

A Double Blind Control Study of Antihypertensive Agents

I. Comparative Effectiveness of Reserpine, Reserpine and Hydralazine, and Three Ganglionic Blocking Agents, Chlorisondamine, Mecamyamine, and Pentolinium Tartrate

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During the past decade a number of drugs have been developed for the specific purpose of reducing blood pressure in hypertensive patients. Attempts to evaluate these agents definitively have been hindered either by lack of suitable controls, failure to eliminate bias, or by insufficient numbers of patients. Inevitably, under such circumstances, differences of opinion have arisen as to the relative effectiveness, tolerability, and safety of the various antihypertensive agents now in general clinical use. Furthermore, well-controlled data have been lacking on the value of blood pressure reduction in preventing or delaying cardiovascular-renal damage in hypertensive disease of mild and moderate severity.

In view of the obvious importance of the problem it was decided to institute a program which would permit more reliable comparisons of the therapeutic effectiveness of antihypertensive agents. A cooperative investigation was best suited for the purpose, since it encompasses a sufficiently large series of patients to permit valid comparisons among various treatment groups. It also is possible to incorporate in the experimental design various safeguards to protect the investigators against false im-

pression and personal bias. The present communication is concerned with the original treatment protocol in which eight Veterans Administration Hospitals have collaborated.† A preliminary report seems justified at this time since 232 patients have completed one year of continuous treatment with drugs or placebos.

Plan of Investigation

Criteria for Selection of Patients.—To qualify for admission to the study it was required that the patient's diastolic blood pressure average 90 mm. Hg or above during the period from the fourth through the sixth hospital day. New medical admissions were surveyed for the presence of patients exhibiting elevated levels of blood pressure. In such patients blood pressures were recorded four times daily. The average of all values of diastolic pressure from the fourth through the sixth hospital day was used (1) in determining admissibility, (2) in grading severity, and (3) for pretreatment control level of blood pressure. If a patient had been receiving Rauwolfia alkaloids immediately prior to admission, he was furloughed for two weeks without medication and then returned for a six-day period of pretreatment evaluation. Occasional patients with diastolic pressures above 140 mm. Hg and symptoms and signs of acute hypertensive encephalopathy, who were considered to be in urgent need of antihypertensive therapy, were treated before the six-day observation period was completed. They received known antihypertensive agents, usually administered parenterally until the symptoms of encephalopathy had cleared. Treatment was then withdrawn for

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†These include the following Veterans Administration Hospitals: Brooklyn; Chicago West Side; Iowa City; Oklahoma City; Richmond, Va.; San Juan, P.R.; Seattle, and Washington, D.C.

several days in order to obtain an estimate of the pretreatment blood pressure. The number of patients managed in this way was small.

The following conditions warranted exclusion from the investigation:

1. Surgically curable with conditions such as unilateral renal disease, coarctation of the aorta, or pheochromocytoma.
2. Hypertensive on admission but whose diastolic pressure averaged less than 90 mm. Hg from the fourth through the sixth hospital day.
3. Inability to attend follow-up clinic.
4. Inability or unwillingness to provide a record of blood pressure readings taken at home.
5. Terminal uremia as judged by BUN levels above 100 mg. % after restoration of dehydration or treatment of congestive heart failure.
6. Concomitant fatal disease not associated with hypertension such as malignant tumors.
7. Myocardial infarction demonstrated by ECG within three months of hospitalization.
8. Age 70 or over.
9. Female patients (since the great majority of Veterans Hospital patients are men).

The number of patients excluded was large, being more than 50% of those hypertensive on admission. The majority of these fell into Category 2 (average diastolic falling below 90 mm. Hg) with considerable numbers also being excluded on the basis of Items 3 or 4.

Initial Examinations.—At the time of admission the history form was filled out by the physician participating in the study. This form included the following information: age, weight, occupation (past and present), family history, prior hospitalization, previous treatment for hypertension, prior blood pressure levels including date of last knowledge of normal blood pressure, cardiac symptoms, previous treatment for cardiac disease, estimation of salt intake, central nervous system symptoms, prior history or symptoms of renal disease, peripheral vascular disease, and past history of peptic ulcer or history of same. The latter was included because of the possible relationship between reserpine and hydralazine and peptic ulceration.

In order to obtain uniformity of historical data amongst the various participating hospitals and to facilitate later analysis, a check-list format was adopted. For example, under "Dyspnea" there were four boxes marked, respectively, (1) none, (2) on heavy effort only, (3) on ordinary activity, and (4) at rest.

The remainder of the workup included single recordings of blood pressure in the lying, sitting, and standing positions, in both arms, and in a lower extremity. In addition the blood pressure was determined by the ward nurses four times daily, with the patient in the sitting position. The optic fundi were graded separately on the basis of arteriosclerotic and hypertensive changes. Only

the latter was used in determining severity. A check list was provided for the various abnormalities, such as arteriolar narrowing, tortuosity, light reflex, segmental spasm, etc., each of which were graded as normal, slight, moderate, or marked changes. In some hospitals, the optic fundi were photographed and the transparencies forwarded after coding for separate review and analysis. The transverse diameters of the heart and thorax were measured by roentgenography. Electrocardiographic abnormalities were reported. Gross neurological changes, such as paresis, memory defects, and encephalopathy, were noted. The tests for estimation of renal status included three routine urinalyses, total excretion of phenolsulfonphthalein during the two hours following injection, blood urea nitrogen, or NPN, and an intravenous pyelogram. Renal blood flow and glomerular filtration rate were estimated by standard methods in one of the participating hospitals. Other examinations included the sodium amytal sedation test, phentolamine hydrochloride (Regitine) test, hematocrit, fasting blood sugar, and cholesterol. Finally, a brief summary of the present illness was included with a statement as to relative importance of the hypertension, other organic conditions, or functional disturbances in contributing to the patient's symptomatology.

Classification of Severity.—Severity was estimated by clinical data obtained in five prognostic indices: basal diastolic blood pressure, optic fundi, and cardiac, cerebral, and renal complications. In each of these categories severity was graded in increments of one to four as follows:

A. Diastolic blood pressure (average of fourth through sixth hospital day): (1) 90 through 99 mm. Hg; (2) 100 through 114 mm. Hg; (3) 115 through 129 mm. Hg, and (4) 130 mm. Hg or above.

B. Optic fundi: (1) mild generalized narrowing (arterioles no narrower than one-half the caliber of veins); (2) generalized narrowing (arterioles reduced to one-third the caliber of veins and/or focal constriction or definite irregularity of arterioles); (3) same as above with hemorrhages and/or exudates, and (4) same as 2 or 3 with definite papilledema.

