An evaluation of the sodium Amytal sedation test in male hypertensive patients

Veterans Administration Cooperative Study on Antihypertensive Agents

The sodium Amytal sedation test is said to have prognostic significance in that the greater the fall in blood pressure during sleep induced by sodium Amytal the better the prognosis and response to treatment. The Amytal test was described first by Allen and his associates,[1,2] who applied it as an aid in selecting patients for sympathectomy. They postulated that, in general, the greater the reduction in blood pressure during the test the better the amelioration of the hypertension after sympathectomy. Smithwick[3] used the test for the same purpose, and later[4] included it with other criteria to divide patients into prognostic categories of hypertensive cardiovascular disease. Hammarström,[5] on the other hand, found no correlation between the Amytal test response and the extent of reduction in blood pressure after sympathectomy. Schroeder[6] indicated that the blood pressure during the sodium Amytal test decreased less in nephrogenic than in essential hypertension. He also applied the test as an index of the severity of the hypertension. Werkö and Brody[7] observed diminished antihypertensive responses after sodium Amytal in patients with toxemia of pregnancy. Duncan[8] advised against the use of ganglionic blocking agents in those patients with essential hypertension whose diastolic blood pressure fell below an arbitrary level of 100 mm. Hg during the Amytal sedation test.

The present report is concerned with correlating the sodium Amytal test with the extent of cardiovascular damage and the levels of blood pressure prior to treatment, as well as with the response and mortality rate after treatment.

Methods

Details of the manner of selection of patients, classification of severity of disease, treatment, and repeated annual examinations may be found in the first report of the Veterans Administration Cooperative Study on Antihypertensive Agents.[9] The Amytal sedation test was performed during the pretreatment examination of 817 male patients with hypertension in Veterans Administration hospitals. Sodium Amytal, 0.2 Gm., was administered orally every hour for 3 hours, beginning at 7:00 P.M. The blood pressure was recorded by the ward nurse before each dose, and every hour thereafter until 7:00 A.M., that is, for 12 hours.

The information from reports of initial examination and annual re-examination was numerically coded, and punched into IBM cards by key-punch machines. A single card contained all of the pertinent,

The following Veterans Administration hospitals collaborated in this study: Birmingham; Brooklyn; Chicago, West Side; Iowa City; Oklahoma City; Richmond; San Juan, Puerto Rico; Seattle; Washington, D.C.; West Haven; and West Roxbury. The data were analyzed by Alvin D. Oscar (medical student in the Veterans Administration Summer Scholarship Program), Edward D. Freis, M.D., and John H. Williams, Jr., B.A.
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Table I. *Relation between age and response of blood pressure during Amytal sedation test*

Number of patients and test parameters	*Age at time of test (yr.)*				
	20-29	*30-39*	*40-49*	*50-59*	*60-69*
Number of patients	19	150	250	123	275
Per cent fall under sedation*					
Systolic	23.3	22.3	21.8	21.1	23.6
Diastolic	20.7	21.6	19.3	19.8	20.1

*Group averages of the falls in blood pressure from the presedation reading to the lowest values obtained during the Amytal sedation test.

available information for one patient. The cards were grouped into four categories according to the per cent fall in the patients' blood pressure from the 7:00 P.M., or presedation, reading to the lowest values after the administration of sodium Amytal. The four grades of response, which were made separately for both systolic and diastolic pressure, were as follows: Grade 1—0 to 9 per cent reduction, indicating the poorest response; Grade 2—10 to 19 per cent reduction; Grade 3—20 to 29 per cent reduction; and Grade 4 (the best response)—30 per cent or more reduction in systolic or diastolic pressure.

The punch-card records of the 817 patients were examined for correlations between the sodium Amytal response and the following: age, race, history of familial hypertension, level of pretreatment basal blood pressure, per cent fall in blood pressure from that at time of admission to the hospital to the average blood pressure for the fourth through sixth hospital days, extent of organic damage in the optic fundi, heart, kidneys, and central nervous system, "treatment failure," and death.

