the cells at the time of addition of hadacidin or the amount of time the cells are exposed to it during growth.

The technical assistance of Mrs. Mary Lucas, Mrs. Carolyn Woolley, Mr. R. T. Blackwell, and Mr. C. W. Davis is appreciatively noted. We are indebted to Dr. H. Adler, Oak Ridge National Laboratory, Oak Ridge, Tenn., and to Dr. J. Miraglia, Bryn Mawr College, Bryn Mawr, Pa., for various strains of *E. coli* and *Salmonella typhimurium*. The advice and support of Dr. F. M. Schabel, Jr., are gratefully acknowledged.

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Received October 26, 1964. P.S.E.B.M., 1965, v118.

Mental Functioning and Premarin Therapy in Cardiovascular and Cerebrovascular Disease.* (29897)

RAY B. EVANS AND JESSIE MARMORSTON

Department of Psychiatry, Loma Linda University School of Medicine; Department of Medicine, University of Southern California School of Medicine, and Los Angeles County Hospital, Los Angeles

Improved mental functioning has been reported in patients with atherosclerosis treated with conjugated equine estrogens (Premarin) in comparison with similar patients given placebos(1). Improvement was evident in patients with myocardial infarction and those with cerebral thrombosis. Caldwell and Watson(2,3) also reported improved intellectual functioning in aged women treated with estrogens, but Lifshitz and Kline(4) found no difference between estrogen- and placebo-treated men with psychosis associated with cerebral atherosclerosis. In studying sex hormone replacement in the elderly, Pauker, Kheim, Mensh, and Kountz(5) observed no difference in post-therapy psychological evaluations between patients treated with androgens-estrogens and control patients.

* Aided by grants from the Bella and André Meyer Foundation. Appreciation is also given to Dr. Gertrude Baker, psychological consultant in the early planning, and to Dr. Oliver T. Kuzma and Dr. Edward H. Davis, who were in charge of the research clinics.

The purpose here is (a) to report a second testing of the hypothesis that mental impairment decreases in patients with cardiovascular and cerebrovascular disease treated with Premarin, and (b) to present an analysis of the results with patients from the two studies combined. The hypothesis was tested with the use of the Rorschach inkblot technique, a sensitive indicator of mental impairment accompanying organic damage to the brain.

Methods. Included in the study were 77 new male patients who were participating in a prolonged clinical trial of the effects of Premarin therapy in cardio- and cerebrovascular disease at the Los Angeles County Hospital. There were 45 men who had recovered from an acute myocardial infarction and 32 who had had a cerebral thrombosis. After careful medical evaluation to ensure accurate diagnosis, the patients were randomly assigned to Premarin or placebo treatment by a statistical control office, and were thereafter seen in special outpatient clinics at approximately 6-week intervals. Relatively small

doses of Premarin were administered orally, 1.25 mg daily for the cerebral patients and 0.625 or 1.25 mg daily for the cardiac patients. There were 16 cerebral patients given Premarin and 16 placebo treatment, and 34 cardiac patients on Premarin and 11 on placebo.

The Premarin-treated patients with cerebral thrombosis had a mean age of 59 (*S.D.* 8.5) years, and those given placebos averaged 60 (*S.D.* 7.4) years of age. Among the patients with myocardial infarction, those given Premarin had a mean age of 58 (*S.D.* 7.9) and those on placebo a mean of 54 (*S.D.* 8.6) years. Neither difference was significant.

