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Results of a Department of Veterans Affairs Cooperative Study**

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Original Contributions

Treatment of Hypertension in the Elderly: I. Blood Pressure and Clinical Changes

Results of a Department of Veterans Affairs Cooperative Study

Barry J. Materson, William C. Cushman, Gerald Goldstein, Domenic J. Reda,
Edward D. Freis, Eli A. Ramirez, Frederick N. Talmers, Thomas J. White, Stewart Nunn,
Robert H. Chapman, Ibrahim Khatri, Harold Schnaper, J.R. Thomas,
William G. Henderson, and Carol Fye

for the Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents

We compared the efficacy and adverse effects of antihypertensive drug regimens in 690 men past age 60 with diastolic blood pressure 90–114 mm Hg and systolic blood pressure less than 240 mm Hg. They received either a low (25–50 mg) or high (50–100 mg) dose of hydrochlorothiazide daily. Of 644 patients who completed the hydrochlorothiazide titration, 375 (58.2%) were responders (diastolic blood pressure <90 and ≤ 5 mm Hg below baseline) and 92.8% of these completed a 6-month maintenance period. Blood pressure was reduced from 157.6/98.5 mm Hg by 18.3/9.5 mm Hg with low dose hydrochlorothiazide and by 20.4/9.6 mm Hg with high dose hydrochlorothiazide; more patients achieved goal blood pressure with the high dose. Whites and blacks responded equally. Serum potassium less than 3.5 mmol/l occurred in 104 of 321 (32.3%) of the high dose versus 62 of 333 (18.6%) of the low dose hydrochlorothiazide patients. The 269 nonresponders to hydrochlorothiazide were randomly assigned in a double-blind study to receive hydralazine, methyldopa, metoprolol, or reserpine in addition to hydrochlorothiazide; 79.2% responded to the addition of the second drug and 87.3% of these completed a 6-month maintenance phase. Overall, there were no significant efficacy differences among the step 2 regimens. We conclude that the lower dose of hydrochlorothiazide was nearly as effective as the higher dose, and the addition of a second drug was effective and generally well tolerated in elderly patients. (*Hypertension* 1990;15:348–360)

Treatment of hypertension in the elderly has been demonstrated to reduce cardiovascular morbidity and mortality.^{1–5} Nevertheless, antihypertensive agents have been reported in less rigorously controlled situations to impair function or quality of life in the elderly.^{6–12} Most of these reports are anecdotal and do not examine the effects of these drugs on cognitive or behavioral function, nor do they compare the efficacy or adverse effects of different antihypertensive regimens. The Quality of Life Study from the University of Connecticut Health Sciences Group specifically excluded patients above age 65.¹³ Miller et al¹⁴ used psychometric testing to demon-

strate improvement in previously demonstrated behavioral deficits in young men and women after long-term antihypertensive therapy.

This study was designed to evaluate the effect of various antihypertensive regimens on blood pressure, biochemical values, symptomatology, and cognitive and behavioral function in an elderly hypertensive population. We performed a double-blind, randomized, multicenter trial that included detailed psychometric testing. The objective of the psychometric testing was to assess the effects of various blood pressure-lowering regimens on memory, motor skills, and other cognitive functions, activities of daily living, and mood for those patients whose blood pressure was controlled. We wanted to determine both the antihypertensive efficacy and comparative adverse effects of 50 mg hydrochlorothiazide (HCTZ) daily compared with 100 mg daily and, in those patients who were nonresponsive to the diuretic, the comparative efficacy and adverse effects

From the Cooperative Studies Program of the Medical Research Service of the Department of Veterans Affairs.

Address for correspondence: Barry J. Materson, MD, Associate Chief of Staff for Education (141), Veterans Administration Medical Center, 1201 N.W. 16th Street, Miami, FL 33125.

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of the addition of one of four "step 2" drugs: hydralazine, methyldopa, metoprolol, or reserpine.

The data are presented in two parts. In part I, the antihypertensive efficacy, adverse effects, and laboratory test changes of the various drugs are compared. In Part II, the results of the cognitive and behavioral tests are presented.

Methods

Patient Inclusion

This study was a seven-hospital, cooperative, randomized, double-blind clinical trial. It was planned in 1980, initiated in October 1981, and concluded in 1986. Hypertensive men 60 years of age or older were entered into the trial after appropriate informed consent if they met criteria described below. The visit blood pressure was defined as the median of three blood pressure readings taken in the sitting position with a mercury manometer. Patients not currently receiving treatment for hypertension were accepted in the trial if the diastolic (phase V) blood pressure (DBP) was 90–114 mm Hg with a systolic blood pressure (SBP) below 240 mm Hg. Patients under treatment for hypertension were accepted if their SBP was below 220 mm Hg and their DBP was below 110 mm Hg and if they met the previous inclusion blood pressure criteria after at least 2 weeks without medication.

Patients were excluded if they had a severe complication of hypertension, secondary hypertension, a serious medical or psychiatric disease, or a contraindication to treatment with any of the study drugs. Patients were excluded if they had a history of congestive heart failure, intracranial bleed, atherothrombotic stroke or myocardial infarction within the past 6 months, or angina pectoris greater than New York Heart Association Class II; left ventricular hypertrophy by electrocardiogram was not disqualifying. Patients were also excluded if they were unable to attend clinic visits throughout the duration of the study or could not be withdrawn safely from concomitant medications that would interfere with the trial.

Prerandomization Period

There was a prerandomization, single-blind placebo period of 2–5 biweekly visits to obtain baseline data and to determine eligibility for randomization. Tablet counts were used to assess compliance and considered acceptable if the patient had taken within 80–110% of the prescribed amount.

A patient was considered eligible for randomization if he were compliant at two consecutive visits at which the DBP was 90–114 mm Hg with the SBP below 240 mm Hg within a maximum of five visits over 8 weeks. Patients were excluded if the SBP was over 239 mm Hg or the DBP was over 114 mm Hg at any one visit, or if the DBP was below 90 mm Hg at any two consecutive visits. In addition, they were excluded if the SBP was 230–239 mm Hg or the DBP was 110–114 mm Hg at two consecutive visits during

which the patient could not be randomly assigned to a group because of noncompliance.

The baseline SBP and DBP was defined as the averages of the median pressures at the randomization visit and the visit immediately preceding. The goal blood pressure (GBP) was defined as a DBP below 90 mm Hg and at least 5 mm Hg below baseline DBP with a SBP below 160 mm Hg.