Results

Per cent of patients in the various grades of response to the Amytal test. In respect to the response of the systolic blood pressure during the sedation test, 30 per cent of the patients exhibited a Grade 4 response, that is, a fall of 30 per cent or more from the presedation level; 55 per cent of the patients exhibited a reduction of 10 to 29 per cent (Grades 2 and 3), and 15 per cent exhibited a fall of less than 10 per cent. In respect to the diastolic blood pressure, approximately 20 per cent of the patients had a maximal fall of 30 per cent or more, 60 per cent had intermediate responses, and 20 per cent exhibited reductions that were less than 10 per cent of the presedation level.

Correlation between age, race, and duration and severity of hypertension and the results of the sedation test. There was no correlation between lability of systolic or diastolic blood pressure according to the sodium Amytal sedation test and age, history of familial hypertension, or duration of known hypertension (Tables I, II, and III). The average sedation test response was greater in the 9 patients who were known to have had hypertension for 30 years or longer, but their number was so small that the result lacked statistical validity (Table III). Furthermore, patients who had had hypertension for 21 to 30 years exhibited no greater responses to Amytal than did patients who had hypertension of shorter duration. There also was no correlation with race: the mean fall in blood pressure during sedation was 22.6/20.0 (systolic/diastolic) per cent in 461 Caucasians, and 22.3/19.9 per cent in 356 Negroes.

The fall in systolic blood pressure during the sodium Amytal sedation test failed to correlate in any way with the levels of pretreatment, "basal,"[8] blood pressure. In regard to the change in diastolic blood pressure during the sedation test, the patients with the poorest responses exhibited slightly higher pretreatment, basal, levels of diastolic blood pressure than did those with the greatest falls during the

Amytal test (diagonal-lined columns in Fig. 2). The differences were small, however, and there was no correlation with the pretreatment, basal, systolic blood pressure (Fig. 1). The patients who received treatment with ganglionic blocking drugs were then analyzed separately, since they included those who had severe hypertension.[8] The results indicated that in these patients with the more severe hypertension the group with the poorest diastolic response during the sedation test exhibited higher pretreatment, basal, levels of systolic and diastolic blood pressure than did the other groups (Figs. 3 and 4).

Correlation between Amytal test responses and extent of organic complications. Grades of severity which indicated the extent of organic damage in the optic fundi, heart, kidneys, and central nervous system were arrived at as described previously.[8] There were fewer patients with Grade 4 organic changes than with the other grades of changes, but these patients with the most severe organic damage exhibited lesser falls in blood pressure during the sodium Amytal sedation test than did patients in the other groups (Table IV). For example, the 22 patients who had Grade 4 changes in the optic fundi (papilledema, hemorrhages, and/or exudates), and the 43 patients who had Grade 4 renal damage (azotemia which failed to clear after therapy for congestive heart failure) exhibited an average fall of 15.7 per cent in diastolic blood pressure during the sedation test, as compared to reductions of 19 to 21 per cent in the other groups. Patients with Grade 4 cardiac changes exhibited a fall of only 13.3 per cent in diastolic blood pressure after sodium Amytal, as compared to reductions of 19 to 21 per cent in the patients with less severe cardiac complications. Since the Grade 4 classification included only patients with congestive heart failure who were not responsive to routine therapy, it would be expected that their sleep might be disturbed even after the administration of sodium Amytal, and that, consequently, their response to the test would be poor.

Relationship between the sodium Amytal sedation test and mortality and "treatment failures." Over an average follow-up period of 2½ years there was a greater percentage of deaths and "treatment failures" in the patients who had minimal falls in diastolic pressure during the sedation test than in those who had greater responses (Table V). Death occurred in 20 per cent of the 188 patients who exhibited a fall of 0 to 9 per cent in diastolic pressure during the Amytal

Table II. *Relation of history of familial hypertension to average response of blood pressure during Amytal sedation test*

Number of patients and test parameters	*History of familial hypertension*		
	Yes	*No*	*Unknown*
Number of patients	237	169	411
Per cent fall under sedation*			
Systolic	23.1	21.5	22.1
Diastolic	21.0	19.3	20.1

*Same footnote as to Table I.