C. Cardiac: (1) either one of the following: (a) ECG evidence of hypertrophy or damage and/or roentgenographic evidence of hypertrophy but without angina or dyspnea on exertion, (b) angina and/or dyspnea on exertion without ECG or roentgenographic evidence of hypertrophy or damage; (2) both roentgenographic and/or ECG evidence of hypertrophy or damage and symptoms of angina or dyspnea on exertion but without objective evidence or history of cardiac decompensation; (3) history of myocardial infarction, or history or presence of congestive heart failure clearing on routine therapy such as digitalis and

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mercurial diuretics; (4) objective signs of congestive heart failure such as elevation of venous pressure, prolongation of circulation time, pulmonary edema, hepatomegaly, or dependent edema which failed to clear following routine cardiac therapy.

D. Cerebrovascular: (1) frequent headaches or dizzy spells of recent origin; (2) single cerebrovascular accident judged clinically to be a thrombosis; (3) cerebrovascular accident judged clinically to be a hemorrhage or multiple cerebrovascular accidents of either type; (4) acute hypertensive encephalopathy or subarachnoid hemorrhage.

E. Renal: (1) any two of the following: (a) proteinuria 1+ or more in any one of three daily urine specimens, (b) specific gravity of 1.020 or less in all three specimens, and (c) PSP excretion of 45% or less in the two-hour pooled specimen of a well-hydrated patient; (2) any two of the following: (a) proteinuria 1+ or more in all three daily specimens, (b) specific gravity of 1.015 or less, and (c) PSP excretion of 35% or less in two-hour pooled specimen; (3) presence of all three items listed under Grade 2; (4) elevation of BUN greater than 25 mg. % or NPN above 40 mg. % with failure to fall below these values after routine treatment of congestive heart failure.

Scores obtained in each of these panels were added together with *double weighting of the optic fundi and diastolic blood pressure* to obtain the total weighted severity index for each patient. In the early stages of the investigation, double weighting had been applied to the optic fundi and the renal scores. However, it was soon found that elderly patients with impaired renal function but only moderate elevations of blood pressure were being classified as severe hypertensives, and, hence, were treated with blocking agents. Similarly, younger individuals without advanced renal damage, but with high levels of basal diastolic pressure, were being classified and treated as mild hypertensives. Despite its prognostic importance, therefore, double weighting of scores in the renal panel was discontinued, and diastolic pressure substituted.

The 425 patients were divided into three major groupings on the basis of severity as follows: mild cases—total weighted scores of 7 or less (121 patients); moderately severe—total weighted scores from 8 through 15 (238 patients); severe cases—total weighted scores of 16 or above (66 patients).

Treatment Regimens.—In determining the basic design of the study the primary considerations were (1) the evaluation of agents most commonly used in clinical practice at the time the investigation was instituted, and (2) the elimination of bias in determining the effectiveness of these agents. It was decided to evaluate reserpine both alone and in combination with hydralazine (Apresoline) in

the mild cases. In patients with severe hypertension three blocking agents, pentolinium tartrate (Ansolysen), mecamlamine hydrochloride (Inversine), and chlorisondamine chloride (Ecolid) each in combination with reserpine were compared for antihypertensive effectiveness and tolerability. In the moderately severe group, both series of therapeutic regimens were utilized in order to compare ganglionic blocking agents with the less drastic forms of antihypertensive drug therapy in such patients.

The specific therapeutic regimens were as follows:

A. Mild cases (severity scores 1 through 7): 1. Reserpine 0.25 mg. before meals and at bedtime (1.0 mg. per day) for two weeks followed by 0.50 mg. daily thereafter. In addition, hydralazine 25 mg. before meals and at bedtime increasing after four days to 50 mg. four times daily (200 mg. per day) thereafter. 2. Same as regimen one except that hydralazine tablets were placebos. 3. Same as regimen one except that both reserpine and hydralazine were placebos.

B. Severe cases (severity scores 16 and above): The three ganglionic blocking agents were tableted in dosage units so that each unit strength of any of the blocking agents was approximately comparable in potency to a similar unitage of the other two blocking agents. Thus, one-unit tablets contained either 1 mg. of mecamlamine, 8 mg. of chlorisondamine, or 10 mg. of pentolinium tartrate. For convenience in dispensing, the drugs were manufactured in 1, 5, and 10-unit tablets. A special effort was made to prepare the tablets so that the appearance, consistency, disintegration time, and taste of the three blocking drugs were as nearly uniform as possible. The dosages of the ganglionic blocking agents were adjusted in accordance with the amount required to reduce the blood pressure within the limits of tolerable side-effects. In addition, reserpine was administered to all patients given blocking drugs in a dose of 1.0 mg. per day for the first two weeks followed by a maintenance level of 0.50 mg. daily thereafter. The choice of regimens in the severe cases, therefore, was reserpine plus one of three ganglion blocking agents. Since the latter were identified only by code numbers and unit strengths, the investigator did not know which of the three blocking agents he was using in any particular case.

C. Moderately severe cases (severity scores 8 through 15): The patients were divided into two groups. Group 1 received the same alternative treatment regimens as the mild cases. Group 2 received reserpine plus one of the three blocking agents as in the severe cases.

Elimination of Bias.—Since antihypertensive agents may produce characteristic side-effects, it seemed possible that the identity of the active agents might be discovered by the investigators if

a simple code-numbering system was used. Therefore, it was decided to identify each of the test agents with more than one complex code number. For example, reserpine and its placebo were given the code name "Antipressor." Three separate six-digit code numbers were then assigned to reserpine-containing Antipressor, and an additional set of three separate six-digit numbers to placebo-containing Antipressor. Thus there were six distinct complex (and hence difficult to remember) code numbers for reserpine and its placebo. A similar scheme was used for hydralazine and its placebo, which were identified by the code name "Reductin." The ganglion blocking agents were identified by the code name "Hypotensive" followed by three separate six-digit code numbers for each blocking drug, making a total of nine sets of such numbers assigned to the code name Hypotensive. Because of the complexities so introduced, investigators were discouraged from attempting to identify given code numbers with particular antihypertensive agents. In practice, it was found that they were unable to differentiate drug from placebo or one blocking agent from another.

By utilizing three separate treatment regimens for the mild and severe patients and six regimens for the moderately severe cases, the effects of variables such as age, lability, organic complications, reliability in following directions, seasonal changes, and unknown factors would tend to cancel out if adequate numbers of patients were accumulated in each group.

After the patient was classified according to severity, assignment to a given therapeutic regimen was determined by opening a sealed envelope containing a card listing the code-numbered agents to be used in his case. For example, if the first patient in the study in any hospital had a severity index of 6, Envelope 1 in the mild series was selected. The cards were prepared by a statistician who had no contact with the patients.

Evaluation of Antihypertensive Effect.—To provide an adequate sample of blood pressure values and also because of the variability so often evident in weekly or biweekly clinic readings, each patient was equipped with an apparatus for recording the blood pressure in the home.‡ A work sheet was provided on which a member of the family or the patient himself recorded the blood pressure values taken twice daily with the patient in the sitting position. The appropriate individual was taught by the previously trained clinic secretary to determine the blood pressure prior to the patient's discharge from the hospital. The home recordings were averaged by the secretary and a record kept of the average and range for each

month. In addition, during each clinic visit, the secretary determined the blood pressure after the patient had rested supine for fifteen minutes. Readings were then taken by the secretary with the patient in the supine, sitting, and erect positions. Finally the blood pressure was recorded by the interviewing physician with the patient in the sitting position. The monthly averages of these various clinic readings also were reported. When marked discrepancies were observed between home and clinic readings, the individual recording the blood pressures at home again was tested for his or her ability to obtain accurate values. In the few instances in which it was impossible to obtain valid home recordings, the patients were dropped from the study.

