1990

# Causes of resistant hypertension in patients referred to a tertiary care clinic

Marko Yakovlevitch
*Yale University*

# CAUSES OF RESISTANT HYPERTENSION IN PATIENTS REFERRED TO A TERTIARY CARE CLINIC

Marko Yakovlevitch

YALE UNIVERSITY

1990

Permission for photocopying or microfilming of "Causes of Resistant Hypertension in Patients Referred to a Tertiary Care Clinic" for the purpose of individual scholarly consultation or reference is hereby granted by the author. This permission is not to be interpreted as affecting publication of this work or otherwise placing it in the public domain, and the author reserves all rights of ownership guaranteed under common law protection of unpublished manuscripts.

Marko Yakovlevitch

April 8th, 1990

# Causes of Resistant Hypertension in Patients Referred to a Tertiary Care Clinic

A Thesis Submitted to the Yale University School of Medicine in Partial Fulfillment of the Requirements for the Degree of Doctor of Medicine

by

Marko Yakovlevitch

1990

## ABSTRACT

**CAUSES OF RESISTANT HYPERTENSION IN PATIENTS REFERRED TO A TERTIARY CARE CLINIC**



**Marko Yakovlevitch, Henry R. Black, Section of Cardiology, Department of Internal Medicine, Yale University School of Medicine, New Haven, CT**



Current estimates regarding the prevalence, and the frequency of causes, of resistant hypertension (HTN) vary with clinical setting. We evaluated 301 consecutive patients referred to a tertiary care hypertension clinic, 81 of whom were referred by a physician because of resistant HTN. Sixty-one (75%) of those patients met our criteria for resistant HTN: failure to achieve blood pressure (BP) control with three or more drugs, and absence of a known secondary cause at the time of referral.

The cause of resistant HTN was found in 52 patients (85%): suboptimal medical regimen in 23, medication intolerance in 13, primary noncompliance in 5, secondary HTN in 5, psychiatric disorders in 4, white coat HTN in 4, alcohol abuse in 1, and a drug interaction in 1.

BP control was defined as diastolic BP (DBP) $\leq$ 90mmHg and systolic BP $\leq$ 140mmHg ($\leq$ 150mmHg for age > 50 and $\leq$ 160mmHg for age > 60). Control was achieved in 30 (55%)

of those 55 patients who met criteria for resistant HTN and returned to clinic at least once, and significant improvement ($\geq$ 15% fall in DBP) was achieved in another six.

In conclusion, resistant HTN is common in a tertiary care setting and is most frequently caused by a suboptimal medical regimen; furthermore, the majority of these patients can be successfully treated. Of patients who were controlled after having been on a suboptimal regimen, 61% needed initiation of diuretic therapy, and 52% needed initiation of therapy with a relatively new agent (calcium antagonist or angiotensin-converting enzyme inhibitor).

**ACKNOWLEDGEMENTS**

I would like to thank Dr. Henry R. Black for his expert assistance and support throughout my work on this project. His guidance has been indispensable.

This research was supported by a Short-term Research Training Stipend from the National Institutes of Health National Research Service Award, a Yale University School of Medicine Student Research Fellowship, and the assistance of the Yale University Section of Cardiology.

CONTENTS



**Index to Figures and Tables**

# INTRODUCTION

The prevalence of resistant hypertension, and the frequency of the various causes underlying resistance, will change as greater information about this condition becomes available and as more effective therapy is developed. Hypertension that is resistant now may not be considered resistant in the future when more powerful and better tolerated drugs come into wider use. Even now, hypertension that is considered resistant in some settings would not be considered resistant in others by virtue of varying levels of sophistication from one clinic to another. Physicians who have not yet begun to use the newest agents, or who neglect the oldest ones, will encounter resistance where others would not.

Despite variability in the classification of resistant hypertension, delineating the characteristics of patients referred with this diagnosis to a specialty clinic will help elucidate the reasons for resistance and enable primary physicians to manage this problem more successfully. Numerous studies have evaluated potential therapies: calcium antagonists[1-5] including experimental agents such as felodipine,[6-9] angiotensin-converting enzyme inhibitors,[10-15] vasodilators,[16-23] doxazosin (also an experimental agent),[24,25] furosemide,[26,27] and labetalol[28-31] have all shown some effectiveness in the

treatment of "resistant hypertension."

There are very few epidemiological studies of resistant hypertension, and it is commonly held that resistant hypertension is very unusual.[32-34] One study which supports this view was reported in 1988; the authors sought to determine what proportion of an employed hypertensive population have resistant hypertension.[32] Of 1,781 hypertensive patients, only 2.9% were found to be resistant, and 63% of those were controlled in subsequent years. Since there was some component of noncompliance in 14 of the 19 patients who remained resistant, the investigators concluded that the incidence of resistance was 0.3%. However, this population of employees who were identified by workplace screening and who elected on-site treatment is not representative of the general population of hypertensive patients. It should also be noted that diagnosing a cause of resistance, such as noncompliance, does not necessarily ensure ability to control blood pressure. For this reason, I would still categorize noncompliant patients with uncontrolled hypertension as resistant to therapy. A noncompliant patient requires education, a simplified regimen, and possibly other therapeutic interventions before blood pressure becomes controllable; therefore noncompliance is a form of patient-derived resistance.

The goals of the present study are to determine:

1) The frequency of resistant hypertension in a tertiary care clinic.
2) The medical regimens employed by the referring physician in those patients.
3) The frequency of causes of resistance, including curable secondary causes.
4) The proportion of patients meeting criteria for resistant hypertension who can ultimately be controlled, and the intervention required.

This information will then be used as the basis for a set of guidelines for the evaluation of patients with resistant hypertension.

A set of categories for resistant hypertension is presented below using a modification of the schema proposed by Frohlich.[35]

A) Patient-derived resistance
   1) Patient is unable or unwilling to tolerate side effects. Excluded from this category are disease-related side effects, such as medically unacceptable cardiovascular or renal side effects which the patient's physician needs to avoid through the selection of appropriate drugs.
   2) Noncompliance with the therapeutic regimen. This is believed by some investigators to be among the most likely dominant causes.[32,36]

3) Psychological causes such as panic attacks in patients with anxiety disorders, or subjective medication intolerance resulting from the misinterpretation of physical and/or psychological stimuli as side effects of medication.

