

Results of Prolonged Treatment with Pentolinium Tartrate

with Special Reference to the Addition of Rauwolfia, Hydralazine or Both

By EDWARD D. FREIS, M.D., AND ILSE M. WILSON, M.D.

A series of 96 patients with severe hypertension has been treated with pentolinium tartrate for an average period of 12 months. Seventeen patients died. Therapy was more effective in arresting changes in the optic fundi and in the heart than in the kidneys. Various combinations of hypotensive agents were tested and it was concluded that in general the combination of pentolinium tartrate, Rauwolfia and hydralazine resulted in the greatest reduction of blood pressure with the least degree of side effects due to ganglionic "blockade."

SOON after pentolinium tartrate was synthesized by Libman, Pain and Slack,¹ pharmacologic studies by Wein and Mason² indicated that it was a potent ganglionic blocking agent with a prolonged duration of action. Preliminary clinical results were reported by Campbell and Maxwell,³ Smirk⁴ and from this clinic.⁵ These reports indicated that pentolinium tartrate was an orally effective, potent, antihypertensive drug that appeared to be useful in the treatment of patients with more severe, fixed types of hypertension. In the present report, the long-term experience with pentolinium tartrate both alone and in combination with certain other hypotensive agents is presented.

MATERIALS AND METHODS

The treatment group consisted of 96 patients selected because of severe, sustained hypertension (table 1). Their ages ranged from 27 to 65 years,

From the Cardiovascular Research Laboratory, Georgetown University Hospital, the Department of Medicine, Georgetown University School of Medicine and the Veterans Administration Hospital, Washington, D. C.

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with an average age of 47 years. All except 15 of these patients were hospitalized prior to or during the initiation of treatment with pentolinium. Prior to therapy, 56 per cent exhibited grade III or more changes in the optic fundi and 39 per cent had some degree of nitrogen retention.

Electrocardiograms were taken of 83 patients and 66 exhibited the pattern of left ventricular hypertrophy. Frank congestive heart failure was diagnosed in 13 of the patients, although lesser degrees of cardiac decompensation as manifested by exertional dyspnea were common. Cardiac enlargement was present in 58 of 76 patients who had roentgenograms taken prior to treatment.

The method of adjusting dosages of pentolinium tartrate has been described in previous communications.⁶⁻⁸ The duration of treatment ranged from 3 to 27 months, with a mean of 12 months. Seven were treated for 24 months or longer, 44 were treated from 12 to 24 months, 26 from 6 to 12 months, and 18 from 3 to 6 months. In the majority of the cases, various other hypotensive agents were added to pentolinium tartrate for periods of time as are described below.

RESULTS

Over-all Results of Treatment

Mortality

There were 17 deaths in the entire series. Of these, 10 exhibited grade IV fundi; 4, grade III; and 3, grade II fundi prior to therapy. The survival from beginning of treatment to death in this group averaged 11 months, and in the malignant group, 13 months. The causes of death were as follows: nephrosclerosis with uremia in 11, cerebral hemorrhage in 4, rup-

TABLE 1.—*Severity Indices of Patients Prior to Treatment with Pentolinium Tartrate*

Parameter	No. of Cases	% of Total
Male.....	71	74
Female.....	25	26
Optic fundi: grade IV.....	34	35
grade III.....	20	21
grade II.....	40	42
grade I.....	1	1
Unclassified*.....	1	1
Elevation of blood urea nitrogen or nonprotein nitrogen.....	38	40
Albuminuria: 2 to 4 +.....	37	39
trace to 1 +.....	27	28
total.....	64	67
15 min. excretion phenolsulfonphthalein (55 cases) under 15 per cent.....	35	
Electrocardiogram (83 cases) LVH pattern.....	66	
Increased transverse diameter of heart (76 cases).....	58	

* Corneal opacities prevented examination.

ture of an aortic aneurysm in 1, and myocardial infarction in 1. Twenty-four of the grade IV patients still survive, 9 have been under treatment for periods varying from 19 to 27 months, 7 from 12 to 18 months, and 8 from 3 to 10 months.

Morbidity

Myocardial infarction occurred in only one case listed above. Two patients developed persistent angina with electrocardiographic evidence of myocardial ischemia. In these two and in one other patient with electrocardiographic changes, it was necessary to discontinue pentolinium tartrate because of angina. In one other patient the routine "check-up" electrocardiogram revealed the development of a pattern consistent with an old myocardial infarction although the patient had experienced no symptoms.

In addition to the four who died with cerebrovascular hemorrhages, two patients developed cerebrovascular accidents of slight degree while under treatment. Only one patient required hospitalization.