Table III. *Relation between duration of known hypertension and average response of blood pressure during Amytal sedation test*

Number of patients and test parameters	*Duration of known hypertension (yrs.)*						
	0	*1-5*	*6-10*	*11-15*	*16-20*	*21-30*	*Over 30*
Number of patients	180	297	124	113	52	26	9
Per cent fall under sedation*							
Systolic	22.9	21.5	22.4	22.4	24.8	21.6	33.1
Diastolic	21.9	18.8	20.0	21.4	20.6	18.7	27.6

*Same footnote as to Table I.

Table IV. *Relation between organic damage, measured in terms of grades of severity, and the response of blood pressure during Amytal sedation test*

Organ area	*Number of patients and test parameters*	*Grades of severity**				
		0	*1*	*2*	*3*	*4*
Optic fundi	Number of patients	48	368	256	120	22
	Per cent fall under sedation†					
	Systolic	22.9	22.9	22.2	22.2	19.3
	Diastolic	19.6	20.3	20.2	18.7	15.7
Kidneys	Number of patients	475	174	73	48	43
	Per cent fall under sedation†					
	Systolic	22.3	21.5	22.1	20.5	18.5
	Diastolic	20.8	19.2	20.6	20.1	15.7
Heart	Number of patients	172	362	145	121	16
	Per cent fall under sedation†					
	Systolic	24.2	23.3	21.8	18.5	17.9
	Diastolic	20.9	20.6	18.6	19.0	13.3
Central nervous system	Number of patients	320	383	87	14	12
	Per cent fall under sedation†					
	Systolic	21.2	22.0	25.1	18.1	16.6
	Diastolic	20.3	19.7	22.7	13.1	15.3

*Severity graded from 0 (no abnormalities) to 4 (most severe impairment), according to criteria given in prior publication.[7]
†Group averages of the falls in blood pressure from the presedation reading to the lowest values obtained during the Amytal sedation test.

test, as compared to 10 per cent in 183 patients who showed a fall of 30 per cent or more in diastolic blood pressure. The difference was significant ($p < 0.02$). Similarly, there were 18 per cent "treatment failures" (development of severely elevated blood pressure or acute hypertensive complications) in the group with the poorest diastolic responses during the Amytal test, and only 7 per cent in those with the greatest response of diastolic blood pressure after sodium Amytal. There was no significant correlation between the percentage fall in systolic blood pressure under sedation and either death rate or "treatment failures" (Table V).

An investigation of the circumstances surrounding the deaths that occurred in the two groups of patients, those with the least and those with the greatest response to sodium Amytal, failed to reveal significant differences between the two groups. They were essentially alike in regard to the interval of treatment prior to death, age range, and cause of death. Approximately 30 per cent of the deaths in both groups occurred during the first year of observation (Table VI). Slightly more of the deaths in the group most responsive to sodium Amytal were among patients who defaulted, but this fact did not account for the difference in death rates in the two groups. The average age at death in the least responsive groups was 46, and in the most responsive it was 45 years.

In a comparison between the two groups as to the causes of death the facts were made obscure because the reason for death could not be established in 10 of the patients in the least responsive group. When these cases were excluded, it was found that there were more deaths from coronary artery disease and cerebral vascular accident, about the same percentage from renal disease, and fewer from congestive heart failure in the group with more than 30 per cent fall in diastolic blood pressure than in the least responsive group. With the exception of the fewer deaths due to congestive heart failure, the numbers of

patients were too small to ascribe any significance to these differences.

