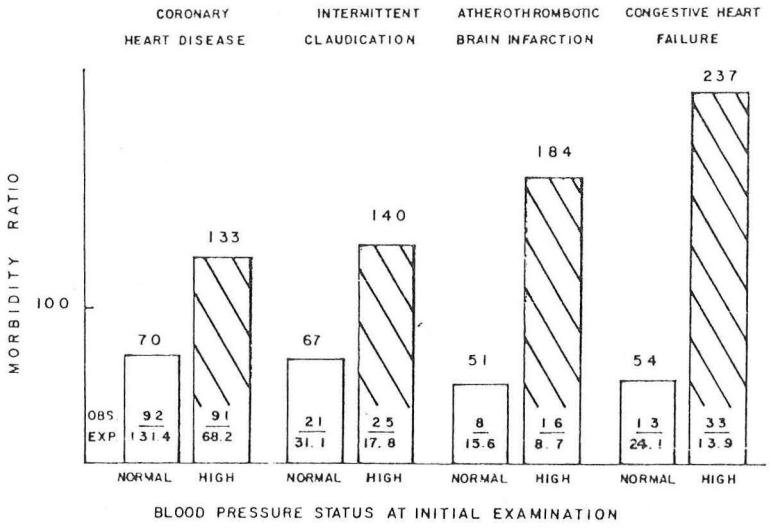
INTRODUCTION

The Gains To Be Made:

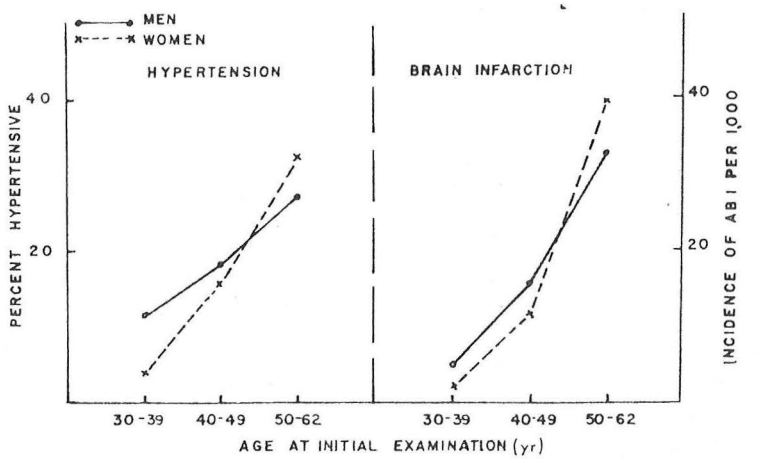
Classic epidemiological studies have focused on hypertension as a major risk factor for coronary artery disease, cerebrovascular and peripheral vascular disease, and congestive heart failure, as well as a common cause for renal failure (1-3) (Figure 1). Morbid, and oftentimes lethal consequences, result when hypertension is either left untreated or "partial control" is accepted for whatever reason.

FIGURES 1, 2, 3 and TABLE 1:

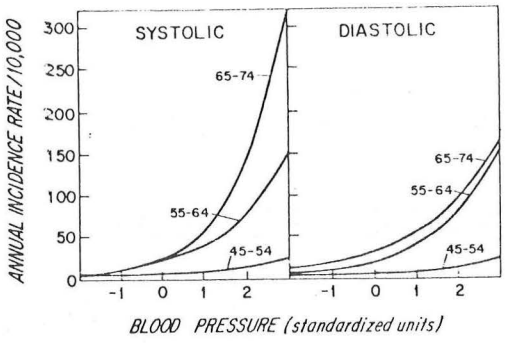
COMPOSITE OF EPIDEMIOLOGICAL DATA
FROM THE FRAMINGHAM STUDY



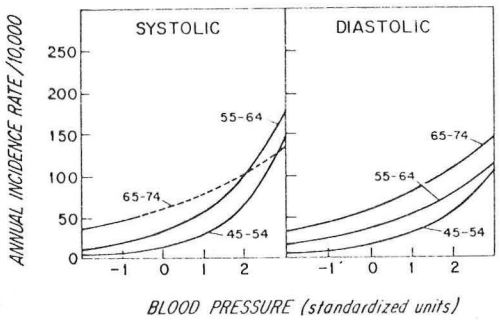
Risk of cardiovascular disease (14 years) according to blood pressure status. Men aged 30 to 62 years at entry.



Prevalence of hypertension and incidence of ABI by age and sex. Men and women aged 30 to 62 years at entry.



A



B

. Smoothed Average Annual Incidence Rate for CHF According to Blood Pressure, by Age for Men (A) and for Women (B), Framingham Heart Study, at 16-Year Follow-up Examination.

1. Incidence of CHF According to Hypertensive Status at Examination and According to Sex and Age.*

Age at Examination	Person-Yr at Risk at Examination			Incidence in Examination Interval			Average Annual Rate/10,000			Relative Risk
	Total	Normal	Hypertension	Total	Normal	Hypertension	Total	Normal	Hypertension	
Men:	16,814	8,586	2,964	80	13	45	24	8	76	7.9†
35-44	4,568	2,701	522	4	0	3	4	0	29	
45-54	6,321	3,272	1,100	24	3	15	19	5	68	14.9
55-64	4,539	2,061	1,020	35	8	19	39	19	93	4.8
65-74	1,386	552	322	17	2	8	61	18	124	6.9
Women:	21,426	11,181	4,013	61	12	36	14	5	90	4.2†
35-44	5,627	4,277	331	4	3	0	4	4	0	
45-54	7,907	4,370	1,226	10	4	3	6	5	12	2.7
55-64	5,956	2,087	1.726	32	4	22	27	10	64	6.7
65-74	1,936	447	730	15	1	11	39	11	75	6.7

*Source: Table 11-18-B of Section 26 of the monograph by Shurtleff D. Some Characteristics Related to the Incidence of Cardiovascular Disease and Death: the Framingham Study: an epidemiological investigation of cardiovascular disease. Bethesda, Maryland, National Heart Institute, 1970, Section 26.

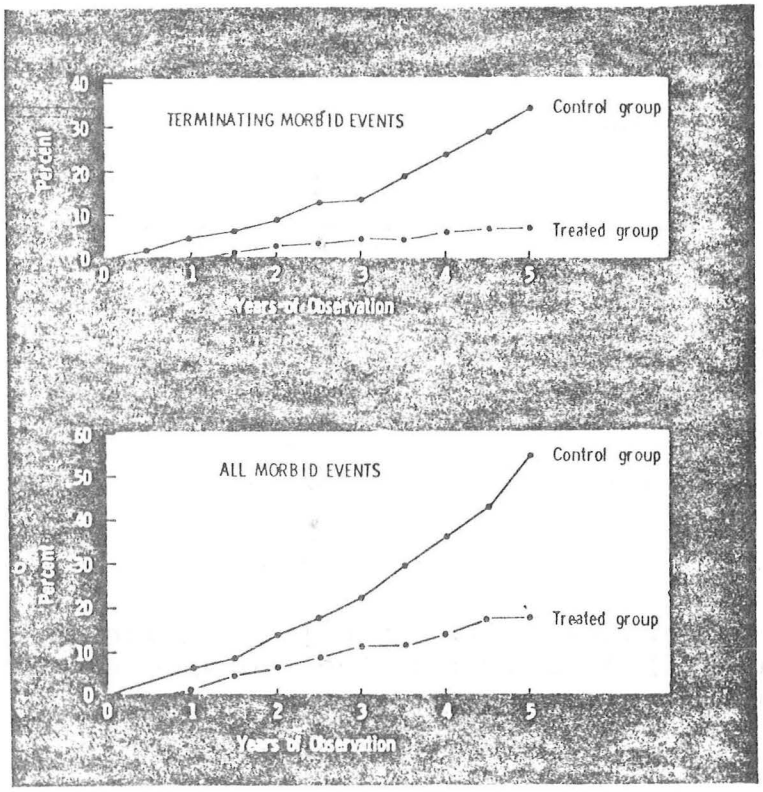
†Age-adjusted by indirect method using as standard rates the sex-age-specific incidence rates for the entire study.

The VA Cooperative study on mild to moderate and severe hypertension (4-6) demonstrated the therapeutic gains derived from blood pressure control.

FIGURE 4 and TABLE 2: VA COOPERATIVE STUDY ON MILD TO MODERATE AND SEVERE HYPERTENSION

MORBID EVENTS, VA COOPERATIVE STUDY
(Men with diastolic pressure between 90 and 115 mm Hg)

	Patients Receiving	
	Placebos	Antihypertensive Drugs
Number of Patients	194	186
Total morbid events	76	22
Congestive failure	11	0
Sudden death	8	4
Total deaths	19	8
Severe cerebrovascular accident	12	1
Mild cerebrovascular accident	8	4
All cerebral thrombosis	12	4
All cerebral and subarachnoid hemorrhage	5	0



Estimated cumulative incidence of morbidity over a five-year period as calculated by life-table method. Terminating morbid events (top) *and all morbid events* (bottom).

Although hypertension has been arbitrarily defined as 160/95 mm Hg, it should be thought of as a continuous variable. Insurance life tables show a consistent, inverse relationship between longevity and blood pressure, even in the normotensive range.

Each year 60,000 deaths are directly related and one million cerebrovascular accidents and myocardial infarctions indirectly related to hypertension at an estimated cost exceeding five billion dollars per year (2). Individual patient suffering serves to magnify these impersonal statistics. The application of available clinical tools to first identify, and then control the estimated 23 million hypertensive Americans is perhaps the most important preventive health care imperative for this nation today.

The Barriers to Recognize:

Major advances in the understanding of the pathophysiology of various types of hypertension, the realization that secondary forms of hypertension are rare (9, 10, 11) Table 2), and the development of effective, better tolerated, and safe* antipressor drugs would seem to place the primary care physician in a key position to manage most hypertensive patients.

TABLE 3: INCIDENCE OF "SECONDARY HYPERTENSION" IN REFERRAL POPULATIONS

	Ferguson (9)	Gifford(10)	Tucker(11)
Renal artery stenosis	2.8%	4.4%	0.18%
Pheochromocytoma	0	0.2%	0.04%
Primary aldosteronism	0.4%	0.4%	0.01%

*The term "safe" being used here in comparison to the untreated hypertensive state.

Nonetheless, population surveys reveal large numbers of previously unidentified hypertensives, and many patients with only partial control or actual "drop-out" from prescribed therapeutic programs (12). In Kaplan's recent review (13) only a minority (16-45%) of patients were considered to be well-controlled (Table 3).

TABLE 4: FINDINGS OF SIX HYPERTENSION SURVEYS (Ref. 13)

	National Health Survey 1960-1962	Atlanta Community 1970	Chicago 1967-1971	National Community Evaluation Clinic 1973-1975	Health & Nutrition Examination Survey 1971-1974	Detection Follow-up Program 1973-1974
Number of people examined	6,672	6,012	22,929	1,049,225	17,796	158,906
% with BP > 160/95	15	23	20	22	17	23
% unaware of hypertension	43	19	59	28	57	25
% with hypertension being treated	36	57	25	62	25	54
% with hypertension under control	16	36	11	45		38

Rarely the failure of a therapeutic regimen to achieve goal blood pressure results from accelerated hypertension, unrecognized "secondary" hypertension or progression of underlying disease. In most cases the explanation is less exotic. Our own clinical experience in the Parkland patient population suggests that more than 95% of hospitalized hypertensives can be controlled with one, two or three drug combinations. Despite the effectiveness of the drugs utilized, ambulatory control of blood pressure is more elusive. Common reasons for compromise or failure to achieve and maintain therapeutic goals include:

- .Patient (or physician) noncompliance
- .Excessive sodium ingestion
- .Renal insufficiency (often mild-"subclinical")
- .Pseudotolerance
- .Poor initial choice of adrenergic blocker
- .Adverse drug effects or interactions
- .Undiagnosed "secondary" hypertension
- .Progression of an underlying disease process

(The latter two problems are beyond the scope of this presentation).

The Liabilities to Pay:

The "labeling" of an individual patient as hypertensive may have both psychological and socioeconomic impacts, as yet not nearly well enough studied. An obvious example is the effect on insurability (however good blood pressure control for two years will allow a return to more favorable rates with most insurance companies) and employability. For example, military and commercial aviators diagnosed as hypertensive must submit to rigorous and frequent medical evaluation. If more than a diuretic is necessary for blood pressure control, the pilot is grounded (14). The economic losses are felt by the pilot and by his training sponsor, whether military or corporate and the losses may exceed hundreds of thousands of dollars.

A second and more general problem, is the effect that "labeling" may have on life-style and work performance. Sackett and Haynes, et al (15) demonstrated an increase in absenteeism exceeding one week per year in newly detected hypertensive steelworkers. The degree of increase in absenteeism was no different between individuals seeking, and those choosing not to seek, physician care and followup. [*The phenomenon of labeling (particularly with a psychiatric diagnosis) is being more extensively studied to assess the impact on the patient and on the health care provider's attitudes and abilities to make appropriate therapeutic decisions.*]

Finally, the attendant risks of known, and as yet unknown, adverse effects and end-organ toxicities of various antipressor agents must be weighed against the likelihood of realistic therapeutic gains. In this regard, therapeutic evangelism, conflicting marketing claims, and short-term clinical trials bearing little or no relationship to the management of this chronic illness, serve only to confuse or intimidate.

Therefore, in addition to discussing the problems of noncompliance, this Grand Rounds will attempt to present a balanced view of the advantages, disadvantages, complications, and adverse drug interactions associated with each commonly used antipressor agent. Negative "word-associations" will be explored and placed into perspective. The intent of this communication is not to discourage or recommend one drug over available alternatives, but to encourage a more knowledgeable application of these clinical tools toward the achievement of the therapeutic goals set for the individual patient.

NONCOMPLIANCE

"...(the physician) should keep aware of the fact that patients often lie when they state they have taken certain medicines..."

-Hippocrates

"Unfortunately, attempts to understand noncompliance (the better to control it) have revealed its complexity without yielding much useful information about its management"

-Haynes, Sackett, et al.
Clin Pharm Ther
22:125, 1977

The Magnitude of the Problem:

The most common reason for loss of blood pressure control is patient noncompliance. Methodologies to assess the degree of noncompliance or the beneficial effects of maneuvers designed to enhance compliance have been difficult to develop due to the lack of quantifiable end points. Methods currently employed to assess compliance include:

- .Patient interview (nonthreatening)
- .Pill counts or prescription refills
- .Attainment of therapeutic goals
- .Presence of side effects or pharmacological effect (orthostasis, tachycardia or bradycardia, effects on serum uric acid, etc.)
- .Surprise home visits

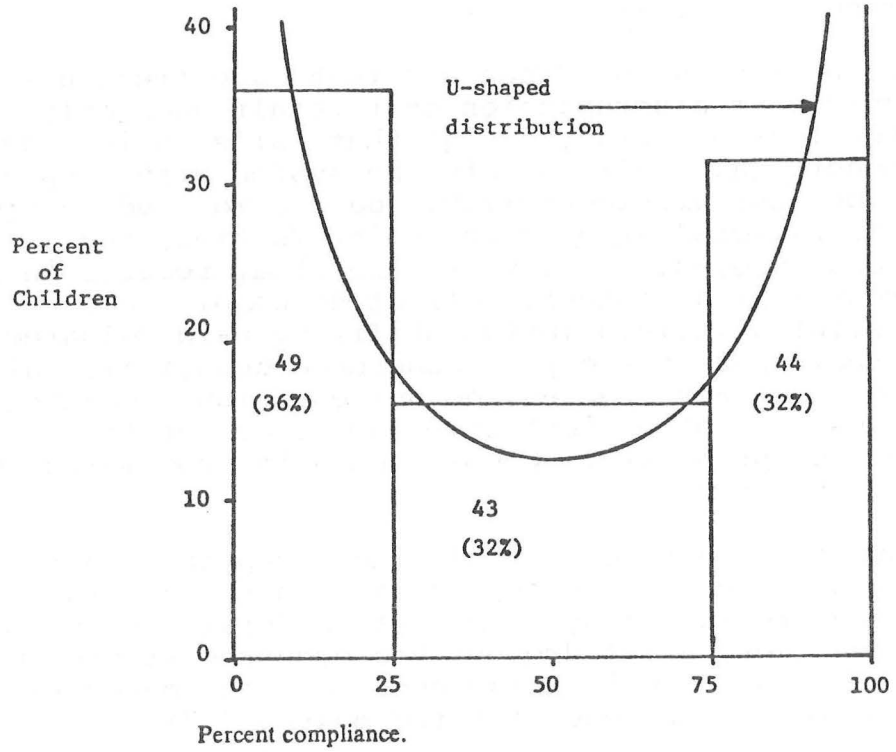
Studies utilizing more than one technique frequently display significant discrepancies that result when only one method is considered. Study design that fails to include an inception cohort (all entries into the system with a specific diagnosis) does not provide reliable data. To study a group of patient "survivors" at only one point in time, and largely ignore "drop-outs" prior to the study results in a gross underestimation of total patient noncompliance. Short-term clinical trials (often utilizing paid volunteers, picked for their past history of adherence behavior), while necessary for efficacy studies, do not contribute meaningfully to dicussions of patient compliance, or for that matter, drug acceptability. Compliance data from marketing studies is best ignored.

Good prospective studies utilizing inception cohorts reveal alarming rates of noncompliance. In the Australian blood pressure program studying mild to moderate asymptomatic hypertensives, a 19% dropout had occurred at the end of two years. Closer review disclosed that the majority of dropouts withdrew by the end of three months (17).

Sackett and Haynes' group in Hamilton, Ontario, has studied two inception cohorts. One study group came from a community population. Individuals volunteering for blood pressure screening, and subsequently seeking physician care as a result of the information received, still had a dropout rate of 21% at the end of one year. Of the remaining patients, only 60% claimed to be fully compliant with medications (18).

The second study group consisted of 144 hypertensive steelworkers. Despite various compliance maneuvers, only 53% of the subjects took at least 80% of the prescribed regimen(19). This sort of "U-shaped" distribution of compliance may be common to long-term preventive programs. Supporting this possibility is the report by Gordis (20) concerning compliance with penicillin-prophylaxis for rheumatic fever (Figure 5).

FIGURE 5: COMPLIANCE WITH ORAL PENICILLIN PROPHYLAXIS IN RHEUMATIC FEVER:



-Gordis L, Markowitz M and Lilienfeld M: Studies in the epidemiology and preventability of rheumatic fever. Pediatrics 43:173-182, 1969

The achievement of goal blood pressure is not solely dependent on compliance; some patients achieve therapeutic goals with less than perfect compliance.

FIGURE 6: FACTORS AFFECTING THE RELATIONSHIP BETWEEN COMPLIANCE AND ACHIEVEMENT OF GOAL BLOOD PRESSURE (Ref. 21)

		GOAL BLOOD PRESSURE	
		ACHIEVED	NOT ACHIEVED
COMPLIANCE	HIGH	• IDEAL	• INADEQUATE THERAPY • DEFINITION OF HIGH COMPLIANCE TOO LENIENT
	LOW	• MISDIAGNOSIS • OVERADEQUATE THERAPY • DEFINITION OF LOW COMPLIANCE TOO STRINGENT	• INTERVENTION NEEDED

Assuming that the patient's diagnosis is correct and the prescribed regimen is effective, one must consider multiple factors at work in each individual patient when trying to insure that adherence behavior will result from the provider/physician-patient interaction. For convenience, five general areas should be considered (22):

1) Patient characteristics
2) The prescribed regimen
3) Physician (or other health care provider's) characteristics
4) The interaction between primary parties in the therapeutic program.
5) The type of illness

Patient Factors:

The relationship between patient and physician may "styleflex" under the burden of various clinical situations (Table 5). With chronic illness, particularly hypertension, a mutual participation model is mandatory. The inability to achieve a "therapeutic partnership" often lies at the root of the problem of noncompliance.

Table 5: STYLEFLEXING IN PHYSICIAN-PATIENT INTERACTIONS

	Physician	Patient	Clinical Example
Active-passive	Does something to patient	Inertly responds	Coma, anesthesia, surgical procedure, etc.
Guidance-cooperation	Tells patient what to do	Cooperates	Acute infection
Mutual	Helps patient to help himself	Participates in partnership	Psychoanalysis, chronic disease (diabetes, hypertension, etc.)

Noncompliance occurs more often at the extremes of age. At one end of the spectrum, the physician must depend on the parent as a provider. The parent's view of the severity of the illness is an important factor. In the geriatric patient similar dependency may be present. If self-medicating, lapses in memory, self-neglect, depression and the resetting of priorities imposed by a fixed income serve to impact negatively on adherence to medications.

Women are more likely to utilize health care resources than men so the impact of gender on the issue of compliance may be somewhat skewed. Studies conducted on patients with tuberculosis revealed that women (particularly young women) are twice as likely to default with medication taking as men (23). Educational level, economic and ethnic factors (especially if a language barrier is present) each play a role. Becker (24) in a review of multiple compliance studies found

that black, blue collar workers, with lower educational levels comply least well. For such patients, obvious structural barriers can be modified in the health care delivery system to improve adherence behavior.