Psychological impairment resulting from organic damage to the brain is often reflected in the manner in which the Rorschach inkblots are described. In order to systematize assessment of impairment, and any changes therein resulting from treatment, a checklist scale was assembled consisting of 46 Rorschach signs known to be associated with disrupted cerebral functioning. The checklist facilitated judgments concerning such things as memory, capacity for abstract thinking, perceptual accuracy, and flexibility of thought. Validity of the scale as an indicator of organic impairment was verified by means of a comparison between 81 patients with known damage to the brain and 53 comparable patients without known damage, in which the Rorschachs of the organic patients showed significantly more signs of impaired thinking. A detailed description of the scale, which was used in its 46-item form in the initial testing of the present hypothesis(1), has been published(6). Subsequently, the checklist was further refined through a comparison of 139 brain-damaged and 136 non-damaged patients(7). The final scale consisted of the 26 signs which individually differentiated those groups at the .01 probability level, with the most highly discriminating items given greater weight. The development of the checklist as a measure of organic impairment was entirely independent of its use to gauge change with treatment.

Each patient was given the Rorschach at the time of allocation to Premarin or placebo therapy or shortly thereafter, and the test was repeated 6 to 16 months later. The tests were administered and scored without knowledge of the patient's form of treatment. For each patient change in mental functioning after treatment was determined by substracting his retest score from his initial score on the 26-item Rorschach impairment scale. The difference signified either an increase or a decrease in signs of impairment; that is, either decline or improvement in mental functioning.

Results were also analyzed using a combined group consisting of the 77 new patients and 76 male patients previously reported(1). There were 86 men with myocardial infarction (57 Premarin treated, 29 placebo) and 67 with cerebral thrombosis (31 Premarin, 36 placebo). In age, the cardiac patients ranged from 39 to 76, with those on Premarin averaging 56 (*S.D.* 8.8) and those on placebo averaging 55 (*S.D.* 9.0), a non-significant difference. The cerebral patients ranged from 47 to 79 years of age, with the Premarin treated averaging 60 (*S.D.* 8.9) and the placebo patients also averaging 60 (*S.D.* 7.7).

Cardiac patients on Premarin averaged 7.4 (*S.D.* 1.4) months of treatment, and those on placebo averaged 8.9 (*S.D.* 2.6) months, a difference significant at less than the .01 level. Premarin-treated cerebral patients averaged 8.0 (*S.D.* 2.0) months of therapy, and the placebo-treated averaged 9.3 (*S.D.* 3.3) months, a difference approaching significance ($P<.10$).

In order to eliminate degree of initial impairment as a factor influencing the results, it was necessary that the Premarin- and placebo-treated groups begin from a comparable base. Among the patients with cerebral thrombosis, the median pre-treatment impairment score was identical for the Premarin and placebo groups(19) and the range was highly similar (0 to 44 and 2 to 42, respectively). Pre-treatment scores for cardiac patients on Premarin ranged from 0 to 37 with a median of 12, and for those on placebo they ranged from 0 to 26 with a median of 8. While that tendency for the Premarin-treated cardiac patients to have greater initial impairment than the placebo patients did not reach sig-

TABLE I. Significance of Differences Between Premarin- and Placebo-Treated Patients in Improvement in Mental Functioning.

	Number		Mann-Whitney *U* test	
	Premarin	Placebo	*z*	*P*
Present study				
Myocardial infarction	34	11	.78*	.22
Cerebral thrombosis	16	16	1.53	.06
Total MI and CT	50	27	.53	.30
Previous study†				
Myocardial infarction	23	18	2.14	.02
Cerebral thrombosis	15	20	2.58	.005
Total MI and CT	38	38	3.14	.001
Combined studies				
Myocardial infarction	57	29	.91	.18
.625 mg Premarin	26	29	.02	.49
1.25 mg Premarin	31	29	1.46	.07
Cerebral thrombosis	31	36	2.67	.004
Total MI and CT	88	65	2.69	.004

* Placebo patients improved more. In all other comparisons the Premarin-treated patients showed greater improvement.

† Rorschach records rescored with revised 26-item scale.

nificance ($P<.08$), it may have affected the results, inasmuch as the greater the pre-treatment impairment in thinking, the more opportunity there is to show improvement with treatment.

In view of the fact that the Rorschach scores cannot be considered truly numerical, nonparametric techniques were used in the analysis. Significance levels of differences between groups were calculated with the Mann-Whitney *U* test, which requires only that scores be ranked.