Estimation of Side-Effects.—The various side-effects known to occur with reserpine, hydralazine, and ganglion blocking agents were listed on a separate score sheet. This was arranged in the form of a check list with each side-effect graded in degrees of increasing frequency and/or severity. For example, under the side-effect "Dry Mouth" the interviewer was required to check one of the following: (1) none, (2) less than two times per week, (3) more than two times per week but does not require pilocarpine, (4) more than two times per week and does require pilocarpine, (5) sore mouth resulting from continuous marked dryness. By providing such a check list it was assured that the interviewer did not omit any pertinent information, and also that the criteria for grading the severity of side-effects were uniform in all hospitals. The initial interview was carried out prior to treatment so that drug effects would not be confused with symptoms experienced before therapy. Subsequent interviews were completed one month following the initiation of treatment and quarterly thereafter. If symptoms of mental depression appeared during treatment, the regimen was discontinued and the patient referred to the psychiatric service for confirmation of the diagnosis.

Evaluation of the Effects of Treatment on the Progress of the Disease.—At six-month intervals in the severe cases and yearly intervals in the remainder the physical and laboratory examinations were repeated. Current symptoms and any significant medical events occurring during the period since the last examination were recorded. Patients usually were readmitted to the hospital for this evaluation but it occasionally was carried out on an outpatient basis if the patient was unable to take sufficient time out from his employment. Recalculation of the severity index provided a convenient means of assessing improvement or further deterioration in the patient's clinical status. It is realized that one year is too brief a period for determining the effects of blood pressure control on organic progression.

‡ Baumanometer Rx Model with Simplex Cuff, W. A. Baum Co., Copiague, Long Island, and Bowles-type Stethoscope.

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Modifications of Treatment.—It was decided that some modification of treatment should be made when the patient exhibited elevation of blood pressure of sufficient degree to be considered an imminent threat to his welfare. Discontinuation of the regimen and substitution of known antihypertensive agents were permitted only if the following conditions were met: (1) Home diastolic blood pressure averaged 130 mm. Hg or above for three weeks or longer. (2) Home diastolic levels averaged 140 mm. Hg or more for one week or longer. (3) Evidence of serious organic progression appeared, such as acute hypertensive encephalopathy accompanied by high diastolic blood pressure, advancing congestive heart failure despite usual therapy employed for this condition, or the development of hemorrhages, exudates, or papilledema in the optic fundi.

Modification of dosages without discontinuation of code-numbered drugs was permitted in the patients taking reserpine, or reserpine plus hydralazine, or placebos, under the following conditions: (1) home diastolic blood pressures average 115 mm. Hg or higher for one month, or (2) average 125 mm. Hg or above for two weeks. However, modification of dosages could not be made within the first three months of treatment. The dosages then could be gradually elevated to double the recommended amounts. These regulations as to modifications of dosage obviously did not apply to the patients receiving ganglionic blocking agents since the dosages of the latter were adjusted routinely to obtain the best possible control of blood pressure.

Results

From the inception of the investigation in 1956 to February, 1958, 425 patients were placed on one of the 6 treatment regi-

mens included in the study plan. Of these 425, only 232 were continuing therapy on the same regimen at the end of one year.

Losses During the First Three Months of Treatment.—Approximately one-half of the patients lost to study discontinued treatment within three months of beginning therapy. The preponderance of losses to the study occurring within the first three months resulted from inability or unwillingness of the patient to continue treatment (Table 1). Since most of these patients did not report back for examination, post-treatment recordings of blood pressure were not available. Thus, it was not possible to include these cases in the analysis of therapeutic results. This exclusion, while restricting the type of patient under study, should not affect any comparisons made between treatment regimens for those patients who remained in the study. Such an assumption seems justified in view of the low probability that the patient's failure to cooperate was related to the ability of the drug to reduce blood pressure during this short period of treatment. It is conceivable that the early drop-outs are related to the side-effects produced by the drugs. The relatively low rate of loss within the first three months among the patients taking only placebos suggests such an event, but, unfortunately, follow-up data was lacking to evaluate this possibility.

TABLE 1.—Number of Patients Starting Study and Subsequent Losses

	Regimen					
	Reserpine & Hydralazine	Reserpine Alone	Placebo	Ganglion Blocking Drugs		
				Mecamylamine	Chlorisondamine	Pentolinium
Total cases randomized	101	106	40	63	75	40
Lost before third month	21	26	2	10	28	12
Death	1	3	0	4	8	3
Side-effects	5	2	0	0	3	0
Could not or would not cooperate	15	21	2	6	17	9
Total with three months' therapy	80	80	38	53	47	28
Lost between third and twelfth month	21	19	11	14	19	10
Death	3	1	1	3	2	3
Treatment failure	0	7	5	3	3	1
Side-effects	4	1	1	3	5	3
Uncooperative	9	8	3	1	5	2
Other	5	2	1	4	4	1
Total with twelve months therapy	59	61	27	39	28	18

Aside from unwillingness or inability to continue treatment, the next most frequent cause for losses from the study during the first three months was death of the patient. Sixteen of the 32 deaths within the first year occurred during the first three months. As expected, the death rate was highest among the more severe cases being treated with blocking agents (Table 1). Since adequate post-treatment blood-pressure readings were not available for the patients who died within the first three months, these cases have not been included in the analysis of the efficacy of the various regimens for reducing blood pressure. In the 13 patients who died after the first three months, and who were included in the analysis, the average of the last month of home diastolic pressure readings was 115 mm. Hg, which was the same as the average pretreatment value for this group. This result was due in part to the fact that 4 of the 13 exhibited a rise of diastolic pressure greater than 10 mm. Hg above the control level. The third most frequent cause for losses from the study in the first three months was the occurrence of side-effects. Only 10 such occurrences were reported among the 425

TABLE 2.—Percent of Cases with Indicated Background Characteristics, All Patients Entering Study