Since the percentage of patients who died over an average follow-up period of 2½ years was twice as great in the group which had the least fall in diastolic blood pressure as it was in the group which exhibited the greatest response to sodium Amytal, the test appeared to have some prognostic value. It was possible, however, that a similar estimate could have been made using other available criteria, particularly the severity of organic changes. If such were the case, the test would be somewhat redundant and its clinical usefulness would, therefore, be reduced considerably.

In order to examine this question, the

Table V. *Relation between the response of the systolic and diastolic blood pressures to Amytal sedation and deaths and "treatment failures"*

Grouping	*Per cent fall in systolic blood pressure during Amytal sedation test*				*Total*	*Per cent fall in diastolic blood pressure during Amytal sedation test*				*Total*
	0-9	*10-19*	*20-29*	*30+*		*0-9*	*10-19*	*20-29*	*30+*	
Total patients	130	204	252	231	817	188	217	229	183	817
Deaths	24	29	43	38	134	38	40	37	19	134
Per cent deaths*	18	14	17	16		20	18	16	10	
"Treatment failures"	18	32	26	21	97	34	23	27	13	97
Per cent	14	16	10	9		18	11	12	7	

*Per cent deaths over an average observation period of 2½ years.

Table VI. *Time and cause of death in patients who exhibited the greatest and least response during Amytal test*

Time and cause of death	*Response of diastolic blood pressure during sedation test*			
	*Least response**		*Greatest response†*	
	Number of patients	*Per cent of patients*	*Number of patients*	*Per cent of patients*
Total deaths	38		19	
Time of death from start of treatment:				
Within 6 mo.	9	24	3	16
6 mo. to 1 yr.	4	11	3	16
1 yr. to 18 mo.	10	26	4	20
18 mo. to 2 yr.	8	21	2	11
More than 2 yr.	7	18	7	37
Died after leaving study	13	34	8	42
Cause of death:				
Cerebral vascular accident	3	8	3	16
Coronary artery disease	10	26	9	47
Congestive heart failure	7	18	1	5
Renal disease	5	13	3	16
Other unrelated causes	3	8	2	11
Unknown	10	26	1	5

*Fall of 0 to 9 per cent.
†Fall of 30 per cent or more.

Table VII. *Comparison between severity of organic changes in the optic fundi and kidneys and diastolic pressure during Amytal sedation in relation to mortality*

*Grades of severity**	*Per cent fall in diastolic pressure during Amytal sedation test*						*p value*
	0-9			*30+*			
	Total cases	*Deaths*	*Deaths (per cent)*	*Total cases*	*Deaths*	*Deaths (per cent)*	
Optic fundi							
0 through 2	150	22	15	149	15	10	>0.05
3 and 4	37	16	43	30	4	13	<0.01
Renal							
0 through 2	163	26	16	165	16	10	
3 and 4	23	12	52	14	3	22	Borderline at 0.05

*See first footnote to Table IV.

deaths were classified into two groups according to the extent of damage in the optic fundi and kidneys: those patients with the least and those patients with the greatest response of diastolic blood pressure after sodium Amytal. Renal impairment and changes in the optic fundi were chosen as the pertinent indices because they are considered generally to have the greatest prognostic significance. If the increased death rate among poor responders to Amytal was only a reflection of the fact that this group contained more patients with the most severe organic changes, then there should be no essential difference in *percentage* deaths among patients with the most severe damage in the optic fundi and kidneys regardless of their response to Amytal sedation.

The results indicated that with the same degree of impairment in the optic fundi or kidneys the per cent of deaths was higher in the group with the least reduction in diastolic blood pressure during the sedation test (Table VII). For example, in patients who exhibited Grades 3 (hemorrhages and/or exudates) and 4 (papilledema) changes in the optic fundi, 43 per cent of those in the group with the poorest response to Amytal died, as compared to 13 per cent in the group with the greatest falls in diastolic pressure during the test ($p < 0.01$). Similarly, in the patients with Grades 3 and 4 renal changes, there were 52 per cent deaths among the poor responders and 22 per cent among the best responders to Amytal ($p = 0.05$). Grade 3 renal complications included proteinuria of 1+ or more, urine specific gravity of 1.015 or less, and PSP excretion of 35 per cent or less in a 2-hour pooled specimen. Grade 4 severity included all cases of azotemia which failed to clear after the patient had been treated for congestive heart failure. Similar trends were seen in the patients with less damage in the optic fundi and kidneys, but the differences between good and poor responders to Amytal were of no, or only borderline, significance.