Results. As in the previous study, there was a great deal of overlap in scores for Premarin- and placebo-treated patients, and change in cognitive functioning was not great for individual patients. Although the 50 new patients on Premarin improved more than the 27 placebo-treated patients, the difference was far from statistically significant, as shown in Table I. When the results were analyzed by diagnostic group, however, the Premarin-treated patients with cerebral thrombosis were found to have improved more than those on placebo, with the difference just missing the .05 level of significance. In contrast, the cardiac patients on placebo improved slightly, but not significantly, more than those on Premarin.

The Rorschach protocols from the previous study which tested the same hypothesis(1) were re-scored in accordance with the revised 26-item scale, and results for those patients are also shown in Table I. Among the cardiac and the cerebral patients, and the two combined, there was greater improvement in those given Premarin.

With the populations from both studies combined, there was a difference favoring those on Premarin for the total group of 153 patients and also for the 67 patients with cerebral thrombosis (Table I). Among the 86 combined patients with myocardial infarction, the superiority of those on Premarin over those on placebo was not statistically significant. A contingency coefficient of .23 ($P=.02$) between form of treatment and change in impairment also indicated a positive relationship between Premarin therapy and improvement in mental functioning among the cerebral patients. No such relationship was apparent for the cardiac patients, where the contingency coefficient was zero.

The results for the combined patients with myocardial infarction appeared in a rather different light when analyzed in terms of Premarin dosage strength (as shown in Table I). Cardiac patients had been given Premarin in 2 dosages, 1.25 mg or 0.625 mg daily, and from the combined studies there were 31 men on the larger and 26 on the smaller dosage. A comparison of the "improvement" scores (*i.e.*, pre-treatment minus

post-treatment) of those 2 groups, without reference to patients on placebo, revealed a tendency for those on 1.25 mg to improve more than those on 0.625 mg, although the difference was not significant ($P=.16$). When the 31 patients on 1.25 mg Premarin were compared with the 29 men on placebo treatment, the Premarin-treated showed greater improvement, and that difference bordered on significance ($P=.07$). In contrast, when the 26 patients on 0.625 mg Premarin were compared with the 29 placebo patients, there was no difference ($P=.49$).

The improvement in Premarin-treated patients was in part a function of worsening in the placebo-treated control patients. Among patients with cerebral thrombosis there was a median decrease in impairment of 4 scale points for those treated with Premarin and an increase in impairment of 2 points for those given placebos. For cardiac patients on 1.25 mg Premarin there was a median decrease in impairment of 1 scale point, but for those on 0.625 mg there was an increase in impairment of 1 point, exactly the same as for cardiac patients on placebo treatment. In other words, patients with cerebral thrombosis treated with Premarin tended to improve in their mental functioning and those given placebos tended to decline, so that when considered in relation to each other, the difference favored the Premarin-treated. There was slight improvement among the cardiac patients on 1.25 mg Premarin and slight deterioration among placebo-treated cardiac patients, but the difference between the two forms of treatment was not quite sufficient to attain statistical significance. Cardiac patients treated with 0.625 mg Premarin and those with placebo both deteriorated slightly, so that there was no difference between them.

To determine whether amount of change with therapy was related to degree of initial impairment, Spearman rank correlations were calculated between pre-treatment and "improvement" scores. Among the cardiac patients on Premarin that correlation was .47 ($P<.001$) and for those given placebos it was .30 ($P<.20$). For the cerebral patients on Premarin the correlation was .51 ($P<.01$), and for those on placebo it was .32 ($P<.10$). There was thus a definite positive association between degree of initial impairment and improvement with Premarin therapy in both cerebral and cardiac patients. There was also a tendency for greater initial impairment to be associated with improvement with placebo treatment.