Effect on Symptoms

The results (table 2) indicate that the symptoms of headache, dizziness, palpitation and

dyspnea usually improved, whereas in the case of angina a few improved but an equal number were made worse. Nocturia usually decreased but in some it increased, particularly in those who exhibited considerable postural hypotension, the latter tending to produce oliguria during the day.

Seven patients had cerebral vascular accidents with residuals prior to treatment. None showed any striking improvement, and there

TABLE 2.—*Changes in Symptoms Following Treatment*

Symptom	No. of Patients	Complete Relief	Improved	Unimproved or Worse	% Improved
Headache.....	53	14	30	9	83
Exertional dyspnea.....	25	2	17	6	76
Dyspnea at rest.....	15	7	6	2	87
Paroxysmal nocturnal dyspnea.....	5	2	3	0	100
Palpitation.....	6	2	2	2	67
Angina.....	5	0	2	3	40
Nocturia.....	70	21	28	11	70
Dizziness.....	15	5	10	0	100
CVA residuals.....	7			7	0

TABLE 3.—*Changes in the Optic Fundi Following Treatment with Pentolinium in Ninety-Five Cases*

Grade	No. of Patients	No. of Patients in Each Grade After Treatment				% Improved
		IV	III	II	I	
IV	34	2	6	22	4	94
III	20	0	3	13	4	85
II	40	0	0	22	18	45
I	1	0	0	0	1	0

TABLE 4.—*Changes in Cardiac Diameter as Measured Roentgenographically and Electrocardiograms Following Treatment with Pentolinium Tartrate*

Parameter Pretreatment	No. of Cases	After Treatment No. of Cases in Each Grouping				% Improved
		Normal	Improved	Unchanged	Worse	
Cardiac diameter.....	76					
Enlarged.....	58	2	33	19	6	57
Normal.....	18	14			4	
Electrocardiography.....	75					
LVH pattern.....	65	4	8	56	1	12
Normal.....	11	10				