Relationship between the response of blood pressure to the sedation test and improvement of blood pressure or of organic changes during treatment. Data derived from repeated annual examinations were available in 209 patients who were followed for a period of 2 years after the beginning of treatment. Each of these patients had been administered one or another of the following regimens: placebo, reserpine alone or in combination with hydralazine, or reserpine plus one of the following ganglionic blocking drugs—pentolinium tartrate, mecamylamine, or chlorisondamine.[8] All regimens were grouped together to give a larger sample for analysis. This

grouping was justified by the fact that treatment was not based on response to the sedation test, and patients with varying degrees of response to the test were distributed approximately equally among the different therapeutic regimens.

After 2 years of treatment, the reduction in both the systolic and diastolic blood pressures of patients with poor responses to sodium Amytal was as great as that which occurred in those with the most marked responses during the test (Figs. 1 and 2). The patients who died or became "treatment failures" prior to 2 years, which represented the majority of such cases, would not be included in this series.

A separate analysis of those patients treated with ganglionic blocking agents disclosed a significant reduction in blood pressure after 2 years of treatment. The extent of the reduction in blood pressure, however, was not correlated with the degree of response to the sodium Amytal test (Figs. 3 and 4).

Changes in severity as related to the optic fundi, kidneys, heart, and central nervous system at the end of 2 years of treatment were also examined. The patients were divided into four groups according to the response of systolic and diastolic pressures during the Amytal sedation test. The scores reported under

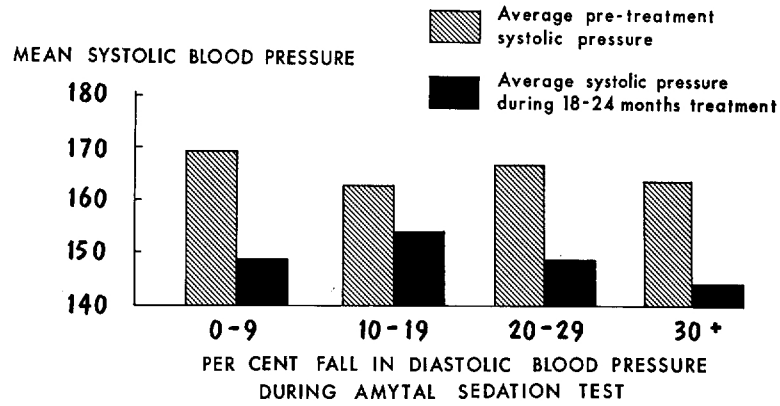

Fig. *1*. Chart showing means of pretreatment (*diagonal-lined columns*) and post-treatment (*solid columns*) systolic blood pressure in 209 patients receiving various antihypertensive regimens for 2 years or longer. The patients have been divided into groups according to the degree of fall in *diastolic* blood pressure during the sodium Amytal sedation test.