Titration Phase I

Eligible patients were randomly assigned in a double-blind fashion to begin with either 25 or 50 mg HCTZ once daily. Dosage titration was performed at a maximum of five biweekly regular visits. The daily drug dose could be halved or increased to twice daily to achieve GBP without adverse effects. A patient was considered to be a treatment responder if he achieved GBP without adverse effects at two consecutive visits on the same drug dose level.

Patients were withdrawn from the study during this titration if the SBP was over 239 mm Hg or the DBP over 114 mm Hg at any visit, or if intolerable side effects or severe hypotension developed while receiving one half tablet a day. Treatment responders were maintained on the same drug regimen for an additional 6 months. Potassium supplementation was withheld unless the serum potassium level fell below 3.0 mmol/l. Those with no drug intolerance but still not at GBP after the maximum number of visits entered a second phase of this study in which they were continued on diuretic therapy and were randomly assigned one of four additional drugs: hydralazine, methyldopa, metoprolol, or reserpine.

Maintenance Phase I

Patients whose blood pressure was controlled on diuretic therapy were seen every 4 weeks for six visits. They were continued in the maintenance phase even if not at GBP if, after dose adjustment, the SBP was not over 169 mm Hg and the DBP was not over 99 mm Hg. Patients were withdrawn during this phase for the following reasons: 1) SBP over 239 mm Hg or DBP over 114 mm Hg at any visit, 2) SBP over 169 mm Hg or DBP over 99 mm Hg on three consecutive visits, 3) drug intolerance at the lowest dosage level, 4) SBP over 219 mm Hg or DBP over 109 mm Hg at maximal dosage, or 5) if the patient was drug intolerant and was not at GBP.

Titration Phase II

Patients who were diuretic nonresponders were continued on the same HCTZ dosage and were randomly assigned in a double-blind parallel design to receive the addition of either hydralazine, methyldopa, metoprolol, or reserpine. Because these drugs do not have the same appearance, the double-blind was maintained by assigning bottles of medication for two of the additional agents; one bottle contained active drug and the other placebo. Titration was performed to GBP, adverse effects, or maximum dosage. Dosage levels for titration were as

follows: hydralazine 25, 50, and 100 mg b.i.d.; methyldopa 250, 500, and 1,000 mg b.i.d.; metoprolol 50, 100, and 200 mg b.i.d.; and reserpine 0.05, 0.10, and 0.25 mg once daily. Half of the lowest dose level was also permitted as well as decreasing a previously prescribed dosage if there were side effects.

Patients were withdrawn from the study during titration if the SBP was over 239 mm Hg or the DBP over 114 mm Hg at any visit, if there was drug intolerance at the lowest dosage level of therapy, if the SBP was over 219 mm Hg or the DBP over 109 mm Hg at maximum dosage, or if GBP was not achieved at two consecutive visits at maximum tolerated dosage. A maximum of five biweekly visits was allowed to achieve GBP, but weekly visits were scheduled if there was drug intolerance or the SBP was 180–239 mm Hg or the DBP 105–114 mm Hg. Patients were advanced to a maintenance phase if they achieved GBP on two consecutive visits without drug intolerance.

Maintenance Phase II

Patients were seen every 4 weeks for six visits. Provisions were made to titrate the nondiuretic antihypertensive medication upward to maximum dose as needed if blood pressure rose above goal. The criteria for withdrawing a patient from the study were identical with those for Maintenance Phase I.

Discontinuation From Protocol

In addition to the blood pressure and drug tolerance criteria already specified, discontinuation of protocol therapy was allowed at any time at the patient's own request, for severe adverse study drug reactions, with a major hypertensive or arteriosclerotic complication, a serum creatinine over 2.1 mg/dl and 50% higher than baseline, after interruptions of therapy of over 21 days, and at any time that an investigator thought that it was in the patient's best interest. Interruptions of known active therapy limited to 10–21 days were handled by restarting the coded medication in a stepwise fashion over a period of 2 weeks to avoid hypotensive reactions. Concomitant medications were monitored to ensure that the patient took no other antihypertensive agents or any other potentially confounding drugs.

Examinations and Testing

Physical examinations, side effects assessment, psychometric testing, electrocardiograms, and routine laboratory studies (complete blood count, urinalysis, and biochemical profile) were performed during the placebo phase, at the end of both titration phases, and at the end of the maintenance phase. In addition, at each visit patients were encouraged to report any adverse effects experienced since the previous visit.

Statistical Analysis

This study was designed by a committee that included biostatisticians, some of whom participated in the analysis of the data and in the monitoring of the study. The sample size calculation was based on

a power requirement of 0.80 to detect moderate treatment differences in psychometric test results across the four step 2 treatment groups. This resulted in a target sample size of 45 patients per step 2 treatment group. We estimated the number of patients that we needed to randomize to diuretic therapy from assumptions based on response data from prior studies and the step 2 target sample size. The data were analyzed on an IBM mainframe computer at the University of Chicago Computation Center using the SAS statistical package.^{15,16} The *p* values for all statistical tests were based on two-tailed tests of significance. A *p* value at or less than 0.05 was considered to be statistically significant.

The Student's *t* test for independent groups was used to compare all baseline data, changes from baseline to end of titration, changes from baseline to end of maintenance, and changes from end of titration to end of maintenance by dosage regimen. When more than two groups were compared, a one-factor analysis of variance was used. When significant differences occurred, Duncan's multiple range test was used to make pairwise comparisons between groups. Changes within each dosage regimen over time were analyzed using the Student's *t* test for paired data. When changes over time were analyzed, each patient served as his own control.

The χ^2 test was used to analyze all associations between categorical variables and dosage regimens. McNemar's test was used to analyze changes in categorical data over time within each dosage regimen.

Results

Baseline Characteristics

The overall scheme of the study with the number of patients in each subgroup is displayed in Figure 1. Of the 757 patients entered into the study, 690 were randomly assigned to one of two groups in Titration Phase I. There were no significant differences in baseline characteristics between the two randomly assigned "low dose" and "high dose" groups. Mean age (\pm SD) was 64.3 ± 4.1 years; 12.1% of the patients were 70 years of age or older, the oldest being 88 years old; 48.3% of the patients were black. Mean baseline blood pressure was $157.3 \pm 17.2/98.3 \pm 5.2$ mm Hg. Mean heart rate was 75.6 ± 10.9 beats/min. Mean weight and height was 83.7 ± 13.5 kg and 174.2 ± 7.4 cm, respectively; 28.8% of the patients were current cigarette smokers; 5.2% of the patients consumed more than three alcoholic drinks per day. Hypertension was under current treatment in 69.4%, had been previously treated in 18.6%, and never treated in 12.0%. Left ventricular hypertrophy was present by electrocardiographic voltage criteria in 12.3% and by voltage and "strain" pattern in 3.9%.