Background Characteristics	Regimen						
	All Regimens	Reserpine & Hydralazine	Reserpine Alone	Placebo	Ganglion Blocking Drugs		
					Mecamylamine	Chlorisondamine	Pentolinium
Total cases	425	101	106	40	63	75	40
Age							
Under 40	18	13	21	20	24	22	10
40 to 59	43	48	40	30	46	38	50
60 and over	39	39	39	50	30	40	40
Race							
White	61	65	60	65	59	60	55
Nonwhite	39	35	40	35	41	40	45
Parents with cardiovascular disease							
No	32	33	29	28	27	29	50
Cardiovascular	28	28	28	40	21	29	28
Hypertension	24	23	26	20	30	24	15
Unknown	14	16	17	12	22	17	7
Sibling with cardiovascular diseases							
No	69	68	65	72	79	70	62
Cardiovascular	17	18	21	18	9	16	23
Hypertension	6	3	5	5	6	5	15
Unknown	8	11	9	5	6	9	0
Previous hospitalization for hypertension							
None	68	76	73	77	64	62	50
Once	18	12	15	13	22	23	36
More than once	14	12	12	10	14	15	14
Prior therapy for hypertension							
None	43	53	46	45	33	41	30
Surgery	2	3	0	0	3	1	5
Chemotherapy	51	39	47	55	60	58	60
Diet	4	5	8	0	3	0	5
Prior chemotherapy for hypertension							
None	45	56	51	42	37	40	35
Reserpine alone	16	11	16	18	24	17	12
Ganglion blocking drugs	7	3	2	0	19	7	15
Other or unknown	32	30	31	40	20	36	38
Weight							
Less than 140 lbs.	16	14	18	14	13	23	15
140-159 lbs.	25	24	21	28	31	23	22
160-179 lbs.	28	24	25	32	31	30	32
180-199 lbs.	16	24	17	10	8	12	15
200+ lbs.	15	13	18	16	17	11	16

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cases. These patients will be discussed further in a later section.

Background Characteristics of Patients.—The background characteristics of the patients in each regimen are presented in Table 2. In regard to the criteria assessed (age, race, family history, previous hospitalization or prior therapy for hypertension, and weight) there were no significant differences among the patients treated with the various reserpine-hydralazine and ganglion blocking regimens. There were slightly fewer Caucasians and patients with no previous history of treatment for hypertension among those taking reserpine alone than there were in either the reserpine-hydralazine group or the placebo cases, but these differences represent fewer than six patients.

The relative antihypertensive effectiveness of each regimen was determined in the patients who exhibited a similar background characteristic. For example, all patients under 40 were analyzed separately as to comparative responses to the various treatment regimens. A similar analysis was carried out for patients between ages 40 to 59, for all white patients as a separate group, and so on for each of the categories listed in Table 2 where sufficient numbers of patients were included to make such a comparison possible. In each classification of background characteristics the comparative effectiveness of treatment regimens was similar to that observed in the total series of patients.

Thus, not only was each background characteristic well distributed through the various treatment groups, but, in addition, none of the characteristics appeared to influence comparative antihypertensive effectiveness.

Cases Included in the Analysis.—The material presented in succeeding tables and charts is based on the 326 patients who completed at least three months of unchanged therapy. If only those patients who remained on the same regimen for the entire year are considered, it is necessary to assume that the patients lost to study achieved the same change in pressure as the group remaining. However, this obviously cannot be the case, since some of the losses were due to death or to changes in regimens necessitated by adverse developments such as a threatening elevation of blood pressure, serious organic complications, or severe side-effects. Omission of these cases would make a therapeutic regimen appear to be more effective than it actually was, especially with the passage of time as the nonresponders dropped out. As will be discussed subsequently, the conclusions as to the efficacy of each regimen were the same for both methods of analysis. Therefore, the decision was made to use the last reported pressure readings for patients lost to study at all periods subsequent to three months. This method seemed to provide the best estimate of drug efficacy in that it made use of all available material in the least biased manner.

TABLE 3.—Average Home and Clinic Blood Pressure Recordings at the Third, Sixth, Ninth, and Twelfth Months for Patients on Reserpine-Hydralazine Regimens*

Regimen	Systolic					Diastolic				
	Pre-Rx †	3d	6th	9th	12th	Pre-Rx †	3d	6th	9th	12th
Average home pressures										
Reserpine & hydralazine	161	153	153	153	153	103	90	90	89	92
Reserpine alone	161	157	160	162	161	102	99	100	100	100
Placebo	162	167	165	165	168	104	106	104	105	106
Clinic pressure										
Reserpine & hydralazine	161	161	156	161	159	103	98	101	100	99
Reserpine alone	161	166	168	169	167	102	107	107	109	108
Placebo	162	175	171	172	168	104	112	111	112	110

* For patients lost prior to 12 months, but after 3 months, last monthly pressures used. † Pre-Rx levels are an average of the hospital blood pressure recordings from fourth through sixth day.

TABLE 4.—Average Rise or Fall of Blood Pressure from Hospital Control to Twelfth Month Home Pressures for Reserpine-Hydralazine Regimens *

Regimen & Type	No. of Cases	Systolic		Diastolic	
		Av. Diff., Mm. Hg	0.90 Confidence Interval †	Av. Diff., Mm. Hg	0.90 Confidence Interval †
Total					
Reserpine+Hydralazine	80	-5.79	- 2.59 to - 8.99	-11.25	- 8.97 to -13.53
Reserpine alone	80	+0.67	+ 5.08 to - 3.74	- 3.70	- 0.96 to - 6.44
Placebo	38	+5.34	+10.75 to - 0.07	+ 0.82	+ 4.28 to - 2.64
Mild					
Reserpine+Hydralazine	36	-2.25	+ 2.54 to - 6.04	- 8.27	- 5.09 to -11.45
Reserpine alone	45	+0.37	+ 6.60 to - 5.86	- 3.27	- 0.09 to - 6.45
Placebo	22	+4.60	+11.98 to - 2.78	+ 0.77	+ 6.25 to - 4.71
Moderate					
Reserpine+Hydralazine	44	-8.56	- 5.28 to -11.84	-13.68	-10.60 to -16.76
Reserpine alone	35	+1.00	+ 7.18 to - 5.18	- 4.26	+ 0.40 to - 8.92
Placebo	16	+6.30	+13.48 to - 0.88	+ 0.88	+ 4.29 to - 2.53

* For patients lost prior to 12 months, but after 3 months, last monthly home pressures used. † Two average differences whose corresponding range estimates do not overlap differ at the 0.02 level of significance.

The blood pressures were evaluated at the third, sixth, ninth, and twelfth months, since results were reported quarterly. The stability of the average blood pressure for each group on the same regimen made it evident that the results of analysis would be the same at whatever time (from three months to one year) that the data were evaluated (Table 3).

Comparison of Reserpine, Reserpine-Hydralazine and Placebo Regimens.

1. Reserpine-Hydralazine Versus the Other Regimens: The regimen of reserpine-plus-hydralazine was more effective in lowering blood pressure than either reserpine alone or placebo. In the 80 patients on this regimen the average systolic pressure changed from a basal pretreatment hospital level of 161 mm. Hg to a post-treatment home average of 153 mm. Hg. The diastolic average fell from 103 in the control to 92 mm. Hg post-treatment (Table 3). Contrasted with this reduction in average systolic pressure of 8 and diastolic of 11 mm. Hg, the 80 patients on reserpine alone exhibited no change in average systolic and a drop of only 2 mm. Hg in the diastolic pressures. In the group of 38 patients receiving placebos, the average systolic pressure rose from 162 pretreatment to 168 mm. Hg post-treatment and the diastolic from 104 to 106 mm. Hg.