B) Physician-derived resistance

1) Failure to identify drug interactions, such as those that can arise from nonsteroidal anti-inflammatory drugs and oral contraceptives.[33,35,37]

2) Failure to identify hypertension-promoting drugs or behaviors (such as alcohol abuse) and to educate the patient to modify such behaviors.[37-39]

3) Use of a suboptimal medical regimen.

a) Use of suboptimal dosages of standard medication in the absence of dose-limiting side effects or patient intolerance. This is also believed to be among the most likely dominant causes.[36]

b) Failure to prescribe standard medication or inappropriate choice of medication. For example, failure to prescribe diuretics in patients with volume-dependent hypertension, and failure to substitute loop diuretics for thiazides in patients with renal insufficiency.[40,41]

4) Failure to identify and treat correctable secondary causes of hypertension, such as renal artery stenosis, pheochromocytoma, and primary aldosteronism.

C) Disease-derived resistance

Resistant essential hypertension in a compliant patient who fails to be controlled with optimal dosages of three concurrently administered antihypertensive agents.

D) Pseudoresistance

1) White-coat hypertension: normotension outside of the clinic setting.
2) Pseudohypertension: normal intra-arterial blood pressures in a patient with sclerotic brachial arteries.

This study was designed to test the hypothesis that resistant hypertension is not an uncommon reason for referral to a tertiary hypertension clinic, and that a large proportion of the patients referred for resistant hypertension have been on a suboptimal medical regimen. We have defined resistant hypertension as uncontrolled blood pressure despite attempted therapy with at least three antihypertensive agents in a patient who is considered resistant by a referring physician. Criteria for blood pressure control are outlined in table 1.

Table 1. Criteria for blood pressure control.

| | Age (years) | | |
|---|---|---|---|
| | ≤ 50 | 51 - 60 | > 60 |
| Systolic blood pressure | ≤ 140 | ≤ 150 | ≤ 160 |
| Diastolic blood pressure | ≤ 90 | ≤ 90 | ≤ 90 |

The criteria for blood pressure control are based upon a goal blood pressure independent of the blood pressure on referral; this contrasts with the definitions accepted by some other investigators.[32,37] Predicating loss of resistance on the achievement of blood pressure control, rather than on a proportionate lowering of blood pressure, is in keeping with the aims of antihypertensive therapy. Even blood pressures that are moderately decreased from their initial levels can be unacceptably high; patients who have elevated blood pressures should be considered resistant to therapy because the goal of therapy is to control, not merely to affect, blood pressure.

# PATIENTS AND METHODS

## Enrollment

The charts were sought of all patients whose initial visit to the Yale Hypertension Clinic was made between January 1, 1986 and March 30, 1988. In consultation with the clinic attending physician, each patient was categorized as to the source of the referral, and self-referred patients were distinguished from those who were referred by a physician. Those patients who were physician-referred were further categorized according to the reason for their referral.

The study group was composed of those patients who were physician-referred for assistance with the management of "resistant hypertension," and who did not have an identified secondary cause for resistance at referral. The patients from that group who had been tried on at least three antihypertensive agents and whose blood pressure was not controlled on their initial visit to the hypertension clinic (according to the criteria in table 1) were studied in detail.

## Evaluation and Follow-up

Standard initial evaluation for all patients included a complete medical history, past medical history, physical

examination, and laboratory studies (unless recent laboratory data was provided by the referring physician). Initial laboratory evaluation in most patients included a urinalysis, complete blood count, determination of serum potassium, calcium, creatinine, and glucose, and measurement of serum cholesterol and triglyceride levels. Further laboratory evaluation for secondary causes of hypertension was pursued when history, physical examination, or routine laboratory evaluation raised the clinical suspicion of such. The criteria used for initiation of studies for particular secondary causes have been described elsewhere.[42]

Dosages of antihypertensive medications were interpreted according to the dosage guidelines given in the 1984 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure;[43] for newer agents not included in the 1984 report, the 1988 report[38] was used. The only exception to this is indapamide, which was not included in either report; dosage guidelines for indapamide were taken from the 1988 Physician's Desk Reference.[44]

All blood pressures reported in this study are an average of two readings (one supine and one standing) taken on the same visit, unless the patient's position during measurement is stated along with the pressure (in which case a single reading is being reported).

Achievement of blood pressure control was defined as controlled blood pressure on two consecutive visits or on the final clinic visit without unacceptable or intolerable side effects. The only exception to this is demonstration of normotension by 24 hour ambulatory monitoring, with greater than 85% of blood pressure readings recorded in the normotensive range (according to the criteria in table 1). In the context of elevated clinic pressures, this established the diagnosis of white-coat hypertension. Blood pressure was considered "significantly improved" if there was at least a 15% fall in diastolic blood pressure (the average of two readings on the final visit compared with the average of those on the initial visit).

Patients were followed until systolic blood pressure was less than or equal to 140mmHg and diastolic blood pressure was less than or equal to 90mmHg, or control was documented by ambulatory monitoring. Those patients in whom blood pressure control was not achieved were followed until their last clinic visit.

**Final Diagnosis**

The criteria for the diagnosis of specific causes of resistance are as follows:

Patient-derived resistance

Multiple medication intolerance: inability to

achieve therapeutic levels of antihypertensive drugs without intolerable side effects despite multiple attempts with a variety of agents.

Noncompliance: patient acknowledgement during interview in a consistent clinical setting.

Psychological causes:

1) Symptoms of panic disorder with episodic elevations in blood pressure.

2) Misinterpretation of psychological and/or physical stimuli as side effects of medication, resulting in subjective but non-physiological medication intolerance.

Physician-derived resistance

Alcohol abuse: temporal correlation of blood pressure resistance with high alcohol consumption (at least 1.5 ounces of ethanol, or two average drinks, per day) such that blood pressure came under control only with abstinence from alcohol.

Suboptimal medical regimen: submaximal dosages of antihypertensive agents and/or failure to prescribe an indicated agent.

Secondary causes:

1) Renal artery stenosis: positive angiographic findings in the context of abnormal captopril renal scintigraphy and a consistent clinical setting.

2) Primary aldosteronism: positive urinary aldosterone studies under a scrupulous protocol, which has been described elsewhere,[44] in a consistent clinical setting. Surgery is pursued when the cause is presumed to be an aldosterone producing adenoma, and in those cases provides the opportunity for pathological confirmation.

3) Pheochromocytoma: positive urinary catecholamine studies, with positive magnetic resonance imaging and/or consistent pathological findings in a surgical specimen.

Pseudoresistance

White-coat hypertension: normotension outside the clinic setting confirmed by 24-hour ambulatory monitoring, with greater than 85% of blood pressure readings in the normotensive range (according to the criteria in table 1).

## Statistical Methods

All means are arithmetic means, and when reported as $x \pm y$, the y value is the standard deviation of the sample. Means were compared using critical ratio calculations (student's t-test). Categorical data was analyzed with chi-square calculations when E (expected

value) for each cell was $\geq$ 5; if this condition was not met, then Fisher's exact test was used. The requirement for statistical significance was set at $p \leq 0.05$, and p values are reported only when $p \leq 0.10$. When $p > 0.10$, the result is reported as "statistically insignificant."