Response to Diuretic Treatment

The blood pressure response to HCTZ is given in Table 1. Although weight loss was significantly greater in the higher dose regimen ($p < 0.01$), blood

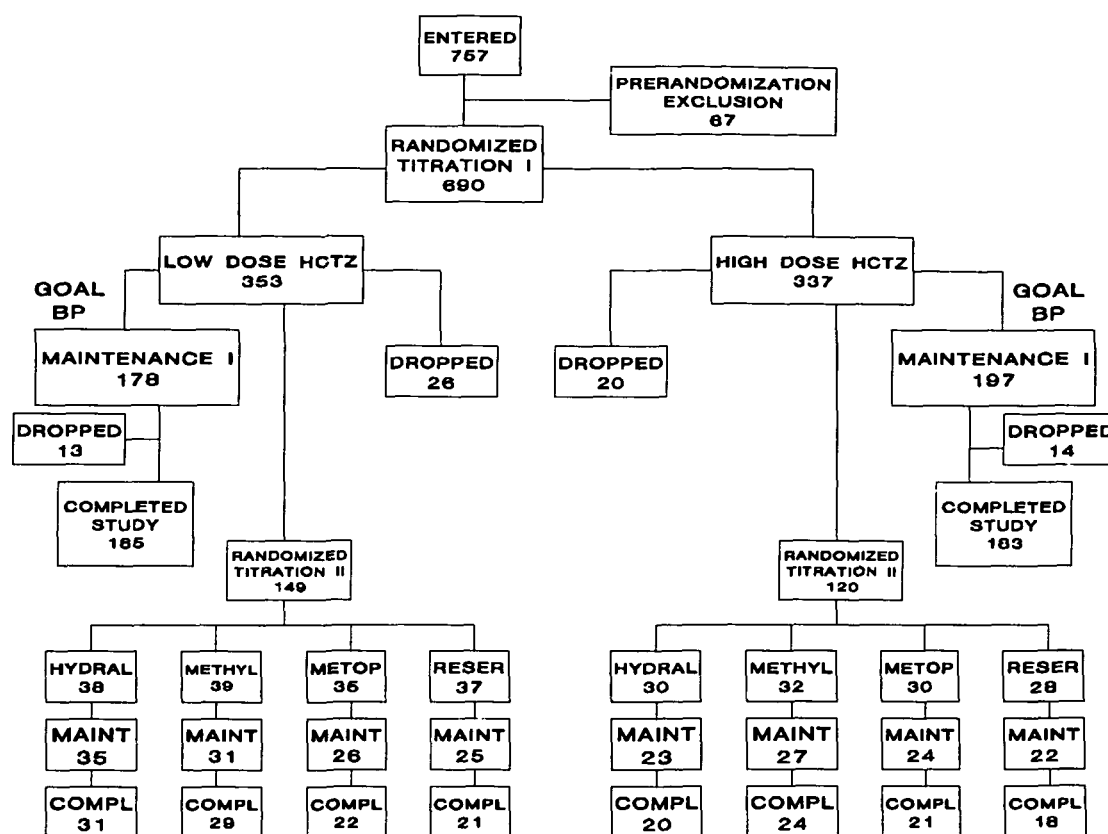


FIGURE 1. Flow chart of the study. First step randomization was to either a lower or higher dose of hydrochlorothiazide (HCTZ). Second step randomization was to hydralazine (HYDRAL), methyldopa (METHYL), metoprolol (METOP), or reserpine (RESER). MAINT refers to Maintenance Phase II and COMPL to patients who completed study. Numbers refer to number of patients in each cell. BP, blood pressure.

pressure reduction in the two groups was similar. Of those patients completing the lower dose HCTZ regimen, 20.4% remained on 25 mg once daily, 79.3% were titrated to 25 mg twice daily (50 mg/day), and only one patient required a reduction to 12.5 mg once daily. With the higher dose HCTZ regimen, 22.8% remained on 50 mg once daily, 76.9% were titrated to twice daily (100 mg/day), and only one patient was reduced to 25 mg once daily. Three hundred seventy-five patients (54.3%) had their blood pressure controlled on one of the two HCTZ regimens and entered the 6-month Maintenance Phase I.

Response Related to Patient Characteristics

There were no significant differences in the blood pressure responses between diuretic regimens in either blacks or whites. Also, there were no significant differences between the races in the blood pressure responses. The patients 70 years or older had higher SBP, but lower DBP, heart rate, and weight compared with those 60–69 years of age. There were no significant differences in reduction of blood pressure between the two dosage regimens for either age group, but the older patients had a greater average fall in SBP (–25.8 mm Hg) in the higher

dose HCTZ group ($p < 0.05$) compared with –19.7 mm Hg in the younger patients.

Baseline characteristics of patients achieving GBP were compared with those of patients not achieving goal to determine which parameters were associated with treatment success. Patients achieving GBP with either regimen were similar to those not achieving goal in terms of smoking or alcohol history, age, weight, race, history of prior treatment for hypertension, and compliance rate. However, those achieving GBP did have significantly lower baseline SBP, DBP, heart rate, and uric acid level. In addition, those whose blood pressure was controlled also had significantly greater decrease in SBP and DBP and increase in heart rate after HCTZ titration. Thirty-six percent of those achieving goal remained on once daily dosing. Those whose blood pressure was controlled had less of a rise in hemoglobin and hematocrit and less of a fall in potassium and chloride.