Table 4 presents the average change in blood pressures from the pre-treatment, hospital, basal level to the final month's, home average. Adjacent to the column indicating the average difference in pressure expressed in millimeters of mercury is a column indicating the 0.90 confidence interval for these estimates of mean change. Such confidence intervals are a function of the number of cases studied and the variability of the patients included in the sample. The probability of the true estimate of the mean change being outside these limits is less than 1 in 10. If the confidence intervals for two means do not overlap, the probability that the difference between the means is the result of chance is less than 1 in 100.

Table 4 lists the average change in systolic and diastolic pressures according to whether the patients were classified as mild or moderately severe (as defined by the scoring system described earlier in this report). The difference in antihypertensive efficacy among the three regimens is greater in the group with moderately severe hypertension. The patients classified as moderate and treated with hydralazine and reserpine showed a change of -8.6 mm. Hg in systolic and of -13.7 mm. Hg in diastolic pressure. These changes were significantly greater than those observed in the patients treated with either reserpine alone or

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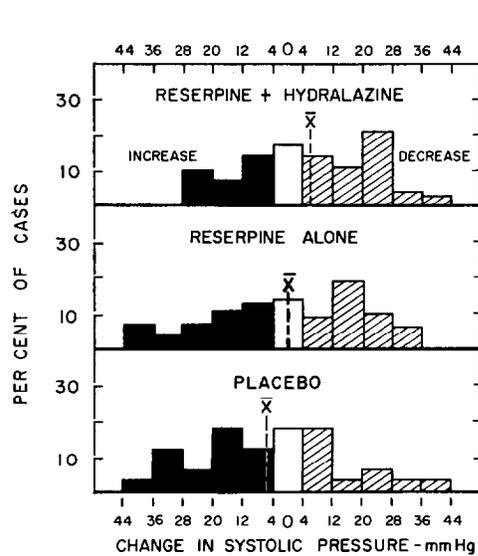


Fig. 1.—Percentage distribution charts (comprising 198 patients) of the changes in systolic blood pressure after three months or more of treatment with either reserpine and hydralazine, reserpine alone, or placebos. The mean changes are indicated by \bar{X} . See text for further details.

placebo. The differences between regimens were less in the mild patients, although in these cases also the effect upon the diastolic pressure was greater in patients on both agents than in those treated with either reserpine alone or no drug.

2. Reserpine Alone Versus Placebo: The mean reduction of blood pressure for patients treated with reserpine alone was consistently greater than the corresponding change in patients treated with placebo, but in no instance was this difference of sufficient magnitude to exclude the possibility of chance effect. The inability to detect a statistically significant difference between the reserpine and the placebo regimens was in part due to the large variance in pressure response among patients treated with reserpine alone. This increased spread is shown in Figures 1 and 2, which illustrate the percentage distribution of the differences between pretreatment levels and the twelfth or final monthly pressure readings. The unshaded block depicts the per cent of cases with a change between +4 and -4 mm. Hg. The columns to the right of the un-

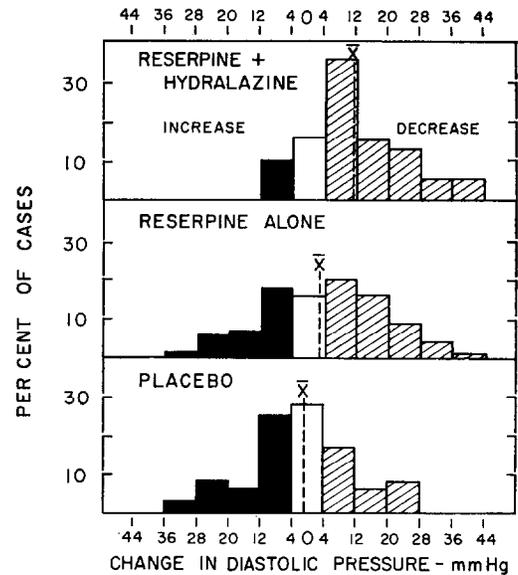


Fig. 2.—Percentage distribution charts of the changes in diastolic blood pressures in patients treated with either reserpine and hydralazine, reserpine alone, or placebo regimens. Other notations as in Figure 1.

shaded block indicate the per cent of cases (ordinate), with the indicated fall in pressure on the abscissa, while the columns to the left indicate the per cent of cases with a gain of blood pressure. For example, in Figure 2, 10% of the patients on reserpine plus hydralazine exhibited an elevation of diastolic pressure varying from 4 to 12 mm. Hg. None exhibited elevations greater than 12 mm. However, 18% of the patients on reserpine alone showed a rise of diastolic pressure of from 4 to 12 mm. Hg and 14% showed elevations greater than 12 mm. On the other hand, 30% of the reserpine-treated patients exhibited a reduction of more than 12 mm. Hg in diastolic pressure whereas this occurred in only 13% of the placebo-treated group.

3. Clinic Versus Home Recordings of Blood Pressure: Table 5 and Figure 3 summarize the results of clinic pressure recordings. The clinic blood pressures are proportional to the home pressures, but for each group the average of the clinic pressures is higher (Figures 3 and 4). This is not true for all individuals, since there were some patients whose clinic blood-pres-

TABLE 5.—Average Home and Clinic Blood Pressure Recordings at the Third, Sixth, Ninth, and Twelfth Months for Patients on Ganglion Blocking Drugs*

Regimen	Systolic					Diastolic				
	Pre-Rx †	3d	6th	9th	12th	Pre-Rx †	3d	6th	9th	12th
Average home pressures										
Mecamylamine	183	166	166	167	167	118	101	101	102	102
Chlorisondamine	178	162	164	164	166	115	103	103	103	103
Pentolinium	185	166	166	166	165	116	101	102	103	102
Clinic pressures										
Mecamylamine	183	178	178	177	179	118	111	112	108	111
Chlorisondamine	178	166	173	170	168	115	106	110	110	109
Pentolinium	185	179	183	175	180	116	115	114	113	113

* For patients lost prior to 12 months, but after 3 months, last monthly pressures used. † Pre-Rx levels are an average of the hospital blood pressure recordings from the fourth through the sixth day.

sure readings were lower than their home recordings. On the average, however, the pressures were 6 to 10 mm. Hg higher than those reported for similar months by the patients. The present analysis relied mainly on the home pressure recordings for drug appraisals for the following reasons: (1) Consecutive home readings were less variable than the clinic recordings taken at consecutive visits. It will be noted also in Figure 4 that the mean diastolic value in the placebo group as obtained from the home recordings lies close to the mean pre-treatment level. In addition, the distribution about this mean approaches a normal curve. (2) Since home recordings were taken daily they were more representative of the average response throughout each month. (3)

The greater number of home readings (60 or more per month) provided ample material for statistical analysis. Despite the greater variation in clinic blood pressures, the mean values indicated the same relative effectiveness of the three regimens as had been determined using the home blood pressure readings.