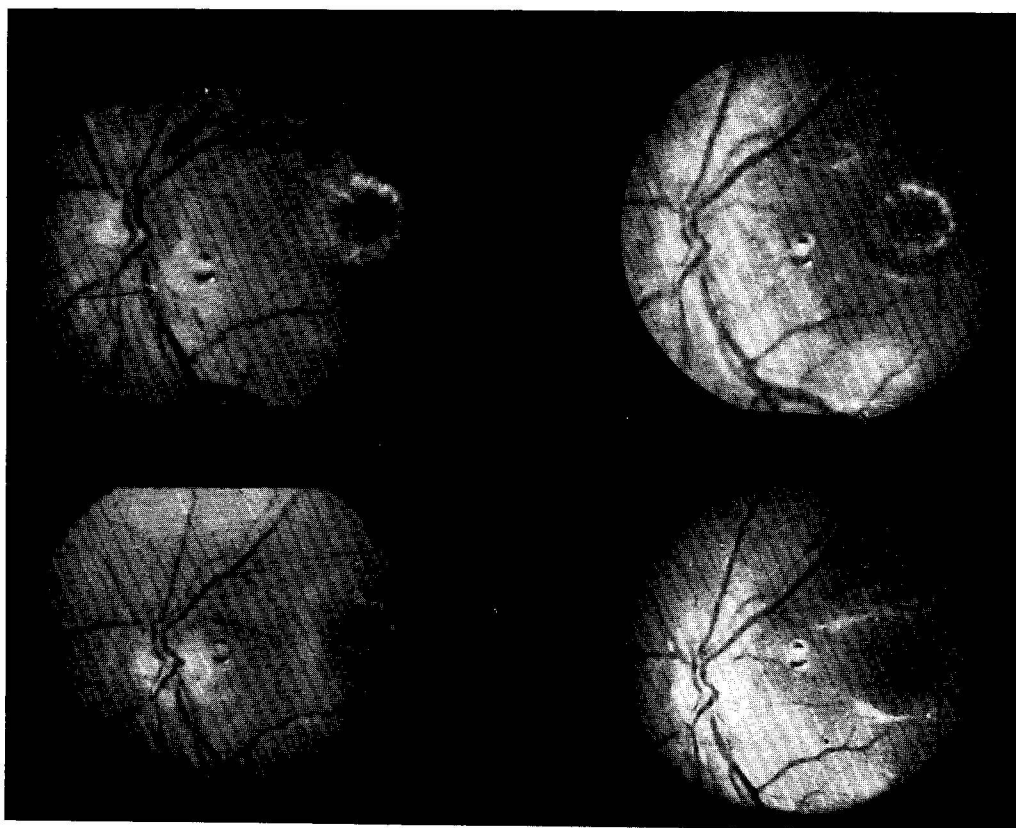


FIG. 1. Photographs of the left optic fundus in W. A., a 32 year old merchant seaman who entered the hospital with an accelerated hypertension. This could not be arrested by his family physician who had tried reserpine and hydralazine. The patient was treated with pentolinium tartrate and after 3 months returned to work as a carpenter. The upper left photograph taken prior to treatment reveals typical neuroretinitis with papilledema, a large macular "star" and a hemorrhage above the disk. The upper right photograph taken 1 month after treatment with pentolinium shows resorption of the hemorrhage and diminution in the papilledema and exudates. The lower left photograph was taken 3 months and that on the right 9 months after treatment. The fundus has reverted to grade II with residual scars in the macular area.

was a temporary return of paresis or difficulty in speech in four of these cases during periods of marked hypotension.

Effect on Objective Findings

1. *Optic Fundi.* As shown in table 3 in the total series, 67 patients, or 71 per cent, exhibited improvement in the optic fundi (fig. 1); 28 cases, or 29 per cent, remained unchanged.

2. *Transverse Diameter of the Cardiac Silhouette.* Roentgenograms of the chest were taken before and after treatment in 76 of the patients (table 4). Fifty-eight were believed to show cardiac enlargement. Thirty-three exhibited a decrease in cardiac diameter, averaging

1.3 cm. (range 0.5 to 4.5 cm.), 19 were unchanged and 6 showed an increase averaging 1.0 cm. The cardiac diameter was considered normal prior to treatment in 18 patients. Fourteen of these exhibited no significant change, while in four there was an increase in size, averaging 1.2 cm.

3. *Electrocardiographic Changes.* The electrocardiogram was recorded in 75 patients before and after treatment (table 4). Sixty-five exhibited the pattern of left ventricular hypertrophy. After treatment, 4 reverted to normal, 4 showed improvement toward normal, 56 were unchanged and 1 exhibited further progression. Of 11 patients whose electrocardio-

TABLE 5.—Changes in Blood Nonprotein Nitrogen or Urea Nitrogen Levels, Degree of Albuminuria and Fifteen-Minute Excretion of Phenolsulfonphthalein Following Treatment with Pentolinium Tartrate

Parameter Pretreatment	No. of Cases	After Treatment No. of Cases in Each Grouping				% Improved
		Normal	Improved	Unchanged	Worse	
Blood nonprotein nitrogen or urea nitrogen.....	64					
Elevated.....	31	8	14	3	14	45
Normal.....	33	28			5	
Albuminuria.....	76					
4 plus.....	10		10			100
3 plus.....	13	2	7	5	1	54
2 plus.....	7	3	6		1	86
1 plus.....	8	1	5	2	1	62
trace.....	21	4	4	8	9	19
negative.....	17	12		12	5	
Excretion of phenolsulfonphthalein..	45					
Less than 15%.....	19		7	4	8	37
15 to 25%.....	26		4	3	19	15

grams were normal before treatment, 10 remained normal while 1 developed changes characteristic of left ventricular hypertrophy.

4. *Renal Function.* The blood nonprotein nitrogen or urea nitrogen was estimated in 64 cases before and after treatment. The results (table 5) indicate no consistent trend, some showing improvement and an equal number increasing azotemia.

The presence of albuminuria was estimated semiquantitatively using the heat and acetic acid method on freshly voided specimens of urine in 76 patients. The results (table 5) indicate that 73 per cent of the 38 patients with 1 plus or more albuminuria showed improvement.

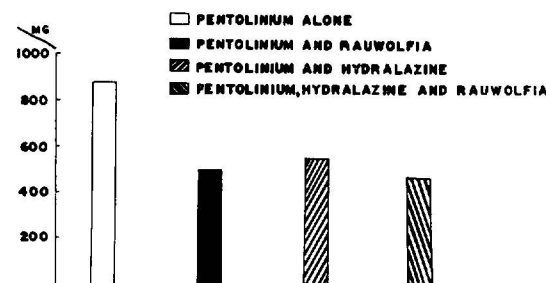
The percentage of phenolsulfonphthalein excreted 15 minutes after injection was determined in 45 cases before and after treatment (table 5). In 26 of the cases prior to therapy, the 15 minute excretion ranged between 15 and 25 per cent of the injected dye. After treatment there was an increased excretion averaging 7 per cent above control values in 4 of the patients, no essential change in 3 cases, while in 19 patients there was a de-

creased excretion averaging 10 per cent below the pretreatment level. In the remaining 19 cases the control excretion was less than 15 per cent of dye in 15 minutes; of this number 7 showed an increase following therapy averaging 8 per cent of the injected phenolsulfonphthalein, 4 were unchanged, and 8 exhibited a further decrease averaging 5 per cent.