Maintenance Phase I

The baseline characteristics of the patients whose blood pressure was controlled during the HCTZ titration phase and who entered the 6-month maintenance phase were similar between the lower and higher dosage regimens. The average changes in

TABLE 1. Effect of Lower Dose and Higher Dose Hydrochlorothiazide Regimens on Blood Pressure During Titration Phase

Variables	Hydrochlorothiazide regimen		<i>p</i> value
	Lower dose (<i>n</i> =342)	Higher dose (<i>n</i> =330)	
Systolic BP (mm Hg)			
Baseline	158.3±19.1	156.8±18.8	0.29
End titration	139.9±16.6	136.2±15.6	
Change from baseline	-18.3±16.9	-20.4±15.6	0.08
Diastolic BP (mm Hg)			
Baseline	98.7±6.0	98.4±5.8	0.55
End titration	89.1±7.7	88.8±7.4	
Change from baseline	-9.5±7.2	-9.6±7.2	0.87
Heart rate (beats/min)			
Baseline	75.1±11.5	76.1±10.2	0.22
Change from baseline	0.0±9.1	0.7±9.9	0.34
Weight (pounds)			
Baseline	184.3±31.3	184.8±28.1	0.82
Change from baseline	-2.3±4.8	-3.5±4.1	<0.01
Treatment response (intention to treat)			
% Achieved goal BP	50.4	58.5	0.10
% No goal BP	42.2	35.6	...
% Drop-out	7.4	5.9	...
Treatment response (remaining on therapy)			
% Achieved goal BP	54.4	62.1	0.05
% No goal BP	45.6	37.9	...

Data are expressed as mean±SD and *p* values reflect differences between regimens. Changes from baseline were significant (*p*<0.001). BP, blood pressure. Lower dose hydrochlorothiazide, 25 mg q.d. or b.i.d.; higher dose, 50 mg q.d. or b.i.d.

blood pressure from the placebo baseline period to the end of maintenance were not significantly different between the 173 patients on the lower dosage regimen (-20.9/-13.3 mm Hg) and the 187 patients on the higher dosage regimen (-22.0/-13.6 mm Hg). There were no significant differences between dosage regimens in SBP or DBP change from the beginning to the end of the maintenance phase.

Although the protocol allowed an increase in dosage during maintenance to bring blood pressure back down to goal if the patient was not already at the maximum dose, 96.1% of the lower dose and 97% of the higher dose group stayed at the same dose level. There was no significant difference between the percentage of patients of each group who remained on once daily dosage regimen at the end of maintenance (34.8% receiving 25 mg vs. 35.5% receiving 50 mg). Only one and two patients, respectively, were reduced to half of the initial dose level.

There were no important changes in blood pressure in white or black patients from the end of titration to the end of maintenance. Patients 70 years of age and older had a significant further average change in blood pressure of -4.3/-4.1 mm Hg on lower dose HCTZ, which was also significantly different from the 3.8/0.3 mm Hg average increase on higher dose HCTZ.

Side Effects and Discontinuations

There were no differences in incidence of side effects or discontinuations from the protocol between the lower and higher dose regimens. Although side effects were uncommon, those increasing in prevalence were weakness, muscle cramps, abdominal pain, constipation, and nocturia. There was no change in the prevalence of sexual dysfunction. The expected changes in serum laboratory values associated with thiazide diuretic therapy were observed in this study (Table 2), but the changes were significantly greater in the higher dose group compared with the lower with respect to urea nitrogen, uric acid, potassium, sodium, and chloride. In particular, serum cholesterol increased more than twice as much with the higher dose during short-term therapy.

Serum Potassium Concentration Distribution

The group mean values or mean decrements from baseline for serum potassium concentration are important but may mask the number of patients who experience hypokalemia of potentially clinically important magnitude. The frequency distribution of serum potassium for low and high dose HCTZ by intention-to-treat is recorded in Table 3. A dose-response relation is evident: serum potassium was less than 3.5 mmol/l in 18.6% of patients taking the

TABLE 2. Significant Laboratory Data Changes in Serum Between Lower and Higher Dose Hydrochlorothiazide

Serum measurements	Hydrochlorothiazide		p value
	Lower dose	Higher dose	
Triglycerides (mg/dl)			
Baseline	143.6±105.3	156.5±108.8	0.75
Change	23.2±73.0	25.3±87.4	
Cholesterol (mg/dl)			
Baseline	220.0±42.1	217.8±42.6	0.010
Change	6.2±28.1	12.5±32.0	
Urea nitrogen (mg/dl)			
Baseline	14.5±4.6	15.2±4.8	0.023
Change	2.6±4.5	3.4±4.4	
Glucose (mg/dl)			
Baseline	105.8±27.2	104.3±23.0	0.82
Change	8.2±23.3	8.7±24.6	
Uric acid (mg/dl)			
Baseline	6.4±1.5	6.3±1.6	0.0003
Change	1.3±1.3	1.6±1.3	
Potassium (mmol/l)			
Baseline	4.32±0.4	4.33±0.47	0.0002
Change	-0.47±0.51	-0.63±0.57	
Sodium (mmol/l)			
Baseline	142.4±2.9	142.7±2.8	0.0007
Change	-0.8±3.7	-1.8±3.7	
Chloride (mmol/l)			
Baseline	105.9±3.2	106.3±5.1	0.0002
Change	-4.4±4.2	-5.9±5.9	
Bicarbonate (mmol/l)			
Baseline	27.8±3.0	27.8±2.9	0.08
Change	2.0±3.3	2.5±3.4	

Values are mean±SD. All changes within each dose regimen are significant at $p<0.0001$. Lower dose hydrochlorothiazide, 25 mg q.d. or b.i.d.; higher dose, 50 mg q.d. or b.i.d.

lower dose and in 32.3% on the higher dose HCTZ regimen.

There were no patients with a serum potassium concentration of less than 3.0 mmol/l and only eight (11.8%) below 3.5 in the group whose final dose of HCTZ was 25 mg ($n=68$). In contrast, seven (2.1%) were below 3.0 and 64 (18.9%) were less than 3.5 mmol/l in the 50 mg HCTZ final dose group ($n=338$) while 21 (8.5%) were below 3.0 and 94 (37.9%) less than 3.5 mmol/l in the 100 mg HCTZ final dose group ($n=248$).

Response to the Addition of a Second Drug

After therapy with 50 or 100 mg HCTZ daily, 269 patients maintained a DBP of 90 mm Hg or greater and were randomly assigned to the addition of one of the four nondiuretic antihypertensive medications: hydralazine ($n=68$), methyldopa ($n=71$), metoprolol ($n=65$), or reserpine ($n=65$). Two hundred thirteen (79.2%) of these patients then achieved GBP and entered the 6-month maintenance phase; 186 (87.3%) of these patients completed maintenance.