## Ethical Controls

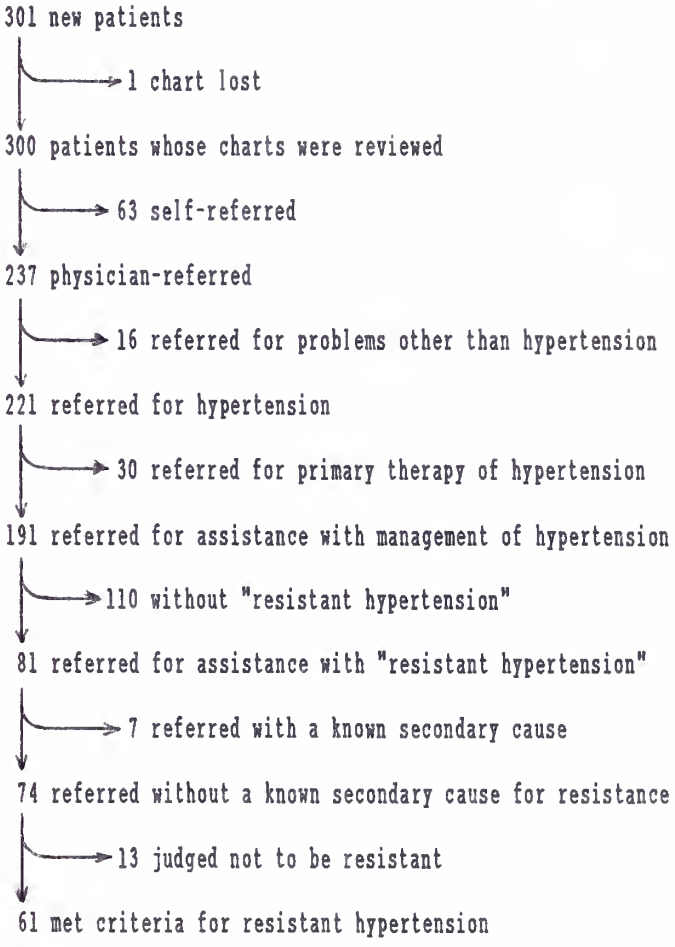
The protocol for this study (HIC # 4892) was approved by the Human Investigation Committee of the Yale University School of Medicine.

# RESULTS

## Demographic Data and Initial Evaluation

301 new patients were seen at the Yale Hypertension Clinic between January 1, 1986 and March 30, 1988. The charts of all but one of these patients were recovered and reviewed. The sources of, and reasons for, their referrals are outlined in figure 1.

**Figure 1.** Sources of, and reasons for, referrals.



Of the 74 patients referred for "resistant hypertension" without a known secondary cause, six (8%) had had a complete work-up for common secondary causes of hypertension prior to their referral, 33 patients (45%) had had a limited work-up, and 35 (47%) had none. Sixty-one patients (82%) met our criteria for resistant hypertension, and they comprised the study group. Their demographic and baseline clinical data are presented in table 2. Neither age, gender, or race, correlated significantly with whether or not a patient satisfied our criteria for resistance.

Table 2. Demographic data.

| | | Range |
|---|---|---|
| Age | 58 ± 15 | 29-85 |
| Female | 34 (56%) | |
| White | 51 (88%) | |
| Black | 6 (10%) | |
| Asian | 1 | |
| Smoking history | 36 (59%) | |
| Current smokers | 14 (23%) | |
| Alcohol history* | 3 | |
| Current alcohol* | 2 | |
| Family Hx. HTN | 33 (54%) | |
| Hx. of HTN (years) | 15 ± 11 | 0.2- 50 |
| Highest SBP by Hx. | 205 ± 36 | 138-300 |
| Highest DBP by Hx. | 118 ± 19 | 70-170 |
| Supine SBP | 181 ± 24 | 130-240 |
| Supine DBP | 103 ± 15 | 60-140 |
| Standing SBP | 178 ± 28 | 122-246 |
| Standing DBP | 106 ± 17 | 60-150 |

*Consumption of at least 1.5 ounces of ethanol (two average drinks) per day.

Abbreviations: Hx. = history, SBP = systolic blood pressure (in mmHg), DBP = diastolic blood pressure (in mmHg), HTN = hypertension.

The incidence of other medical conditions in these patients is reported in table 3. Coronary artery disease was established by a history of typical angina and/or electrocardiographic, radionuclide, or other objective evidence of ischemia. Diabetes mellitus included diet-controlled as well as insulin-dependent diabetic patients. Seven of the 13 patients with known renal parenchymal disease had renal insufficiency at the time of referral.

No patient had a history of pheochromocytoma, primary aldosteronism, or congestive heart failure.

**Table 3. Comorbid diseases.**

| | Patients |
|---|---|
| History of myocardial infarction | 3 |
| Coronary artery dis. without MI* | 6 |
| Diabetes mellitus | 12 |
| Renal parenchymal disease | 13 |
| Renal failure | 0 |
| Renal artery disease** | 1 |
| History of gout | 3 |
| History of hyperthyroidism | 3 |
| Medically treated anxiety | 10 |
| No comorbid disease | 23 |
| One comorbid disease | 27 |
| Two comorbid diseases | 9 |
| Three comorbid diseases | 2 |

*Patients with coronary artery disease without a history of myocardial infarction.

**Hemodynamically insignificant renal artery disease.

The drugs being used at the time of referral in these patients' regimens are enumerated in table 4 ("INITIAL" column). The mean number of agents in those regimens was 2.3 $\pm$ 1.1. In this and all subsequent tables, labetalol has been included in the category "beta-adrenergic blockers." These patients also had a history of having been tried on 4 $\pm$ 3 agents (on average) that were discontinued because of side effects or ineffectiveness.

Table 4. Frequency of medication use and adjustment of medical regimens.

| Agent | N = 61 | N = 49* | | | |
|---|---|---|---|---|---|
| | INITIAL | FINAL | Added | Removed | Increased | Decreased |
| Diuretics | 36 | 36 | 22 | 10 | 5 | 4 |
| Thiazides | 16 | 19 | 12 | 3 | 2 | 1 |
| Thiazide/Potassium-sparing** | 6 | 8 | 5 | 1 | - | - |
| Loop diuretics | 10 | 8 | 5 | 3 | 3 | 2 |
| Potassium-sparing | 3 | 1 | 0 | 2 | - | 1 |
| Indapamide | 1 | - | - | 1 | - | - |
| Beta-adrenergic blockers | 33 | 22 | 4 | 10 | 4 | 1 |
| Central-adrenergic inhibitors | 11 | 3 | - | 8 | - | - |
| Reserpine | - | 1 | 1 | - | - | - |
| Alpha$_1$-adrenergic blockers | 1 | - | - | 1 | - | - |
| Vasodilators | 5 | 3 | 1 | - | - | 1 |
| ACE inhibitors | 34 | 31 | 11 | 6 | 3 | 5 |
| Calcium antagonists | 19 | 30 | 18 | 1 | 5 | 3 |

*Does not include patients with alcohol abuse or a secondary disease causing resistance.