4. Losses Due to Failure of Therapy: As previously mentioned, an analysis of the patients remaining on an unchanged regimen for one year demonstrated a significant difference between patients on reserpine plus hydralazine, and those on reserpine alone or on placebo. However, the differences among the regimens were less than those indicated in the analysis of all cases receiving at least three months of therapy.

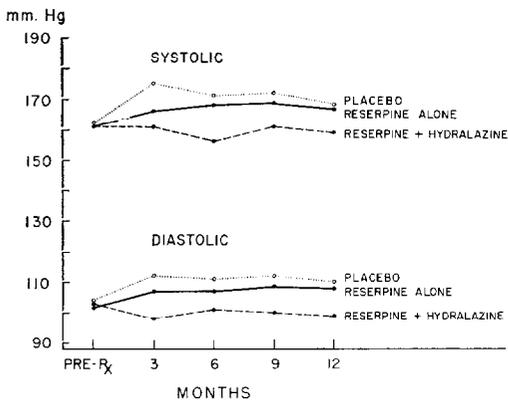


Fig. 3.—Mean systolic and diastolic blood pressure values as recorded in the clinics at 3, 6, 9, and 12 months in all patients treated with either reserpine and hydralazine, reserpine alone, or placebos. Pretreatment values represent the mean hospital control blood pressure readings.

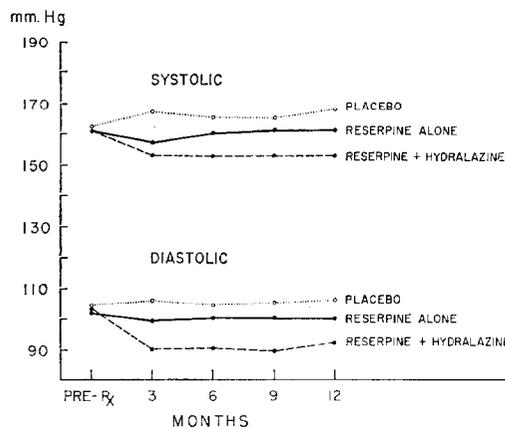


Fig. 4.—Mean systolic and diastolic blood pressure values as recorded in the home, compared to mean hospital control readings. Other notations as in Figure 3.

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This, of course, was the result of changes in regimen among patients whose responses to therapy were felt to be unsatisfactory. For example, only one of 80 patients treated with reserpine-hydralazine was considered a treatment failure and placed on another regimen, while there were 7 such instances among the 80 patients on reserpine. There were 5 treatment failures among the 38 cases on placebo. These differences have considerable significance in view of the double-blind nature of the study.

Among the 80 patients on reserpine alone, 14 were classified as dosage failures and the dose of the drug was doubled. For purposes of this analysis, doubling of the dose was ignored in the evaluation of treatment effect, since, if any bias were introduced, it would have been in favor of the drug regimen found to be inferior. In fact, however, doubling the dose did not seem further to reduce the blood pressure in the patients so managed.

5. Toxicity in Reserpine and Reserpine-Hydralazine Regimens: Among these three regimens, drugs were discontinued because of side-effects in 13 cases. Nine of the thirteen patients were taking the double-drug regimen of reserpine and hydralazine; three were on reserpine alone, and one was taking placebos. Five of the discontinuations of the reserpine-hydralazine regimen occurred during the first three months of

therapy. Two were due to severe headache, one to depression, and the other two to gastrointestinal upset, in one of which there was a severe gastrointestinal hemorrhage. It is probable that the depression and possibly the gastrointestinal hemorrhage were due to the reserpine. Two additional cases of severe depression occurred in the series taking reserpine and ganglion blocking drugs. The two early discontinuations of reserpine alone were caused by the appearance of nausea, coupled with possible depression.

Six cases were dropped from the study because of side-effects subsequent to the first three months. Four of the six were taking reserpine-hydralazine combined therapy. The reasons were: one because of possible depression, although there were no suicidal thoughts; one because of nervousness; one because of edema of the legs, and the last because of dermatitis and nightmares. In the only patient on reserpine alone, whose regimen was changed after three months because of side-effects, the complaint was impotence. Therapy was discontinued in one patient taking placebos because of insomnia. The incidence of less important side-effects will be reported on in subsequent communications.

Ganglionic Blocking Agents Plus Reserpine Regimens.—Two special circumstances must be considered in evaluating the gan-

TABLE 6.—Average Rise or Fall of Blood Pressure from Hospital Control to Twelfth Month Home Pressures for Ganglion Blocking Drugs

Regimen & Type	No. of Cases	Systolic		Diastolic	
		Av. Diff., Mm. Hg	0.90 Confidence Interval †	Av. Diff., Mm. Hg	0.90 Confidence Interval †
All cases					
Mecamylamine	53	-18.41	-12.87 to -23.95	-16.79	-13.19 to -20.39
Chlorisondamine	47	-12.27	- 5.05 to -19.47	-11.32	- 7.07 to -15.57
Pentolinium	28	-19.92	-12.20 to -27.64	-12.82	- 7.75 to -17.89
Moderate					
Mecamylamine	34	-12.32	- 6.58 to -18.06	-12.41	- 8.67 to -16.15
Chlorisondamine	35	- 7.93	+ 0.39 to -15.47	- 7.86	- 3.65 to -12.07
Pentolinium	16	-20.20	-11.67 to -28.73	-10.94	- 4.38 to -17.50
Severe					
Mecamylamine	19	-28.29	-18.73 to -39.05	-24.63	-17.94 to -31.32
Chlorisondamine	12	-23.18	- 6.94 to -39.42	-20.58	-10.85 to -30.31
Pentolinium	12	-19.55	- 5.45 to -33.65	-14.50	- 6.71 to -22.29

* For patients lost prior to 12 months, but after 3 months, last monthly home pressures used. † Two average differences whose corresponding range estimates do not overlap differ at the 0.02 level of significance.

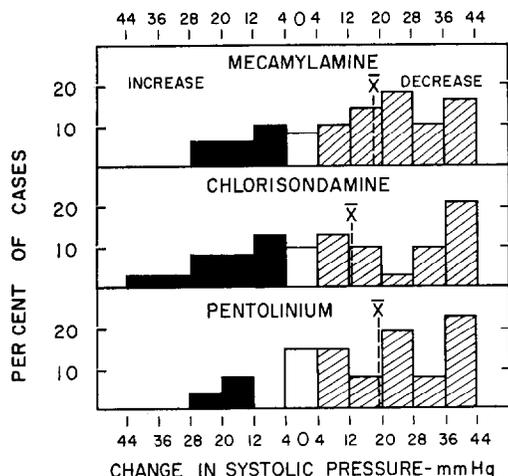


Fig. 5.—Percentage distribution charts (comprising 128 patients) of the changes in systolic blood pressure after three months or more of treatment with reserpine plus either mecamylamine, chlorisondamine, or pentolinium tartrate. The mean changes are indicated by X.