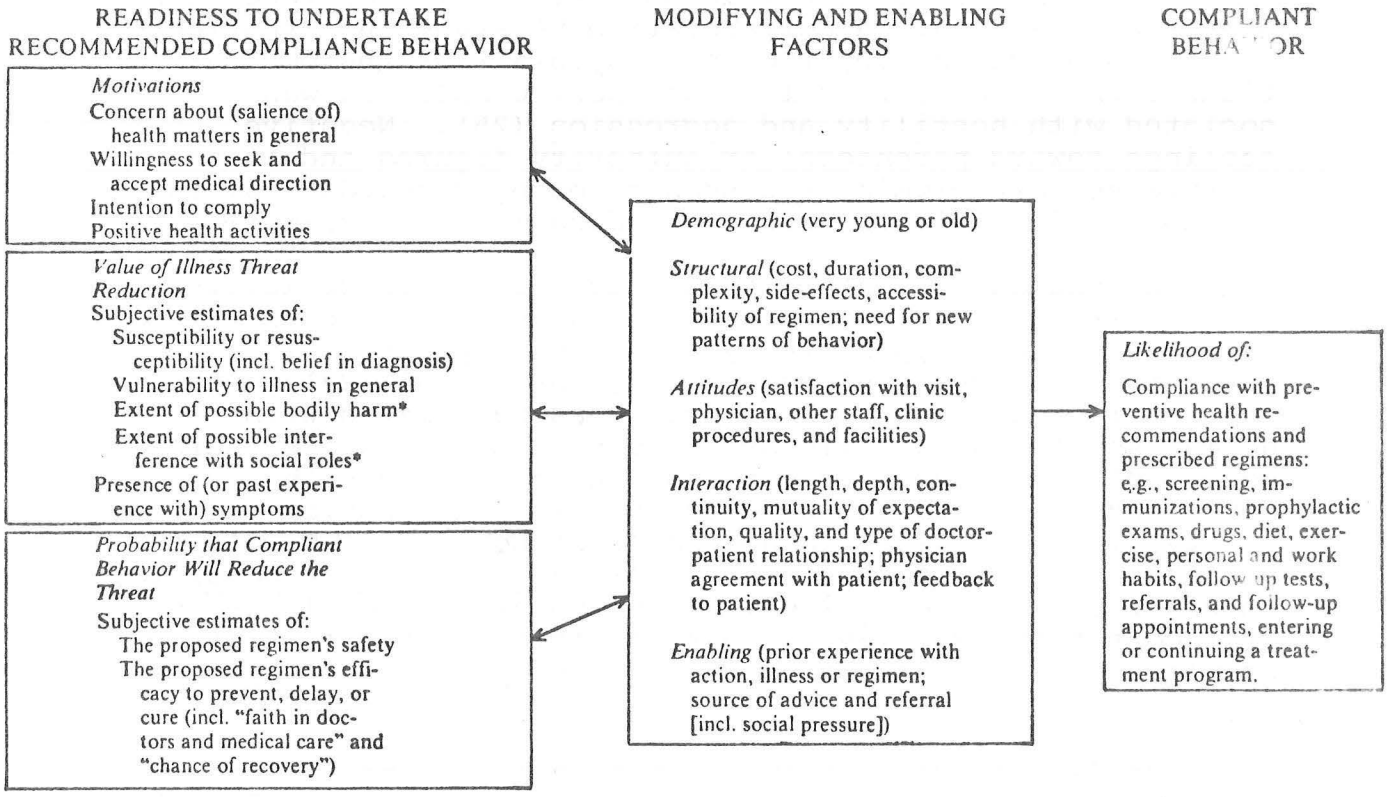
A more difficult type of patient to understand is the individual who comes to clinic but never fills or takes his prescribed regimen. A collaborative VA study in outpatients receiving psychotherapy from one psychiatrist and medications from another, revealed that poor compliance was associated with hostility and aggression (25). Negative feelings toward parenteral or authority figures and institutions were prominent causes cited by Richards (26) in schizophrenic patients refusing medications (neuroleptics).

Personality inventories such as the Minnesota Multiphasic Personality Inventory (MMPI) have been used to try to identify patient types likely to be noncompliant. In patients with peptic ulcer disease, Roth et al (27) found that poor compliance with antacids was associated with normal scores on the "lie scale" of the MMPI. While there seems not to be overt deceit, the author suggests that covert psychological components (possibly aggression-hostility) may be at work in noncompliant behavior. Similar personality profiles describe as "immature and irresponsible, impulsive, and risk taking", women who are noncompliant on oral contraceptives (28). Fear of medications will limit compliance in personalities flavored by paranoia or hypochondriasis.

One of the most difficult personality types to deal with is the Type A personality. Such individuals fear "loss of control" or dependency and will comply poorly unless allowed to "co-pilot" therapeutic decisions concerning their illness. A skilled physician can usually guide such a patient with very little real compromise. *(On the other hand, the physician with a Type A personality may have some difficulty with this concept.)*

One of the most important constructs dealing with the patient's contribution to compliant behavior has been the "Health Belief Model" (29). Central to this conceptualization, and directly related to desired behavior, is the degree of perceived threat" the illness represents to the patient, and secondly, the degree to which the threat can be reduced by adherence to recommendations. The actual seriousness of the disease process (by physician estimation), and the amount of intellectualized data (patient education) seems to have less influence than what the patient perceives (or feels).

FIGURE 7: BECKER'S HEALTH BELIEF MODEL (Ref. 24)



*At motivating, but not inhibiting, levels.

Hypothesized model for predicting and explaining compliance behavior.

Marshall H. Becker: "Sociobehavioral Determinants of Compliance" In Compliance with Therapeutic Regimens, Ed. Sackett and Haynes, Johns Hopkins University Press, pg. 48, 1976

Ultimately, four patient behaviors are critical to the achievement of a "therapeutic partnership" and long-term blood pressure control (30).

The patient must make the decision

.to control the blood pressure

.to take the medication as prescribed

.to monitor the progress toward goal blood pressure

.to resolve problems blocking goal achievement.

The following table 6 can be used by health care providers to assess patient knowledge, attitudes, and skills or it can be used as a framework for patient education with the basic hypothesis being that active participation by the patient favors successful management of the illness. Such a model casts the physician as the "prime diagnostician and initiator", "advisor and guide", while the patient is viewed as "decision-maker and problem solver".

The patient's peer group and family's attitude toward physicians, medicines and hospitals can be extremely influential (31). It often pays to educate and inform "significant others" when trying to influence the patient.

TABLE 6 (Reference No. 30)

Four Critical Behaviors With Concomitant Knowledge, Attitudes, and Skills		
Knowledge	**Attitude**	**Skill**
Make Decision to Control Blood Pressure (BP)		
The patient is able to state:	The patient believes that:	The patient is able to:
His BP and normal limits	His BP exceeds normal	Differentiate between normal and abnormal
That high BP can be asymptomatic	His BP is high even if there are no symptoms	. . .
That untreated high BP can lead to stroke, kidney failure, or heart disease	Although consequences may not occur for years, they are nevertheless real and serious	. . .
That drug therapy can control high BP and reduce risk of these complications	Drug therapy and high BP control lessen risk of stroke, kidney failure, or heart disease	Explain the benefits of high BP control, eg, increased length and quality of life
The necessity of lifelong therapy for control of high BP	Potential problems can be resolved	Differentiate between control and cure
. . .	The benefits of control outweigh the costs	Identify potential problems related to medication regimen, fear of medication, time, and money
Take Medication as Prescribed		
The patient is able to state:	The patient believes that:	The patient is able to:
Medical regimen: which pill to take, when to take it, what to do if doses are missed	Prescribed medicine will lower BP, is needed every day for BP control, should not be stopped without medical advice	Develop habit of taking medicine by tailoring plan to fit personal schedule
. . .	Folk remedies are not substitutes for prescribed medication	Cue medication taking (if necessary) by associating with daily activities, storing in a prominent place, marking medication calendar
. . .	. . .	Select accessible source to obtain medications
. . .	. . .	Make financial plan and arrangements to obtain medications
. . .	. . .	Renew prescription before supply exhaustion
Monitor Progress Toward BP Goal		
The patient is able to state:	The patient believes that:	The patient is able to:
His BP goal	As a partner with physician, he has the right to understand what is expected of him, follow own progress, interact with advisor concerning progress	Identify and communicate progress toward goal: state of health, problems encountered with therapy
That BP readings vary and the trend during time is the basis for therapeutic decisions	Accepts daily BP fluctuations (within range physician defines) without undue concern	Keep track of his BP trend (if the physician recommends home BP measurement, then additional skills need to be developed)
That medications may need to be changed	. . .	. . .
Date and time for next appointment	Continuous therapy is important, including appointment keeping	Make arrangements necessary to keep appointment: travel, time from work, financial, reminder systems
What to do if he cannot keep appointment	Continuous therapy is important, including appointment keeping	Reschedule appointment
Resolve Problems That Block Achieving BP Control		
A. Communication		
The patient is able to state:	The patient believes that:	The patient is able to:
That BP control requires a combined effort by both physician and patient	Physician is interested in his concerns	State concerns; ask questions
. . .	As a partner, he has responsibility to know what is expected, state what he expects of physician	With the physician: identify possible solutions, select and try out solutions, evaluate progress
That other health professionals can help solve problems	Others can assist him to solve problems	Select appropriate health professional
. . .	Aforementioned attitudes apply here as well	Aforementioned skills apply here as well
That BP control requires emotional support from friends and relatives	He can ask and will gain empathy, support, and assistance with high BP therapy from friends and relatives	State when and how family members can help and ask for that assistance
. . .	. . .	Request instruction for friends and relatives about BP control and its management
. . .	. . .	Accept and use reinforcement and support
B. Medication regimen		
The patient is able to state:	The patient believes that:	The patient is able to:
Important side effects of his BP drugs	Side effects occur	Recognize symptoms as possibly being drug-induced
Action to be taken if symptoms occur	Physician will correct problems that pose danger to health	Consult physician about bothersome symptoms
Methods of minimizing side effects, eg, dosage scheduling, dietary supplements, activity precautions	. . .	Utilize methods when necessary

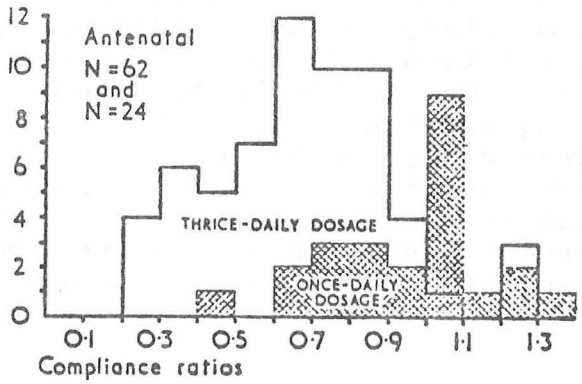
TABLE 6 (continued)

Four Critical Behaviors With Concomitant Knowledge, Attitudes, and Skills (Cont)		
Knowledge	**Attitude**	**Skill**
That other medications are available if side effects are intolerable	Living with minor side effects is more acceptable than consequences of uncontrolled BP	Request that other medication be prescribed if side effects are intolerable
That other drugs can interfere with BP goal, eg, over-the-counter medications such as decongestants	Drug interactions can interfere with BP goals	Inform all providers of current regimen
...	...	Seek advice before taking nonprescription medications
C. Costs Time required for follow-up visits, getting medicine	Time commitment to high BP therapy is as important as conflicting time demands	Inform physician of special time constraints
How this time will be built into his life	...	Request advice on how to minimize time spent on treatment of high BP
Dollar costs of medicine and follow-up visits	Treatment of high BP has high priority in budget	Inform physician of special financial problems
...	...	Request advice on resources to assist with cost

Regimen Factors:

Multiple medications taken at different times during the day can be confusing and too often predisposes to either medication error (32) or noncompliance (33). Weintraub has pointed out that increasing the complexity of a regimen using digoxin by adding a diuretic and potassium supplements significantly decrease compliance for digoxin (34). The frequency of doses per day seems to be more important than the number of medications taken at each dosing interval (Figure 8).

FIGURE 8: PERCENTAGE OF PRESCRIBED DOSES OF FERROUS SULFATE TAKEN ON A ONCE VS THRICE DAILY REGIMEN



Porter AMW. Drug defaulting in a general practice. Br M J 1:218-26, 1969

The above study compares compliance in a group of patients taking one tablet of ferrous sulfate per day vs a group on a thrice daily regimen. The first group displayed much better compliance but only received one-third as much active drug, obscuring the possible impact of adverse GI side effects on compliance in this group. Still the best rule is simplicity! Nearly all antihypertensive agents can be given B.I.D. in full therapeutic doses. B.I.D. in this case should mean breakfast and supper, or bedtime, depending on the drug used, first to prevent the need for taking medication out of the home, and secondly to allow ritualization of dosing.

For patients easily confused, compartmentalized containers can be "set up" by family members or visiting nurses. Visual aids can be developed for patients with poor vision or inability to read. Cardboard posters with medication samples glued to dosing intervals on a clock-face are easy to make and very useful. The use of easily identifiable products (unique color or shape), product labeling, and directions that explain why the medication has been prescribed, will make it easier for the physician and patient to communicate concerning problems with medications. One safeguard to duplication or overmedication is a review of "all medications being taken" at each clinic visit, by having the patient bring in all medication bottles and vials [*pill counts can be done in a nonobtrusive way during the visit*].

In some cases it would seem reasonable to simplify the medication regimen by using combination products ("convenience formulations"), and many marketing claims vigorously imply a resulting improvement in compliance. The FDA requires that combination products be proven efficacious but since this sort of study employs volunteers (with or without reward) interpreting information regarding compliance is difficult. One of the better studies (35) utilized a triple drug regimen: Tablet A (.1 mg reserpine), Tablet B (25 mg hydralazine) and Tablet C (15 mg hydrochlorothiazide). Medication was given in separate tablets compared to a one tablet combination product (SerApEs®), each being given three times per day. In the same patients, an additional lowering of blood pressure occurred with the combination product. (Table 7).

Table 7: Diastolic Pressure Changes on Transfer of Patients from Separate Tablets to One Tablet Combination

Initial Drug Regimen (N=13)	Average Diastolic BP Prior to Therapy	Separate Tablets (9 per day)	Change in BP	Combination Tablet-(SerApEs®) (3 per day)	Further Change in BP
A + B + C	135 mm Hg	99 mm Hg	-36 mm Hg	89 mm Hg	- 10 mm Hg*

* Significant at the 5% level.

Adapted from Clark and Troup (35)

Utilizing both office and ambulatory blood pressure monitoring with a semi-automatic blood pressure recorder (Remler®) as guides to blood pressure control, our group recently studied 24 mild to moderate hypertensives given chlorthalidone 50 mg per day, followed by clonidine (Catapres®) titration to control on a B.I.D. schedule (36). A switch was then made to a single tablet combination (clonidine .1 or .2 with 15 mg chlorthalidone) utilizing an equivalent dose of clonidine, first on a B.I.D. schedule and later the total dose was given as an H.S. dose only. The single tablet combination was as effective as the separate tablet regimen despite an average reduction in the total diuretic dose to 38 mg (Table 8). This was not surprising since chlorthalidone 25 mg has been shown to be as effective as 50 mg or 75 mg per day in mild hypertension, with less chance for hypokalemia (37). The Remler device was used at each step of therapy for comparison of control. Significant control of blood pressure occurred with the single bedtime dose. Clinically, it seemed that smoother control was more often achieved on the B.I.D. schedule, however differences in control between the twice and once daily regimen were not statistically significant ($p > .5$). Initiating therapy with clonidine may be best carried out by using low doses at bedtime only. Even though side effects tend to decrease with time, when B.I.D. regimens are necessary, the largest dose of clonidine can still be given at bedtime.

TABLE 8: MEAN ARTERIAL PRESSURE AS DETERMINED BY THE REMLER RECORDER ON TWICE VS SINGLE H.S. DOSES OF COMBIPRES* (24 PATIENTS)

Time	Step 1 Chlorthalidone (50 mg) Clonidine BID (A.T.D. .385 mg)†	Step 2 Combipres® BID	Step 3 Combipres® H.S. Only
7 AM	104 ± 13	98 ± 10	100 ± 12
10 AM	98 ± 13	99 ± 11	103 ± 12
1 PM	97 ± 11	98 ± 13	104 ± 14
4 PM	99 ± 10	98 ± 10	101 ± 15
7 PM	99 ± 12	99 ± 13	104 ± 13
10 PM	101 ± 12	95 ± 11	104 ± 16

Blood pressure on chlorthalidone 50 mg alone was 121 ± 3 mm Hg

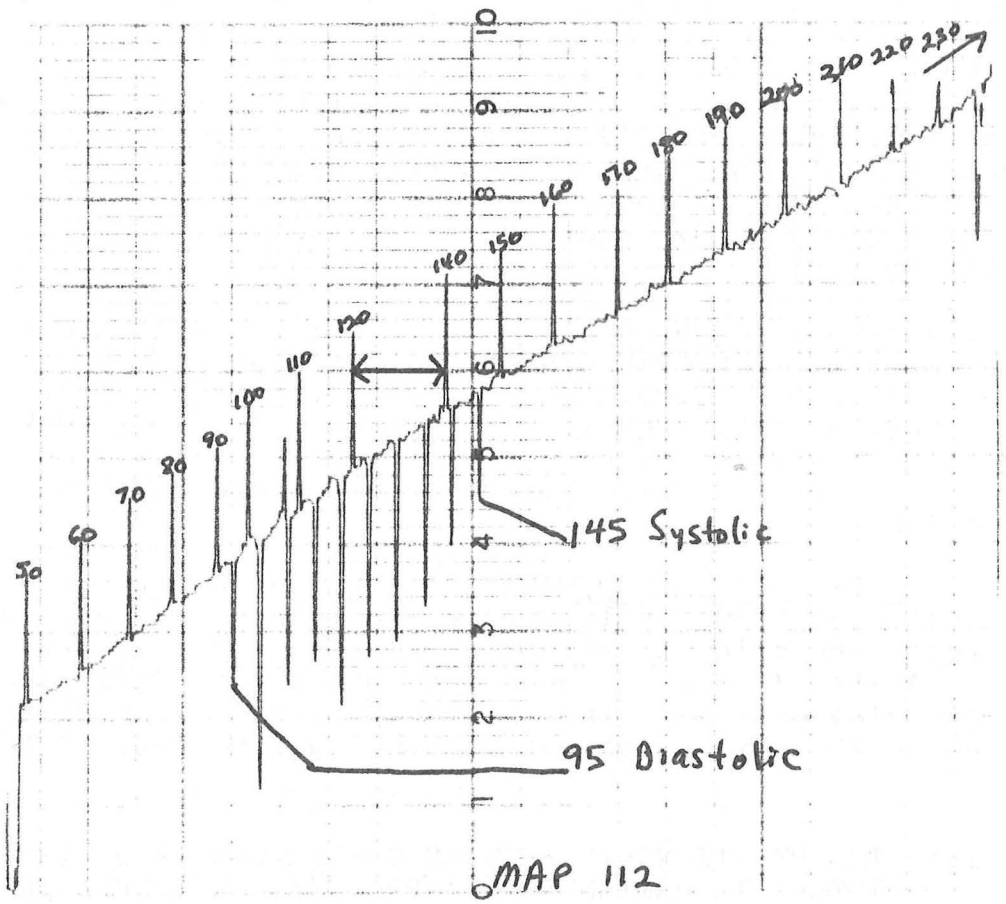
$p > .5$ (No statistically significant difference between Steps 1, 2 or 3. Statistical method: Analysis of variants with repeated measures. Winer BJ: in "Statistical Principles in Experimental Design", McGraw-Hill, New York, 1971, 2nd Ed. pps 514-570.

*This formulation contains clonidine (Catapres®) .1 mg or .2 mg with a fixed dose of chlorthalidone, 15 mg. By design, no patient exceeded a total dose of .8 clonidine/day, therefore use of the fixed ratio combination usually resulted in a reduction of the total chlorthalidone dose.

†A.T.D. = Average Total Dose

During this study, patients were allowed to see their decoded Remler recordings (figure) and the elevation of blood pressure resulting from scheduled withdrawal of the drugs. Common misconceptions held by the patients concerning hypertension could be dissuaded when the recorded blood pressures were compared to a diary of daily activities. Pill counts in this study did not show improved medication compliance by switching to a single daily dose schedule.

FIGURE 9: DECODED READING FROM A REMLER SEMIAUTOMATIC AMBULATORY BLOOD PRESSURE RECORDER



Reserpine and guanethidine can also be utilized when single dose per day schedules are necessary. A recent study utilizing metoprolol, a β-blocker, suggested that it may also be an effective single dose agent (38). This study reported office BP readings taken on one occasion two hours after a daily dose, and again four weeks later, 26 hours after a daily dose. Clearly this is inadequate blood pressure monitoring. Single dose efficacy studies of "sustained release products", one utilizing a propranolol-diuretic combination, and another utilizing clonidine, are currently underway. A recently developed percutaneous system utilizing a small disc saturated with medication hopefully will be

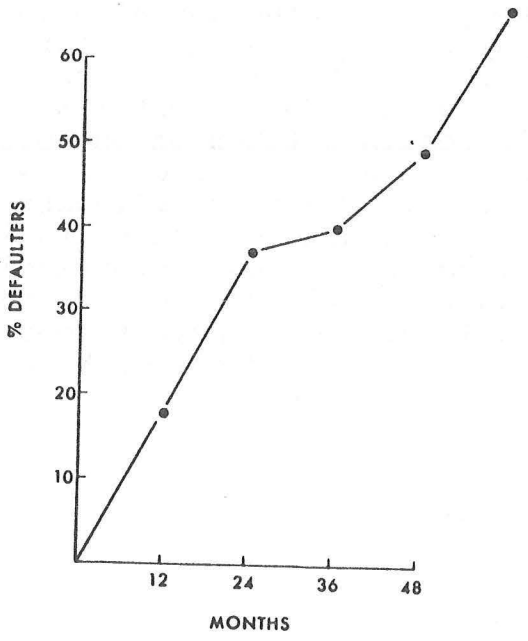
capable of extended periods of controlled medication delivery. Long-acting parenteral antipressor agents (analagous to Prolixin for schizophrenia) may be developed in the future, but presently available antipressor agents do not lend themselves well to such a delivery system.

Nevertheless, as new claims are made for old drugs, as new formulations ("sustained release") of old drugs, or new methods of delivery are developed, we must insist that documentation of blood pressure control for the claimed dosing interval be obtained by either conventional blood pressure readings or by such devices as the Remler semi-automatic monitor.

The degree of change in a patient's life style necessitated by medical recommendations will strongly influence adherence behavior. Occasional oral medication is generally less disruptive than attempting to lose weight, stop smoking or adhere to a strict low sodium diet. Physician recommendations concerning these latter problems are infrequently followed (39).

The duration of therapy necessary in the hypertensive patient has a negative influence on compliance. Even in a more threatening clinical situation such as tuberculosis, Luntz and Austin (40) have shown that compliance diminished in direct relationship to the length of time since hospital discharge, with only 30% of patients being compliant at four years.

FIGURE 10: THE RELATIONSHIP BETWEEN DEFAULTERS (% OF THE TOTAL) IN PATIENTS ON AMBULATORY ANTITUBERCULOSIS THERAPY AND DURATION OF THERAPY. (From Luntz and Austin, Ref. 40)



Side effects of antihypertensive agents are commonly stated physician reasons for patient noncompliance but represent a relatively minor reason for noncompliance according to patient reports. Of a group of 42 hypertensive "dropouts" seen in a Detroit emergency Room for hypertensive emergencies, only 7% cited side effects as the reason for noncompliance (31) (Table 9). The Johns Hopkins Study Center for Health Services Research and Development reviewed side effects with 308 patients; 79% reported no experience with side effects, 15% had one, and 6% had more than one side effect to report although they continued to take medications.