**Fixed combination agents.

Abbreviations: Thiazides = Thiazides and related sulfonamide diuretics, Potassium-sparing = Potassium-sparing diuretics, ACE = Angiotensin-converting enzyme.

Mean cholesterol and triglycerides levels, measured in 46 patients, were 226 $\pm$ 45mg/dL and 174 $\pm$ 96mg/dL respectively. Mean HDL and LDL levels, measured in 19 and 18 patients respectively, were 42 $\pm$ 13mg/dL and 152 $\pm$ 44mg/dL.

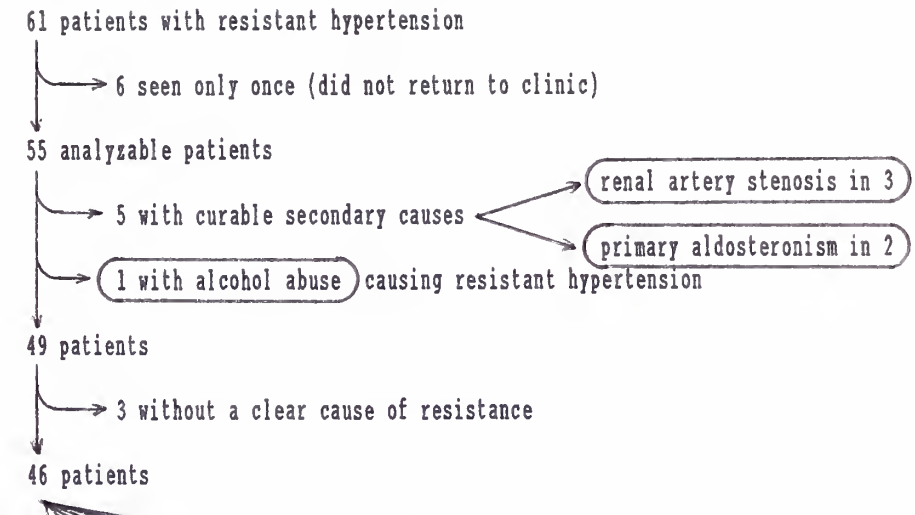
## Follow-up and Outcome

Of those 61 patients who met criteria for resistant hypertension, 55 returned to clinic at least once, and

these comprised the group of resistant hypertensive patients who were analyzable; they were followed for an average of 10.0 ± 9.3 months. The final diagnoses along with the results of treatment in the clinic are summarized in figures 2 and 3. Patients were assigned to categories of causes of resistance based upon their meeting the specific criteria stated under "Final Diagnosis." In some cases, patients met the criteria for more than one cause. When both of these causes were important contributors to resistance, the patient is reported in a combined category; when one was a minor contributor to resistance, the patient is reported in the major category alone. Minor causes are reported in a footnote of figure 2.

Of those 55 patients who returned to clinic at least once, 30 (55%) were controlled, and another 6 had significantly improved blood pressure. Of the remaining 19, diastolic blood pressure was (not significantly) decreased in 9. All three patients with renal artery stenosis responded to angioplasty or surgery, and both patients with primary aldosteronism were treated surgically.

**Figure 2.** Diagnoses and results of treatment.




| | Psychiatric disease | Medication intolerance | Noncompliance | Suboptimal medical regimen | White-coat hypertension | Psychological causes of medication intolerance & noncompliance | Drug interaction | TOTAL** |
|---|---|---|---|---|---|---|---|---|
| Controlled: | - | 3 | - | 1 | 1 | 16 | 1 | 2 | 1 | - | - | 25 |
| Significantly improved: | - | 1 | - | - | - | 4 | - | - | - | - | 1 | 6 |
| Neither: | 1 | 2 | 6 | 3 | - | 1 | - | - | - | 2 | - | 15 |

*In addition to the primary problems enumerated above, six patients had a suboptimal medical regimen, three patients had a drug interaction, and two patients had noncompliance as significant but minor contributors to their resistance.

**Blood pressure control was documented in all but one of the six patients with secondary causes or alcohol abuse; one of the patients with renal artery stenosis was off all medications after angioplasty and had a blood pressure of 138/100mmHg on her final clinic visit. The three patients without a clearly established cause of resistance did not show significant improvement in blood pressure control.

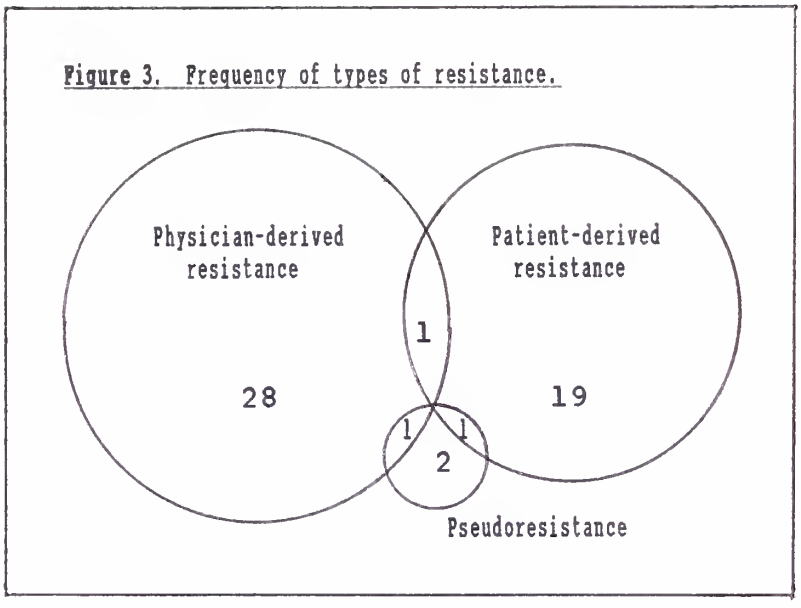



Figure 3. Frequency of types of resistance.

Table 4 also reports agents used in the final regimen of those 49 patients without a curable secondary cause or alcohol abuse causing refractory blood pressures (that is, those 49 patients with essential hypertension) who returned to clinic at least once ("FINAL" column). The mean number of agents used was 2.6 $\pm$ 1.3. The therapeutic interventions according to class of antihypertensive agent used are also recorded in table 4. Fifty-seven new agents were added and 36 were removed, while 17 of the original agents were increased in dose, and 14 were decreased.