Treatment with Pentolinium Alone

Fifty-four patients were treated initially with pentolinium for an average period of 2 months (range 2 days to 19 months, fig. 2). The average pretreatment blood pressure was 222/137 mm. Hg (range 190/110 to 270/155). Following treatment, the average pressure in the supine position was 174/106 mm. Hg (range 145/95 to 208/135), and 161/101 mm. Hg erect (range 130/88 to 200/125). This represented a reduction of "mean" arterial

AVERAGE DAILY DOSE OF PENTOLINIUM TARTRATE



PER CENT REDUCTION OF BLOOD PRESSURE—SUPINE

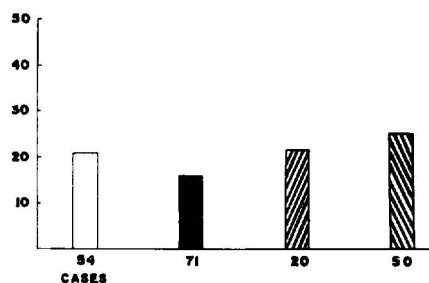


FIG. 2. Chart showing average daily dosage of pentolinium (above) and mean per cent reduction of blood pressure (below) in the group of patients treated with pentolinium tartrate alone as compared to the groups treated with the various combinations of hypotensive agents. The combination of pentolinium, hydralazine, and Rauwolfia resulted in the greatest reduction of blood pressure and the lowest dosage requirement of pentolinium tartrate.

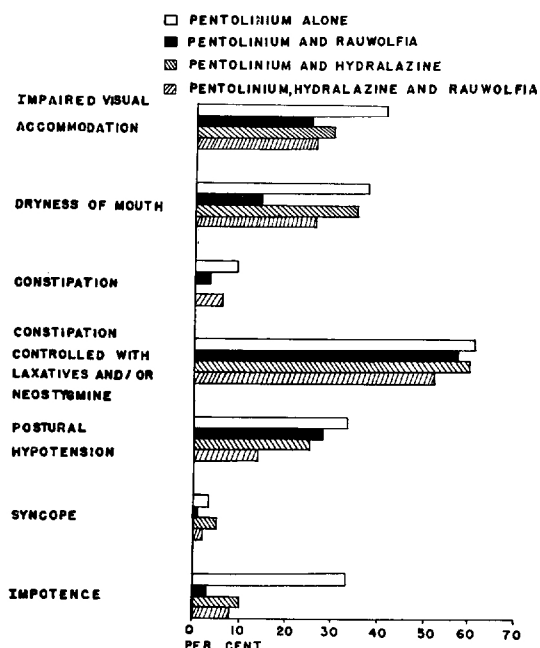


FIG. 3. Chart showing incidence of side effects of ganglionic "blockade" experienced with pentolinium tartrate alone and with the various combinations of hypotensive drugs. The incidence of such side effects appeared to be somewhat reduced with all of the combinations used.

pressure, averaging 22 per cent supine (range 11 to 39 per cent) and 26 per cent erect (range 14 to 41 per cent). The values were obtained from the average of many hospital, home and office readings; in each patient individual readings may have ranged considerably above or below the average reading.

Dosages were administered 3 times daily at approximately 8 hour intervals. The average total daily dosage was 867 mg. (range 60-1400 mg.). In many instances in order to prevent marked fluctuations of blood pressure the morning doses were smaller than the afternoon or night doses.

The incidence of side effects is shown in figure 3. Impotence was complained of in 33 per cent, although probably present in the majority of patients over the age of 45. Difficulty in emptying the urinary bladder was not complained of. Because of the development of tolerance to the hypotensive effect of pentolinium or of marked side effects from ganglionic blockade or because of marked fluctuations in

blood pressure, all, except one patient, were given combinations of pentolinium with reserpine or hydralazine or both.

Pentolinium Tartrate and Rauwolfia

There were 71 cases in this group, the average duration of treatment with *Rauwolfia serpentina* being 6 months (range 9 days to 19 months, fig. 2). Dosages of pentolinium averaged 492 mg. (range 60 to 1800) as contrasted to 867 mg. on pentolinium alone. *Rauwolfia* was administered to 61 patients as reserpine in doses of 0.25 to 1 mg. per day, and as an extract of the crude root (*Rauwiloid*) in doses of 2 to 4 mg. daily in 10 cases.