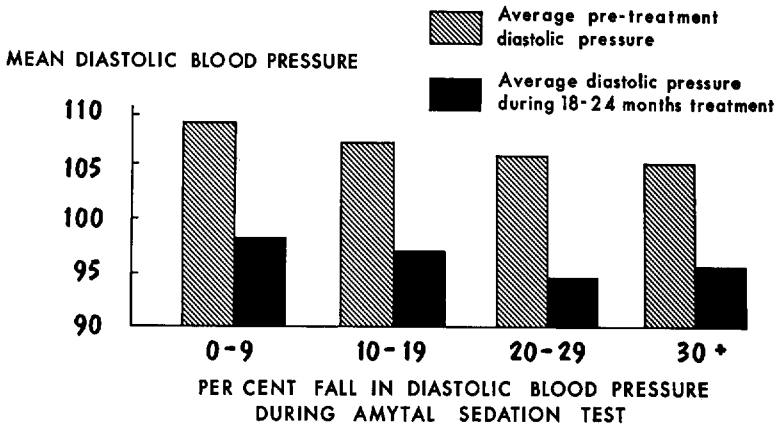

Fig. *2*. Chart showing means of pretreatment and post-treatment diastolic blood pressure in 209 patients receiving various antihypertensive regimens for 2 years or longer. Other notations as in Fig. 1.

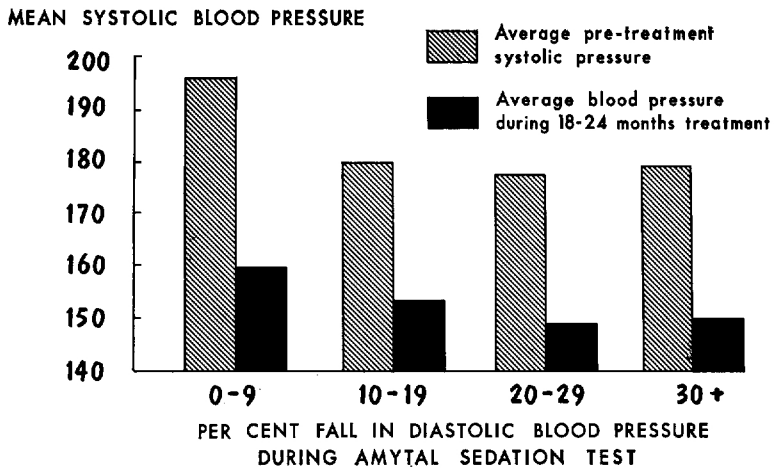

Fig. *3.* Chart showing means of pretreatment and post-treatment systolic blood pressure in patients treated with ganglionic blocking agents for 2 years or longer. Other notations as in Fig. 1.

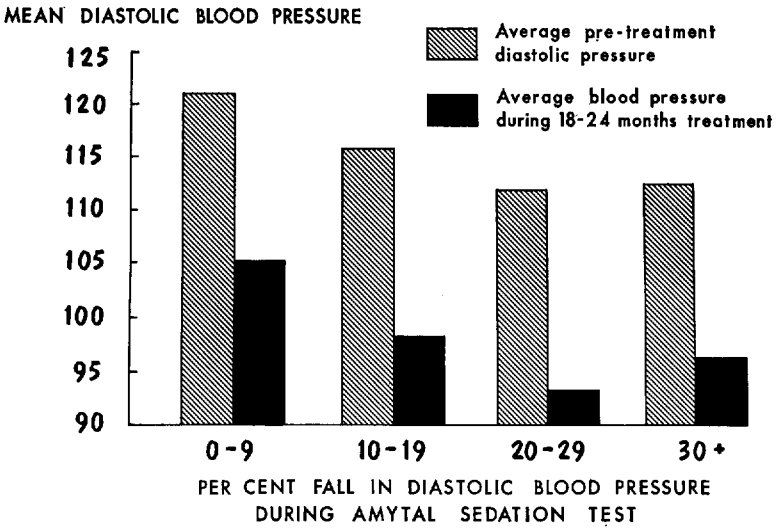

Fig. *4.* Chart showing means of pretreatment and post-treatment diastolic blood pressure in patients treated with ganglionic blocking agents for 2 years or longer. Other notations as in Fig. 1.

the organ systems were arrived at by averaging the individual grades of severity.