Of the 29 patients who were found to have a suboptimal medical regimen as a cause (either major or minor) for their resistance, twenty-eight achieved control or significant improvement in their blood pressure. In those 23 patients who were completely controlled, 32 agents were added and 14 were removed, while 11 of the

original agents were increased in dose, and 9 were decreased. The specific agents (by class) are reported in table 5.

Table 5. Correction of suboptimal regimens.

| Agent | N = 23 Added | Removed | Increased | Decreased |
|---|---|---|---|---|
| Diuretics | 17 | 3 | 2 | 2 |
| Thiazides | 10 | 1 | 1 | - |
| Thiazide/Potassium-sparing* | 3 | 1 | - | - |
| Loop diuretics | 4 | 1 | 1 | 2 |
| Beta-adrenergic blockers | 1 | 5 | 3 | 1 |
| Central-adrenergic inhibitors | - | 4 | - | - |
| Reserpine | 1 | - | - | - |
| Vasodilators | 1 | - | - | 1 |
| ACE inhibitors | 3 | 2 | 2 | 3 |
| Calcium antagonists | 9 | - | 4 | 2 |

*Fixed combination agents.

Abbreviations: Thiazides = Thiazides and related sulfonamide diuretics, Potassium-sparing = Potassium-sparing diuretics, ACE = Angiotensin-converting enzyme.

Of the 23 patients who were on a suboptimal medical regimen and were subsequently controlled, 21 (91%) needed the addition of one or more new agents to their regimen. Fourteen of these 23 patients (61%) needed initiation of diuretic therapy to achieve control, and another three patients needed a change in diuretic agent (one from a loop diuretic to a thiazide, two from a thiazide to a loop diuretic). Sixteen patients (70%) needed initiation or

augmentation of therapy with a relatively new agent: a calcium antagonist (12) and/or an angiotensin-converting enzyme inhibitor (5). Some patients needed an increase in the dosage of medication they were already taking. Of those 29 patients who were on a suboptimal medical regimen, thirteen (45%) were controlled by the addition, or augmentation, of diuretic and/or calcium antagonist therapy alone.

Noncompliance (as a major or minor contributor to resistance) was present in sixteen patients; it was accompanied by medication intolerance in nine. The patients who did not have accompanying medication intolerance were more likely to show significant improvement in blood pressure than those who did ($0.05 \leq p \leq 0.10$). In those seven patients who had noncompliance without medication intolerance, the three whose regimen was increased in frequency did not have significant improvement in blood pressure; the four patients whose regimen was decreased in frequency or unchanged, did have significant improvement ($p < 0.05$). Frequency of a patient's regimen was defined as the frequency of the most frequently taken agent on that regimen.

**Covariate Analysis**

Final outcome (controlled vs. not controlled, and

controlled or significantly improved vs. neither) did not correlate with age, gender, race, presence of particular comorbid diseases, number of comorbid diseases, tobacco use (prior or present), high alcohol consumption (prior or present), duration of hypertension, cholesterol, triglyceride, HDL, and LDL levels, or highest blood pressures by history (systolic or diastolic). There was a trend towards higher diastolic blood pressure (by history) in those patients who could not be controlled: controlled 115 $\pm$ 18mmHg, controlled or significantly improved 116 $\pm$ 19mmHg, no significant improvement 122 $\pm$ 17mmHg; however, the difference was not statistically significant.

## DISCUSSION

Resistance to therapy is a subjective experience as well as an objective phenomenon. Thus, it is not surprising that some patients who are referred for resistant hypertension will not meet objective criteria for such. The criteria used for inclusion in this study were designed to identify those patients who can be justifiably called resistant by a referring physician. The high frequency of resistance found in this clinic population (20% of 300 patients) is in marked contrast to the recent study of employed hypertensive patients identified by workplace screening which found a less than 3% incidence.[32] However, the investigators in that study removed from the "resistant" category all patients who achieved a 10% fall in diastolic and 15% fall in systolic blood pressure even if final blood pressure remained above normal. I disagree with this criterion of categorization because those patients still have unacceptable blood pressures in spite of medical therapy, and are therefore resistant to attempts at controlling blood pressure even if they aren't resistant to attempts at improving it. It has been suggested previously that severe resistant hypertension may be present in 5 to 10% of hypertensive patients[45] and, as this study shows, the frequency varies with clinical setting. The frequency of resistance varies

with both the clinic's population and the clinic's level of expertise in treating the condition.

Of the 61 patients who met criteria for resistant hypertension upon referral, 24 still had resistant essential hypertension at the conclusion of the study. This means that eight percent of patients seen in this tertiary care clinic continued to have uncontrolled blood pressure (by the criteria in table 1) through their final, or most recent, clinic visit. Thus, I would say that in the population of patients seen in this hypertension clinic, 20% had hypertension resistant to community care, and eight percent had hypertension resistant to expert care. The majority of patients in this latter group had medication intolerance or noncompliance causing resistance.

These patients referred for resistant hypertension had (on average) a 15 year history of documented disease, with an average of four drugs having been tried and discontinued in the past because of side effects or ineffectiveness. Nonetheless, the most frequent cause of resistance in the community setting was a suboptimal medical regimen. Almost half the patients referred for resistant hypertension were found to have resistance due to a suboptimal medical regimen, and three-quarters of those patients could subsequently be controlled. In fact, all but one of those 29 patients who were on a suboptimal

regimen achieved at least a 15% fall in diastolic blood pressure if not complete control of systolic and diastolic pressures. Addition of a diuretic or use of a newer agent such as a calcium antagonist, or augmentation of therapy with these agents, proved to be the most successful therapeutic maneuver in this group.
Angiotensin-converting enzyme (ACE) inhibitors were also added in a few patients. All the interventions used were ones generally available to outpatient clinics.

The need for calcium antagonists in patients referred on suboptimal regimens is probably due to less familiarity among referring physicians with these agents. ACE inhibitors, which are a few years older than calcium antagonists, were added less often. Fifty-seven percent of patients who met criteria for resistance at referral were referred on ACE inhibitors, while calcium antagonists were used in only 31%. Treatment in the Hypertension Clinic eliminated the difference; ACE inhibitors were used in 65% of patients with essential hypertension, and calcium antagonists were used in 61%. Use of these agents frequently permitted discontinuation of agents that carry more side effects, such as central-adrenergic inhibitors and beta-adrenergic blockers.