Table 9: Patient Reports Concerning Compliance

Causes for Noncompliance:		Reasons for Continued Compliance:	
Detroit ER Group	(42 "dropouts")	Control Group	(24 Patients with Severe Hypertension)
Felt well	39%	Good knowledge of disease	71%
Poor instruction	36%	Harmful effects of inadequate treatment	50%
Financial need	33%	Harmful effects of hypertension in family	50%
Advice of physician	24%	Emotional satisfaction	51%
Lack of family support	14%	Physical comfort	38%
Dissatisfied	10%	Family support	38%
Discouraged	7%		
Side Effects*	7%		

A comparison of side effects in hypertensive patients treated with placebo (control group) or with active drug (treatment group) in the VA Cooperative Study (6) reveals the high baseline incidence of side effects in this population.

TABLE 10:

Incidence of Specific Side Effects among a Subsample of 56 Control and 68 Treated Patients

Side effect	Control group					Treated group				
	Without prev complaint* (no.)	With complaint postrand				Without prev complaint* (no.)	With complaint postrand			
		Any visit		After 2nd visit			Any visit		After 2nd visit	
		No.	%	No.	%		No.	%	No.	%
Nightmares	52	6	12	4	8	65	4	6	2	3
Depression	53	5	9	5	9	67	6	9	5	7
Skin rash	55	5	9	4	7	64	5	8	5	8
Arthritis	50	19	38	16	32	63	17	27	15	24
Impotence	46	13	28	10	22	62	18	29	13	21
Angina	49	12	24	9	18	64	8	13	6	9
Headache	38	13	34	8	21	52	13	25	4	8
Ulcer symptoms	55	5	9	5	9	68	8	12	6	9
Lethargy or weakness	46	12	26	8	17	64	25	39	13	20
Nasal stuffiness	48	14	29	10	21	63	22	35	10	16
Other complaints	47	20	43	16	34	58	25	43	18	31
Any complaint†	24	16	67	15	63	40	33	82	31	78

*Patients who did not have the specific complaint prior to randomization.

†Patients without any of the above complaints prior to randomization, and those who subsequently developed some complaint.

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Still it is important to minimize symptomatic side effects when possible. Reassurance and a discussion of available alternatives may convince the patient to tolerate minor side effects in favor of therapeutic gains. An open invitation to discuss problems arising from the prescribed regimen should be extended to each patient.

The sheer cost of medications, transportation and follow-up clinic visits may force otherwise conscientious patients to drop out or default with medication taking. Again, discussion concerning these factors allows for the development of a tailored regimen, one that will be more likely complied with since the patient has partially designed the program (See Appendix A for costs of common prescribed drugs at PMH).

Considering the reasons that patients state for non-compliance, patient education, social support programs, and teaching techniques to improve physician communication skills seem to be approaches to the dropout problem that are worthy of further study.

Health Care Provider Factors:

The interaction between health care provider and patient affect the patient's willingness to adhere to a prescribed regimen. The display of such attributes as empathy and concern (42), continuity, comprehensiveness, and accessibility (43) seem to improve patient feelings about their interaction with the physician and are more likely to result in adherence to recommendations. Positive feedback rewarding compliant behavior enhances the likelihood of continued patient participation in the prescribed regimen. Additionally, the specificity and clarity of communications is extremely important. If a physician responds to the question, "Doc, how's my blood pressure doing?" by saying, "Fine", he may imply that the illness has run its course. A better answer would be "Your blood pressure is well-controlled today on your medications". This latter reply does not imply a cure and further emphasizes the positive gains made by the prescribed regimen. Nonverbal communications to the patient may affect compliance as shown in the study by Rickels and Briscoe (43B) where patients were found to be more likely to take drugs when the prescribing physician believed in their efficacy and importance.

Doctors have traditionally overestimated compliance, as well as patient knowledge (44). Multiple studies emphasize that health care providers are usually not successful in identifying noncompliance at the time of an office visit (45-47). These studies point out that medical students are more likely to identify drug defaulters than senior attending physicians and that physicians are better at identifying noncompliance in a colleague's practice than in their own.

Tutorials designed to increase physician awareness of the problem of noncompliance in patients treated at Johns Hopkins for hypertension resulted in improved physician behavior as concerns charting and allocation of patient contact time (39). A significant increase in the number of patients taking 75% of the prescribed regimen and achieving acceptable blood pressure control occurred in the study group (patients of physicians receiving tutorials).

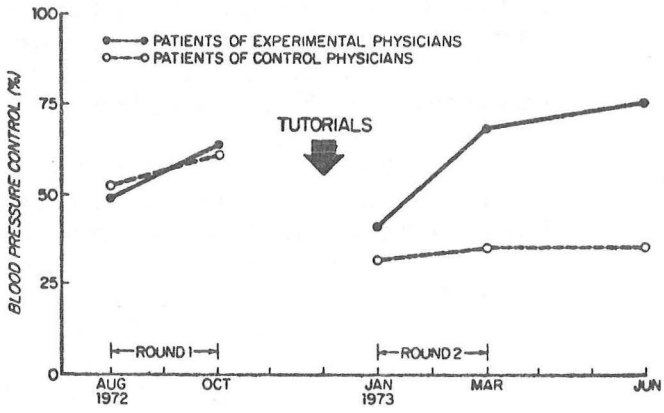
TABLE 11 and FIGURE 11: RESULTS OF PHYSICIAN TUTORIALS ON PATIENT COMPLIANCE.

Physician Behavior: Reported Allocation of Visit Time (Round 2)

Visit Activity	Visit Time Allocated by Study Physicians		Student's *t*-Test, *P* Value
	Control	Experimental	
	%		
Physical examination	27.4	20.4	~0.01
Taking interim history	28.4	22.7	~0.025
Educating patient	20.8	29.6	~0.005
Other	23.4	27.3	NS

Physician Behavior: Chart Notations (Round 2)

Mentioned on Chart Entries	Charts of Study Physicians		Chi-Square Test, *P* Value
	Control	Experimental	
	%		
Dietary recommendations	20.8	61.2	< 0.005
Patient compliance	26.4	73.5	< 0.005
Patient understanding of hypertension	3.8	18.4	~0.05
Patient education	1.9	26.5	< 0.005



Patient Behavior: Compliance (Round 2)*

Patient Activity	Compliant Patients		Chi-Square Test, *P* Value
	Control (*n* = 53)	Experimental (*n* = 49)	
	no.		
Taking 75% of pills	17	30	~0.005
Diet adherence	29	28	NS
Keeping appointments	37	40	NS

* NS = not significant.

To assure patient participation, the health care delivery system and/or health care providers should be flexible enough to change structure and function of service units to meet the needs of the patient population served. A striking example of improved patient compliance and blood pressure control comes from Finnerty's work in Washington, D.C. (48). A compliance rate for followup appointments (not medication taking) of 58% characterized a clinic system where patients waited an average of 2.5 hours to see the doctors, saw him for an average of 7.5 minutes and then waited 1.8 hours to get their prescription filled. Patient knowledge was fair, most considering hypertension as a serious illness. The major complaints voiced by patients were the lack of a stable provider/patient relationship and the excessive waiting periods. After reorganizing one of three parallel clinics (the other two served as controls) to provide continuity of care, accessibility and shorter waiting periods, appointment compliance rose to 84% by eight months of followup. More importantly, goal blood pressure control was achieved in 70% compared to 10% and 17% in the control clinics.

Illness Factors:

The final set of factors that influence compliance relate to the illness itself. As previously stated, perceived threat is more important than the actual seriousness of the illness. Generally, the greater the degree of symptomatology, especially if noncompliance triggers a return of symptoms, the greater the chance for continued compliance. In this regard, the goal of hypertensive control is made more difficult since the illness is usually asymptomatic and noncompliance is usually without untoward effects perceptible to the patient. Sometimes a previous or concurrent serious illness, or a history of hypertensive illness in a family member, serve to improve compliance in a general fashion. The duration of therapy also adversely effects compliance with antihypertensive agents. The longer patients have gone without symptoms or without reinforcement from the physician or family, the more likely noncompliance will result merely from fatigue or the willingness to take a chance.

Important Studies on Methodologies to Improve Patient Compliance:

Americans have long relied on education as an approach to social problems, and its role in compliance enhancement deserves special comment. Sackett and Haynes, et al. (49) studying an inception cohort of hypertensive steelworkers, applied first an " augmented convenience " strategy (follow-up care at work, during working hours with no penalty or payment associated with the visit) followed by a " mastery learning " strategy. Each intervention group was balanced by a control group. In short, neither intervention improved compliance. Patient knowledge levels in the study group rose to 85% (compared to 18% in the control group) without translating into better compliance or the achievement of goal blood pressure.

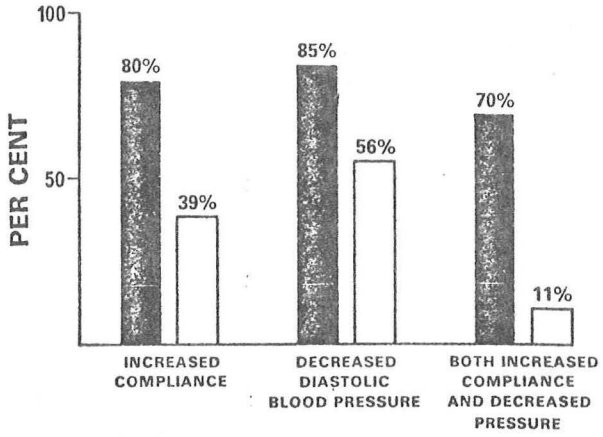
TABLE 12: EFFECTS OF STRATEGIES UPON COMPLIANCE DEFINED AS TAKING AT LEAST 80% OF A PRESCRIBED DOSE

Strategy	(1) No. of men placed on anti-hypertensive drugs	(2) % (and number) of "drop-outs"	(3) % (and number) designated "compliant" at six months	(4) % (and number) designated "compliant" and "at goal B.P."
	—EFFECTS OF STRATEGIES UPON COMPLIANCE			
Augmented convenience	87	7% (6)	54% (47)	23% (20)
Normal convenience	57	7% (4)	51% (29)	19% (11)
Undergoing mastery learning	80	10% (8)	50% (40)	24% (19)
Not undergoing mastery learning	64	3% (2)	56% (36)	19% (12)

Sackett, Haynes, Ref. No. 40

Finally, as a sequel (50) noncompliant patients underwent a variety of behavior modification techniques, including home blood pressure measurement and maintenance of a medication diary. Regimens were tailored and doses timed to coincide with daily patient rituals. Supervision and positive reinforcement (by a nonphysician) were utilized. Compliance for medication taking rose from 39% to 80% and importantly, over 70% of the patients reached goal blood pressure control.

FIGURE 12: CHANGES IN PATIENTS BETWEEN START AND END OF PHASE II



The use of home blood pressure cuffs in various other studies has not been so positive. In fact, mean compliance in the above study fell back to 39% in the experimental group during the year following active intervention despite the fact that patients continued to self-monitor blood pressure. This same group looked at another inception cohort of 136 hypertensive community patients, one group received monthly home visits, and blood pressure kits by a random assignment; the other group received neither (51). Both interventions were ineffective and did not improve compliance.

Carnahan and Nugent (52) randomly assigned 100 new hypertensive patients to receive or not receive a sphygmomanometer with a built-in stethoscope. At the end of six months of therapy, both groups of patients revealed the same degree of decrease in diastolic blood pressure, 10.5 mm Hg, while the experimental group had a significant incremental decrease in systolic blood pressure, 18 mm Hg vs 10.5 mm Hg in the controls ($p < .05$).

The utilization of home blood pressure kits may improve compliance in the individual patient but cannot be relied upon to improve compliance in all new patients or even those previously proven noncompliant.

McKenney (51) studied the impact of pharmacist's supervision and patient education on the number of "doses taken as prescribed"* by hypertensive patients. An increase from 25% to 79% occurred during the study period, but these gains were quickly lost as soon as the monitoring was discontinued (Table 13).

TABLE 13:

PHARMACIST INTERVENTION

	CONTROL			STUDY		
	Before	During	After	Before	During	After
No. of Pts	25	24	19	24	24	24
No. Compliant*	4	4	3	6	19	6
% Normotensive	44	20	14	20	79	42

* ± 10% of prescribed doses

-McKenney et al.
Circulation 48:1104, 1973

The effect of increased patient supervision was further studied by Wilbur and Barrow (53) in a random sample from a community in Georgia. A door-to-door blood pressure screening program identified 220 hypertensive individuals and each subject was offered regular home visits by a public health nurse along with instructions concerning the nature of hypertension and the importance of medication compliance. Only 88 individuals volunteered for this manuver. During the subsequent two years, the percentage of patients on medication rose from 25% to 86%, and the percentage of patients reaching goal blood pressure rose from 15% to 80%. Despite the fact that this study was composed of seemingly motivated volunteers, the two year period following the home visit intervention was characterized by a high rate of patient dropout (only 55% continued on therapy) and loss of blood pressure control (only 29% maintained goal blood pressure).

Simple and inexpensive maneuvers can be readily adapted to private and public clinic systems. Takala, et al (54) using matched pairs, randomly allocated 202 Finnish hypertensives, to an ordinary or "reorganized" treatment group. The latter group received written instructions concerning hypertension, a personal blood pressure followup card, and, for those who failed to attend their appointed clinic visit, an invitation for a new checkup was sent. In this latter group, only 4% dropped out during the first year of follow-up, compared to 19% in the ordinary treatment group ($p < 0.01$). Additionally, 95% of the reorganized treatment group experienced a 10% reduction of blood pressure at the end of one year, compared to 78% in the ordinary treatment group ($p < 0.01$). This article emphasized the need for a simple medication regimen, and of those patients achieving satisfactory control, 60% were managed with a single daily dose of diuretic (chlorthalidone).

The message from each of these studies is that most interventions successful in improving compliance must be continued indefinitely.

One caution is in order if you choose to utilize the "Health Belief Model" to influence your patient's attitudes toward their illness and toward medication compliance. Education concerning the risks of hypertension represents threatening data that the patient may choose to assimilate into a plan of avoidance. This is a healthy response that leads through patient compliance to a reduction in threat. On the other hand, such threat may trigger neurotic anxiety, which can bring about a series of defense mechanisms including denial, repression of information, aggression, etc. These reactions reduce fear by eliminating thoughts about danger, without having any real impact on danger reduction. Individuals who handle fear in this way avoid reminders of illness and hence do not take medications. Leventhal (55) has reviewed the impact of high, moderate and low fear communications on patient acceptance of preventive health practices. In smokers offered a free screening chest x-ray, 53% of the subjects exposed to a moderate to low threat accepted, while only 6% of those subjects exposed to high threat accepted. The percentage of patients attempting to stop or reduce smoking was the same in each fear group, while the high fear group was more often successful. This author describes the development of "invulnerability beliefs" under conditions where warnings are repetitive without the perceptable approach of danger. A "natural" high fear communications, significant illness in a loved one, may result in a break through of invulnerability beliefs, arouse appropriate fear and motivate protective or avoidance behavior.

The wisest approach to the whole issue of fear communication is to present mild to moderate threat coupled with a clear course of action which, if followed, results in a reduction of danger.

"Perhaps you'd care for a home medical encyclopedia that is a little less specific, sir."

Summary:

The achievement of goal blood pressure by improving concordance is attainable only through physician-patient mutual participation. The rewards to society and the individual patient are clear. The following recommendations may prove beneficial in the approach to the individual patient requiring chronic antipressor therapy:

1. Be alert to the problem, indeed likelihood, of noncompliance and the difficulty physicians have detecting it.

2. The patient, the patient's family and/or peer group should be brought into the therapeutic program as far as education is concerned.

3. Continuity, comprehensiveness, and accessibility are physician attributes more likely to result in desired patient behavior.

4. Patients are more likely to comply with enthusiastic recommendations.

5. Medical regimens should be as simple as possible and ritualized to existing daily habits.

6. Successful behavioral modifications must be positively and continually reinforced.

7. Patient education should be utilized to inform the patient of his/her responsibilities as a "decision maker" and "problem solver" in selfcare (mutual participation model). Points to stress include:

   Hypertension

   -is a serious problem, that if left untreated may result in end-organ damage.

   -is usually asymptomatic.

   -is usually a life-long malady, requiring life-long therapy.

   -can be controlled.

   -therapy can be tailored to minimize adverse effects.

8. The physician (or other health care provider) cast his/her role as "guide" and "initiator" of therapeutic maneuvers, inviting dialogue concerning difficulties encountered with the prescribed regimen and offering, when appropriate, effective alternative therapy.

9. Health manpower resources (pharmacists, nurse practitioners, physician assistants, health educators, dieticians, social workers, and lay volunteers) should be used in such a way as to extend and support the individual therapeutic program.

The following table compiled from various articles cited in Compliance with Therapeutic Regimens, David L. Sackett and R. Brian Haynes, Johns Hopkins Press, 1976, and from the body of this text may serve to help predict the likelihood of compliance in the individual patient.

Table 14

DETERMINANTS OF COMPLIANCE

Provider Factors	"Hard" Conclusions	"Soft" Conclusions	No Consistent Relationship Found
Patient Factors:	-Social isolation +Patient perception of susceptibility to disease -Presence of certain psychiatric illness or personality types	-Extremes of age -Female gender -Low income -Lower educational level -Marital status, single or widowed ±Patient education +Family expectation favoring compliance	Patient knowledge about disease Religion
Regimen Factors:	-Complexity -Frequency of dosing -Prolonged duration of therapy -Other behavioral changes necessary	-Number of pills per dose -Side effects +Extent that therapy relieves symptoms ±Type of medication (tablet, capsule, liquid, etc.) +Patient perception of treatment efficacy	
Physician or Clinic	+Positive attitude of physician +Length of clinician-patient relationship +Time clinician spends with patient (or the mother of a pediatric patient) +Regular vs substitute physician +Assignment of a specific physician +Patient satisfaction with encounter +Specificity and clarity of communications +Positive feedback +Personality Accomodation -Long Waiting periods -Extended period between screening and appointment	-Dissatisfaction with clinician ±Clinic setting	Clinician prediction of compliance Physician's knowledge of the actual seriousness of the disease
Illness Factors:	+Previous bout of same illness +Similar illness in family or friends -Duration-chronic -Asymptomatic illness	+Extent to which therapy relieves symptoms +Extent to which recognizable symptoms reappear with noncompliance	Actual seriousness of the illness

+ = Positive Association - = Negative Association

DIETARY SODIUM, RENAL INSUFFICIENCY AND PSEUDOTOLERANCE

The Antipressor Effects of Diuretics:

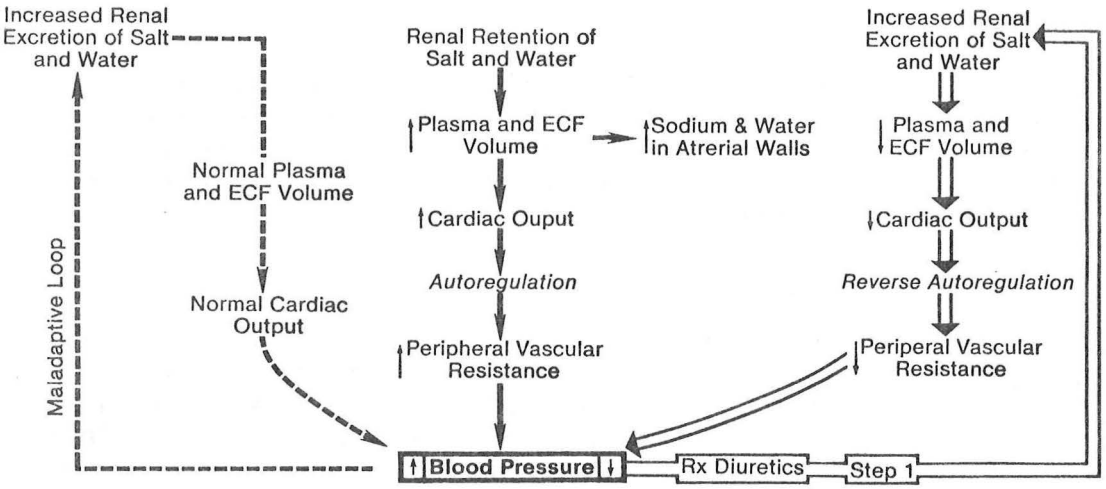
The discovery of orally active, highly efficacious diuretic agents has played an important role in the development of antihypertensive regimens. The wide number of agents with differing dosing intervals, duration of action, sites of action and relative potencies has facilitated our ability to tailor the diuretic regimen to each patient's life style and constellation of physiologic and pathologic variables.

Dustan (56) and Wilson and Freis (57) demonstrated that the antihypertensive effect of thiazide diuretics was dependent on a reduction of extracellular fluid (ECF) including plasma volume (PV). Later Conway and Lauwers (58) described the acute and chronic effects of chlorothiazide. They postulated that diuretics initially reduce blood pressure by contracting ECF and decreasing cardiac output (CO). With chronic therapy they reported an increase in ECF and a return of CO to normal and suggested that the diuretics had vasodilating properties somewhat analagous to diazoxide.

A series of investigators (59-61) confirmed the return of CO to normal after several weeks of diuretic therapy. In each study, peripheral vascular resistance (PVR) was reduced with chronic diuretic administration, however, ECF did not return to normal even after months of therapy. A direct vasodilator action of the thiazide diuretics has not been convincingly shown (62). Since the nonthiazide diuretics (furosemide, ticrynafen, etc.) also reduce blood pressure, it would seem that a continued reduction in ECF is the essential ingredient for the antipressor effect of diuretics.

Tobian (63) has proposed the concept of *reverse autoregulation* to explain the lowered PVR to chronic diuretic therapy. A reduction in ECF would initially cause a reduction in CO followed by autoregulation of resistance vessels to reduce PVR, which in turn would decrease left ventricular afterload and permit CO to return to normal. From a hemodynamic standpoint, just the reverse situation occurs with the induction of the hypertensive state in experimental animals.

FIGURE 13



Tobian's concept of "reverse autoregulation with diuretic therapy of hypertension.

Other mechanisms help to explain the antipressor effects of diuretics. The pressor response to norepinephrine or angiotensin II is blunted by chronic chlorothiazide therapy (64, 65), however, responsiveness can be restored by reexpansion of plasma volume with salt-free dextran (66).

What is the role for sodium then in this scenario? Tobian (67) found that sodium and water content is increased in the small arteries of hypertensive animals. According to Haddy (68), an increase in intracellular sodium activates ATPase and releases free ionic calcium which mediates contraction. In multiple studies (69-71), the electrolyte and water content of small arteries is unchanged by chronic chlorothiazide therapy. In man, the net sodium loss from chlorothiazide therapy can be accounted for by a loss of ECF in isotonic proportions (57). Bennett, et al. (72), administered (by crossover design) hydrochlorothiazide,

metolazone, or placebo to patients with end-stage renal failure on maintenance hemodialysis. In the absence of a natriuresis, there was no reduction in blood pressure and no evidence of direct vasodilating effects from the diuretics.