In addition, an attempt was made to determine whether there was any relationship between age and change with treatment. Spearman rank correlation coefficients revealed that among patients receiving Premarin there was virtually no relationship between age and improvement with therapy (cardiac, $-.03$, $P>.20$; cerebral, .10, $P>.20$). There was a definite negative association between age and improvement for the cerebral patients on placebo treatment ($-.36$, $P<.05$) and a tendency in the same direction appeared among the cardiac patients on placebo, although it was not significant ($-.15$, $P>.20$). Among the older men, then, impairment increased with time alone (placebo treatment).

Discussion. The present findings with an independent second sample gave additional support to the hypothesis that mental functioning improves with Premarin therapy, as far as male patients with cerebral thrombosis are concerned. For patients with myocardial infarction, however, the present findings were at variance with the previous study.

Including cardiac patients treated with 1.25 mg Premarin and those with 0.625 mg in one statistical group obscured the fact that the change in cognitive functioning following therapy tended to be somewhat different for patients on different dosage. In fact, the median change following treatment with 0.625 mg Premarin was identical with that following placebo treatment; that is, slight deterioration. In contrast, there was some improvement following treatment with 1.25 mg Premarin, so that in relation to placebo-treated controls the difference bordered on significance. In terms of change in mental functioning, it would appear that 1.25 mg Premarin is more likely to be helpful than a dosage of 0.625 in men with myocardial infarction.

Another possible explanation of the divergent results following treatment with the 2 dosages of Premarin, however, is the fact that cardiac patients treated with 1.25 mg had higher pre-treatment impairment scores (median 15) than those treated with 0.625 mg (median 9.5), and also higher than the cardiac patients treated with placebos (median 8). The possibility that those pre-treatment differences were a determining factor in the results cannot be disregarded in view of the observed positive relationship between degree of initial impairment and amount of improvement with Premarin therapy. On the other hand, supporting the idea that Premarin therapy was of primary importance in determining the results, and not the degree of initial impairment, is the fact that among cerebral patients, where there was no difference in pre-treatment impairment, greater improvement occurred in those treated with Premarin.

An additional factor of possible relevance was the greater length of treatment (approximately 1.5 months average) for the placebo than the Premarin group among both cerebral and cardiac patients. In view of the observed tendency for older men to deteriorate in their thinking with time alone, it is possible that the difference in length of treatment biased the results in favor of the Premarin-treated. To test that possibility, Spearman rank correlations were computed between time on treatment and degree of intellectual improvement. Only one of those coefficients was anything but trivial. Among the cerebral patients on Premarin, the coefficient of .27 indicated a trend toward greater improvement with longer treatment (more than 6 months) but that tendency did not approach statistical significance ($P>.10$). The slightly longer treatment period for the placebo patients was, therefore, considered inconsequential as far as influencing the results was concerned.

Summary. Tested a second time was the hypothesis that mental impairment decreases in patients with cardio- or cerebrovascular disease treated with Premarin. Forty-five men with myocardial infarction and 32 with cerebral thrombosis were studied by means of the Rorschach test, which was first administered at the time either Premarin or placebo treatment was begun, and was repeated after 6 to 16 months. Each patient received a score denoting amount of increase or decrease in impairment following treatment. There was considerable overlap in scores between Premarin and placebo groups, and gains were relatively small for individual patients. The results paralleled findings from the earlier study in showing improved mental functioning in Premarin-treated patients with cerebral thrombosis compared with placebo-treated controls, but they were at variance with the previous findings regarding similar improvement in cardiac patients. Analysis of the results with the 153 male patients from the 2 studies combined showed superiority of Premarin among the cerebral patients only. However, with the cardiac patients separated into those receiving 1.25 mg Premarin and those given 0.625 mg daily, the improvement of those on the higher dosage compared with placebo-treated patients also bordered on significance. Those treated with 0.625 mg were not different from placebo patients. A positive relationship was found between degree of initial impairment and amount of improvement with Premarin therapy. Among the placebo-treated cerebral patients, an association was observed between age and increased impairment with time.

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Received November 1, 1964. P.S.E.B.M., 1965, v118.