There was no evidence in these data to indicate that the sodium Amytal sedation test was of value in predicting changes in either the optic fundi, heart, central nervous system, or kidneys after treatment. It was possible that some slight effect could have been lost because of the rather crude nature of the scoring. This analysis also excludes those who died, defaulted, or left the study for other reasons prior to 2 years of follow-up.

Discussion

The most important finding of this study was the relationship between the Amytal sedation test and the prognosis. The significant correlation with death and treatment failure was found only in the response of the diastolic, and not in that of the systolic, blood pressure to sodium

Amytal. The present series was composed entirely of male hypertensive patients. If the sample is indeed representative of the male hypertensive population, the results indicate that a male patient with a fall of less than 10 per cent in diastolic blood pressure after sodium Amytal has twice the probability of dying within 2 to 3 years as has the male patient who exhibits a fall in diastolic blood pressure of 30 per cent or more. As indicated in Table V, the patients with intermediate responses of diastolic pressure during the sedation test also exhibited correlative, that is, intermediate, mortality rates. The incidence of so-called treatment failures, who represented survivors, but who developed such severe elevations of blood pressure or organic complications that a change in antihypertensive therapy was indicated, also was significantly higher in the patients with less than a 10 per cent fall in diastolic blood pressure during the Amytal test.

It seems improbable that the prognosis indicated by the Amytal test could have been duplicated using other available clinical criteria. Hypertensive patients with retinal hemorrhages, exudates, or papilledema, who exhibited falls of less than 10 per cent in diastolic blood pressure after sodium Amytal, had a mortality rate that was approximately threefold higher than that of patients who had similar funduscopic changes, but whose diastolic pressures fell more than 30 per cent during the test. A similar trend was found in the patients who had advanced renal impairment. The Amytal sedation test, therefore, appears to supplement rather than duplicate other prognostic criteria. These results also suggest that, if the patient who has advanced organic changes still exhibits a labile diastolic blood pressure as indicated by the sedation test, his disease is not so severe as that of the patient who has a "fixed" diastolic pressure. Although similar trends were found in the patients with less severe organic damage, they were not so marked, which indicates that the test has less prognostic value in milder cases of hypertension.

Although the sodium Amytal sedation test correlated fairly well with the incidence of death and "treatment failures," it was of no value in predicting therapeutic responsiveness in the surviving patients who remained in the study. The lack of correlation also held in the patients treated with ganglionic blocking agents. These results, therefore, supplied no basis for using this test as a means of selecting patients for treatment with ganglionic blocking drugs.

Summary and conclusions

Sodium Amytal sedation tests were carried out in 817 male hypertensive patients. The results are listed below.

1. There was no correlation between the response to the Amytal test and age, race, or duration and severity of the hypertension.

2. In patients with severe hypertension a fall of less than 10 per cent in diastolic blood pressure during the sedation test was associated with higher pretreatment, basal, levels of blood pressure than those in patients with severe hypertension who showed greater responses.

3. Patients with the most advanced organic complications in the optic fundi, kidneys, heart, and central nervous system exhibited a poorer average response to the sodium Amytal test than did the other patients.

4. During the follow-up period there were twice as many deaths and "treatment failures" in the patients who showed the poorest response of diastolic blood pressure to sodium Amytal as in those who showed the greatest response. Such correlation was not found with the response of systolic pressure to sodium Amytal. The combination of severe changes in the optic fundi and kidneys with a poor response to Amytal was a particularly bad prognostic indication: the percentage of deaths was approximately threefold higher in this group than in the patients with similar organic changes but a good response after sodium Amytal. The test was of insignificant prognostic value in patients with less severe organic changes.

5. In 209 patients who survived and remained in the study with unchanged treatment for at least 2 years, there was no correlation between the Amytal test results and the response to antihypertensive agents, including ganglionic blocking drugs.

The fall in diastolic blood pressure

rather than the fall in systolic blood pressure during the Amytal sedation test had prognostic significance and seemed to be of more value in predicting the outcome in patients with severe hypertension than in those with milder forms of hypertension.

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