The control blood pressures averaged 228/135 (range 200/115 to 300/170) mm. Hg. After treatment the mean supine pressure was 197/109 (range 142/92 to 250/150) mm. Hg and in the erect position 163/101 (range 130/80 to 240/145) mm. Hg. The reduction of "mean" arterial pressure averaged 16 per cent in the supine position and 26 per cent in the erect position.

The side effects of ganglionic blockade on this combination are shown in figure 3. Side effects due to the addition of *Rauwolfia* were nasal stuffiness in 18 per cent, severe mental depression in 6 per cent, weight gain in 21 per cent, increase in appetite in 27 per cent, nightmares in 2 patients and diarrhea in 2 cases.

In 43 patients it was possible to determine the dosage requirement of pentolinium after, as compared to before, the addition of *Rauwolfia* (table 6). The average daily dosage of pentolinium when used alone was 550 mg., which produced an average blood pressure fall of 18 per cent in the supine position and 22 per cent in the erect position. After addition of *Rauwolfia*, the average daily requirement of pentolinium was 422 mg. and the mean reduction of blood pressure was 25 per cent in the supine and 29 per cent in the erect position.

The above data represent over-all averages. In not all of the patients was it possible to reduce the dosage. In 23 or 54 per cent of the 43 patients, the dosage of pentolinium could be decreased, in 16 it remained the same and in 4 it was increased. Twenty-four patients exhibited an additional reduction of 5 per cent

TABLE 6.—*The Effect of Added Rauwolfia or Hydralazine or Both on Blood Pressure and Dosage Requirement of Pentolinium Tartrate in the Patients with Three or More Recordings of Blood Pressure Daily for Several Weeks Preceding and Following Combined Drug Therapy*

Drug Combination	No. of Cases	Pentolinium Alone			Pentolinium Combined						Cases in Which Pentolinium Was Reduced %
		Av. Daily Dose mg.	Blood Pressure Av. % Reduction		Average Daily Dose		Blood Pressure				
			Supine	Erect			Av. % Reduction		Additional % Reduction		
					Mg.	Per cent reduction	Supine	Erect	Supine	Erect	
Pentolinium tartrate and Rauwolfia.....	43	550	18	22	422	23	25	29	7	7	54
Pentolinium tartrate and hydralazine.....	13	671	18	24	610	9	24	28	6	4	54
Pentolinium tartrate, Rauwolfia and hydralazine.....	27	642	19	23	418	35	27	31	8	8	70

or more of "mean" arterial pressure after addition of reserpine.

Pentolinium Tartrate and Hydralazine

Twenty patients were given this combination (fig. 2). The average duration of treatment with hydralazine and pentolinium tartrate was 4 months (range 3 days to 8 months). The average daily dose of pentolinium tartrate was 671 mg. before hydralazine was added and 540 mg. afterwards. The average dose of hydralazine was 120 mg. (range 50 to 300 mg.) per day. The dosages of hydralazine were deliberately maintained at a low level because of the reported serious reactions that may occur on long term use.

The pretreatment control blood pressure averaged 227/135 mm. Hg. (range 210/120 to 250/160) in this group of cases. After treatment the average blood pressure was 173/104 mm. Hg (range 153/96 to 200/120) in the supine position. In the erect position the average blood pressure after treatment was 162/100 mm. Hg (range 140/80 to 190/110). The reduction of "mean" arterial pressure averaged 23 per cent in the supine position and 26 per cent erect.

The side effects due to pentolinium tartrate are shown in figure 3. Side effects thought to be due to the addition of hydralazine were: headache in 4, palpitation in 2 and edema in 2. There was no arthritis or dermatitis.

In 13 patients it was possible to compare

dosage requirements and blood pressure response before and after addition of hydralazine. The results are shown in table 6. In seven patients it was possible to reduce the dosage of pentolinium.

Pentolinium Tartrate plus Rauwolfia and Hydralazine

There were 50 patients in this group (fig. 2). The average length of treatment was 4 months (range 9 days to 23 months). The average dose of pentolinium was 458 mg. (range 90 to 1700 mg.). The average dose of hydralazine was 144 mg. (range 50 to 500 mg.). Daily dosage of reserpine varied between 0.25 and 1.0 mg. per day. The average pretreatment blood pressure was 230/136 (range 190/110 to 270/170) mm. Hg. After treatment the average blood pressure in the supine position was 171/106 (range 140/90 to 200/120) mm. Hg and in the erect position was 160/99 (range 130/88 to 200/115) mm. Hg. The reduction of "mean" arterial pressure averaged 25 per cent in the supine position and 28 per cent in the erect.

The incidence of side effects is shown in figure 3. Rauwolfia side effects were: nasal stuffiness in 20 per cent, mental depression in 4 per cent, weight gain in 20 per cent, increase in appetite in 24 per cent, nightmares in 2 per cent, gastrointestinal bleeding in 2 and diarrhea in 4 per cent. Hydralazine side effects were headache in 16 per cent, palpitation in 10 per cent, and dyspnea in 1.