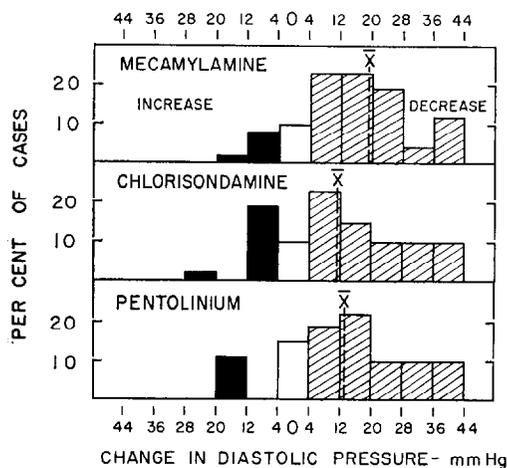


Fig. 6.—Percentage distribution charts of the changes in diastolic blood pressure after treatment with reserpine plus one of the ganglion blocking drugs indicated. Other notations as in Figure 5.

gliconic blocking agents. The first is the variability of dosage. In reality the dosage level was determined in each patient by the clinician's evaluation of the relative importance of blood pressure reduction as opposed to severity of side-effects. The second is the wide range of responsiveness in different individuals. Because of the large variance only considerable differences from one blocking agent to another can be regarded as being significant.

1. Relative Antihypertensive Effectiveness: From inspection of Table 6 and Figure 5, it might be suspected that chlorisondamine was less effective than the other two. It should be noted, however, that there is overlapping at the 0.90 confidence interval (Table 6). Further evidence against a significant difference is provided in the analysis of the three-month results in a group of patients whose treatment was begun subsequent to February, 1958. The data on these patients (which are not recorded here in tabular form because of incomplete follow-up) disclose the following changes from average hospital control blood pressure levels at the end of three months of treatment: for 21 patients taking mecamylamine $-16/-12$ mm. Hg, 20 cases on

chlorisondamine $-15/-13$ mm. Hg, and for 18 patients taking pentolinium tartrate $-13/-11$ mm. Hg. The similarity among the ganglion blocking drugs was again indicated by the fact that the percentage of treatment failures was essentially the same in the three regimens. As indicated in Table 1, there were 3 such cases in the group of 53 patients taking mecamylamine, 3 in the 47 cases on chlorisondamine, and 1 in the 28 patients taking pentolinium tartrate. It seems probable, therefore, that when data are available on the entire series, no significant differences in antihypertensive effectiveness will be apparent among the various blocking agents used in this investigation.

There is no question that the ganglion-blocking-drug—reserpine combination produced a significant average reduction of blood pressure. In the total group of 128 patients treated with ganglionic blocking agents plus reserpine, the average reduction of blood pressure was 16.5 mm. Hg systolic and 13.9 mm. Hg diastolic. However, not all patients responded to this therapy. Fourteen per cent exhibited higher diastolic and twenty-two per cent higher systolic pressures following treatment (Figures 5 and 6). On the other hand, in approximately 20% of patients systolic pressure was reduced by 40 mm. and diastolic by 30 mm.

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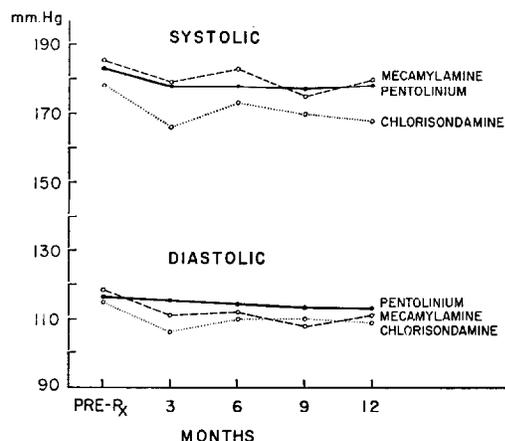


Fig. 7.—Mean systolic and diastolic blood pressure values as recorded in the clinics at 3, 6, 9, and 12 months in all patients treated with reserpine and one of the three ganglion blocking drugs indicated. Pretreatment values represent the mean hospital control blood pressure readings.

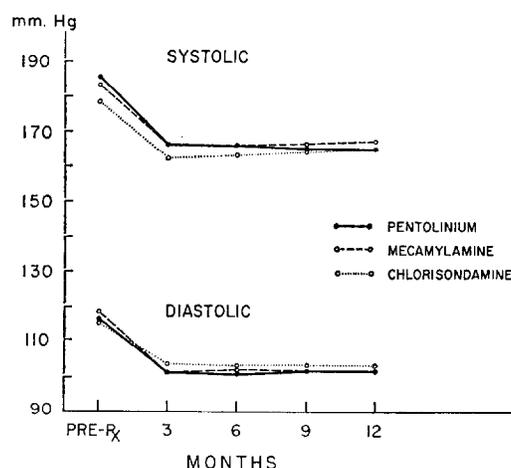


Fig. 8.—Mean systolic and diastolic blood pressure values as recorded in home compared to mean hospital control readings. Other notations as in Figure 7.

Hg. These extreme responses illustrate the wide variability in antihypertensive effectiveness which seems to be characteristic of the ganglion blocking agents.

Further analysis of the data in respect to the responses seen in moderately severe as opposed to the severe cases revealed that the absolute decreases in blood pressure were greater in the severe group (Table 6). This probably was a reflection of the fact that the severe cases began therapy at a higher average level of blood pressure. It is of considerable interest that when the moderately severe cases on blocking agents were compared to the group of similar severity taking the hydralazine plus reserpine combination there were no significant differences between the two types of therapy. Thus, in 44 moderately severe patients taking hydralazine plus reserpine the average change of blood pressure was $-8.6/13.7$ mm. Hg (Table 4), while in 85 patients of comparable severity on ganglionic blocking agents it was $-12/10.3$ mm. Hg. This result may have been influenced by the fact that therapy with blocking agents was not pursued as aggressively in the moderately severe as in the severe group since the general levels of blood pressure were not as alarming in the less severe cases. These trends were evidenced, however, in

all of the participating hospitals, and probably are an accurate reflection of the results to be expected in clinical practice. Since hydralazine was not tested in the severe group of cases, it is not possible to make any comparisons between the effectiveness of this agent as compared to ganglionic blocking agents in severe hypertension.

The clinic pressure recordings provided an unreliable and misleading indication of the effects of therapy with ganglion blocking drugs (Figures 7 and 8). Not only was there considerable variability from one treatment period to another, but the over-all results indicated little change in blood pressure from the pretreatment control level (Figure 7). Because of this extreme variability and unreliability of the clinic readings, no attempt was made at this time to analyze the data for orthostatic effects produced by the blocking agents. The only home records available were those taken with the patient in the sitting position.