TABLE 3. Serum Potassium Distribution as a Result of Lower Dose or Higher Dose Hydrochlorothiazide Treatment at the End of Titration

Serum potassium (mmol/l)	Hydrochlorothiazide					
	Lower dose			Higher dose		
	n	%	Cum. %	n	%	Cum. %
2.3–2.9	6	1.8	1.8	22	6.8	6.8
3.0–3.4	56	16.8	18.6	82	25.5	32.3
3.5–3.9	144	43.2	61.8	125	38.9	71.2
≥4.0	127	38.1	99.9	92	28.7	99.9

Difference in distribution of serum potassium levels between lower and higher dose is highly significant by χ^2 ($p<0.001$). Lower dose hydrochlorothiazide, 25 mg q.d. or b.i.d.; higher dose, 50 mg q.d. or b.i.d.

TABLE 4. Effect of Hydralazine, Methyldopa, Metoprolol, and Reserpine on Blood Pressure, Heart Rate, and Percent of Patients at Goal Blood Pressure During the Titration Phase

	Hydralazine	Methyldopa	Metoprolol	Reserpine	<i>p</i>
Number	68	71	65	65	
<i>Systolic blood pressure (mm Hg)</i>					
End titration	132.3±12.9	130.9±16.4	135.9±15.0	136.3±16.5	
Change	-11.5±10.1*	-15.0±13.7*	-13.0±15.4*	-12.7±11.5*	0.43
<i>Diastolic blood pressure (mm Hg)</i>					
End titration	83.9±6.3	84.9±5.5	86.1±5.8	85.3±5.9	
Change	-11.3±5.9*	-10.6±6.3*	-10.6±6.7*	-9.8±6.3*	0.59
<i>Heart rate (beats/min)</i>					
End titration	78.8±13.5	76.6±9.5	62.6±10.7	68.7±10.9	
Change	1.4±10.5A	-1.6±9.3A	-15.9±11.9*C	-7.9±10.7*B	<0.001
% Achieved GBP	85.3	81.7	76.9	72.3	0.28

Values are mean±SD unless otherwise indicated. A,B,C: Groups having the same letter are not significantly different from each other; different letters indicate that drug groups are significantly different ($p<0.05$) from one another using Duncan's multiple range test. GBP, goal blood pressure (diastolic blood pressure <90 mm Hg and >5 mm Hg below baseline, and a systolic blood pressure <160 mm Hg). * $p<0.001$ significant change with addition of second drug.

Those completing maintenance had been on HCTZ a total of 9–12 months.

Baseline Characteristics

There were no significant differences in baseline characteristics between each of the drug groups at randomization nor were there differences in characteristics between the 690 patients originally randomly assigned to the high or low dose group and the 269 patients who received a second drug. For the patients who received a second drug, blood pressure on HCTZ averaged 146.7/95.6 mm Hg.

Blood Pressure and Heart Rate Changes in Titration Phase II

The blood pressure and heart rate response to the addition of each medication to HCTZ during Titration Phase II is given in Table 4. Across all medications, there was an additional average reduction in blood pressure of 13.1/10.6 mm Hg to a blood pressure level of 133.7/85.0 mm Hg. Hydralazine, methyldopa, metoprolol, and reserpine were equally effective in reducing blood pressure; there were no statistically significant differences in SBP or DBP reductions among the regimens.

The total average reduction of blood pressure from the baseline phase (before beginning HCTZ) to the end of titration of the second drug was 29.4/15.9 mm Hg. Of the 690 patients entering the diuretic titration phase of this study, 85.2% had their blood pressure eventually controlled on either HCTZ alone or after the addition of hydralazine, methyldopa, metoprolol, or reserpine.

Of the patients who were randomly assigned to one of the four regimens, 149 (55.4%) had been previously randomly assigned to 50 mg HCTZ daily (25 mg twice daily) and 120 (44.6%) to 100 mg daily (50 mg twice daily). There were no significant differences in blood pressure response between all 50 mg and all 100 mg HCTZ–second drug combinations during the

titration phase. There were also no differences between hydralazine, methyldopa, metoprolol, and reserpine in the blood pressure responses with 50 or 100 mg HCTZ. Nevertheless, the reduction in DBP with metoprolol was significantly greater ($p=0.02$) with 100 mg HCTZ (12.7±6.9 mm Hg) than with 50 mg HCTZ (8.9±6.1 mm Hg). There was a significant difference ($p=0.01$) in age between the two metoprolol groups (62.8±2.6, 100 mg HCTZ vs. 65.0±4.0 years, 50 mg HCTZ). No other within-drug HCTZ dose comparisons of blood pressure response were significantly different. Heart rate was decreased significantly by metoprolol compared with all other drugs and by reserpine as compared with methyldopa and hydralazine.

Phase II Response Related to Patient Characteristics

The characteristics of patients who achieved GBP (<90 mm Hg) and those who were removed from the study or did not achieve goal were compared. Although responders had significantly lower baseline SBP, the baseline DBP was similar to the nonresponders. There were no baseline differences between responders and nonresponders in age, racial ratio, estimated IQ, education, weight, heart rate, smoking status, alcohol intake, or the proportion of patients recently treated for hypertension. Changes in weight and heart rate during titration also did not differ. In addition, there were no standard laboratory parameters, physical examination findings, or neuropsychological tests at baseline that would have predicted achievement of GBP in this population.

The major postrandomization factors distinguishing the two groups were blood pressure changes, compliance, drug intolerance, and adverse effects. Average SBP ($p=0.01$) and DBP ($p=0.0001$) changed significantly more in the responders (–14.3/–11.8 mm Hg) than in the nonresponders (–8.2/–5.8 mm Hg). The proportion of patients considered compliant was significantly greater in the responders

(85.0% vs. 60.7%, ($p=0.002$). Further analysis of each drug group revealed significantly more of the responding patients were compliant than nonresponders for hydralazine (38% more, $p=0.012$) and methyldopa (32% more, $p<0.01$), but the differences in the metoprolol (10%) and reserpine (20%) groups were not significant.

Drug intolerance was defined as adverse effects leading to downward titration or discontinuation of the study medication. Drug intolerance was present in 23.3% of those not achieving GBP compared with only 2.8% of the responders ($p<0.001$). This was also significantly different within the hydralazine, methyldopa, and metoprolol drug groups, but not with reserpine. Of particular note, nearly half (46.2%) of those terminated in the methyldopa group were considered drug intolerant compared with 23.2% or less with any of the other agents.