The high frequency of inadequate diuretic therapy may reflect a growing reluctance to use these agents because of the criticism they have received with time. Avoiding

diuretics in favor of newer agents causes problems in patients with volume-dependent hypertension, which is particularly common among patients taking peripheral $alpha_1$-adrenergic blockers, central $alpha_2$ agonists, vasodilators, or peripheral sympathetic blockers.[46] The need to adequately control volume in hypertensive patients cannot be overemphasized, for volume overload alone can prevent control of otherwise manageable hypertension;[26,27,41] this phenomenon has been referred to as "pseudotolerance"[35] or "pseudo-resistance"[46].

Five patients were referred on vasodilator therapy. Two of those did not return to clinic, and a third returned only once and was lost to follow-up before a diagnosis was established. The vasodilator dosage was halved in one of the two remaining patients, and it was discontinued in the other. Only one patient was started on vasodilator therapy in the Hypertension Clinic (in this case, with minoxidil). This patient was intolerant of other agents when they were prescribed at dosages that controlled blood pressure. In summary, only two patients were taking minoxidil at the conclusion of the study. Minoxidil is an effective but poorly tolerated treatment for resistant hypertension[16,18,21,47] and, as shown in the present study, is rarely needed now that ACE inhibitors and calcium antagonists are available.

Secondary causes of hypertension, though not common in the general population, were certainly not uncommon in this referred group. Of patients meeting our criteria for resistant hypertension, eight percent had correctable secondary causes. However, the seven patients who were referred with a known secondary cause were excluded from the present study; when these patients are included, the incidence of secondary hypertension becomes 15% of patients referred to the clinic for "resistant hypertension." The Cleveland Clinic has reported an 11% incidence of secondary hypertension among 4,939 patients referred to the clinic with hypertension (not necessarily resistant) over a two year period.[48] Other sources have reported a 0.5 to 10% incidence of secondary hypertension;[42] the broad range arises from variability in the kind of populations studied.

The five percent incidence of renal artery stenosis is similar to that reported by a study of 3,520 patients referred for evaluation for secondary causes of hypertension, which found a three percent incidence,[49] as well as the four percent incidence found in the Cleveland Clinic study mentioned above.[48]

Pheochromocytoma and primary aldosteronism are reported to have an incidence of 0.1 to 0.5%[42,48] in a hypertensive population. Therefore, finding no patients with pheochromocytoma is consistent with what we would

expect, but finding two patients (three percent) with primary aldosteronism is a little surprising. Although the suggestion of a 20% incidence of "normokalemic aldosteronism" in patients with "essential hypertension" made by Conn[50] has been rejected as a lack of appreciation of the syndrome of low renin essential hypertension,[42] estimates of the incidence of primary aldosteronism may suffer from underdetection owing to the difficulty in diagnosing this condition. The small size of that group in this study, however, limits the generalizability of the findings.

Medication intolerance secondary to psychological causes was distinguished in this study from medication intolerance per se. This was done because patients with medication intolerance per se had usual side effects from their antihypertensive drugs, but of a magnitude and frequency that prohibited the use of therapeutic dosages. Those patients who were categorized as having intolerance secondary to psychological causes consistently ascribed to their medications adverse effects which were considered a result of unrelated psychological and physical stresses. Finding an acceptable regimen in these patients is particularly challenging since the intolerance seems largely unrelated to the particular agents prescribed. The majority of patients whose blood pressure could not be

controlled in the Hypertension Clinic had medication intolerance and/or noncompliance causing their resistance.

Noncompliance was surprisingly underrepresented as a cause of resistance; current estimates of noncompliance have been as high as 50%,[51,52] and as low as 4% in patients on simplified regimens.[53] It may be that those patients willing to pursue treatment in a specialty clinic are more likely to be compliant. It is also likely that, with the growing awareness of this problem, the incidence of undetected noncompliance is falling. Slightly more than half of those patients with noncompliance also had medication intolerance. Education alone may be of limited value in these patients since their noncompliance is related to poor tolerance of the agents themselves. These patients should be considered separately from those without medication intolerance since one is likely to use different treatment strategies for the two groups. Minimizing dosages and taking the liberty to try a variety of agents may be the most useful course of action in the patients with medication intolerance and noncompliance, while simplification of the medical regimen may be the most successful approach in the patients without medication intolerance.

The results in this study show a significant correlation between more complex regimens and failure of therapy. An earlier study of compliance in elderly

hypertensive patients also found that compliance improved with reduction in the number of tablets taken, and their frequency.[53] Other research has suggested that failure in understanding is the most frequent problem in noncompliant patients;[54,55] careful counseling is an important part of these patients' management. Compliance was assessed in this study by patient interview, which is not as accurate as pill counts or pharmacist logs, but is probably still quite reliable.[56]

White-coat hypertension was identified in four patients. They all required antihypertensive therapy to achieve ambulatory normotension, thus they had essential hypertension without true resistance. I categorize white-coat hypertension as pseudoresistance because it is not resistance in the hypertension itself, but rather is resistance of a physiological anxiety response: what Pickering calls, "a pressor response to the physician."[57] Although 24-hour ambulatory monitoring of every patient is currently prohibitive, blood pressure measurements at home, or in other settings, may provide clues that a patient has white-coat hypertension, as might signs of unusual variability in blood pressure.

Three patients remained undiagnosed. Although these are potentially disease-resistant cases, they were all lost to follow-up after only two or three visits. It is

likely that a cause would have been found if they had continued to come to the clinic.

Diastolic blood pressure control has been defined as pressure $\leq$ 90mmHg in other studies[24,25] besides this one, though some authors have used 95mmHg[14,23] or 100mmHg.[35,58-60] In this study, 90mmHg was accepted as a ceiling, since this is the level of diastolic control that is believed to be associated with decreased morbidity and mortality.[38] Systolic blood pressure control was adjusted for age to accommodate for isolated systolic hypertension in the elderly. Rather than use a cut-off of 150mmHg[60] or 160mmHg[35] regardless of age, as has been suggested in some discussions of resistant hypertension, the definitions were chosen to reflect goals that would be systematic and yet individualized.

Using an average of two blood pressure measurements when assessing for blood pressure control serves two purposes. Firstly, it decreases the variability associated with single measurements; it is for this reason also that two consecutive visits with controlled blood pressure were required to establish loss of resistance. Secondly, being an average of supine and standing blood pressures, it assures that supine blood pressure is controlled within the limits tolerated by standing blood pressure. Supine blood pressure control can be difficult to achieve because of postural changes, but it should be

included in the definition of control since target organ damage may progress when only supine blood pressure remains uncontrolled.[61]

The criteria for demonstrating control of hypertension included cases of demonstratiion of control on only a single visit if that was the patient's final visit to the Hypertension Clinic. This condition was included because, being a referral clinic, patients were often not seen after control was achieved. Accepting a final visit blood pressure as evidence for control helped eliminate the bias introduced by discounting as uncontrolled all those patients who did not return because their hypertension became controlled.