Renal insufficiency, excessive dietary sodium, and the complex renal, sympathetic and hemodynamic alterations induced by the sympatholytic and vasodilating drugs used in hypertension, diminish (usually by expansion of ECF) the effectiveness of diuretic therapy.

Renal Insufficiency

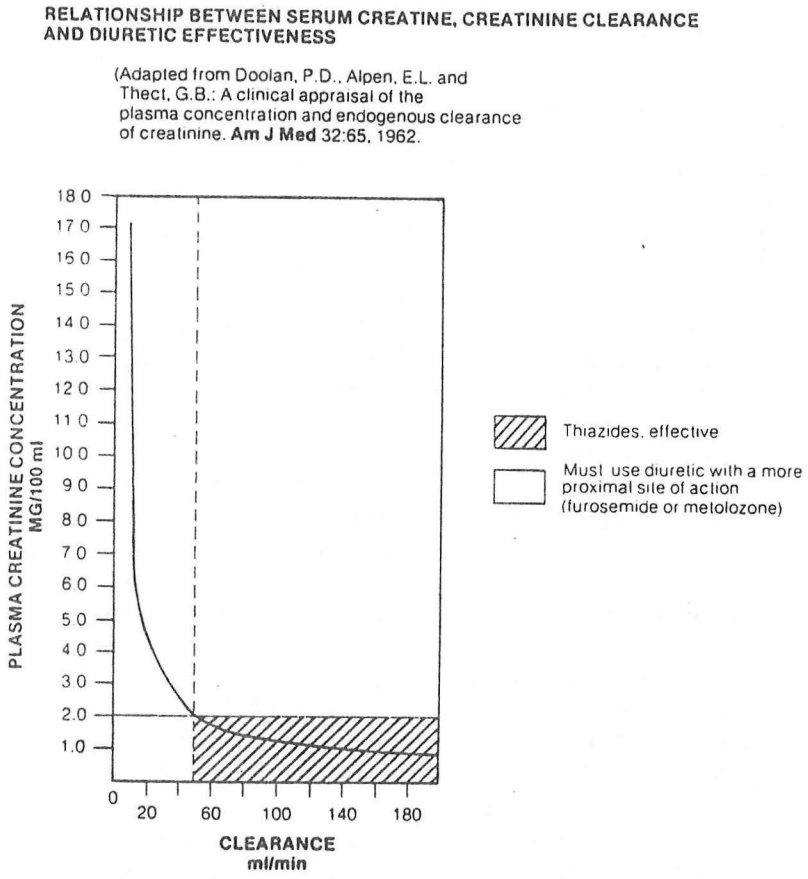
Mild to moderate renal insufficiency is not rare in the hypertensive population, whether it be the result of the hypertensive process, the cause of it, the result of an unrelated intercurrent disease, or a nonspecific manifestation of aging. Advanced renal insufficiency may complicate preexisting hypertension, and its treatment, by significantly compromising the ability of the patient to either excrete excessive dietary sodium loads or to conserve sodium when dietary intake is restricted. However, for our purposes one of the most important complications of mild-moderate renal insufficiency is the ineffectiveness of the thiazide diuretics.

It is now clear that the thiazide diuretics are ineffective below a GFR of 25-35 ml/min (73). It is postulated that in the setting of renal insufficiency, there is a diminished amount of filtrate delivered to the distal nephron, due to more complete proximal reabsorption in functioning nephrons. Since the main site of action of the thiazides appears to be in the cortical diluting segment of the ascending limb of the loop of Henle, it is hypothesized that insufficient filtrate is delivered to this site to allow for significant diuresis (74). Two diuretics with more proximal sites of action, metolazone and furosemide, retain their effectiveness in patients with renal insufficiency. For this reason, these two drugs are preferable in patients with a GFR of less than 40 ml/min.

Unfortunately, it is often difficult to estimate the level of renal function from the serum urea nitrogen or creatinine. In the elderly and those of slight muscular development, the serum creatinine may not exceed 1.5-2 mg%

until the GFR is less than 20-30 ml/min. In patients with a serum creatinine of 1.5-2, in whom thiazides do not seem to be having the desired effect, it would be wise to collect a 24-hour urine and calculate endogenous creatinine clearance. If the clearance is less than 40 ml/minute, the patient should be switched to furosemide or metolazone. These two drugs are the diuretics of choice for all patients with serum creatinine greater than 2 mg%.

FIGURE 14: GFR VS SERUM CREATININE AND RECOMMENDATION FOR DIURETIC TYPE



Excessive Dietary Sodium

The importance of dietary sodium intake in the maintenance of some hypertensive states has been recognized since the days of the strict rice diet (75). It has become increasingly clear that a number of patients with essential hypertension can be controlled to a normotensive range by strict dietary salt restriction. By contrast, patients with certain forms of secondary hypertension, such as pheochromocytoma, may actually experience an increase in blood pressure with strict salt restriction. Unfortunately, most Americans find it very difficult to follow a severely salt restricted diet. The food is often bland and unpalatable, and low salt or salt free foods are next to impossible to find in restaurants, fast food chains, etc. Medical regimens requiring changes in diet will be poorly complied with by most Americans (39).

It is difficult to make blanket statements regarding the daily salt intake of average Americans, as it varies according to race, nationality and multiple other factors. For most of us, however, it wouldn't be an exaggeration to say we literally live in a sea of salt. An average diet will contain at least ten grams of salt daily, and many Americans daily consume 15-30 grams. The daily intake of this amount of sodium may select for individuals with a genetic substrate analagous to the Dahl "S" (salt sensitive) and Dahl "R" (salt-resistant) rat strains. In this model, it has been shown that "S" rats excrete less sodium than "R" rats at each level of renal perfusion pressure (70). The "S" rats must have an elevated pressure to excrete sodium loads and spontaneously develop hypertension. Whether or not this can be applied to man is controversial. Less controversial is the effect that excessive dietary sodium has on control of blood pressure in the hypertensive patient.

The vast majority of hypertensive patients do not need severe salt restriction of the type used in the edematous states. However, evidence has accumulated that moderate salt restriction to 6-10 grams per day may be beneficial. Early in the investigation of the use of diuretics for hypertension, it was found that the antihypertensive effects could be abolished by the infusion of salt-free dextran or saline (66, 77), in other words, by plasma volume expansion. It now appears that the same is true of excessive dietary sodium. Winer (78) has conclusively shown that 15-20 grams of salt per day can reverse the antihypertensive effects

of thiazide diuretics. These results have been confirmed by a number of other investigators and some studies demonstrate that as little as 12 grams of salt may be deleterious. Thus, there are potentially a large number of patients consuming enough salt daily to abrogate the effectiveness of otherwise adequate diuretic regimens.

In addition, it has been shown that the effectiveness of the thiazides can be positively enhanced by moderate salt restriction (79). These studies have demonstrated that salt restriction of 4-8 grams per day in patients on 1 gram of chlorothiazide or 100 mg of hydrochlorothiazide could cause an additional fall in diastolic pressure of 5-6 mm Hg when compared to a 12 gram salt diet and the same dose of diuretics.

Though most Americans cannot tolerate severe salt restriction (500 mg-2 grams), restriction to 6-8 grams per day can be achieved by simply avoiding obviously salty foods, using salt only sparingly during cooking, and adding no salt at the table. This degree of dietary restriction should be easily attainable and satisfactory for most patients. Many authorities now feel that moderate dietary salt restriction of this degree is advisable, at least for patients who do not reach goal blood pressure on diuretics alone. This measure is especially important for those patients with apparently resistant hypertension or those who have slowly slipped out of control, and those with excessive K+ losses (80). (Table 15).

The degree of salt restriction can be assessed by measuring the 24-hour urine sodium, as in most patients this value will accurately reflect daily salt intake. The low sodium diet sheet we currently use in Hypertension Screening Clinic is reproduced on page 42 for your review.

TABLE 15A: LOW VS HIGH DIETARY SODIUM AND $^{42}K_E$ VALUES DURING VARIOUS DIURETIC REGIMENS IN 12 PATIENTS

Drug	Dose	Low NA+ (64 mEq/day)	High NA+ (205 MEq/day)
Furosemide	40 mg B.I.D.	-186	-338
HCTZ	50 mg	-147	-283
Ticrynafen	250 mg	-229	-361
Chlorthalidone	50 mg	-324	-642
Chlorthalidone (n=6)	25 mg	Not Done	-308

TABLE 15B: PAIRED LOW VS HIGH DIETARY SODIUM WITH THE SAME DIURETIC (N = 30 PATIENTS)

Low Na+		High Na+	
U_{na}	$\Delta^{42}K$	U_{na}	$\Delta^{42}K$
71.4 mEq/24 hrs	-212.2 mEq	192.3 mEq/24 hrs	-427.3 mEq

C.V.S. Ram, B. Garrett and NM Kaplan: Diuretics and sodium restriction in the treatment of hypertension: Effects on potassium wastage and blood pressure control, (Ref. No. 80).

LOW SALT DIET

On a low salt diet you can eat many foods such as any type of bread, vegetable, or fruit. You can also eat most meats and poultry--including beef, fresh pork, lamb, and chicken if they are prepared with only light salt seasoning. If the food tastes salty, do not eat it. Do not add salt or seasoned salt (Accent, onion salt, garlic salt, or seasoned salt) at the table.

In cooking, use 1/2 of the amount of salt a recipe requires. Remember that onion salt, garlic salt, Accent meat tenderizer, and seasoned salt are all salt products. Instead, cook with fresh onions and garlic. Do not add salt to food which has been processed with salt, like canned vegetables.* Read the labels on food products. They will tell you if salt has been added. Many sauces contain salt. Catsup, chili sauce, barbeque sauce, soy sauce, and steak sauces are examples. Please avoid them. In addition, do not eat the following foods:

Cheese of any kind
Bread, crackers, or rolls which have a salt topping (pretzels)
Salted nuts (peanuts); unsalted nuts such as pecans are okay
Barbecued, salty, cured, smoked, or canned meats and fish--for example:

chili	ham	herring
dried chipped beef	sausage	frankfurters
corned beef	canned chicken	TV dinners
bacon	anchovies	salt pork
canned tuna	vienna sausages	caviar
sardines	meat pies	luncheon meats

Chips of any kind (potato chips, corn chips, etc.)
Saurkraut and other vegetables prepared in brine

hominy	canned broth	canned pork and beans
pickles	bouillon cubes	prepared horseradish
canned soup	olives	salted popcorn
prepared mustard		

*It is also helpful when cooking canned vegetables to drain off the liquid in the can and cook your vegetables in fresh water.

Pseudotolerance

Shortly after the introduction of the potent ganglionic blocking drugs for the treatment of hypertension, it was found that these drugs initially produced excellent decreases in blood pressure, though the pressure tended to rise toward control values after several weeks or months of treatment (81). This apparent tolerance to the antihypertensive effects of the drug has now been demonstrated for all Step 2 and Step 3 agents, though propranolol and prazosin seem less likely to evoke it. It is now clear that this phenomenon represents not a true tolerance, but a false tolerance or "pseudotolerance".

To understand the phenomenon of pseudotolerance, it is necessary to first review the complex changes in sodium balance, sympathetic nervous system activity and hemodynamics that occur with administration of each of the major classes of antihypertensive drugs. These changes represent the body's attempt to compensate for fall in blood pressure, plasma volume, etc. and, if unopposed, often serve to raise the blood pressure after an initial decline.

Step 1

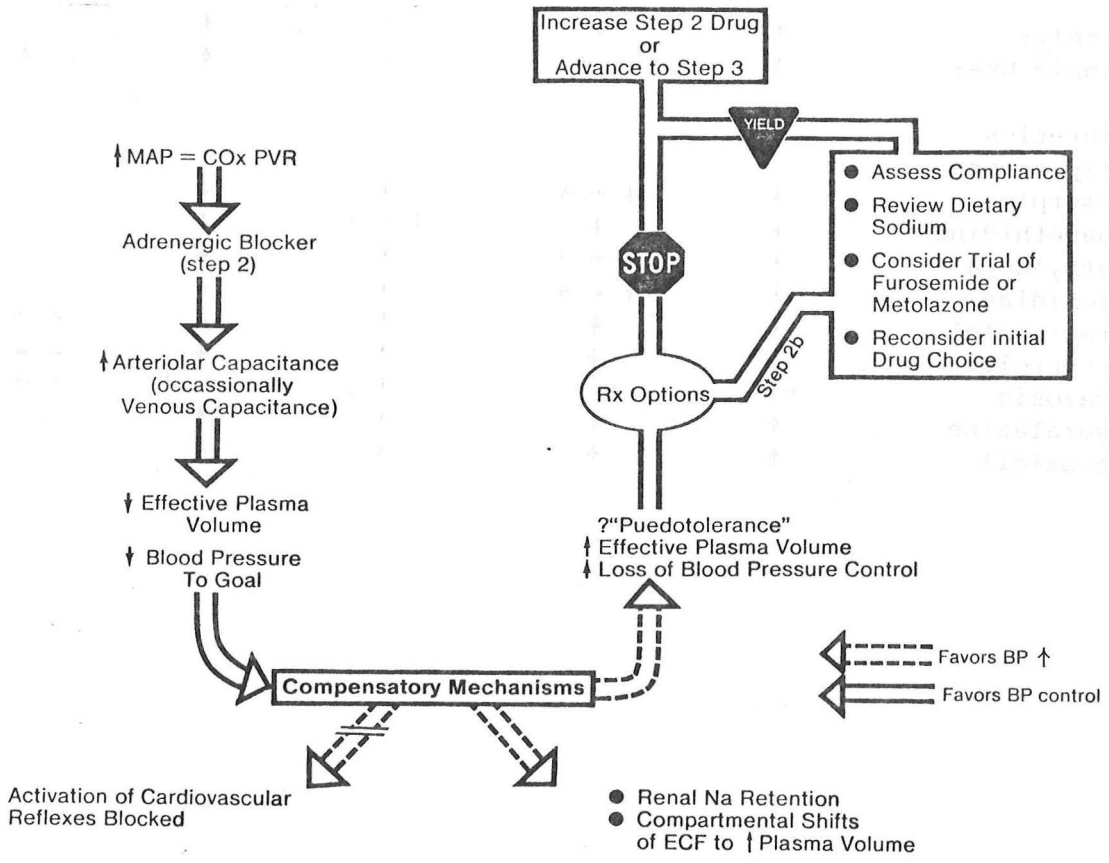
Though we usually think of pseudotolerance with Step II, III, IV drugs, diuretics do trigger compensatory mechanisms that may limit their clinical utility.

Diuretic agents initially induce a natriuresis with negative salt and water balance and a fall in plasma volume. These early changes are accompanied by a slight fall in cardiac output. Over the long term, a mild volume contraction remains while cardiac output tends to return to normal, coincident with a fall in peripheral vascular resistance (82). Plasma renin activity rises with diuretic therapy. In patients with borderline renal function, diuretics may cause a further decrease in GFR and enhance renal reabsorption of sodium and water. Thus, increased plasma renin and enhanced proximal reabsorption of sodium can overcome the antihypertensive effects of the diuretics (85). This pseudotolerance can be abolished by increasing diuretic dosage, changing to a diuretic with a more proximal site of action such as the loop diuretic furosemide or metolazone, cautiously combining two diuretics which act at different sites in the nephron, using an agent which will antagonize the effect of aldosterone (84), or suppressing renin release with adrenergic blocking agents. In truth, pseudotolerance with diuretic agents is rare; indeed, the diuretics are the cornerstones of our efforts to prevent pseudotolerance.

Step 2 and Step 4 (guanethidine)

The major sympatholytic drugs produce complex changes in hemodynamics which tend to limit their effectiveness when used alone. The commonly used drugs cause a decrease in heart rate, a mild decrease or no change in cardiac output, and a fall in peripheral vascular resistance. In addition, the sympatholytics block renin release. Unfortunately, however, when used alone they tend to cause an increase in ECF, including plasma volume. Dustan (85) demonstrated that in the treated patient intravascular volume and blood pressure tended to vary directly, whereas in the untreated patient there is generally an inverse relationship. They found normal or expanded plasma volumes in patients who had responded poorly to combined adrenergic blockers and diuretic therapy. Intensified diuretic therapy tended to restore blood pressure control and to reduce plasma volume below normal. Weil (86) was able to demonstrate that the changes in plasma volume occurring with guanethidine therapy could occur in the absence of sodium retention and appeared to be caused by changes in venous compliance. These changes presumably allow a shift in volume from the interstitial compartment of the ECF to the intravascular compartments. This expansion of the plasma volume, in some cases compounded by absolute sodium retention, accounts for pseudotolerance to the sympatholytic agents. These effects can be blocked by intensified diuretic regimens.

FIGURE 15:



This tendency to plasma volume expansion explains the poor blood pressure control usually seen when Step 2 drugs are used alone. Beta blockers and prazosin have less tendency to cause volume expansion and pseudotolerance, and thus in some cases may be effective monotherapy for hypertension.

COMPENSATORY MECHANISMS INDUCED BY VARIOUS ANTIHYPERTENSIVE AGENTS

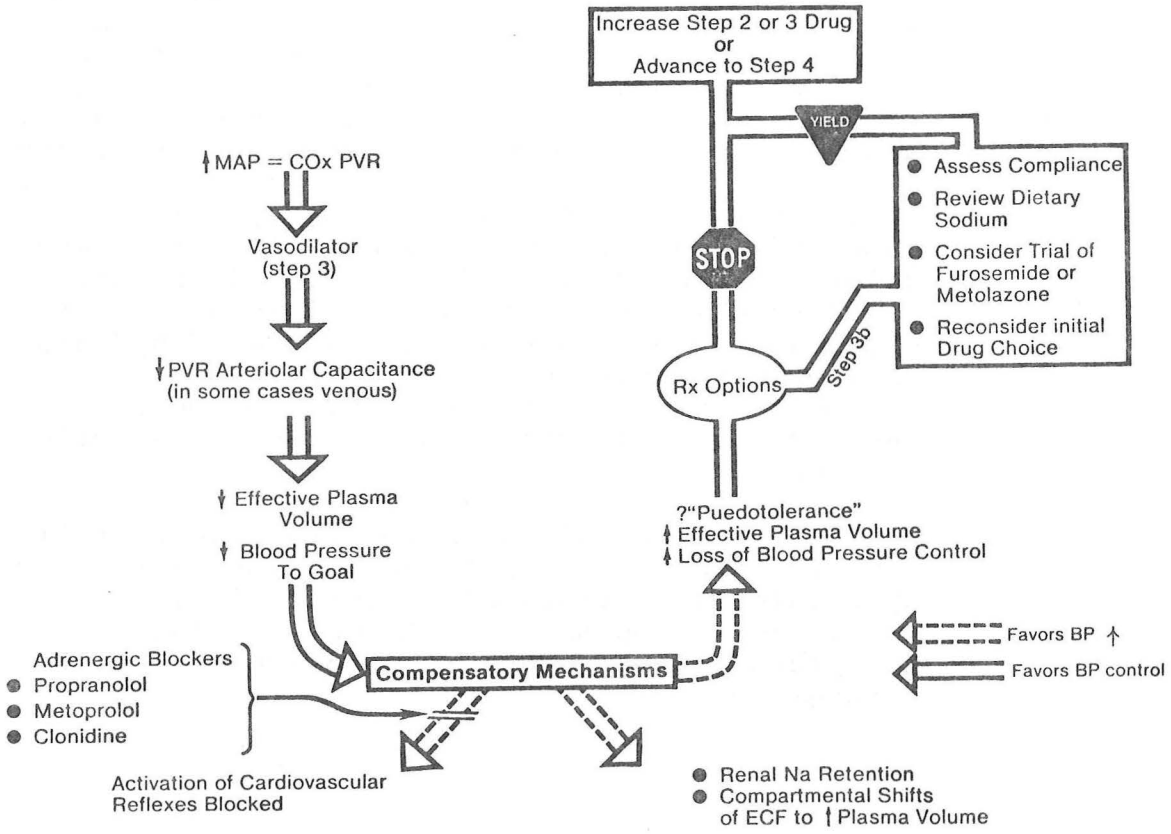
	Heart Rate	Cardiac Output	PVR	Plasma Renin	Plasma Volume
1) Diuretics (Step One)					
Acutely:	±	↓	↑	↑	↓
Chronic Use:	±	← →	↓	↑	↓ ← →
2) Nondiuretics					
Antipressors					
.Reserpine	↓	↓ ← →	↓	↓	↑
.Guanethidine	↓	↓	↓ ← →	↓	↑
.Methyldopa	↓	↓ ← →	↓	↓	↑
.Clonidine	↓	↓ ← →	↓	↓	↑
.Propranolol	↓	↓	↑	↓	← → or sl. ↑
.Metoprolol	↓	↓	↑	↓	← → or sl. ↑
.Prazosin	← →	← →	↓	← → ↓	← → or sl. ↑
.Hydralazine	↑	↑	↓	↑	↑
.Minoxidil	↑	↑	↓	↑	↑

Step 3

The vasodilating drugs such as hydralazine, diazoxide and minoxidil invoke multiple compensatory responses when used alone. These drugs promote fluid retention and volume expansion, and are potent stimuli for renin release (87) and reflex sympathetic stimulation (88). Though any of these factors could potentially limit blood pressure fall, it appears that stimulation of cardiac output and heart rate may be the most deleterious influence (84).

These effects may be blocked by effective diuretic therapy and adrenergic blockade, thus providing the rationale for combining Step 1, 2 and 3 drugs in severe or resistant hypertension. Though drug combinations of hydralazine and a diuretic exist, most patients will need a sympatholytic agent as well to block renin release and reflex sympathetic activity.

FIGURE 16:



Summary

It can be seen that each major class of antihypertensive drug calls into play compensatory hemodynamic, renal and sympathetic responses which tend to limit effectiveness of the drugs in question. Intensive diuretic therapy, with careful attention to the choice of the proper agent for each patient is the cornerstone of our efforts to prevent pseudotolerance and avoid needlessly escalating the antipressor regimen form Step 2 to Step 3 or 4.

The following conclusions can be made about the phenomenon of pseudotolerance:

1. Loss of control of blood pressure in patients initially well-controlled is often due to the development of pseudotolerance; this loss of control may be wrongly attributed to noncompliance.

2. In patients on sympatholytic agents, weight gain or edema may serve as clues to pseudotolerance. It should be emphasized, however, that expansion of plasma volume can occur without salt retention; shifts of fluid from the interstitial to the intravascular compartment are probably responsible. Enhanced diuretic regimens may reestablish blood pressure control and avoid more complicated therapeutic regimens.

3. In patients on vasodilating agents, weight gain, edema and tachycardia are clues to pseudotolerance. Often both diuretics and adrenergic blockers will be required to counteract these effects. In patients on high doses of hydralazine or minoxidil, metolazone or furosemide may be necessary to block plasma volume expansion and avoid come complicated therapeutic regimens.