Side effects of at least moderate severity that were judged to be possibly or definitely related to the study medications were compared between responders and nonresponders: 17.4% of patients achieving GBP had such adverse effects compared with 32.1% of those withdrawn from the study ($p=0.024$).

Blood Pressure During Maintenance Phase II

The 213 patients who achieved GBP during the titration phase entered the 6-month maintenance phase. There were no significant differences across drug groups in any SBP or DBP changes that occurred during maintenance or from baseline to the end of maintenance. There was a further DBP fall during maintenance with reserpine (-1.6 ± 8.5 mm Hg) that approached being significantly different ($p=0.07$) from the rise that occurred with hydralazine (1.8 ± 6.0), methyldopa (1.4 ± 6.9), and metoprolol (1.6 ± 6.9). There were no differences in the proportion of patients completing maintenance in each drug group: the range was from 83.0% with reserpine to 91.4% with methyldopa ($p=0.62$).

Effect of Race on Response

The blood pressure changes from baseline to the end of titration and maintenance were analyzed for white and black patients separately. During the titration phase, all systolic and diastolic changes in each race-drug group were significant, but there were no significant differences between drug groups in the

TABLE 5. Laboratory Values at Baseline and Changes During Titration and From Baseline to the End of Six Months of Maintenance

	Hydralazine	Methyldopa	Metoprolol	Reserpine	<i>p</i>
Number (BL/T/M)	67/65/52	70/66/54	65/59/43	64/60/39	
Glucose (mg/dl)					
Baseline	117	115	115	114	0.93
Titration-BL	4	2	3	-2	0.59
Maintenance-BL	-8*	2	-3	-1	0.24
Potassium (mmol/l)					
Baseline	3.71	3.66	3.67	3.70	0.90
Titration-BL	0.00	0.03	0.12*	0.09	0.41
Maintenance-BL	-0.06 B	-0.02 B	0.27† A	0.01 B	0.01
Cholesterol (mg/dl)					
Baseline	233	229	238	228	0.62
Titration-BL	-11†	-8	-6	-5	0.67
Maintenance-BL	-13†	-12†	-9*	-16†	0.84
Triglycerides (mg/dl)					
Baseline	197	172	180	203	0.53
Titration-BL	-37†	31	37*	41	0.07
Maintenance-BL	-47† C	9 AB	39* A	-13 BC	<0.001
Uric acid (mg/dl)					
Baseline	7.6	7.9	8.3	8.2	0.18
Titration-BL	-0.6‡ B	0.2 A	0.2 A	0.1 A	<0.01
Maintenance-BL	-0.3	-0.0	0.1	0.1	0.46
Creatinine (mg/dl)					
Baseline	1.18	1.26	1.26	1.23	0.22
Titration-BL	0.02	0.02	0.04*	-0.02	0.13
Maintenance-BL	0.00	-0.01	0.03	-0.01	0.49

All parameters are mean values. Baseline refers to end of titration of hydrochlorothiazide. * $p<0.05$, † $p<0.01$, ‡ $p<0.0001$ significant change from baseline.

A,B,C: Groups having the same letter are not significantly different from each other; different letters indicate that drug groups are significantly different ($p<0.05$) from one another using Duncan's multiple range test. BL, baseline; T, titration; M, maintenance.

blood pressure changes or percent achieving GBP within each racial group. Nevertheless, during maintenance white patients had an average 4.1 mm Hg ($p<0.01$) further fall in DBP with reserpine, which was different from the other three agents ($p<0.01$) and from black patients ($p<0.05$). No other race-drug group had an average fall in DBP during maintenance, although blacks whose blood pressure was controlled with hydralazine sustained a 2.9 mm Hg average rise in DBP ($p<0.05$). The net changes from baseline to the end of maintenance, however, were not significantly different between drug groups.

When whites were compared with blacks within each drug group, whites had a 7.4 mm Hg greater fall in SBP with methyldopa during titration and a 6.7 mm Hg greater fall from the beginning of titration to the end of maintenance. The only other difference was the previously mentioned fall in DBP with reserpine in whites during maintenance. There were no significant racial differences in DBP changes or percent achieving GBP during titration or in diastolic changes from the beginning of titration to the end of maintenance. Equal proportions of whites and blacks completed the maintenance phase within each drug group.

Discontinuations From Protocol During Phase II

Of the 269 patients who were randomly assigned to one of four regimens to receive a second drug, 56 were dropped from the study during the titration phase and 27 were removed during the 6-month maintenance phase. The termination rate was the same whether they had been assigned to the low or high dose HCTZ group and for blacks and whites.

Although most (85.9%) of the terminations were deemed to be for medical rather than administrative reasons, the majority ($n=35$) were for inability to achieve or maintain GBP. Intercurrent illnesses such as newly discovered cancer or necessity to treat other disease processes with excluded drugs was also a major factor. There were 27 terminations because of drug-related adverse effects (10.0%). There were 3

for hydralazine (chills and fever, headache, sexual dysfunction), 8 for methyldopa (chills and fever, depression, hepatitis, dry mouth, drowsiness), 9 for metoprolol (wheezing, nasal stuffiness, impotence, paresthesia, weakness), and 7 for reserpine (fatigue, dyspepsia, insomnia, nervousness, depression). There were two terminations in the methyldopa-treated group (both taking 1,000 mg methyldopa; 50 mg HCTZ) and one in the reserpine-treated group (0.1 mg reserpine; 100 mg HCTZ) for depression. One death from an acute myocardial infarction occurred in a patient who was receiving 100 mg HCTZ and 100 mg metoprolol. He was in the fifth month of the maintenance phase.

Laboratory Data

Laboratory values at the end of titration of HCTZ, the changes that resulted after titration of the step 2 drugs, and the changes from the end of HCTZ titration to the end of maintenance with the step 2 drugs are shown in Table 5. Glucose, which was increased an average of 8 mg/dl with HCTZ, was reduced significantly only with hydralazine: -8 mg/dl long-term. Potassium increased both during titration (0.12 mmol/l) and from baseline to the end of maintenance (0.27 mmol/l) with metoprolol only. Cholesterol, however, which had increased 7.3 mg/dl from a baseline value of 218.9 mg/dl with short-term HCTZ and to 226.5 mg/dl at the end of HCTZ monotherapy, decreased significantly in combination with all four other drugs long-term: hydralazine -10.4 mg/dl, methyldopa -11.5 mg/dl, metoprolol -6.0 mg/dl, and reserpine -11.4 mg/dl. Triglycerides, which had increased 25 mg/dl with HCTZ titration, increased further (39 mg/dl) with metoprolol but decreased (-47 mg/dl) with hydralazine. There were no net long-term changes in uric acid or creatinine in any of the drug groups.