In 27 patients, hydralazine and Rauwolfia were added almost simultaneously (interval of 3 weeks or less). The results are shown in table 6. In 19 of the 27 patients the dosage of pentolinium could be reduced. In 9 of the patients the additional reduction of blood pressure averaged 10 per cent or more.

Development of "Tolerance"

The development of "tolerance" was estimated by comparing the dosage requirement and blood pressure reduction at the initiation of treatment with that required at the end of the period of this study. The initial effective daily dosage averaged 374 mg. and the most recent effective dosage 520 mg., an average increase of 36 per cent. In the early treatment period there was a 22 per cent reduction of supine and 26 per cent in erect blood pressure and at the end of study, 21 per cent supine and 28 per cent erect. It should be pointed out that in most instances Rauwolfia and hydralazine had been added. Thus, these figures do not accurately reflect the development of tolerance to pentolinium tartrate alone but rather to our treatment regimen.

DISCUSSION

The symptoms that are related to hypertension or to associated cardiac decompensation often were relieved following treatment. Thus, the symptoms of headache, dizziness, dyspnea and palpitation were improved in more than two thirds of the individuals who suffered from these complaints. On the other hand, none of the patients with symptoms resulting from residuals of old cerebrovascular accidents showed improvement and in some, reduction of blood pressure aggravated these symptoms. Similarly, less than half of the patients with angina noted improvement and an equal number complained of increased discomfort. It would appear that "hypertensive" symptoms and those that arise from cardiac "strain" frequently will be improved, whereas those due to vascular sclerosis often do not improve and may become worse.

In regard to objective signs of improvement other than blood pressure, regression was noted in the optic fundi in more than four fifths of

the patients with grade III and IV changes and in slightly less than half of the patients with grade II changes. Thus, the most marked effects were on the hemorrhages, exudates, and papilledema, although diminution in the degree of arteriolar narrowing also was seen in some of the cases.

In the patients with cardiomegaly diminution of cardiac size was observed in approximately one half of the cases. Since the majority of these cases had the usual therapy for congestive heart failure prior to being placed on pentolinium tartrate, the improvement appeared to result from the antihypertensive therapy per se. In fact, in many of these patients the need for salt restriction or diuretics was reduced or even abolished. In contrast to these evidences of improvement in cardiac status only 12 per cent of patients showed partial or complete reversal of the electrocardiographic pattern of left ventricular hypertrophy.

The extent of improvement in the kidneys was less impressive than in the fundi and the heart. In the patients with nitrogen retention, as many showed increasing uremia as showed clearing, and five patients developed elevations of blood urea nitrogen or nonprotein nitrogen from normal to abnormal while under treatment. The degree of albuminuria in general tended to lessen under therapy. On the other hand the ability of the patients to excrete phenolsulfonphthalein dye decreased more often than it improved.

It seems possible that the decrease in albuminuria and improvement in nitrogen retention seen in some of the cases might be expected in part on the basis of improvement in latent or overt cardiac decompensation. The same might be said for the decrease in nocturia that was frequently noted. The appearance or worsening of nitrogen retention in other patients while under therapy and the frequent observation of reduced ability to excrete phenolsulfonphthalein dye may be accounted for on the basis of two factors: (1) effect of ganglionic blocking agents on renal hemodynamics⁹ and (2) further progress of the renal lesions despite antihypertensive therapy. The fact that the majority of the deaths in this

series were due to renal failure tends to support this thesis. It would appear, therefore, that treatment with pentolinium tartrate is least effective against the renal complications of severe hypertension. If nephrosclerosis results from sustained hypertension these observations provide an argument for beginning treatment earlier, before the renal arterioles have become irreparably sclerosed.

Confirming our previous experience¹⁰ and those of others^{11, 12} the addition of reserpine not only produces a further reduction of blood pressure in many patients but also may permit reduction of the dosage of pentolinium and, hence, lessen the incidence of disabling side effects produced by ganglionic "blockade." This combination while effective and generally better tolerated by the patient must be instituted with an awareness that serious mental depression can occur in patients treated for long periods with *Rauwolfia* preparations.¹³

The additive hypotensive effect of hydralazine alone was studied in only a small number of patients and the dosages used were smaller than those employed by Perry and Schroeder in a similar study.¹⁴ Nevertheless, the present results confirm their observation that the addition of hydralazine produced a further lowering of blood pressure. It is interesting that in our cases, where the dosages of hydralazine were small, the development of the syndrome resembling disseminated lupus erythematosus did not occur; whereas it was not an infrequent complication in Perry and Schroeder's series. On the basis of the various observations on small doses of hydralazine and of *Rauwolfia* we have concluded that therapy combining all 3 agents produces the greatest reduction of blood pressure and the smallest dosage requirement of the blocking agent. We believe, however, that each drug be added separately in order to judge its effects in the particular case.