4. Patients who cannot tolerate effective diuretic therapy because of hyperglycemia, hyperuricemia or hypercalcemia, propranolol, metoprolol, and prazosin appear to have less propensity for pseudotolerance and may provide effective monotherapy.

ADVERSE SIDE EFFECTS AND DRUG INTERACTIONS

Introduction:

While the importance of side effects and adverse drug reactions in limiting successful antihypertensive therapy have been overstated, a working knowledge of problems peculiar to each class of antihypertensive, and to different agents in each class, can allow the physician to better tailor the therapeutic regimen to the individual patient. To be maximally effective, the clinician must establish an open communication with his patients concerning side effects and adverse reactions which will allow the patient to identify problems and encourage their reporting. While a "trade-off" is often necessary to achieve good blood pressure control, the patient should not suffer needless side effects if effective alternative therapy is available. Because most potent antihypertensives have easily identifiable drug effects, the patient must realize the benefits of long-term therapy and his role in the therapeutic partnership. The term "adverse side effects" covers a number of problems coincident to any therapy. Important adverse effects may be behavioral, metabolic, related to sleep-arousal states, etc., or may directly refer to end-organ damage. These adverse side effects will be reviewed in detail.

Most patients on antihypertensive drugs have other major medical illnesses requiring various drug therapies. Since many drugs may interact to diminish the effectiveness and safety of antihypertensives, an adequate base of information concerning clinically important interactions will be presented. Some reported interactions are not likely to be clinically significant, therefore, this review will be directed at clinically relevant interactions.

A caution is necessary at this point prior to the discussion of adverse drug effects attributable to individual drugs. Blanc, et al (88B) reviewed 672 admissions to a general medicine service over a five month prospective period. One hundred and ten clinical manifestations considered possible adverse drug reactions were received. Of these, 42 were excluded because of inadequate documentation or because they failed to meet the definition of an adverse reaction. The 68 remaining cases were independently submitted to three pharmacologists who then tried to establish

cause and one of five degrees of probability for the reaction. Of the 68 reactions, 54 were considered as certain or probable by at least two observers, yet only 27 of these reactions were attributed to the same drug by all three observers (40% of the total reactions, and only 25% of the total events reported).

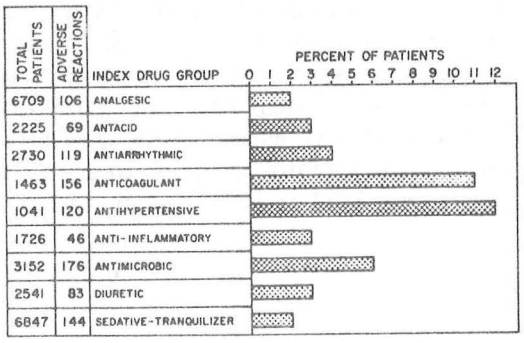
Difficulties have also arisen in two similar studies. Koch-Weser, Sellers, and Zaust (88C) rejected 154 of 500 reactions because of the disagreement of one of three clinical pharmacologists consulted. Of 346 remaining reactions, complete agreement as to the responsible drug could be reached in only 63% of the cases. Karch, et al (88D) submitted 60 reactions (due to drugs or alcohol) to three clinical pharmacologists and a unanimous judgement was rendered in only 50% of the cases.

Letters to the editor and poorly documented case reports often help establish a negative "word association" for a given drug. These communications serve as warnings to the prescriber but must be taken with a grain of salt, (so to speak).

Diuretics - Adverse Metabolic Consequences:

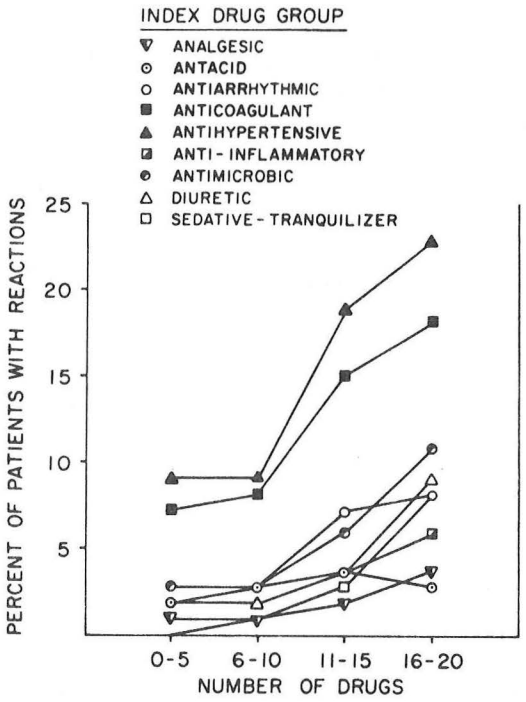
Many hypertensive patients (30-40%) can be adequately controlled by a diuretic alone; additionally, patients requiring a postganglionic blocker, beta blocker, central sympatholytic, or vasodilator exhibit a synergistic therapeutic response from diuretic therapy. These agents, compared to nondiuretic antihypertensives, enjoy a relatively low incidence of side effects severe enough to require physician discontinuation of therapy or cause patient noncompliant behavior (89), and diuretics display fewer drug interactions when multiple medications must be administered (90) (Figures 17 and 18).

FIGURE 17: PERCENTAGE OF PATIENTS WHO EXPERIENCED ADVERSE DRUG REACTIONS IN THE HOSPITAL BY INDEX DRUG GROUP.



May, Stewart and Cluff
Clin Pharm Ther 22:322, 1977

FIGURE 18: RATE OF ADVERSE DRUG REACTIONS BY NUMBER OF DRUGS FOR EACH INDEX GROUP



May, Stewart and Cluff
Clin Pharm Ther 22:322, 1977

Many thiazide diuretics are available and the various formulations yield products of similar clinical efficacy, the most important difference between agents being the therapeutic half-life. The site of action of each drug in this class is the cortical diluting segment; a proximal tubule effect is present but insignificant except in the case of metolazone (91, 92). Each drug appears to lower blood pressure by causing sodium depletion and reduction of extracellular fluid and plasma volumes (93). Furosemide, a "loop diuretic", with its major site of action in the ascending limb of Henle's loop, is an effective antihypertensive agent, particularly useful in patients on adrenergic blockers or vasodilators who have developed plasma volume expansion (94) and in patients with renal insufficiency (95, 96). As would be expected, a number of adverse reactions

are shared by the thiazides and furosemide. Volume depletion with azotemia, hypokalemia, hyperuricemia, hyponatremia (97), hyperglycemia and hyperlipidemia (98, 99) may occur with either drug. Hypokalemia is less common with furosemide and hypocalcemia instead of hypercalcemia may occur. Furosemide may cause hypochloremia which is not a feature of thiazide administration.

TABLE 17: A SUMMARY OF THE ADVERSE METABOLIC CONSEQUENCES OF DIURETIC THERAPY

	Thiazides	Ticrynafen	Furosemide
.Volume depletion with azotemia	+	+	++
.Hypokalemia	++	++	+
.Hyponatremia	+	+	+
.Hypochloremia	-	-	+
.Hyperuricemia	++	-*	+
.Hyperglycemia	+	+	+
.Hyperlipidemia	+	?-	±
.Cholesterol Elevation	+	?-*	±
.Hypercalcemia	+	+	-

*See Ref. 103

In the usual patient, these effects are rarely significant enough to require cessation of therapy, however, they may be poorly tolerated in patients with diabetes, gout or hyperparathyroidism. Less commonly, nausea, vomiting, weakness, orthostasis, dry mouth, dermatitis and photosensitivity may develop. Very rarely, hemolytic anemia, pulmonary edema, blood dyscrasias and pancreatitis have been reported. With furosemide, ototoxicity, usually transient, has followed large intravenous doses. Very rarely have anaphalactoid reactions been mentioned. Many listed complications of both of these diuretic classes represent a single or small number of cases.

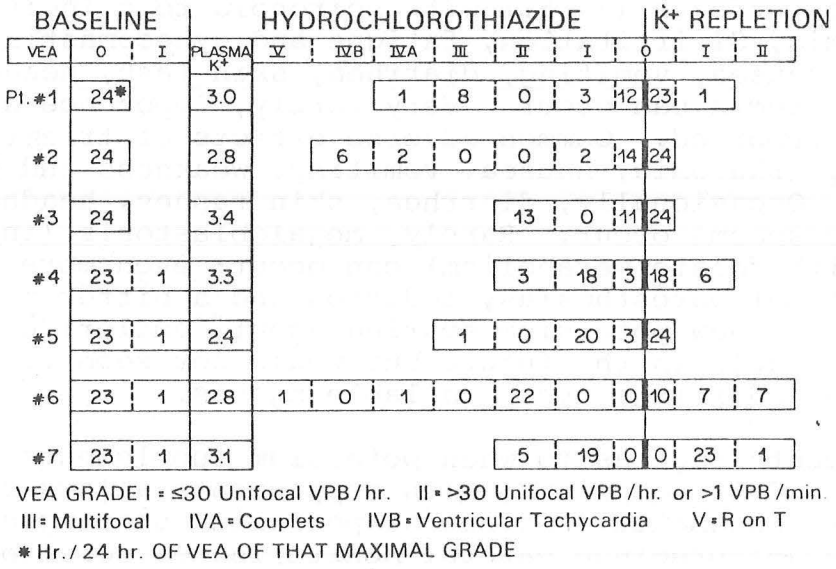
The potassium sparing diuretics commonly used in this country include spironolactone and triamterene. Both work

in the distal tubule, but at different sites. By comparison, these drugs are weak natriuretic agents most commonly used in combination with a thiazide diuretic. Triamterene alone is not considered an effective antihypertensive agent. Common side effects (> 5%) with spironolactone include hyperkalemia, GI irritation, fatigue and gynecomastia. Less commonly, nausea, vomiting, diarrhea, skin rash, headache and hyponatremia can occur. Very rarely, impotence and drug fever are reported. Common adverse effects of triamterene include hyperkalemia, nausea, vomiting, weakness and hyperuricemia. Occasionally, diarrhea, skin rashes, headaches, and muscle spasms occur. Rarely, megaloblastosis (interference with folate metabolism) can occur; even more rare are reports of paresthesias, sedation and a bitter taste in the mouth. A new potassium sparing agent, amiloride (100), may be available in the future but would not seem to offer significant advantage over available agents.

Arguments rage as to when potassium supplements should be given, and if compliance with supplements allows for adequate replacement. The use of potassium sparing diuretics does not preclude careful monitoring of serum potassium; in fact, since hyperkalemia is more lethal than modest potassium depletion, even closer monitoring is necessary. These agents should not be used with potassium supplements, with each other, or in patients with even mild renal insufficiency.

Holland, et al (101) has recently presented data that will force a closer look at diuretic-induced hypokalemia and its contribution to ventricular ectopy and possibly to sudden death. Figure 19 represents ventricular ectopic activity (VEA) developing in 7 of 21 patients with uncomplicated essential hypertension and normal baseline 24-hour ambulatory Holter monitoring. Monitoring was repeated after the development of hypokalemia during treatment with HCTZ 50 mg B.I.D. and again after potassium repletion and spironolactone. The lowest serum potassium level and the maximal grade of VEA, as well as the number of hours of this grade, during the individual 24-hour periods is depicted. Further studies concerning hypokalemia and cardiac arrhythmias are clearly warranted.

FIGURE 19: VEA GRADE AND DURATION VS POTASSIUM STATUS ON DIURETIC THERAPY



A uricosuric diuretic called ticrynafen has been recently released by the FDA. This drug is equivalent to HCTZ as an antihypertensive agent (Figure 20) and they share similar durations of activity (101-103). Patients initially receiving this drug must be well-hydrated and off of previous diuretic therapy for three days to avoid potential problems with uric acid stone formation. Since the diuretic response parallels the uricosuric response, this likely will not be a significant clinical problem during chronic administration(Fig. 21)

FIGURE 20: BLOOD PRESSURE, SUPINE. LAST DAY OF WASHOUT PERIOD IS DAY 0 OF ACTIVE THERAPY. SOLID LINE INDICATES HYDROCHLOROTHIAZIDE THERAPY: DOTTED LINE, TICRYNAFEN

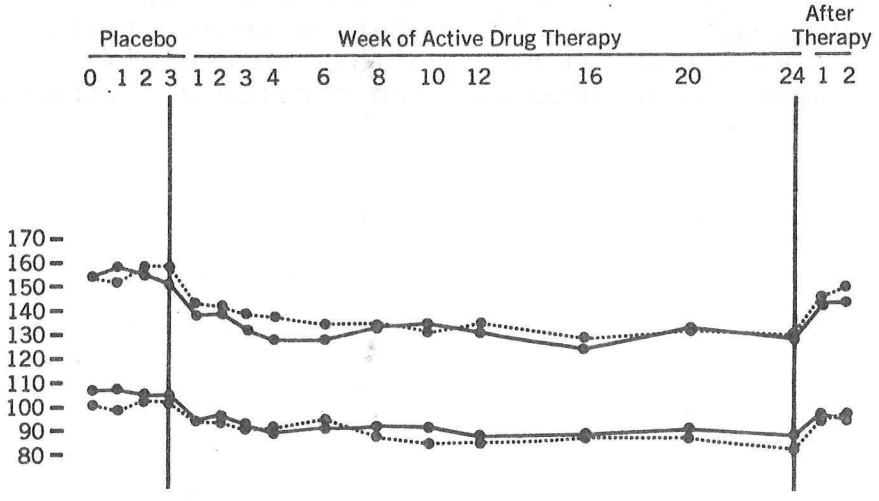
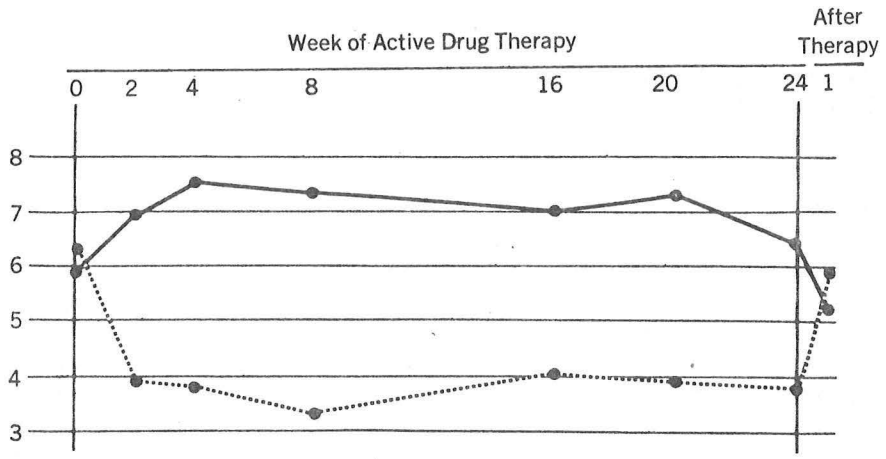


FIGURE 21: URIC ACID LEVELS, MG/DL. LAST DAY OF PLACEBO IS FIRST DAY OF ACTIVE THERAPY. SOLID LINE INDICATES HYDROCHLOROTHIAZIDE THERAPY; DOTTED LINE, TICRYNAFEN



Diuretics - Drug Interactions

Drug interactions with diuretics may be beneficial as in the synergistic antipressor response achieved with diuretics and adrenergic blockers or vasodilators. Also, thiazides and furosemide may be used with potassium sparing diuretics to reduce potassium loss while providing a modicum of synergism for natriuresis. Most other drug interactions with diuretics are deleterious.

A. Thiazide Diuretics

1. With indomethacin (Indocin®) It has been recently demonstrated that the administration of indomethacin to patients on either thiazides or furosemide leads to substantial decreases in salt and water excretion. Brater (104) found that the administration of indomethacin to patients on 1 gm chlorothiazide led to an average 35-40% reduction in sodium excretion over an eight hour period (105). The test dose of indomethacin was large, 100 mg. Other authors have reported similar results using doses of indomethacin commonly utilized in clinical practice (106). As of yet, it is not known whether increasing the dose of diuretic will overcome this effect, or whether the effect persists beyond the first few hours

or days of indomethacin administration. If patients on thiazides or furosemide are to be placed on indomethacin, it would seem prudent to follow weight and blood pressure control closely.

2. With digitalis - Depletion of potassium and magnesium may predispose the patient to digitalis toxicity at significantly lower serum digoxin levels (107, 108, 109).

3. With lithium carbonate - Diuretic agents reduce the renal clearance of lithium and thus elevate its blood levels. Toxicity may occur on doses previously producing therapeutic blood levels. Any patient on lithium who must take diuretics should be followed closely with serum lithium levels until a steady state is reached. Careful observation in the steady state period is still necessary since sodium intake and other antihypertensives can affect lithium balance (110, 111). Recently, in a study using normal volunteers, hydrochlorothiazide administration for two weeks, 50 mg per day, caused a significant rise in serum lithium levels, whereas furosemide, 40 mg per day did not (112).

4. With Warfarin Compounds - Thiazides diminish the effectiveness of coumadin and larger doses may be required to achieve the desired anticoagulant effect (113). Withdrawal of thiazides may then result in greatly prolonged clotting times and frank bleeding episodes.

5. With corticosteroids, the potassium wasting qualities of the thiazides are potentiated (114).

6. With diazoxide (HyperStat®), the hyperglycemic tendencies of both drugs seem to be enhanced (115).

Less common adverse interactions include those with succinylcholine or tubucurare (enhanced effect of neuromuscular) blockers (116), with norepinephrine (diminished response to pressors), (117) and with colestipol (diminished absorption of thiazide if administered concurrently) (118).

B. Furosemide (Lasix®)

Furosemide shares interactions 1, 2, and 3 above with the thiazide diuretics, as well as the interactions with skeletal muscle relaxants, norepinephrine and corticosteroids. Unique interactions include:

1. With salicylates - Furosemide competes with salicylates for the same renal tubular excretory site. Thus, the concomitant administration of furosemide and high doses of salicylates (12 to 16 gms/day) may lead to unusually high levels of salicylates and toxicity (119). Patients felt to require both drugs should have salicylate levels measured frequently until a steady state is achieved. The onset of tinnitus which occurs frequently at serum salicylate levels greater than 35 mg% may serve as a guide to toxicity.

2. With cephloridine (Loridine®) and gentamicin (Garamycin®) - Furosemide has been reported to potentiate nephrotoxicity associated with cephloridine (120) and to actually prolong gentamicin's plasma clearance which could result in toxicity (121).

3. With probenecid (Benemid®) - Onset of furosemide natriuretic effect may be blunted while the duration of activity is extended, hence the total diuretic response is not adversely changed and may even be greater over an eight hour period (122, 123).

4. With metolazone (Diulo® or Zaroxolyn®) and furosemide, the natriuretic qualities of both drugs are remarkably enhanced (124). Even in patients with massive edema and renal insufficiency, careful hemodynamic monitoring and frequent determinations of serum potassium are necessary to avoid complications. The most serious complications include: severe hypokalemia, alkalosis, volume contraction, etc. This may set the stage for cardiac arrhythmias and pulmonary embolism.

5. Chloral hydrate when used with furosemide may cause chaotic blood pressure, diaphoresis, hot flashes and uneasiness (125). Their concomitant use should be discouraged. This reaction has not occurred with furosemide and flurazepam (Dalmane®).

6. Clofibrate (Atromid-S®) and furosemide utilized in hyperlipoproteinemic patients with the nephrotic syndrome resulted in excessive diuresis, muscle aches, and stiffness (126).

C. Spironolactone

1. With digoxin - Spironolactone may lead to unexpectedly high serum digoxin levels because the renal secretory pathway which accounts for a significant portion of total digoxin excretion is blocked by this drug (127, 128).

2. With potassium supplements - Marked, and even fatal hyperkalemia may occur.

3. With salicylates - Administration of only two 5 grain aspirins per day with spironolactone may result in a markedly reduced natriuresis (about 30%) (29). As with the thiazide or furosemide and indomethacin interaction, it is not known whether this effect can be overcome with time or increased diuretic dosage.

4. Spironolactone, like thiazides and furosemide, may decrease vascular responsiveness to norepinephrine which may be of importance, especially when a patient must be subjected to general or regional anesthesia.

5. Spironolactone used with other diuretics may potentiate the chance for hyponatremia.

D. Triamterene

1. With potassium supplements - Marked, and even fatal hyperkalemia may occur.

2. With ticrynafen (Selacryn®) - BUN elevations have been noted and the manufacturer cautions against concomitant use. These two drugs are also incompatible from a medicinal chemistry standpoint.

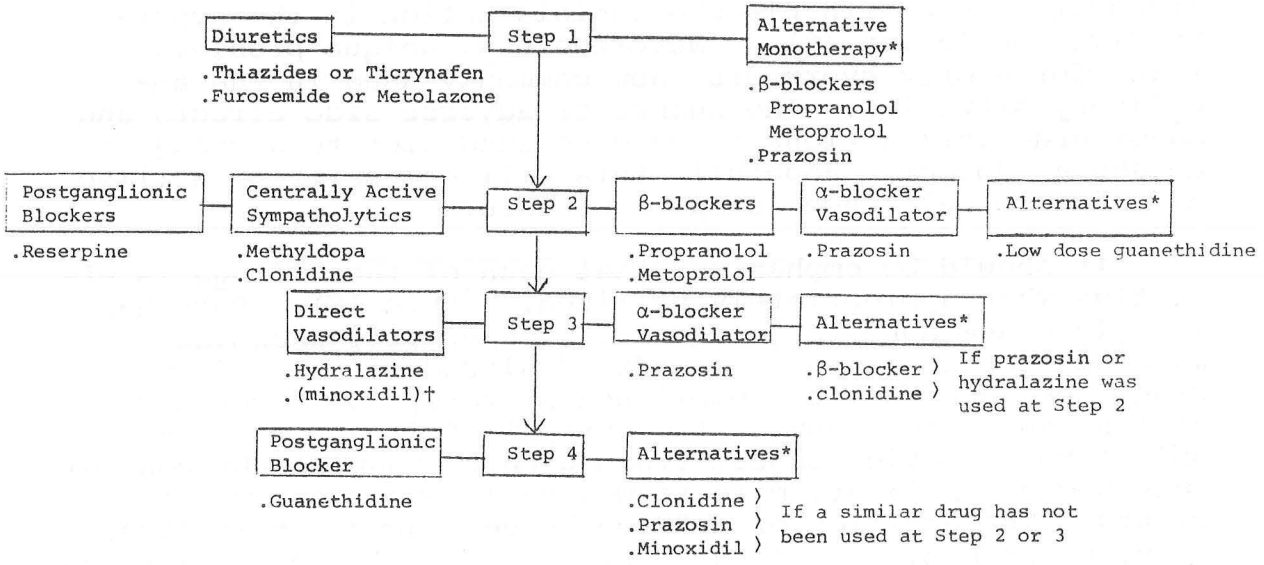
Nondiuretic Antipressor Agents (Part II)

Many of the side effects associated with various nondiuretic anti-pressor agents are similar and some are frequently seen with placebo administration in the hypertensive population (6). Nevertheless, unique problems exist for nearly every drug now commonly used in the ambulatory situation. The number of adverse side effects and major drug interactions to be discussed dictate a change to a tabular format. Hopefully this will be easier to utilize as a future reference for patient care.