Volunteered Side Effects

During Titration Phase II (Table 6), methyldopa was associated with significant increases in six volun-

TABLE 6. Prevalence (%) of Selected Patient Complaints During Titration With Hydralazine, Methyldopa, Metoprolol, and Reserpine

	Hydralazine	Methyldopa	Metoprolol	Reserpine
(Number in group)	(68)	(71)	(65)	(65)
Postural dizziness	5.9	11.3*	7.7	4.6†
Fatigue/tiredness	11.8	28.2*	0.0	10.8
Weakness	5.9	15.5‡	7.7	9.2
Sexual dysfunction	1.5	9.9*	7.7	1.5
Dry mouth	2.9	8.5*	3.1	1.5
Headache	19.1	9.9	4.6†	4.6†
Indigestion	0	0	7.7‡	1.5
Backache	1.5	2.8	1.5†	3.1
Drug intolerance	2.9	15.5§	4.6	4.6

Drug intolerance was defined as adverse effects leading to downward titration or discontinuation of the study medication. ‡ $p<0.05$, * $p<0.01$, § $p<0.001$, significant increase from baseline (McNemar test). † $p\leq 0.01$, significant decrease from baseline (McNemar test).

teered patient complaints. Almost 30% of patients complained of fatigue or tiredness with methyldopa, compared with less than 12% in any other drug group. The other volunteered complaints that increased significantly with methyldopa were postural dizziness, weakness, sexual dysfunction, dryness of the mouth, and drug intolerance. Among the other agents, only metoprolol was associated with a significant increase in any complaint (indigestion). Headaches significantly decreased with both metoprolol and reserpine, as did postural dizziness with reserpine and backache with metoprolol.

There were several complaints that increased in prevalence from the end of HCTZ titration to the end of the maintenance phase within each of the four drug groups: fatigue (or tiredness) and backache with methyldopa; diarrhea and arthritis with hydralazine; indigestion and arthritis with metoprolol; and weakness with reserpine.

The overall incidence of volunteered nonterminating moderate or severe adverse effects was significantly greater ($p < 0.01$, χ^2) with methyldopa (31%) and hydralazine (25%) than with reserpine (15%) or metoprolol (9%).

Discussion

Elderly hypertensive patients will number approximately 20 million by the year 2030 and, when compared with their normotensive age-matched controls, will be at increased risk for stroke, congestive heart failure, left ventricular hypertrophy and its associated cardiac dysrhythmias, renal failure, accelerated and malignant hypertension, decrease in functional IQ, reduced motor skills, and impaired activities of daily living.^{14,17-19} When the present study was designed, there was no clear proof that treatment of the elderly hypertensive patient provided a benefit. On the other hand, overzealous treatment of elderly patients was thought to result in a serious deterioration of the quality of life for many of them because of side effects.^{20,21}

An earlier Veterans Administration Cooperative Study²² used doses of HCTZ as high as 200 mg without any dramatic adverse effects. In that study, some patients responded when the dose of HCTZ was increased from 100 to 200 mg. The dose-response curve for blood pressure reduction in this dose range was not entirely flat. On the other hand, the absolute decrement of serum potassium concentration was clearly related to diuretic dose.²³

When the present study was designed, 50 mg was considered to be a low effective dose of HCTZ; the 25 mg dose had not been sufficiently explored to base a major study on its exclusive use. Therefore, we decided to compare 50 and 100 mg regimens but elected to begin with half doses for safety reasons.

The excellent blood pressure response achieved in this group of elderly patients is consonant with that observed in the elderly cohorts of the Veterans Administration trial,² the Hypertension Detection and Follow-up Program,^{3,24} the Australian Thera-

peutic Trial in Mild Hypertension,⁴ and the European Working Party on Hypertension in the Elderly.¹ The diuretics were well tolerated and associated only with the clinical and laboratory side effects that occur with thiazides.

Although our lower and higher doses of HCTZ were nearly equally effective, there were fewer biochemical changes associated with the lower dose. This dissociation between the diuretic dose-response curves for blood pressure reduction and those for serum potassium and uric acid levels, for example, is now well known.²⁵ In this study, however, there were no observed differences in subjective side effects between the two dose groups.

The design of this study does not permit valid statistical comparison of the groups of patients taking 25, 50, and 100 mg HCTZ. To make this comparison, patients would have to have been randomly assigned initially to one of the three dose groups. Nevertheless, about one fifth of the patients in the low dose group were controlled by 25 mg HCTZ once daily. This was the same as the proportion controlled by 50 mg in the high dose group. We can only speculate as to how many more patients on the "half" doses would have been controlled if they had been given a longer time before titrating to the "full" dose.

In contrast to previous studies, we did not show a difference in blood pressure response to HCTZ between the black and white patients. This may be because of the known low plasma renin status of elderly white patients.²⁶ Both groups would then be expected to be diuretic sensitive. Our group of patients 70 years old who were responsive to 25 mg HCTZ had a further decline in blood pressure during the maintenance period. There was no loss of control in any of the dose groups. We did not measure plasma renin activity in our patients because we have previously determined that it is not a reliable predictor of diuretic sensitivity for individual patients.²⁷

At the time this study was designed, it was generally recommended that antihypertensive therapy be initiated with a diuretic and then an adrenergic inhibiting agent added if blood pressure was not controlled.²⁸ Although recent recommendations have expanded to include the consideration of other approaches and initial monotherapy, such as with a calcium channel blocker,²⁹ all of the long-term morbidity and mortality trials demonstrating benefit in the elderly used diuretic-based "stepped care" or combination therapy including a diuretic.^{1-4,24} The adrenergic inhibitors in these studies were either reserpine, methyldopa, or a β -adrenergic blocker. Therefore, we believe these regimens are still relevant at this time. Our inclusion of a hydralazine regimen in the present study was because of the expectation that it should produce little, if any, central nervous system adverse effects and because of previously demonstrated efficacy in patients over 50 years of age when given in combination with a diuretic.^{30,31}