The size of the sample in this study limited the likelihood of demonstrating associations between factors which may be identified on an initial visit and the final categories of resistance (or outcome). Factors that may be associated with particular categories of resistance according to a previous study include gender, blood pressure, body mass index, funduscopic changes, serum cholesterol, and fasting blood sugar.[32] As in this study, age, race, smoking history, and a history of angina were not found to be significantly associated with final diagnosis. Other studies have shown particular agents to be more effective in certain subpopulations. For example,

diltiazem seems to be more effective in older and female patients.[62]

I would conclude from the present study that resistant hypertension, the reason for referral in 26% of physician-referred patients in this tertiary care clinic, is not unusual. Excluding drug interactions and noncompliance is the first step in managing these patients; likewise, white-coat hypertension and pseudohypertension should be considered at the outset. The large majority of those patients remaining resistant are likely to be on suboptimal medical regimens, and can be controlled with changes in their regimens. Many patients will be volume expanded, and most will require the addition or augmentation of appropriate diuretic therapy; some will require adjustment of diuretic therapy, such as replacing thiazides with loop diuretics in patients with renal insufficiency. Although calcium antagonists were also important in achieving control, the need for this intervention probably reflects the time lag between the introduction of new agents and their widespread use. Evaluation for secondary causes of hypertension will identify curable diseases in some of the patients who remain resistant. Those remaining patients without a secondary cause will typically be resistant as a result of medication intolerance with or without noncompliance. These two problems are often interrelated

and difficult to correct. Simplifying regimens and minimizing adverse side effects will provide some degree of success with these patients. An algorithm for the management of patients with resistant hypertension follows; it is an adaptation of a schema presented elsewhere by Black.[46]

1. Exclude drug interactions and noncompliance.
2. Be sure the patient doesn't have white-coat hypertension or pseudohypertension.
3. Be sure the patient isn't volume expanded.
4. Evaluate the patient for secondary causes of hypertension.
5. Simplify the regimen, if possible, and minimize adverse side effects.

Although the patients referred to a tertiary care clinic represent a biased population of hypertensive patients, the present study offers some suggestions as to approaches that may be productive and effective in patients with resistant hypertension, and also provides another perspective on the frequency of resistant hypertension and its subtypes.

## REFERENCES


1. Spritzer N, Spritzer TS, Rodriguez R. Treatment of resistant hypertension: 3 years of follow-up with the combination of verapamil and methyldopa. J Cardiovasc Pharmacol 1989; 13(suppl 4):65-7.

2. Heagerty AM, Bing RF, Thurston H, Swales JD. Nifedipine substituted for minoxidil in the treatment of refractory hypertension. J Hum Hypertens 1987; 1(2):83-6.

3. White WB, Viadero JJ, Lane TJ, Podesla S. Effects of combination therapy with captopril and nifedipine in severe or resistant hypertension. Clin Pharmacol Ther 1986; 39(1):43-8.

4. Murphy MB, Bulpitt CJ, Dollery CT. Role of nifedipine in the treatment of resistant hypertension. Am J Med 1984; 77(2B):16-21.

5. Sloan PJ, Beevers DG. Nifedipine in combination therapy for resistant hypertension. Pharmatherapeutica 1983; 3(5):349-53.

6. Seideman P, Ekeroth M, Ostman J. Effects of felodipine in refractory hypertension. Drugs Exp Clin Res 1988; 14(9):587-92.

7. Herlitz H, Bjorck S, Nyberg G, Granerus S, Aurell M. Clinical evaluation of felodipine in patients with refractory hypertension. Drugs 1987; 34(suppl 3):151-5.

8. Maclean D, Mitchell ET, Readman AS. Felodipine compared to nifedipine as "third-line drug" in resistant hypertension. Angiology 1986; 37(11):840-5.

9. Collste P, Danielsson M, Elmfeldt D, et al. Long term experience of felodipine in combination with beta-blockade and diuretics in refractory hypertension. Drugs 1985; 29(suppl 2):124-30.

10. Laher MS, ORegan P, ODonohoe JF, Counihan TB. Captopril for refractory hypertension in patients with impaired renal function. J R Soc Med 1985; 78(5):367-72.

11. Forslund T, Fyhrquist F, Hortling L. Sustained antihypertensive effect of captopril combined with diuretics and beta-adrenergic blocking drugs in patients with resistant hypertension. Acta Med Scand 1983; 213(4):299-303.

12. Raine AE, Ledingham JG. Clinical experience with captopril in the treatment of severe drug-resistant hypertension. Am J Cardiol 1982; 49(6):1475-9.

13. Maskill MR, Orme ML, MacIver M, Serlin MJ, Breckenridge AM. Efficacy and adverse effects of captopril in severe refractory hypertension. J Cardiovasc Pharmacol 1981; 3(6):1287-95.

14. Pigott PV, Hill JF, Weston-Davies WH. The use of captopril in severe treatment resistant hypertensive patients. Drugs Exptl Clin Res 1980; 6(6):533-40.

15. White NJ, Rajagopalan B, Yahaya H, Ledingham JG. Captopril and frusemide in severe drug-resistant hypertension. Lancet 1980; 2(8186):108-10.

16. Spitalewitz S, Porush JG, Reiser IW. Minoxidil, nadolol, and a diuretic. Once-a-day therapy for resistant hypertension. Arch Intern Med 1986; 146(5):882-6.

17. Andreucci VE, Usberti M, Federico S, Pecoraro, Balletta M, Meccariello S. Long-term follow-up of minoxidil therapy in refractory hypertension. A prospective trial in patients with various degrees of renal insufficiency. Clin Nephrol 1983; 19(2):55-60.

18. Mackay A, Isles C, Henderson I, Fife R, Kennedy AC. Minoxidil in the management of intractable hypertension. Q J Med 1981; 50(198):175-90.

19. Rosenthal T, Swartz J, Teicher A, Boichis H. Minoxidil in the treatment of refractory hypertension. Angiology 1980; 31(3):176-84.

20. Mitchell HC, Pettinger WA. Long-term treatment of refractory hypertensive patients with minoxidil. JAMA 1987; 239:2131-8.

21. Kleiner JP, Ball JH, Nelson WP, Norton JD. The outpatient treatment of resistant hypertension with minoxidil. South Med J 1977; 70(7):814-7.

22. Zacest R, Frewin DB, Robinson MA, et al. Clinical and hemodynamic effects of minoxidil in refractory hypertension. Drugs 1976; 11(suppl 1):177-84.