It should be emphasized that each of these drugs is effective when appropriately utilized. (Table 18). Each has its place and none is "out-dated", especially when the approach to the patient is individualized for secondary diagnoses, occupation, compliance history, socioeconomic status, age, etc. Any of the "Step Two" drugs, with an effective diuretic, should yield greater than an 80% control rate among compliant, mild to moderate, hypertensive patients. The addition of a "Step Three" agent, or if necessary, guanethidine, a "Step Four" drug, will capture all but a rare patient, even if he has severe hypertension. The rate limiting factors in this last population include poor compliance, collagen-vascular disease, missed secondary forms of hypertension, or progressive renal parenchymal disease.

In the following section, each drug's mechanism of action will be described, and a table will follow to summarize points with which the clinician should be familiar. With the wide array of potent antipressor agents now available, effective therapy can be tailored to fit the individual patient's and physician's needs.

TABLE 18: STEP THERAPY OF HYPERTENSION



*Alternatives not necessarily recommended by the Joint National Committee on Detection, Evaluation and Treatment of Hypertension

†Release by the FDA anticipated shortly.

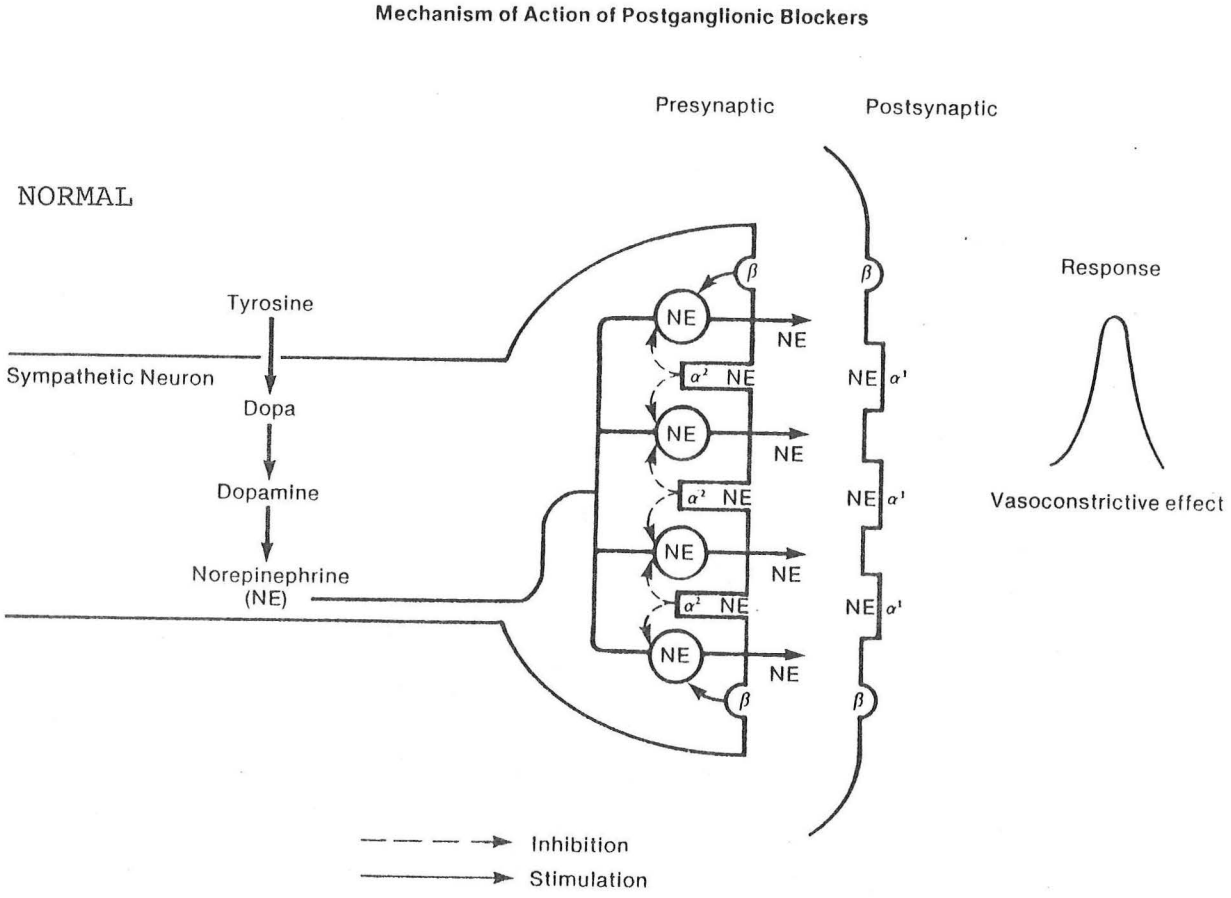
NONDIURETIC ANTIPRESSOR AGENTS:

I. Postganglionic Blocking Agents:

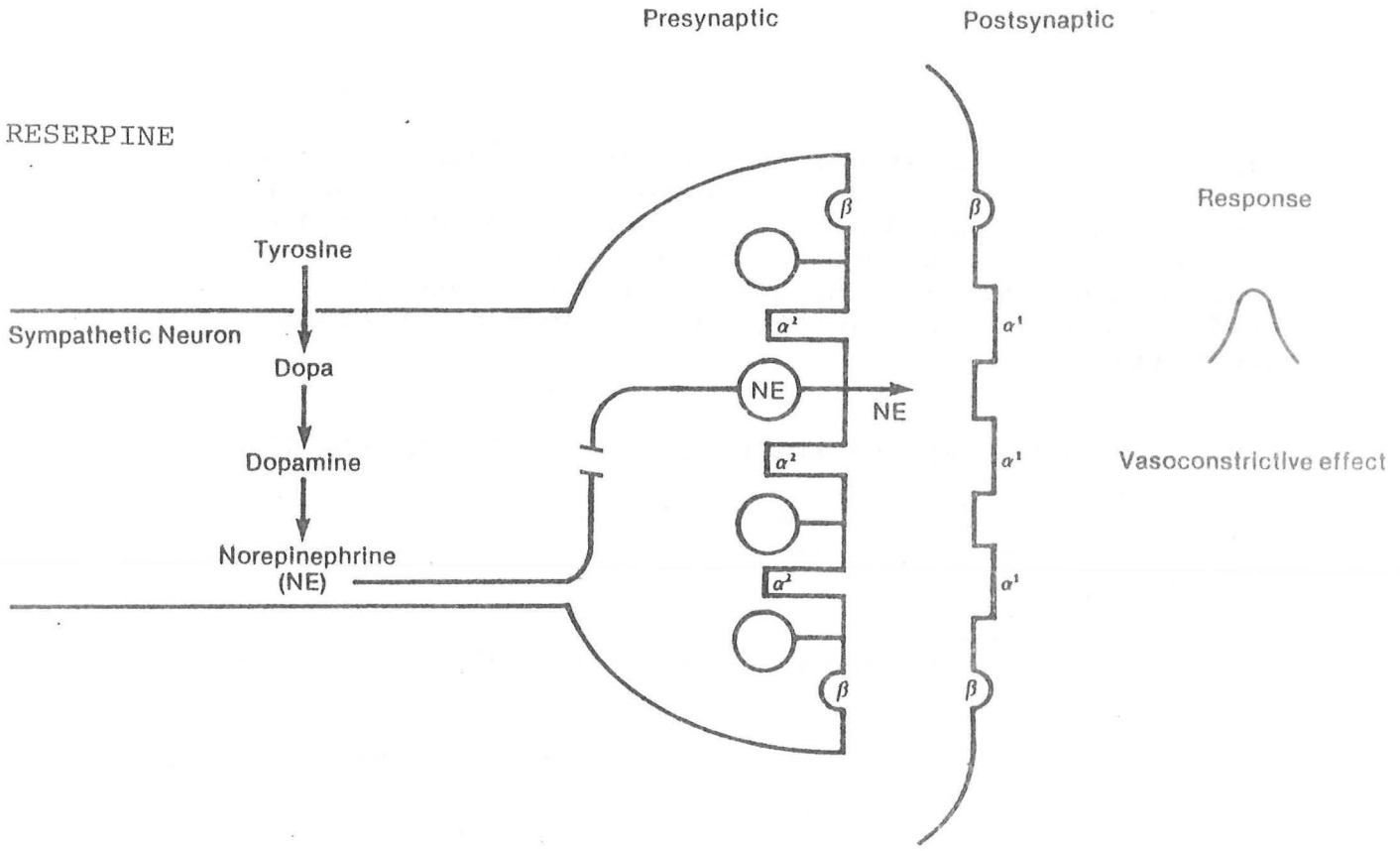
Reserpine and other rauwolfia alkaloids prevent the binding of norepinephrine (also serotonin and dopamine) in the granular pool, which leads to cytoplasmic degradation of the neurotransmitter by mitochondrial monoamine oxidase (130). Depletion of these neurotransmitters occurs in the central and peripheral nervous systems accounting for this drug's major side effects. Guanethidine interferes with norepinephrine release in peripheral sympathetic nerves and also causes norepinephrine depletion (31). The drug is taken up by the same amine-"reuptake" mechanism that terminates the action of norepinephrine after physiological release. The drug is then stored in norepinephrine storage vesicles replacing neurotransmitter by concomitant release.

Guanethidine has no effect on the adrenal medulla and seems to exert its antihypertensive action mainly by interfering with neurotransmitters at the adrenergic postganglionic nerve terminals, thus decreasing arteriolar vasoconstriction. Drugs that block norepinephrine reuptake (tricyclic antidepressants) also block guanethidine's antipressor effect (132).

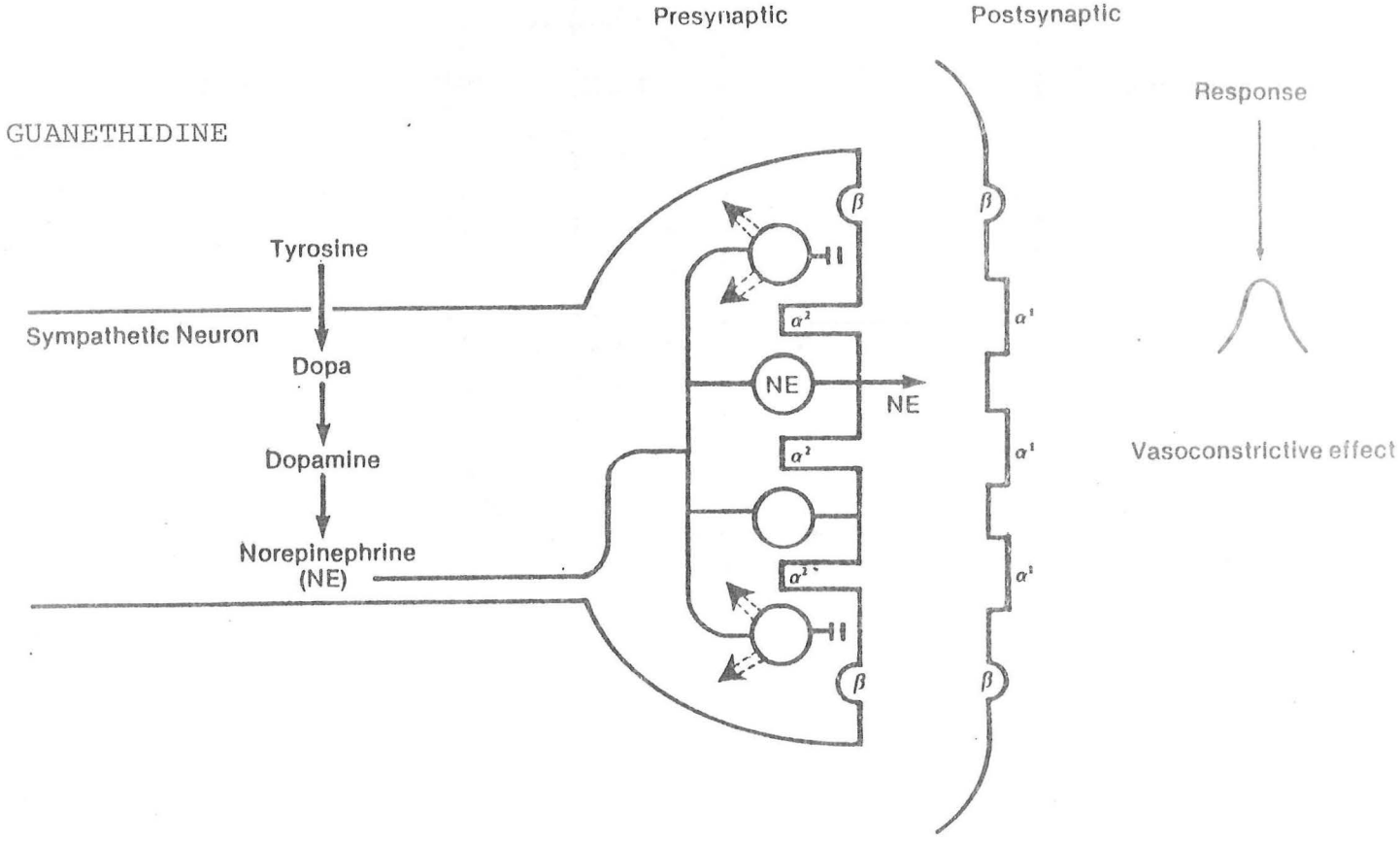
FIGURE 22: MECHANISM OF ACTION OF RESERPINE AND GUANETHIDINE



Continuation of Figure 22



Summary: Norepinephrine transport into storage granules is blocked eventuating in neurotransmitter depletion.



Summary: Norepinephrine exit from the storage pool is blocked; neurotransmitter depleted (replaced with drug).

I. Postganglionic Blocking Agents:

A. Drug and Dose: Reserpine (Step II) 0.1 to 0.25 mg

Advantages: Inexpensive
Single daily dose

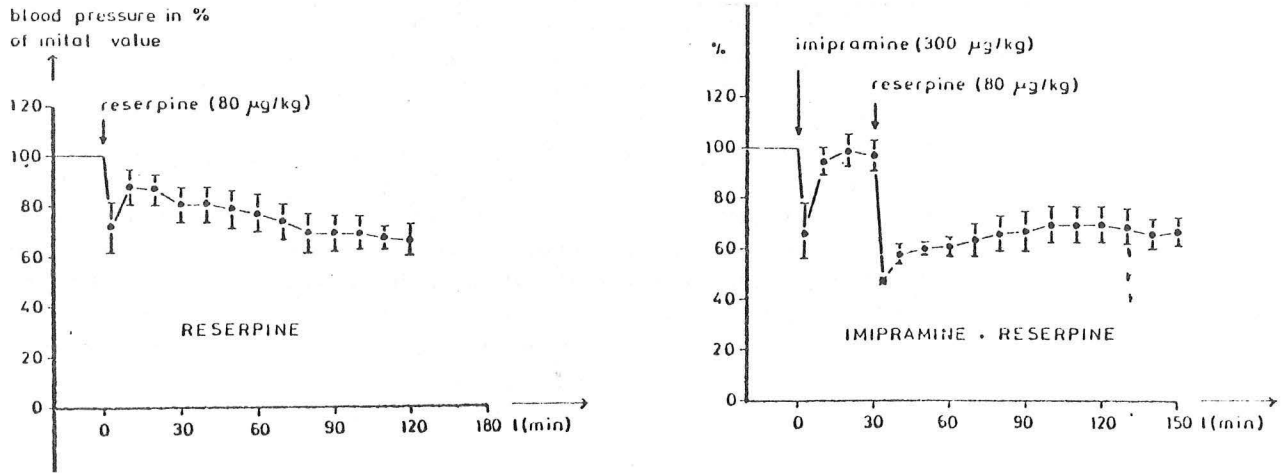
Adverse Effects: Minor:
- Lethargy
- Lassitude
- Diarrhea
- Nasal Stuffiness
- Dry Mouth
- Impotence

Major:
- Bradycardia (rarely AV conduction delay)
- Activation of peptic ulcer disease (133)
- Parkinsonism
- Depression (134)
- Breast and visceral tumors? (135, 136)

Medical Contraindications: Past or present history of:
- Peptic ulcer disease
- Parkinsonism
- Depression
- During electroconvulsive therapy

Major Drug Interactions:
plus:
-MAO inhibitors = CNS excitation and worsening of hypertension (137)
-Anesthesia, general = Hypotension (138, 139)
-Levodopa = Antagonism of anti-Parkinsonism effect (140)
-Ephedrine = Adrenergic effect decreased because of norepinephrine depletion
-Tricyclic antidepressant = May result in transient hypotension (141)

FIGURE NO. 23: INTERACTION BETWEEN RESERPINE AND TRICYCLIC ANTIDEPRESSANTS (REF. NO. 141)



B. Drug and Dose: Guanethidine (Step IV-Ocassionally Step II)
10 mg to 150 mg

Advantages:
Relatively inexpensive
Very potent
Single dose

Adverse Effects:

Minor:
- -Weakness
- -Diarrhea
- -Nasal Stuffiness
- -Retrograde ejaculation
- -Impotence

Major:
- -Bradycardia
- -Exercise and orthostatic hypotension
- -Decreased cardiac output and fluid retention may result in CHF
- -May aggravate bronchial asthma

Medical Contraindications:
- .Known or suspected pheochromocytoma
- .Congestive heart failure
- .Hypersensitivity

Major Drug Interaction:

plus:

Reserpine = Very little synergism except for side effects of increased postural hypotension, bradycardia and depression

MAO inhibitor = Hypertensive crisis (contraindication) (142)

General anesthesia = Hypotension (143, 139)

Alcohol = Exaggeration of orthostatic hypotension

Amphetamines, ephedrine or methylphenidate = Neuronal blockade induced by guanethidine is antagonized causing blood pressure elevation (144). More dangerous however, is the possibility of inducing cardiac arrhythmias (145).

Over-the-counter sympathomimetics or decongestants, (Phenylpropranolamine, phenylepherphine, etc.) = may result in a hypertensive episode (144).

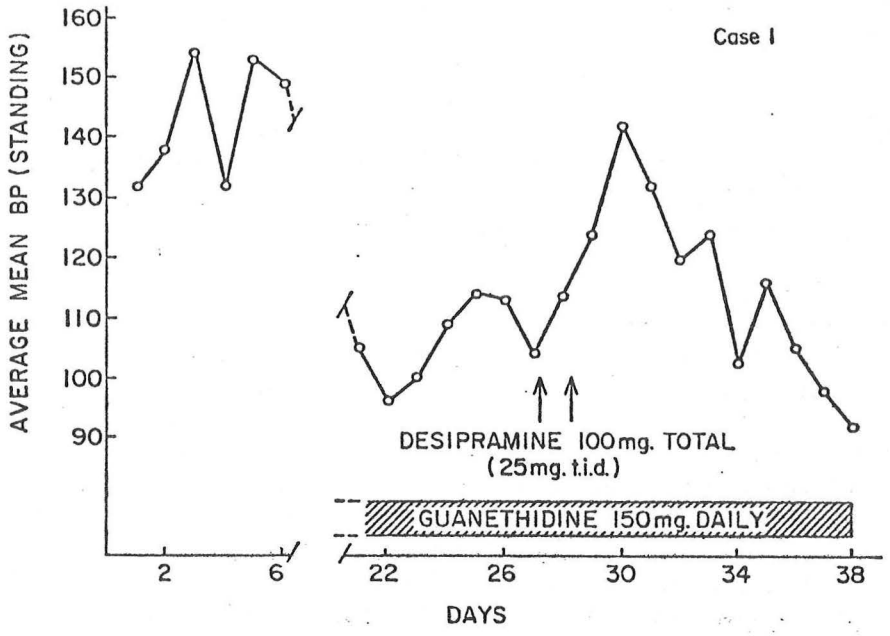
Phenothiazines = Reduction in antipressor effect (146)

Tricyclic antidepressants (two possibilities)

Norepinephrine uptake pump is blocked, therefore, guanethidine cannot reach its storage site, blood pressure control is lost (132).

If both drugs have been given together for a prolonged time, guanethidine, while still ineffective, may be present in large amounts since tricyclics partially inhibit guanethidine's hepatic metabolism. In this situation, if the interaction is recognized and the tricyclic suddenly stopped, relieving the block at the norepinephrine reuptake pump, the equivalent of a guanethidine overdose could result (147, 148). Guanethidine should be stopped for 2 to 3 weeks prior to discontinuation of the tricyclic antidepressant.

FIGURE 24: CLINICAL INTERACTION BETWEEN GUANETHIDINE AND TRICYCLIC ANTIDEPRESSANTS RESULTING FROM BLOCKADE OF THE NOREPINEPHRINE REUPTAKE PUMP



-Mitchell, et al.
JAMA 202:975, 1967

II. Centrally Acting Sympatholytics

Methyldopa is metabolized to alpha-methyl-norepinehrine which can be stored in sympathetic nerve endings (displacing norepinephrine) and serve as a "false neurotransmitter". The fact that this metabolite is still a vasoconstrictor suggests that another mechanism of action is operative (149). It is now believed that this metabolite exerts its antipressor effect in much the same way as clonidine, by stimulating alpha-adrenergic inhibitory CNS pathways (α_2) thereby reducing sympathetic outflow from the central nervous system (150) (Fig 25). Clonidine when injected intravenously causes a transient rise in blood pressure, followed by a prolonged antipressor effect. The initial rise in blood pressure is caused by clonidine's peripheral vasoconstrictor effect which can be prolonged in the experimental animal by "pithing" to abolish any central

effect (144). The vasoconstrictor effect of either drug is not operative in ordinary clinical usage unless a β-blocker is concurrently employed (151, 152). The enhanced peripheral effect induced by β-blockade may diminish the central antipressor effect of clonidine (152) and most likely methyldopa.