Our results demonstrate that hydralazine, methyldopa, metoprolol, and reserpine have similar antihypertensive effects when added to a diuretic in elderly men with mild-to-moderate hypertension, uncontrolled by HCTZ monotherapy, and that the antihypertensive effect is well maintained for 6 months. The proportion of patients achieving GBP is similar to what has been reported in younger populations.^{31,32}

A variety of patient characteristics, including age, race, education, intelligence, smoking status, and alcohol intake, were examined as predictors of achieving GBP, but none of these distinguished responders from nonresponders. However, observed blood pressure changes and medication compliance were greater in responders, and adverse effects and drug intolerance were more common in nonresponders. It is probable that patients experiencing bothersome adverse effects took less medication and therefore had less antihypertensive effect, but alternative reasons are possible. For example, patients with more resistant hypertension may have been titrated to higher doses of medication, resulting in more side effects and subsequent poor compliance. In any case, elderly patients should be carefully questioned about medication side effects and changed to better tolerated regimens if bothersome adverse effects are present.

Serum cholesterol, which had increased with short-term HCTZ therapy, was reduced to prediuretic levels after long-term therapy in each step 2 drug group. A significant fall was seen early with hydralazine and later with reserpine. There may be a loss of the hypercholesterolemic effect from thiazides after a year or more of therapy.^{22,33} The total duration of HCTZ therapy was between 9 and 12 months. On the other hand, triglycerides and glucose were reduced significantly only with hydralazine, and triglycerides were increased only with metoprolol. The increase in triglycerides with β -adrenergic blockers is well known,²² and the apparent hypolipidemic and hypoglycemic effects of hydralazine have been known since 1962.³⁴ Reserpine also had a favorable lipid profile with the greatest decrease in cholesterol (16 mg/dl) and a modest decrease in triglycerides (13 mg/dl), qualitatively similar to a previous Veterans Administration Cooperative Study.³⁵ The 0.6 mmol/l decrease in potassium after HCTZ titration was only ameliorated by metoprolol (0.3 mmol/l increase). These biochemical effects may be important to consider in individual patients.

Volunteered side effects and drug intolerance were frequent with methyldopa: the complaints increasing in prevalence were not unique to this study (fatigue, lethargy, weakness, dizziness, sexual dysfunction, and dry mouth), but over 30% of patients complained of moderate or severe adverse effects on methyldopa, and drug intolerance was more than three times more common with methyldopa than with any other agent. The only complaint increasing significantly in any other drug group was indigestion with metoprolol. It is possible that lower

doses of methyldopa would have had comparable efficacy with less adverse effects, but the design of this study did not permit examination of this question.

We believe the absence of significant increases in patient complaints with reserpine or hydralazine is important, although moderate or severe adverse effects with hydralazine (headache was the most common complaint) developed in 25% of patients. Hydralazine, if tolerated, has many advantages, but many patients will require at least twice daily dosing of currently marketed preparations.

Reserpine plus HCTZ seems to have some advantages for treatment of hypertension in the elderly³⁶: 1) low cost; 2) long duration of action leading to convenient dosing, slower loss of blood pressure control; and no "rebound"; 3) little titration; 4) experience in morbidity and mortality trials; 5) good antihypertensive efficacy; and 6) favorable side effects profile according to the present results. It is probable that the reputation that reserpine has for adverse effects is based on previous studies that used comparatively high doses. Small doses of reserpine combined with HCTZ were used in this trial.

That newer classes of agents, such as angiotensin converting enzyme inhibitors or calcium channel blockers, are better tolerated in the elderly in equally effective regimens seems possible, but this has yet to be clearly demonstrated. For the present, low dose reserpine plus HCTZ appears to be a cost-effective reasonable combination for many elderly patients with essential hypertension.

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Appendix

Participants in Department of Veterans Affairs Cooperative Study

Chairman: Barry J. Materson, MD (Miami, Florida); Senior Consultant: Edward D. Freis, MD (Washington, DC); Forms Reviewers: J.R. Thomas, MD, Janice Ivie (Memphis, Tennessee).

Principal Investigators: Frederick N. Talmers, MD (Allen Park, Michigan); William C. Cushman, MD (Jackson, Mississippi); J.R. Thomas, MD (Memphis, Tennessee); Stewart Nunn, MD (Memphis, Tennessee); Robert H. Chapman, PhD, MD (Miami, Florida); Barbara Coplowitz, MD (Miami, Florida); Ibrahim Khatri, MD (Washington, DC); Eli A. Ramirez, MD (San Juan, Puerto Rico); Harold Schnaper, MD (Birmingham, Alabama).

Nurses: Chris Grant, RN (Allen Park, Michigan); Pauline Derrington, RN (Jackson, Mississippi); Anita

McKnight, RN (Memphis, Tennessee); Mary Smith, RN (Miami, Florida); Madeline Metcalfe, RN (Washington, DC); Maria Natal, RN (San Juan, Puerto Rico); Bill Hackett, PA (Birmingham, Alabama).

Biostatistician: Domenic Reda, MS (Chicago, Illinois).

Coordinating Center (Chicago, Illinois): William G. Henderson, PhD (Chief), Jean Rowe (Administrative Officer), Carol Colby-Moritz, Dolly Koontz, Mike Barnick, Sherry Jackson, Barbara Lizano, Gary Tesdal.

Research Pharmacists: Larry Young, RPh, John vanEckhout, RPh, Jane Weber, PharmD, Nancy Morgan, RPh, Carol L. Fye, RPh.

Psychometric Testing Laboratory: Gerald Goldstein, PhD, Marilyn Kanagy, Kathy Barry.

Human Rights Committee: Sydney D. Krampitz, RN, PhD, Reverend Douglas Hall, Mary Davidson, PhD, Horace Dudley, PhD, Dr. Lauren Lawson, Edgard Perez, Nancy Cahill, Esq., Dr. Paul Peterson, Dr. William Upholt, Reverend Martin Feldbush.

Operations Committee: Edward D. Frohlich, MD, Stevo Julius, MD, ScD, John M. Lachin, III, ScD, W. Gibson Wood, PhD.

Veterans Administration Central Office: Daniel Deykin, MD (Chief, Cooperative Studies Program), James A. Hagans, MD, PhD (Past Chief, Cooperative Studies Program), Janet Gold (Administrative Officer), Ping Huang, PhD (Staff Assistant).

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