23. Hunyor SN. Hydrallazine and beta-blockade in refractory hypertension with characterization of acetylator phenotype. Aust N Z J Med 1975; 5(6):530-6.

24. Englert RG, Mauersberger H. A single-blind study of doxazosin in the treatment of essential hypertension when added to nonresponders to angiotensin-converting enzyme inhibitor therapy. Am Heart J 1988; 116(6 Pt 2):1826-32.

25. Lindner UK, von Manteuffel GE, Stafunsky M. The addition of doxazosin to the treatment regimen of hypertensive patients not responsive to nifedipine. Am Heart J 1988; 116(6 Pt 2):1814-20.

26. Ramsay LE, Silas JH, Freestone S. Diuretic treatment of resistant hypertension. Br Med J 1980; 281(6248):1101-3.

27. Wilson M, Morgan T, Gillies A. A role of frusemide in resistant hypertension. Med J Aust 1977; 1(7):213-5.

28. Hedstrand H. Labetalol in resistant hypertension. Acta Med Scand Suppl 1982; 665:125-8.

29. Williams LC, Murphy MJ, Parsons V. Labetalol in severe and resistant hypertension. Br J Clin Pharmacol 1979; 8(suppl 2):143S-7S.

30. Morgan T, Gillies A, Morgan G, Adam W. The effect Of labetalol in the treatment of severe drug-resistant hypertension. Med J Aust 1978; 1(7):393-6.

31. Dargie HJ, Dollery CT, Daniel J. Labetalol in resistant hypertension. Br J Clin Pharmacol 1976; 3(4 suppl 3):751-5.

32. Alderman MH, Budner N, Cohen H, Lamport B, Ooi WL. Prevalence of drug resistant hypertension. Hypertension 1988; 11(3 Pt 2):II71-5.

33. Ram CV. Management of resistant hypertension. Chest 1987; 92(6):1096-7.

34. Gifford RW Jr, Tarazi RC. Resistant hypertension: diagnosis and management. Ann Intern Med 1978; 88(5):661-5.

35. Frohlich ED. Classification of resistant hypertension. Hypertension 1988; 11(3 Pt 2):II67-70.

36. Vidt DG. The patient with resistant hypertension. Cations, volume, and renal factors. Hypertension 1988; 11(3 Pt 2):II76-83.

37. Gifford RW Jr. An algorithm for the management of resistant hypertension. Hypertension 1988; 11(3 Pt 2):II101-5.

38. The 1988 Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure: the 1988 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. Arch Intern Med 1988; 148:1023-88.

39. Frohlich ED, Gifford RW Jr, Horan M, et al. Nonpharmacological approaches to the control of high blood pressure. Report of the Subcommittee on Nonpharmacologic Therapy for the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure, 1984. Hypertension 1986; 8(5):444-67.

40. Johns DW, Peach MJ. Factors that contribute to resistant forms of hypertension. Pharmacological considerations. Hypertension 1988; 11(3 Pt 2):II85-95.

41. Dustan HP, Tarazi RC, Bravo EL. Dependence of arterial pressure on intravascular volume in treated hypertensive patients. N Engl J Med 1972; 286:861-6.

42. Black HR. The diagnosis and treatment of secondary hypertension. Develop Cardiol 1989; 1(9):1-17.

43. The Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure: the 1984 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. Arch Intern Med 1984; 144:1045-57.

44. Barnhart ER, pub. Physicians' desk reference. 42nd ed. Oradell: Medical Economics Company Inc., 1988:1802-4.

45. Raftos, J. The difficult hypertensive. Drugs 1976; 11:55-60.

46. Black HR. Distinguishing resistant hypertension. Cardio 1988; 5(12):61-70.

47. Berlyne GM, Giovanelli S, ed. Minoxidil therapy in refractory hypertension. Analysis of 155 patients. Nephron 1978; 21:1-15.

48. Gifford RW Jr. Evaluation of the hypertensive patient with emphasis on detecting curable causes. Milbank Mem Fund Q 1969; 47(3 Pt 2):170-86.

49. Anderson GH, Blakeman N, Streeten DH. Prediction of renovascular hypertension. Comparison of clinical diagnostic indices. Am J Hypertens 1988; 1:301-4.

50. Conn JW, Cohen EL, Rovner DR, Nesbit RM. Normokalemic primary aldosteronism. JAMA 1965; 193:200-6.

51. Becker MH. Patient adherence to prescribed therapies. Med Care 1985; 23:539-55.

52. Sackett DL, Haynes RB, Gibson ES, et al. Randomized clinical trial of strategies for improving medication compliance in primary hypertension. Lancet 1975; 1:1205-7.

53. Morgan TO, Nowson C, Murphy J, Snowden R. Compliance and the elderly hypertensive. Drugs 1986; 31(suppl 4):174-83.

54. Morse GD, Douglas JB, Upton JH, Rodgers S, Gal P. Effect of pharmacist intervention on control of resistant hypertension. Am J Hosp Pharm 1986; 43(4):905-9.

55. German PS. Compliance and chronic disease. Hypertension 1988; 11(3 Pt 2)II56-60.

56. Klein LE. Compliance and blood pressure control. Hypertension 1988; 11(3 Pt 2):II61-4.

57. Pickering TG. Blood pressure monitoring outside the office for the evaluation of patients with resistant hypertension. Hypertension 1988; 11(3 Pt 2):II96-100.

58. Barnett AJ, Taubman I. Current status of treatment of severe hypertension. Med J Aust 1976; 2:563-6.

59. Forslund T, Fyhrquist F, Hortling L. Sustained antihypertensive effect of captopril combined with diuretics and beta-adrenergic blocking drugs in patients with resistant hypertension. Acta Med Scand 1983; 213:299-303.

60. Gifford RW Jr. Resistant hypertension. Introduction and definitions. Hypertension 1988; 11(3 Pt 2):II65-6.

61. Kincaid-Smith PS. The treatment of resistant hypertension. Drugs 1976; 11(suppl 1):78-86.

62. Massie B, MacCarthy EP, Ramanathan KB, et al. Diltiazem and propranolol in mild to moderate essential hypertension as monotherapy or with hydrochlorothiazide. Ann Intern Med 1987; 107(2):150-7.

YALE MEDICAL LIBRARY

Manuscript Theses

Unpublished theses submitted for the Master's and Doctor's degrees and deposited in the Yale Medical Library are to be used only with due regard to the rights of the authors. Bibliographical references may be noted, but passages must not be copied without permission of the authors, and without proper credit being given in subsequent written or published work.

This thesis by has been used by the following persons, whose signatures attest their acceptance of the above restrictions.

| NAME AND ADDRESS | DATE |
| --- | --- |
| | |
| | |