It is interesting that all of the "toxic" reactions to pentolinium tartrate seemed to be due to the acute effects of ganglionic "blockade." Unlike hexamethonium^{15, 16} no cases of chronic interstitial pneumonitis occurred in this series, nor to our knowledge have there been any reports of this complication in the literature on pentolinium tartrate.

The proof of the effectiveness of any form of treatment in hypertension is its ability to prevent morbidity and mortality. The duration of treatment in this series still is too short to draw any conclusions in regard to mortality. In regard to morbidity, however, it is important to note that the majority of the patients who had lost their jobs because of severe hypertension were able to return to some sort of gainful occupation. This was also the case in many of the patients who eventually died but who were able to work until shortly before exitus. The clearing of symptoms of cardiac decompensation or hypertensive encephalopathy produced considerable subjective improvement in these severe cases. In addition, due to the postural hypotension produced by pentolinium tartrate, the control of blood pressure was as good or better when the patient was up and active than when he was inactive.

The arrest and seeming reversal of ever worsening symptoms in these most severe cases provided a tremendous boost to the patient's morale, and as such was an important additional therapeutic dividend. In less desperate situations and particularly in the asymptomatic hypertensive, the side effects resulting from therapy blunted the patient's desire to continue with treatment. In such cases various techniques were used to assure the patient's cooperation. These included (1) gradual elevation of dosage to the effective level, (2) explanation of side effects and instructions in minimizing their severity⁵ and (3) the use of home blood pressure recordings.

SUMMARY AND CONCLUSIONS

A series of 96 patients with severe, fixed hypertension was treated with pentolinium tartrate alone or in combination with *Rauwolfia* or hydralazine, or both, for periods varying from 3 to 27 months (average 12 months) with the following results:

1. Ten of the 34 patients with grade IV changes in the optic fundi and 7 of the remaining cases have died. In addition, 1 case developed a myocardial infarction and 2 developed mild cerebrovascular accidents while under treatment.

2. Typical hypertensive symptoms such as

headache, dizziness and those relating to cardiac decompensation often were relieved; whereas those due to vascular sclerosis, such as angina or residuals of old cerebrovascular accidents, usually did not improve or were made worse.

3. Improvement in the optic fundi was observed in more than 80 per cent of the patients with grade III and grade IV changes and in slightly less than half of the patients with grade II changes.

4. Decrease in cardiac size frequently was observed. Improvement in the electrocardiographic pattern of left ventricular hypertrophy also occurred but less frequently than the former.

5. The degree of albuminuria usually tended to lessen during treatment. Approximately half of the patients with nitrogen retention showed clearing, whereas the other half developed increased retention. The ability of the patients to excrete phenolsulfonphthalein decreased more often than it increased following treatment. The reasons for these apparent discrepancies are discussed and it is concluded that treatment was more effective in arresting or reversing changes in the optic fundi and in the heart than in the kidneys.

6. Data are presented to demonstrate the additive effects of Rauwolfia or hydralazine, or both, to the regimen. Combining all three agents generally resulted in the greatest reduction of blood pressure with the least degree of symptoms resulting from ganglionic "blockade."

7. In view of the severity of the hypertension in the present series, it is concluded that this method of treatment is beneficial. It was especially effective in restoring semi-invalided or invalided hypertensive patients back to more useful and active modes of living.

SUMMARIO IN INTERLINGUA

Un serie de 96 patientes de sever hypertension fixe esseva tractate durante periodos de inter 3 e 27 menses (durantia median 12 menses) con tartrato de pentolinium sol o in combination con Rauwolfia o hydralazina o ambes. Le resultatoss esseva le sequente:

1. Dece del 34 patientes con alterationes de grado IV in le fundos optic e 7 del altere patientes ha morite. In plus, un patiente disveloppava un infarcimento myocardiac e duo disveloppava leve accidentes cerebrovascular quando illes esseva sub tractamento.

2. Typic symptomatos hypertensive—mal de capite, vertigine, symptomatos pertinente al discompensation cardiac, etc. esseva alleviate in multe casos. Symptomatos debite a sclerosis vascular—angina, residuos ab ancian accidentes cerebrovascular, etc. non se meliorava in general, e in certe casos illos deveniva pejor.