2. Side-Effects: Side-effects were considered to be sufficiently severe in 13 patients to warrant discontinuation of therapy. In two of these the complaint was severe depression verified by psychiatric consultation. Since this probably was the result of treatment with reserpine, only 11 of the cases can be suspected of being the result of gan-

glionic blocking agents per se. Of this number, three patients were taking mecamlamine, six patients chlorisondamine, and three patients pentolinium tartrate. No single side-effect predominated as the major cause for deciding to discontinue therapy. The most common complaint was that of general discontent with the multiple side-effects of ganglionic blockade. Gastrointestinal symptoms predominated in two cases; in one reserpine and mecamlamine were discontinued after nine months of treatment because of reactivation of a peptic ulcer with epigastric pain. In the other, severe diarrhea occurred each of three times the patient was given reserpine-chlorisondamine.

There was a higher percentage of patients with impaired visual accommodation among the patients on chlorisondamine than on the other agents. This was evidenced both in regard to difficulty in near vision and in lack of adjustment to bright light. Thus, 20% of the patients on chlorisondamine required sunglasses while these were needed in only 12% of the patients on the other regimens. Patients taking mecamlamine experienced more difficulty with dry mouth and with micturition than did those on the other ganglion blocking drugs. There was no evidence to suggest an increase in side-effects after the third month although these comparisons were limited by the loss of patients to observation at a later time period.

No attempt has been made in this report to compare the incidence of side-effects with either dosage levels or antihypertensive effectiveness. The presently available data are considered too preliminary for analysis in this fashion. However, such an analysis will be carried out when results become available on a larger series of patients.

Comment

The objectives of this cooperative investigation are twofold. First, over the short term, it is designed to evaluate the most effective and best tolerated regimens for achieving reduction of blood pressure. The

present report covers the preliminary results of one aspect of the program as it relates to the five antihypertensive agents herein reported. Other drugs, such as chlorothiazide and *Veratrum viride*, are at present under study, and will be reported on as significant data accumulate. As new and clinically promising antihypertensive drugs appear, they too will be subjected to similar evaluation. It is not the intention of this program to screen previously untried compounds.

The second and long-range purpose of the cooperative study is to determine whether control of blood pressure at reduced levels effectively prevents the progression of organic deterioration in mild and moderate (as defined herein) degrees of hypertension. While maintaining the integrity of the placebo-treated control group, antihypertensive agents of demonstrated effectiveness will be added to or substituted for the treatment regimens of patients receiving active agents in order to obtain optimal reduction of blood pressure. Methods for accomplishing these changes without destroying the "double-blind" technique used in the present study will be described at a subsequent time. It seems probable that no valid estimation of the effectiveness of reduced blood pressure in preventing organic damage can be made in less than 5, or possibly 10, years.

No large-scale or long-term double-blind assessment of antihypertensive agents has been attempted previously. However, double-blind studies of reserpine alone or reserpine and hydralazine have been reported in small series in which the drugs were administered for relatively short periods of time. Bello and Turner¹ gave reserpine or a placebo for five-week periods to ambulatory clinic patients and were unable to demonstrate any significant antihypertensive effects. Dorsett and his associates² evaluated the effects of phenobarbital, reserpine, reserpine-hydralazine, and of placebos in groups of 4 ambulatory patients each (total 16 patients). All cases received placebos for 8 weeks, treatment for 16 weeks, and placebos again for an additional 8 weeks. No signif-

icant blood pressure changes occurred in the four patients receiving placebos throughout, and in the four receiving phenobarbital. Reserpine produced a slight but not statistically significant decrease, whereas reserpine-hydralazine brought about a significant fall in blood pressure. Lee and associates³ concluded, on the basis of a double-blind evaluation in 25 patients, that hydralazine alone or in combination with reserpine, but not reserpine alone, produced a significant antihypertensive effect in certain patients of the series. Thus, the previous placebo-controlled studies are in essential agreement with the conclusions of the present investigation that oral reserpine in the doses employed has only minimal antihypertensive effects, whereas the addition of hydralazine produces a significant reduction of blood pressure in mild and moderate hypertension.

It would appear from the present investigation that any one of the three ganglion blocking drugs tested is about as effective as the other two. Chlorisondamine produced more disturbance in visual accommodation, whereas mecamlamine caused dryness of the mouth and difficult micturition more frequently than the other drugs. In view of the comparable antihypertensive effectiveness of hydralazine in moderately severe hypertension and the lack of evidence for serious toxicity (lupus-like syndrome) in the dosages used (200 mg. per day), it would appear desirable to undertake a trial of this agent in the less severe cases before subjecting such patients to the ganglion blocking drugs.

The incidence of severe depression was not as great as in other reported series of patients treated with reserpine.^{4,5} The reason for this may be dependent on the population sampled in this study. It has been noted previously that depressions produced by reserpine were uncommon in clinic patients, in contrast to their frequent occurrence in higher income groups, especially the professional classes.⁶ The lack of female patients in this series also cautions against the unqualified application of the

presently reported results to the population as a whole.

Summary and Conclusions

Antihypertensive effectiveness and side-reactions of a variety of therapeutic regimens were compared in a double-blind, control study on 326 male hypertensive patients followed for at least three months, of whom 232 completed one full year of unchanged treatment. In each regimen the average for the final month of home blood-pressure recordings was compared to the average "basal" pretreatment values (average blood pressure from the fourth through the sixth hospital day).

In mild hypertension, reserpine (0.5 mg. per day maintenance dose) plus hydralazine (200 mg. per day) was more effective than reserpine alone or placebos. Reserpine alone may have been slightly more effective than placebos but the difference was not statistically significant.

In moderately severe hypertension, the reserpine plus hydralazine regimen was considerably more effective than either reserpine alone or placebos. The mean change in diastolic pressure was -13.7 mm. Hg with reserpine-hydralazine, -4.3 mm. with reserpine alone, and $+0.9$ mm. Hg with placebos. Reserpine plus hydralazine produced as great a reduction of blood pressure as reserpine plus ganglion blocking drugs in moderately severe hypertension.

All three of the ganglionic blocking agents produced significant reductions of blood pressure. The mean change from hospital control levels in 128 patients was $-16.5/-13.9$ mm. Hg. The range of response was wide, varying from rises of blood pressure in approximately 20% of patients to reductions of 40/30 mm. Hg in another 20%. There were no significant differences in antihypertensive effectiveness among mecamlamine, chlorisondamine, or pentolinium tartrate.

Therapy was discontinued in 9 of 101 patients begun on the reserpine plus hydralazine regimen because of headache in 2, depression in 2, gastrointestinal disturb-

ances in 2 (including severe gastrointestinal hemorrhage in 1), nervousness in 1, edema of the legs in 1, and dermatitis and nightmares in 1. In four patients on reserpine alone, therapy was discontinued because of nausea, possible depression, and/or impotence. Treatment was stopped in one patient on placebos because of insomnia.

Slight differences in frequency of side-effects occurred with certain of the ganglion blocking drugs. Chlorisondamine therapy was associated with more frequent disturbances of visual accommodation, while mecamlamine produced slightly more dryness of the mouth and difficulty in micturition than the other two agents.

Dr. Edward D. Freis, Veterans Administration Hospital, 2650 Wisconsin Ave., North West (7).

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