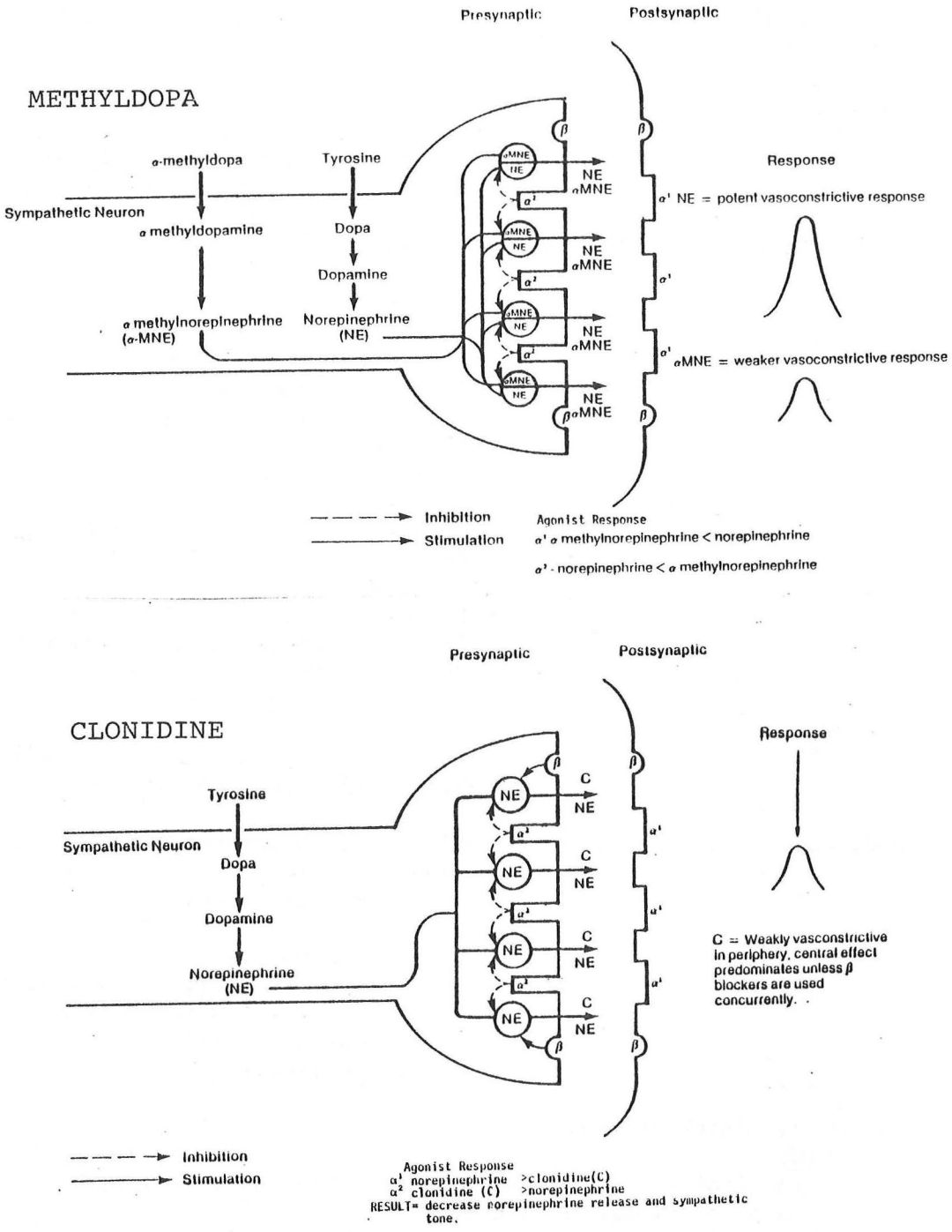
Tricyclic antidepressants are apparently agonists for this alpha receptor system as well. When used with either methyldopa or clonidine, the antipressor effects are blunted, as are the peripheral vasoconstrictor effects of clonidine in the "pithed animal model" (141).

One other agonist for this receptor system is a new drug, guanabenz, which also has a guanethidine-like adrenergic neuronal blocking action (153, 154). Abrupt cessation of methyldopa (155-159), clonidine (160-163) and guanabenz (164) may cause withdrawal symptoms characterized by agitation, tremor, headache, abdominal pain, insomnia, palpitations and malaise. Of interest, extreme agitation has even been reported after tricyclic antidepressant withdrawal (165). Rarely, blood pressure may rapidly return to, or surpass, pretreatment values. Two prospective studies (166, 167) failed to demonstrate significant "overshoot" of blood pressure with abrupt cessation of clonidine in doses commonly used in clinical practice although withdrawal symptoms occurred in a minority of patients. Recently, it has been shown that clonidine will markedly decrease the withdrawal symptoms of addicts previously maintained on methadone (168). The drug stimulates "autoreceptors" (CNS inhibitory pathways) in the locus ceruleus attenuating the extreme adrenergic responses seen in narcotic withdrawal. This effect is not blocked by the narcotic antagonist, naloxone.

Methyldopa lowers renins to some extent while clonidine suppresses renin rapidly and to as great an extent as do β-blockers (169).

Interesting uses for clonidine, not yet cleared by the FDA include prophylaxis for migraine headache (170) and postmenopausal "hot flashes" (171).

FIGURE 25: MECHANISMS OF ACTION OF CENTRALLY ACTIVE SYMPATHOLYTICS



α_1 (post-synaptic receptor system) - Stimulation = Vasoconstriction

α_2 (Presynaptic receptor system*) - Stimulation = Inhibition of sympathetic outflow.

*This is a functional and not truly an anatomical classification, since these receptors may be post synaptic (?).

II. Centrally Acting Sympatholytics:

A. Drug and Dose: Methyldopa (Step II) 250 mg to 3 Gms (in 2 to 4 doses)

Advantages:
-Familiarity
-Can be given B.I.D.
-Maintains renal and cerebral blood flow
-Can be given as a parenteral by IV infusion

Adverse Effects:

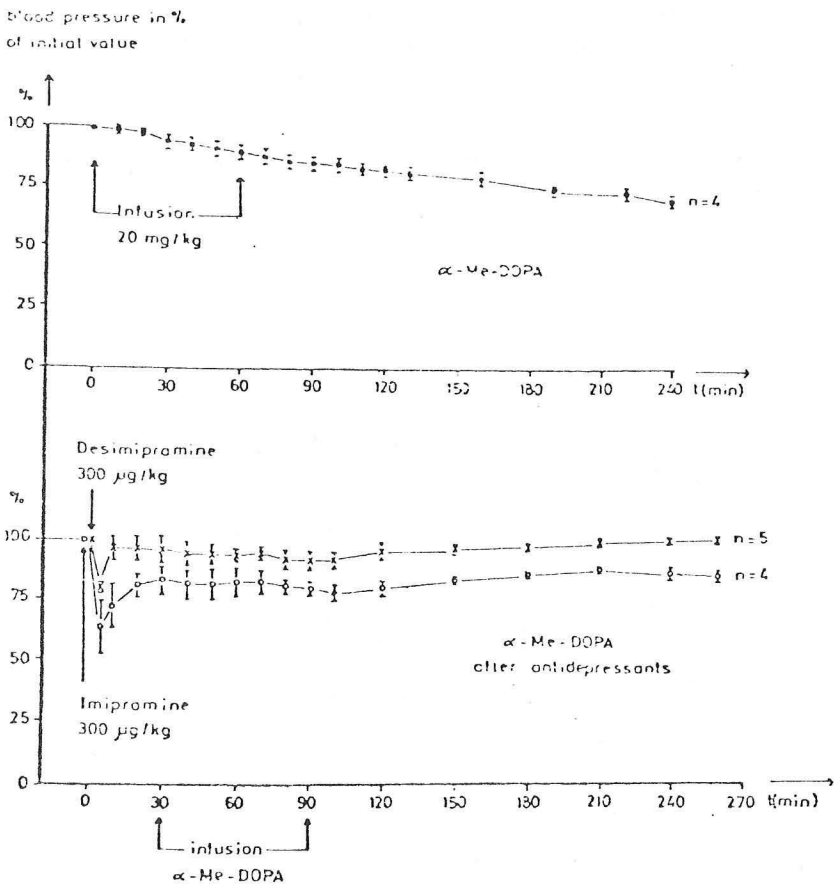
Minor:
-Sedation
-Lethargy
-Dry mouth
-Impotence
-Rarely nasal stuffiness
-+Direct Coombs test (172)
-Interferes with SGOT determination on SMA
-Fluid retention

Major:
-Hyperprolactinemia and lactation (155)
-Bradycardia
-Orthostatic hypotension
-Depression (rarely)
-Acute (possible chronic) hepatitis (173-175)
-Hemolytic anemia (rare)(176)
-Drug fever (177, 178)
-+ ANA or + LE Prep (rare)
-Leukopenia or thrombocytopenia (rare)
-Withdrawal Syndrome (155-159)

Medical Contraindications:
-History of prior methyldopa therapy resulting in:
  .Hemolytic anemia
  .Fever
  .Eosinophilia
  .Hepatitis (active liver disease, even if unrelated to prior methyldopa contraindication)
  .Hypersensitivity

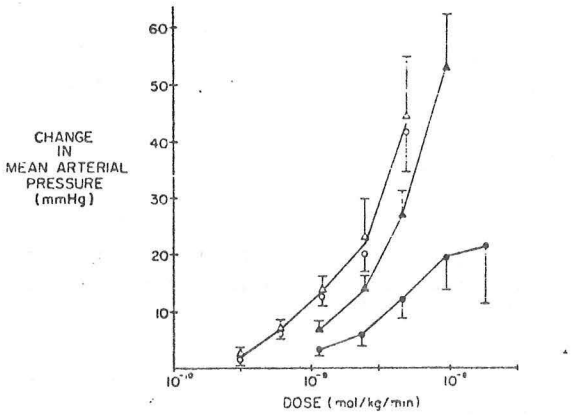
Major Drug Interactions:
plus:
-Clonidine = Synergistic for side effects, very little improvement in blood pressure control.
-MAO inhibitor = Hypertension and hyperexcitability (179)
-Phenothiazine = Paradoxical increase in blood pressure (180)
-Tricyclic antidepressants = Antipressor effect is markedly blunted (141, 181)

FIGURE 26: INTERACTION BETWEEN METHYLDOPA AND TRICYCLIC ANTIDEPRESSANTS (Ref. 141)



-Lithium = increased toxicity for lithium (182, 183)
-Haloperidol = Toxicity of haloperidol is increased (184)
-Levodopa = Anti-Parkinsonism effect is dimished (185) and hypotension may result (186).
-Barbiturates = Hepatic enzyme induction shortens methyldopa half-life.
-Sympathomimetics antagonize methyldopa's antipressor effect.
-β-blockers - Active metabolite of methyldopa becomes a more potent pressor (152).

FIGURE 27: ENHANCEMENT OF PRESSOR EFFECT OF α-METHYL NOREPINEPHRINE BY β-BLOCKADE



Legend: Dose-response relationship for norepinephrine (open symbols) and α-methyl-norepinephrine pressor effects (closed symbols) before (o ●) and after (Δ ▲) propranolol in six mongrel dogs. The pressor activity of α-methyl-norepinephrine (and clonidine) although usually insignificant is enhanced by propranolol.

Nies and Shand
Clin Pharmacol & Ther
14:823-826, 1973.

B. Drug and Dose: Clonidine 0.2 to 2.4 mg/day B.I.D.

Advantages:
-B.I.D. schedule
-Occasionally single HS dose will suffice
-Maintains renal and cerebral blood flow
-Rapid onset of action p.o.
-Blocks tachycardia caused by vasodilators and is a valuable component of "triple drug" regimens not utilizing β-blockers (187-189)
-At usual doses, clonidine has no effect on glucose metabolism and can be safely used in diabetics (190)
-Synergism for antipressor effect likely at any step of antipressor therapy
-Side effects tend to diminish with time.
-Fairly well tolerated.

Adverse effects:

Minor:
-Lethargy
-Drowsiness
-Sedation
-Dry mouth
-Rarely parotid pain
-Constipation
-Impotence
-Fluid retention

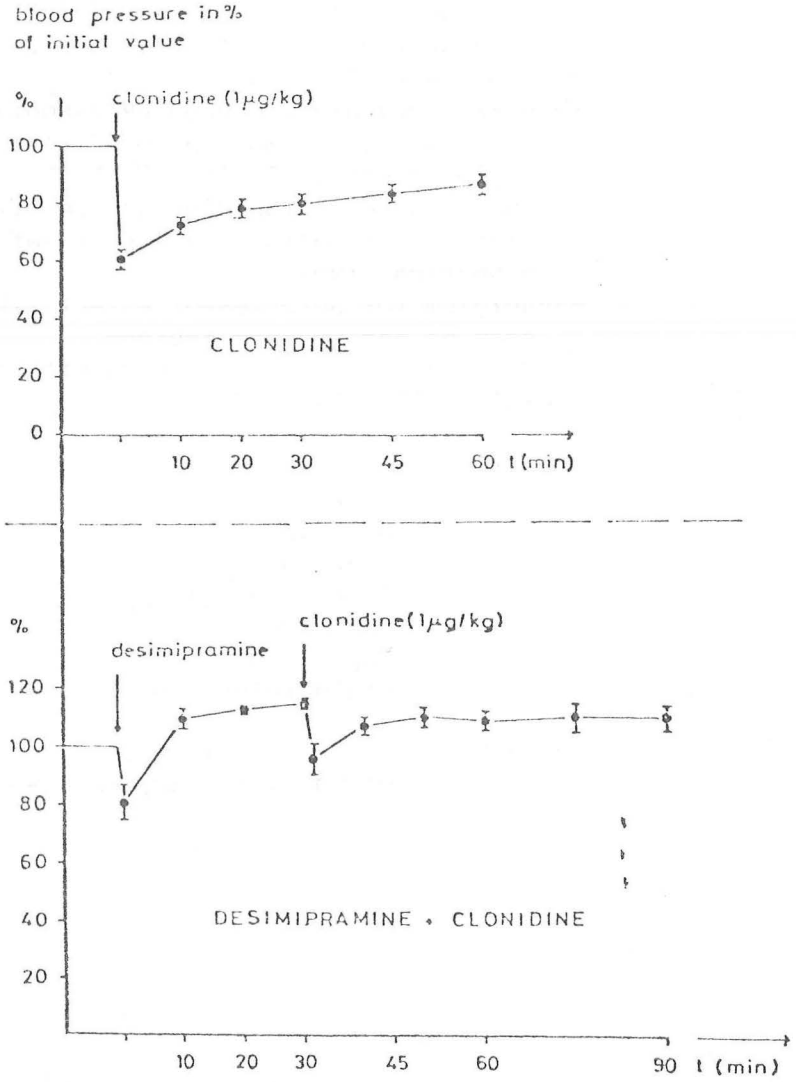
Major:
-Depression (rarely)
-Withdrawal syndrome (159-167)

Medical Contraindications: None

Major Drug Interactions

plus:
-Methyldopa = Synergistic for side effects, very little improvement in blood pressure control.
-β-blockers = Results in an antagonistic effect which compromises goal blood pressure control by enhancing clonidine's peripheral pressor effect (151). This combination is also more likely to cause withdrawal symptoms and blood pressure "overshoot" with abrupt cessation of therapy (193)
-CNS depressants or alcohol = sedation enhanced; caution should be given about driving.
-Tolazoline - hypotensive effect of clonidine reversed by this agent; can be used in cases of clonidine overdose (194)
-Tricyclic antidepressant = Hypotensive effect of clonidine is antagonized by these agents (141, 191, 192)

FIGURE 28: INTERACTION BETWEEN CLONIDINE AND TRICYCLIC ANTIDEPRESSANTS (Ref. No. 141)

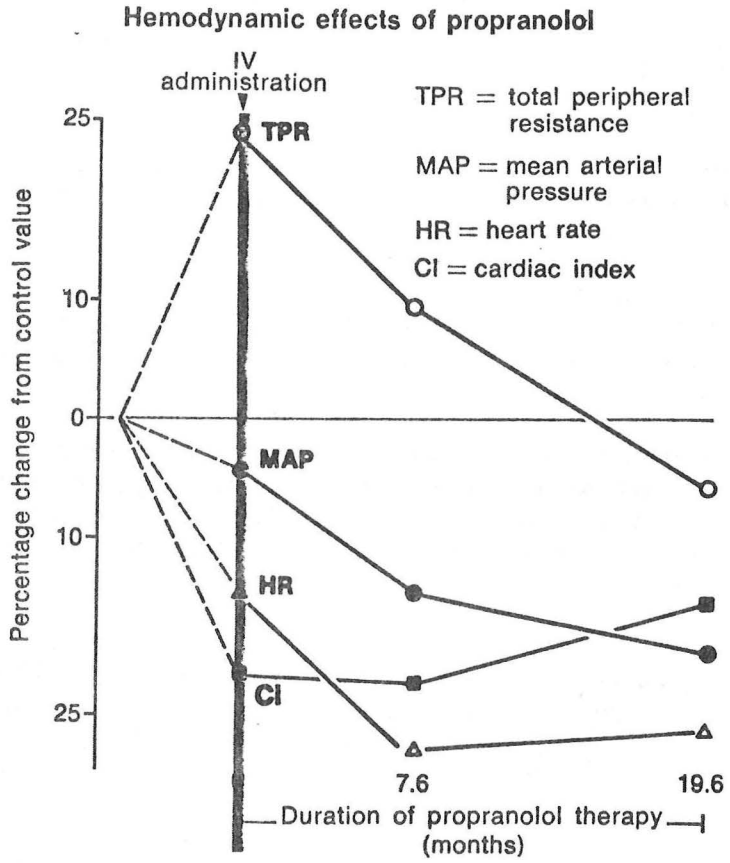


III. Beta Adrenergic Blockers:

Despite greater than ten years of utilization, the precise mode of action of β-blockers in lowering the blood pressure is still unclear. β-blockers diminish heart rate and reduce myocardial contractility. This effect occurs early whereas the antihypertensive effects appear more gradually (195). Nonresponders (patients whose blood pressure doesn't fall) demonstrate similar decrements in cardiac output as do responders (196).

Intravenous propranolol lowers cardiac output abruptly without reducing blood pressure unless the patient is in borderline cardiac decompensation. Finally the dose necessary to achieve blood pressure control, as determined by plasma concentrations, is usually far in excess of that required to decrease cardiac output (197). The negative inotropic and chronotropic qualities of these drugs may contribute to, but cannot account for, the blood pressure control achieved with chronic therapy. Initially, β-blockade results in an increase in peripheral vascular resistance because of unopposed alpha-adrenergic vasoconstriction; however, with time, peripheral vascular resistance tends to fall (not necessarily to normal) (198), as does blood pressure.

FIGURE 29: HEMODYNAMIC EFFECTS OF PROPRANOLOL (Ref. No. 198B)



The secretion of renin from the juxtaglomerular apparatus in the kidney is inhibited by β-adrenergic blockade. Suppression of the renin-angiotensin-aldosterone axis by β-blockers occurs early on and at low doses prior to effects on blood pressure (199). The suppression of the renin-angiotensin-aldosterone axis would theoretically reduce vasoconstrictive tone and the tendency to sodium and water retention. Buhler and co-workers (200) were able to subdivide patients by their renin status and predict subsequent response to propranolol. Similar correlations have been made with metoprolol (201). However, several other studies have shown a convincing lack of correlation between renin activity and the response to propranolol (202-206), and metoprolol (207). Practolol, removed from the market because of its toxicity, was a β-blocker that effectively lowered blood pressure without lowering renins (208). A reduction in plasma volume with propranolol has been reported (209) which may be accounted for by renin and aldosterone suppression. "Pseudotolerance" is not likely to occur with a β-blocker and some patients receive adequate blood pressure control without a diuretic.

Propranolol crosses the blood brain barrier, and small doses given by intracarotid or intravertebral injections result in lowering of blood pressure (210); however, some β-blockers do not penetrate the CNS and yet are quite effective antipressor agents (211). The side effects of propranolol (nightmares, confusion, hallucinosis and depression) reflect some central nervous system effects. Interestingly, propranolol now has an indication for migraine prophylaxis (212-214).

Finally, several hypotheses exist concerning the effects of β-blockers on various neurotransmitters, particularly serotonin (215) and on baroreceptors (216), but as yet no firm evidence in man supports either mechanism as contributory to antipressor effects.

Demographics are useful predictors of response to β-blockers. For example, these drugs seem to be uniformly effective in young whites, while ineffective in black hypertensives. The elderly hypertensive is also less responsive while more likely to have adverse side effects from β-blockers.

Sudden discontinuation of β-blockers may result in a "withdrawal" syndrome. Early reports were anecdotal (217-219), however, Miller et al (220) described 20 patients

undergoing abrupt propranolol withdrawal. Within the following two week period, three patients developed unstable angina, one died from a myocardial infarction, one from a "sudden death" syndrome, and yet another required DC cardioversion for ventricular tachycardia. Four other patients had a significant increase in the frequency and severity of anginal attacks. Alderman (221) reported six patients who similarly developed unstable angina, three going on to myocardial infarction and one dying after abrupt propranolol cessation. It should be emphasized that the patient population affected represented individuals with coronary artery disease, being treated for angina, not hypertension.

As with the centrally active sympatholytics, abrupt discontinuation should be avoided. A two week taper period can be utilized in patients with known or suspected coronary artery disease. This taper should be in conjunction with restriction of physical exercise.

III Beta Adrenergic Blockers:*

A. Drug and Dose: Propranolol (Step II; occasionally Step I)
40-480 mg divided B.I.D. to Q.I.D. (Larger doses, 2 to 4 Gms are utilized in Europe). Titration steps should be several weeks apart.

B. Drug and Dose: Metoprolol (Step II; occasionally Step I)
50 mg B.I.D. to start; titration to 200 mg B.I.D. maximum dose. Titration steps should be several weeks apart.

Advantages:
Few patient complaints (222)
-Can be given B.I.D.
-Not associated with fluid retention except in minority of patients (223)
-May be used without a diuretic if necessary
-Blocks vasodilator induced tachycardia and makes a significant contribution to "triple drug" regimens
-Fewer interactions with psychiatric medications
Oculocutaneous syndromes seen with practolol (224, 225) not yet seen with either β-blocker marketed in U.S.

Adverse Effects:
Minor:
-GI disturbances
-Cold extremities (or worsening of claudication or Raynaud's phenomenon)
-CNS disturbances (226, 226B)
.Headache (common)
.Confusion
.Nightmares
.Hallucinosis
.Depression (rare)

Major:
-Bradycardia
-Congestive heart failure
-AV conduction delay
-Bronchospasm
-Hypoglycemia in insulin dependent diabetics (227-229)
-Rare blood dyscrasias
-Rare dermatologic disorders
-Potentially dangerous withdrawal syndrome (217-221).

Medical Contraindications or Precautions

-Congestive heart failure
-Right ventricular failure secondary to pulmonary hypertension
-Sinus bradycardia (AV conduction disturbances > first degree heart block)
-Brittle diabetes*
-Asthma*
-Severe peripheral vascular disease or Raynaud's
-Past history of anaphylaxis
.Bee sting allergy
.Aspirin-nasal polyp syndrome, etc.
-Pheochromocytoma (unless preceded by an alpha adrenergic blocking drug (250).