3. Melioration in le fundos optic esseva observate in plus que 80 pro cento del patientes con alterationes del grados III e IV e in levemente minus que 50 pro cento del cases de grado II.

4. Reduction del dimensiones cardiac esseva observate. Melioration del figuracion electrocardiographic de hypertrophia sinistro-ventricular esseva etiam observate sed illo occurreva minus frequentemente que le reduction del dimensiones cardiac.

5. In general, le grado de albuminuria monstrava un tendentia a reducir se durante le tractamento. Circa un medietate del patientes con retention de nitrogeno habeva un augmento del clearing; le altere medietate disveloppava un augmentate grado de retention. Le capacitate de excerner phenolsulfonphthaleina esseva plus frequentemente reducite post le tractamento que augmentate. Nos discute le rationes pro iste apparente discrepantias e concluda que le tractamento esseva plus efficace in arrestar o reverter alterationes in le fundos optic e in le corde que in le renes.

6. Es presentate datos pro demonstrar le effectos additive de Rauwolfia o hydralazina o ambes. Le combination de omne tres agentes resultava generalmente in le plus grande reduction del pression sanguinee, con le minus grande grado de symptomatos resultante ab "blockage" ganglionic.

7. Considerante le severitate del hypertension in le presente serie de patientes, nos concluda que iste methodo therapeutic es benefic. Illo esseva specialmente efficace in restaurar semi-invalidate o invalidate patientes hypertensive a plus utile e active formas de vita.

REFERENCES

- ¹ LIBMAN, D. D., PAIN, D. L., AND SLACK, R.: Some bisquaternary salts. *J. Chem. Soc.* **430**: 2305, 1952.
- ² WEIN, R., AND MASON, D. F. J.: Pharmacology of M & B 2050. *Lancet* **1**: 454, 1953.
- ³ MAXWELL, R. D. H., AND CAMPBELL, A. J. M.: New sympatholytic agents. *Lancet* **1**: 445, 1953.
- ⁴ SMIRK, F. H.: Action of a new methonium compound in arterial hypertension, Pentamethylene 1:5-bis-N-(N-methyl-pyrrolidinium bitartrate) (M & B 2050 A). *Lancet* **1**: 457, 1953.
- ⁵ FREIS, E. D., PARTENOPE, E. A., LILLENFIELD, L. S. AND ROSE, J. C.: A clinical appraisal of pentapyrrolidinium (M & B 2050) in hypertensive patients. *Circulation* **9**: 540, 1954.
- ⁶ —: Hypertension; method of treatment. *In* Conn, H. F., *Current Therapy*. Philadelphia, W. B. Saunders Co., 1955. p. 124.
- ⁷ —: The discrepancy between home and office recording of blood pressure in patients under treatment with pentapyrrolidinium. Importance of home recordings in adjusting dosages. *Ann. District of Columbia* **23**: 363, 1954.
- ⁸ —: Letter to the editor. *J.A.M.A.*, **158**: 1390, 1955.
- ⁹ —, ROSE, J. C., PARTENOPE, E. A., HIGGINS, T. F., SCHNAPER, H. W., AND JOHNSON, R. L.: The hemodynamic effects of hypotensive drugs in man. III. Hexamethonium. *J. Clin. Invest.* **32**: 1285, 1953.
- ¹⁰ —: Combinations with ganglionic blocking agents. Symposium on hypotensive drugs. Evans Memorial Research Conference, Sept. 15, 1953, p. 126.
- ¹¹ SMIRK, F. H., DOYLE, A. E., AND McQUEEN, E. G.: Control of blood pressure by combined action of reserpine and pentapyrrolidinium. *Lancet* **2**: 159, 1954.
- ¹² BAIN, C. W. C., ASHTON, F., AND JONES, B. P.: The treatment of essential hypertension with pentolinium tartrate combined with Rauwolfia alkaloids. *Brit. M. J.* **1**: 817, 1955.
- ¹³ FREIS, E. D.: Mental depression in hypertensive patients treated for long periods with large doses of reserpine. *New England J. Med.* **251**: 1006, 1954.
- ¹⁴ PERRY, H. M., JR., AND SCHROEDER, H. A.: The use of pentolinium tartrate with and without hydralazine in the treatment of severe hypertension. *New England J. Med.* **252**: 1057, 1955.
- ¹⁵ MORRISON, B.: Parenteral hexamethonium in hypertension. *Brit. M. J.* **1**: 1291, 1953.
- ¹⁶ MORROW, J. D., SCHROEDER, H. A., AND PERRY, H. M., JR.: Studies on the control of hypertension with Hyphex. II. Toxic reactions and side effects. *Circulation* **8**: 829, 1953.