Major Drug Interactions

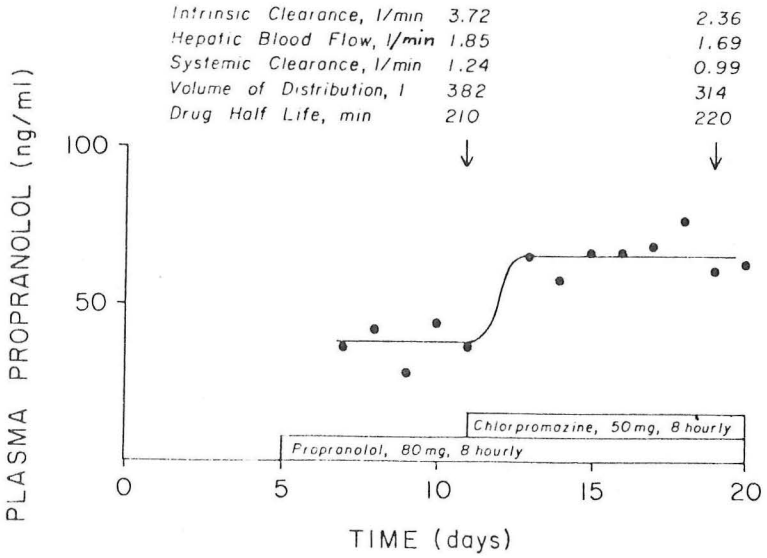
plus:

-MAO inhibitors = Hypertensive crisis
-Amphetamines or other sympathomimetics = May produce exaggerated pressor response.
-Insulin = Potentiates tendency toward hypoglycemia and masks warning signals (adrenergic responses) of hypoglycemia (227-229)
-Oral hypoglycemic = Insulin release from β-cells is partially blocked and diabetic control may be worsened (231)
-Methyldopa = Has resulted in exaggeration of hypertension (152)
-Clonidine = Antipressor effect blunted by β-blockers and withdrawal phenomena more likely when both drugs are suddenly discontinued (151, 193).
-General anesthetics = Must avoid agents that will potentiate myocardial depression. (Isoproterenol and levarterenol may counteract hypotension in this situation). (232)
-Digitalis = Inotropic effect decreased. In patients requiring β-blockers for angina control who have borderline cardiac compensation, concurrent digitalization is wise.

-Tricyclic antidepressants = Half-life is prolonged on occasion by β-blockers; AV conduction disturbances from this combination have been seen twice in our institution (rare considering number of patients so treated).
-Phenothiazine = Inhibit metabolism and increase therapeutic response of propranolol (233).

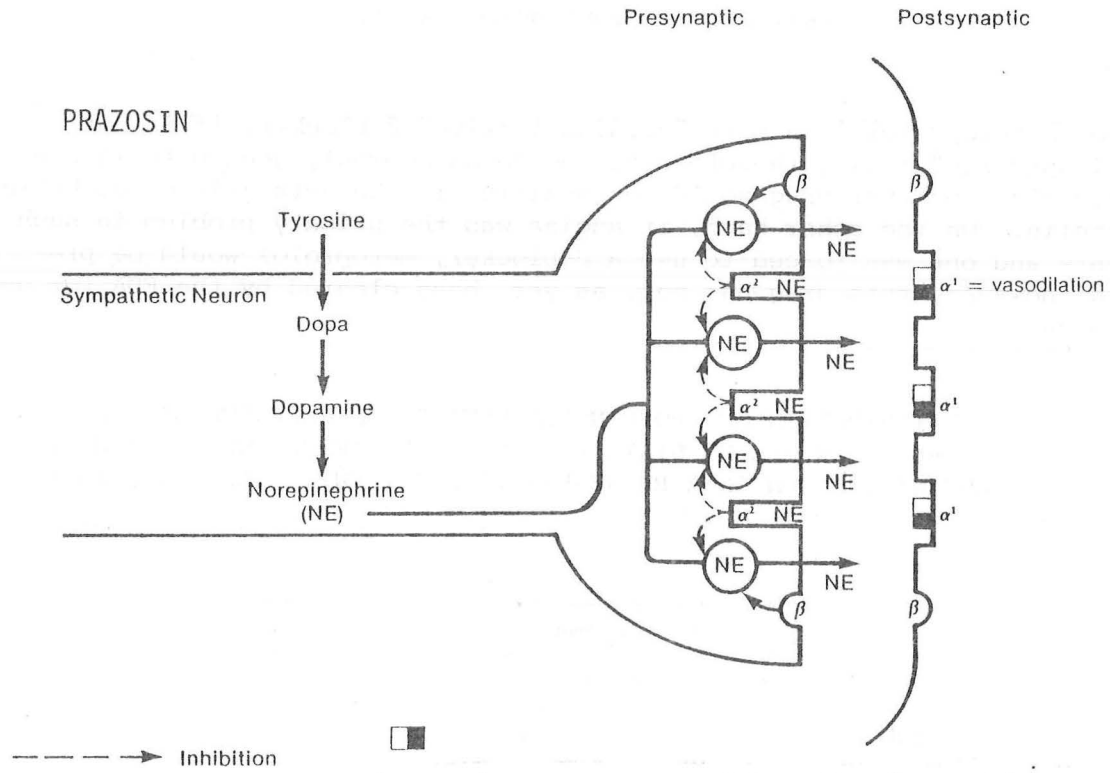
*Although metoprolol is a more "cardioselective" β-blocker, it is not "cardiospecific" (234), therefore at the doses commonly needed to manage hypertension, neither drug would be justified in the asthmatic or diabetic on insulin. On the other hand, if angina was the primary problem in such patients and one was forced to use a β-blocker, metoprolol would be preferred; however, this drug has not, as yet, been cleared by the FDA for use in angina.

FIGURE 30: THE INHIBITION OF PROPRANOLOL METABOLISM REFLECTED BY AN INCREASE IN STEADY STATE PLASMA LEVELS AFTER CHLORPROMAZINE ADMINISTRATION IN A REPRESENTATIVE PATIENT. (REf. No. 233)



IV α-Adrenergic Receptor Blockers (Indirect Vasodilators):

FIGURE 31: MECHANISM OF ACTION FOR PRAZOSIN



Prazosin, a more specific α-blocker, which blocks the α^1 site and still allows NE to stimulate inhibition of further neurotransmitter release, since it does not block the presynaptic α^2 site.

Prazosin, initially thought to be only a direct vasodilator, has been shown to exert its primary effect by α-adrenergic postsynaptic blockade (235, 236). This drug apparently blocks the postsynaptic receptor at the effector cell (α_1) without blocking the presynaptic autoreceptor (α_2). Postsynaptic blockade prevents the vasoconstrictor effect of norepinephrine, while the norepinephrine in the synaptic cleft can still stimulate the presynaptic autoreceptors. Blood pressure goes down without a parallel increase in heart rate. Unlike other vasodilators, prazosin does not cause a rise in plasma renin activity.

Prazosin has an effect on both resistance (afterload) and capacitance vessels (preload) and therefore may be a useful agent in conjunction with digitalis, diuretics, and nitrites in the chronic management of refractory congestive heart failure (237). Two recent studies however, suggest that this effect may not be as sustained as previously thought (238-239).

IV Selective α-Adrenergic Receptor Blocker: (See Figure 32)

A. Drug and Dose: Prazosin (Step II, III, and occasionally Step I)
1 mg at bedtime to start, then titrate starting at 1 mg T.I.D. going up to a maximum recommended dose of 20 mg/day (An occasional patient requires 30-40 mg/day in divided doses.)

Advantages:
-May be added to any therapeutic program if further BP reduction is necessary
-Little or no tachycardia compared to other α-blockers or hydralazine
-Maintains renal blood flow
-Doesn't stimulate renin release
-Side effects tend to decrease with time; fairly well tolerated
-Can be used to "unload" the failing heart by its effect on both preload and afterload
-Can be used safely in renal insufficiency since metabolism is primarily hepatic
-Fewer interactions with psychiatric medications.

Adverse Effects Minor:
-Postural dizziness
-Headache
-Drowsiness
-Weakness
-Nausea or vomiting
-Palpitations
-Edema
-Nasal stuffiness
-Urinary frequency or incontinence

-Blurred vision
-Nervousness
-Depression
-Vertigo
-Constipation
-Diarrhea
-Rash
-Polyarthralgia
-+ANA (240)

Major:

-Primary concern: Sudden syncope (30-90 minutes after the first dose) occurred in approximately 1% of patients receiving 2 mgs as an initial dose (241, 242). More commonly, a "first dose effect" manifested by lassitude weakness, palpitations, orthostasis and transient faintness is seen.
-To avoid:

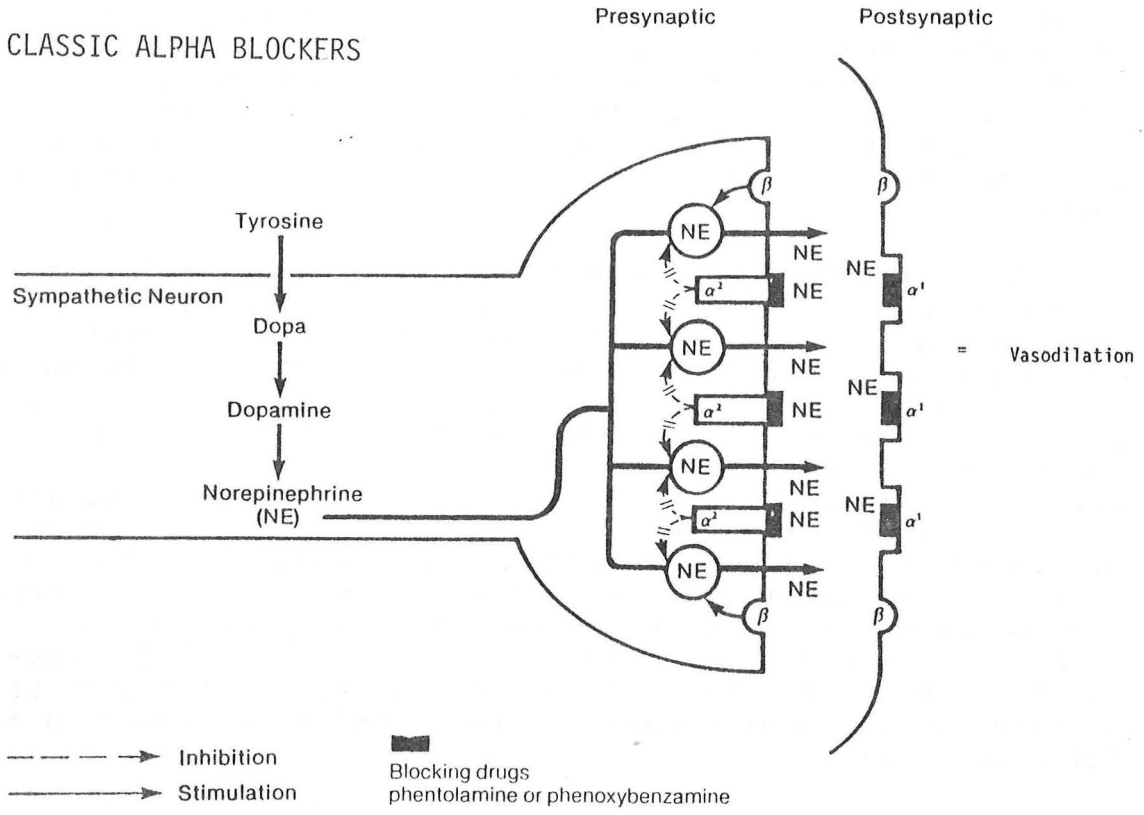
.Never start at more than 1 mg (given at bedtime)
.Upward dose adjustments should be small and several weeks apart
.When adding prazosin to another regimen, it is wise to cut the dose of diuretic, β-blocker or central sympatholytic, usually to "half-dose" and proceed with prazosin titration.
.Cautiously add other antihypertensive agents to prazosin by "back titration" to 1 or 2 mg T.I.D., then retitration can be carried out.
.Sudden syncope may be more likely in patients who are sodium depleted (243) or maximally beta blocked.

Medical Contraindications: None

Medical Precautions: Pheochromocytoma - the first dose of prazosin may be analagous to a "Regitine Test".

Major Drug Interactions:
plus:
-Nitroglycerin = Rare syncope (244).
-Guanethidine = Long half-life and norepinephrine depleting qualities of this drug may be "set up" for syncope when prazosin is added to regimen.

FIGURE 32:



* Phenoxybenzamine HCl and Phentolamine HCl are still available, but their utility is limited due to severe side effects resulting from both pre- and post-ganglionic alpha blockade (postural hypotension, tachycardia, impotence, miosis and nasal stuffiness). Inoperable pheochromocytoma or pheochromocytoma crisis are indications for use.

V. Direct Vasodilators:

Hydralazine diminishes total peripheral resistance by direct relaxation of smooth muscle (245, 246), actually concentrating in vascular walls (247). Relaxation in arterioles and small arteries is much greater than in venules and small veins (248). Its effect on blood pressure is predictable and the drug has great utility when used in a triple drug regimen. Hydralazine has been used in refractory congestive failure in patients managed on nitroprusside infusion, as an agent to decrease left ventricular afterload (249).

The peripheral hypotensive effect of hydralazine is counteracted by several mechanisms that limit its utility. The drug causes a reflex increase in sympathetic drive resulting in an increase in cardiac rate, contractility and output (246,250). Sodium and water retention (251, 252), possibly mediated through renin stimulation and plasma volume expansion from interstitial fluid shifts (253), occurs with this agent and requires that diuretics be utilized if the antipressor effect is to be maintained. β-blockers or clonidine (187) can be used, and are ideally suited, as part of a triple drug regimen utilizing hydralazine. Such a combination limits counter-productive adaptations to therapy and the adverse effects of palpitations and tachycardia. The potent vasodilator, minoxidil, will likely be marketed in the near future and is therefore included in the following table.

VI. Vasodilators:

A.	Drug and Dose:	Hydralazine (Step III, rarely step II) 40-400 mg divided into 2-4 daily doses
	Advantages:	-Synergistic with diuretics and all Step II drugs -Can be given parenterally when necessary -Does not aggravate renal insufficiency -Few interactions with psychiatric medications -May be useful in "unloading" left ventricle in refractory CHF.

Adverse Effects:

Minor

-Headache
-Nausea or vomiting
-Tachycardia
-Palpitations
-Postural hypotension
-Weakness, lethargy, fatigue
-Dizziness
-Diarrhea or constipation
-Anxiety, nightmares, sleep disturbances
-Depression
-Sedation
-Fever
-Myalgias or arthralgias
-Psychosis

Major:

-Increases plasma volume by
  .stimulating renin release
  .Enhancing sodium and water retention
  .Encouraging interstitial fluid shifts toward plasma volume (needs diuretic to remain effective)
-Increases sympathetic drive toward "hyperdynamic" circulation
  .Angina, EKG changes, palpitations reported (254, 255)
  .Has been implicated in several myocardial infarctions (254, 256)
-"Lupus-like" syndromes (257-261)†
-Peripheral neuropathy (262, 263)

† Most individuals suffering from late toxicity of hydralazine (lupus-like syndromes) are "slow acetylators" who are unable to metabolize the drug well. About 50% of the American white and black populations are slow acetylators. While monitoring of the ANA is clearly appropriate, the low incidence of the lupus-like syndrome should not prohibit the clinician from using effective doses (up to 400 mg/day) of this drug. The syndrome when recognized is usually reversible with discontinuation of the drug.

Medical Contraindications;
or Precautions:

-Clinical picture of lupus erythematosus or past history of lupus-like syndrome on hydralazine (264)
-Mitral valvular rheumatic disease (254, 255, 265) (may raise pulmonary artery pressure)
-Severe coronary artery disease (unless preceded with a β-blocker or clonidine to prevent tachycardia)
-Congestive heart failure (unless with digitalis)
-Aortic dissection
-Hypersensitivity

Major Drug Interactions:

plus:
-MAO inhibitor = Hypotensive episodes
-Epinephrine = Pressor response reduced (266)

B. Drug and Dose: Minoxidil (Step IV)
2 to 40 mg/day in divided doses four times per day

Advantages:

-Has been used as a "last resort" drug in azotemic accelerated hypertension avoiding the need for nephrectomy (267, 268)
-No "lupus-like" syndromes reported
-Side effects of orthostasis, impotence and decreased libido are minimal

Adverse Effects:

Minor:
Headache (probably less than with hydralazine)
-Nausea
-Conjunctivitis
-Weight gain or edema

Major:
-Congestive heart failure*
-Tachycardia*
-Angina*
-EKG changes
-Pericardial effusions
-Hair growth (133) (hypertrichosis)
-Right atrial fibrosis in Beagle dogs; evidence for the same lesion in man is not yet convincing (269-271)
-Pulmonary hypertension (probably no more common with this agent (272)

Medical Contraindications:	-Symptomatic coronary artery disease (unless with propranolol) -Congestive heart failure (unless with digitalis) -Mitral valvular rheumatic disease -Pulmonary hypertension
Major Drug Interactions:	Must await broader clinical trials

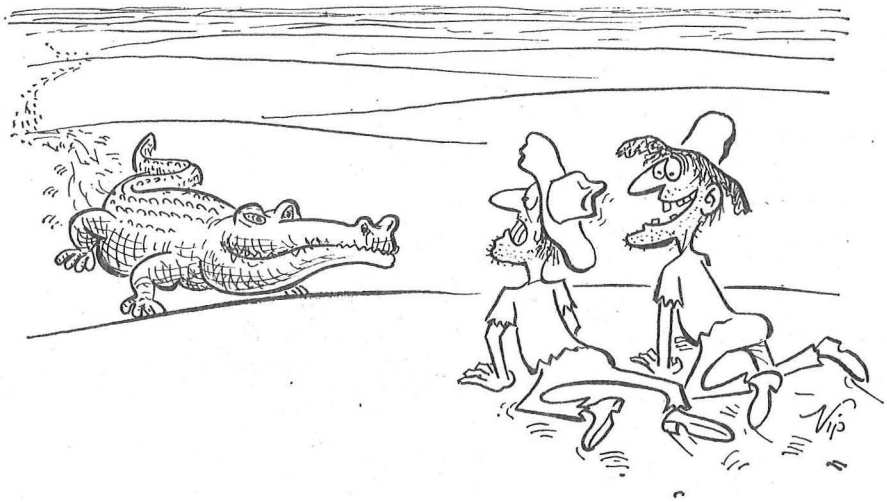
* These adverse effects can be avoided by utilizing aggressive diuretic therapy with furosemide or metolazone and adrenergic blockers, either a β-blocker or clonidine (187).

SUMMARY

This Grand Rounds has focused somewhat "on the other side of the coin", i.e. the barriers to the achievement and/or maintenance of goal blood pressure control. Effective and relatively safe medications are available, but each may have attendant limitations and risks for the individual patient. Noncompliance seems to be less related to the drug utilized than to underlying patient behavior. Obviously, we need to study the impact of various maneuvers on patient compliance with the same rigorous scientific technique we have used to study the drugs.

Physiologic adaptations to drug therapy, adverse drug effects and drug interactions with antihypertensive agents are common, and dictate constant vigilance to achieve the best outcome for your patients.

As new techniques to improve patient compliance or new drugs are developed, I would suggest an attitude of "conservative optimism" in the incorporation of these tools into your practice.



"You know what <u>this</u> means, Slim? We're nearing water!"

DRUG USAGE - 1978

The top ten drug categories dispensed at Parkland Memorial Hospital for ambulatory care patients:

DRUG	UNITS DISPENSED
1. Antihypertensives	3,711,878
2. Iron Supplements	3,218,490
3. Oral Potassium Replacement	2,597,641
4. Diuretics	2,383,299
5. Vasodilators	2,208,417
6. Analgesics & Antipyretics	2,164,713
7. Anti-infectives	1,432,350
8. Oral Hypoglycemics	1,306,980
9. Nonsteroidal Antiinflammatories	1,083,374
10. Bronchodilators	915,812

RANK IN TOP 140 DRUGS: DESCRIPTION	TOTAL NO. DISPENSED	AVG. NO. Rx. @ $/UNIT	Rx CHG. TO PT.
2. Hydrochlorothiazide 50 mg	2,272,027	100 @ 0.090	$ 9.00
4. Methyldopa 250 mg	967,935	200 @ 0.120	24.00
5. Potassium Chloride 8 mEq	884,691	200 @ 0.075	15.00
8. Furosemide 40 mg	692,879	100 @ 0.135	13.50
11. Propranolol 40 mg	600,094	200 @ 0.105	21.00
14. Methyldopa 500 mg	507,821	200 @ 0.225	45.00
15. Propranolol 10 mg	452,076	200 @ 0.060	12.00
27. Hydralazine 50 mg	229,660	200 @ 0.120	24.00
33. Hydralazine 25 mg	202,496	200 @ 0.075	15.00
37. Potassium Chloride 20% (ounce)	171,295	16 @ 0.540	8.64
39. Furosemide 20 mg	152,782	100 @ 0.105	10.50
40. Clonidine HCl 0.1 mg	147,128	200 @ 0.135	27.00
42. Trichlormethazide 4 mg	131,557	100 @ 0.105	10.50
47. Guanethidine 25 mg	111,322	100 @ 0.210	21.00
53. Clonidine HCl 0.2 mg	98,610	200 @ 0.180	36.00
55. Propranolol 80 mg	97,345	200 @ 0.165	33.00
56. Spironolactone 25 mg	96,607	100 @ 0.180	18.00
58. Prazosin	95,657	100 @ 0.105	10.50
67. Triamterene & Hydrochlorothiazide	73,518	100 @ 0.135	13.50
81. Guanethidine 10 mg	55,430	100 @ 0.150	15.00
97. Prazosin 2 mg	42,892	200 @ 0.150	30.00
98. Hydralazine 100 mg	41,995	200 @ 0.165	33.00
100. Chlorthalidone 50 mg (25 mg now available)	41,553	100 @ 0.135	13.50
116. Reserpine-Hydralazine-Hydrochlorthiazide	30,939	100 @ 0.150	15.00
117. Prazosin 5 mg	30,478	200 @ 0.255	51.00
133. Spironolactone & Hydrochlorothiazide	21,951	100 @ 0.195	19.50

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ACKNOWLEDGEMENT

I would like to extend my appreciation to Dr. Norman Kaplan and Dr. Donald W. Seldin for their editorial review of this work. I would also like to express special thanks to Dr. Gary R. Hart for his contributions to the manuscript and to Barneé Goldberg for her secretarial assistance.