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Improved Mental Functioning with Premarin Therapy in Atherosclerosis. (28466)

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Intellectual decline in the elderly is often attributed to atherosclerosis in the cerebral vasculature. Experimental work with animals and studies of patients with coronary artery disease have both suggested that estrogens may be helpful in retarding or even reversing atherosclerosis(1). It has also been reported that survival rate increased with administration of conjugated equine estrogens (Premarin) to men who had recovered from an acute myocardial infarction(2,3). Kountz(4) concluded that administration of estrogens to postmenopausal women reduced atherosclerosis in uterine vessels and also improved the general constitutional condition and some aspects of the mental state. Rivin and Dimitroff(5) reported less severe atherosclerosis of cerebral arteries in patients with carcinoma of the prostate who were treated with estrogens than in those who were not. Their findings were not confirmed, however, by Meissner and Moehring(6). To the extent that estrogens may promote restored cerebral physiological processes in patients with atherosclerosis, improvement in mental functioning might also be anticipated.

This report concerns the effect of Premarin on certain aspects of cognitive funtioning, the hypothesis being that mental impairment decreases in patients with atherosclerosis treated with Premarin. The hypothesis was tested with the use of the Rorschach ink blot technique, which has frequently proved to be sensitive to impaired mental functioning accompanying organic changes in the brain(7).

Methods. One hundred and one patients were included in the analysis, 51 who had had cerebral thrombosis and 50 who had had myocardial infarction. They were participating in a long-term, controlled study of the effects of Premarin therapy in cardiovascular and cerebrovascular disease, in progress at the Los Angeles County Hospital. Prior to assignment to treatment all patients had been carefully evaluated to ensure accuracy of diagnosis. They were free of concomitant illness threatening survival, and were free of clinical need for hormone therapy other than insulin or thyroxin. In general they came from low socioeconomic backgrounds and had had limited education. Patients were randomly allocated by a statistical control office to either Premarin or placebo treatment, and were then seen in special outpatient research clinics at approximately 6-week intervals.

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Relatively small doses of Premarin were administered orally, 0.625 mg daily for women, and from 0.625 to 2.5 mg for men, most frequently 1.25 mg daily.

Of the 51 cerebral patients, 23 received Premarin and 28 placebo treatment. There were 25 cardiac patients on Premarin and 25 on placebo. Altogether there were 10 women and 38 men on Premarin, and 15 women and 38 men on placebo, a nonsignificant difference in sex composition ($p>.40$). In age the patients ranged from 39 to 80 years, with the Premarin-treated averaging 58.5 (*SD* 10.4) and the placebo patients 59.1 (*SD* 9.4), also a nonsignificant difference ($p>.38$).

Rorschach test. The Rorschach was selected as the primary technique for testing the hypothesis, but several other psychological tests were also used at the beginning of the study. When it became necessary to limit the amount of testing in order not to discourage patients from continuing in the treatment program, the other tests were discontinued in favor of the Rorschach. The Rorschach test consists of 10 inkblots which are shown to the patient one at a time with the request that he report what he sees in the blot. The psychological impairment which accompanies disturbed brain functioning consequent to cerebral damage, known as "organicity," is often reflected in the ways the inkblots are described. To systematize the assessment of impairment, and any changes therein resulting from treatment, a checklist scale was assembled consisting of 46 specific Rorschach signs known to be associated with disrupted cerebral functioning(8). With the use of the scale judgments were made about each patient concerning such things as memory, capacity for abstract thinking, perceptual accuracy, flexibility of thought, organizing skill, and subjective feelings of adequacy. The items comprising the scale included Piotrowski's 10 signs(9); 9 signs from Aita, Reitan, and Ruth(10); 8 from Baker(11); 6 from Ames, Learned, Metraux, and Walker(12); 4 from Hertz and Loehrke(13); and 9 signs suggested by early work on the atherosclerosis study. A more detailed description has been published(8).

Validity of the checklist scale as an indicator of organic impairment was verified by comparing Rorschach scores (before treatment) for 81 patients with cerebral thrombosis, who were thus known to have damage to the brain, and 53 patients with myocardial infarction but no known brain damage. The two groups of patients were similar in age, sex, education, and socioeconomic background. The cerebral patients showed more signs of impaired thinking (z 5.87, $p<.001$). Retest reliability of the scale based on scores for 31 cerebral patients on placebo was found to be .77, $p<.001$, after 6 to 16 months. Rescoring reliability after approximately 6 months was .97, $p<.001$.

Procedure. Each patient was given the Rorschach at the time of assignment to treatment or shortly thereafter, and the test was repeated after 6 to 16 months of treatment, so that each person served as his own control. Change in cognitive functioning after treatment was determined by subtracting each patient's retest score on the Rorschach impairment scale from his initial score. The difference represented either an increase or a decrease in the number of Rorschach signs of impairment; that is, either decline or improvement in mental functioning. The test was administered and scored according to Klopfer's system(14), and without knowledge of the patient's form of treatment.

Among the cerebral patients those on Premarin averaged 8.8 (*SD* 2.2) months of treatment between the first and second testing; those on placebo averaged 9.2 (*SD* 2.9), a nonsignificant difference ($p>.27$). However, the cardiac patients on Premarin averaged 7.2 (*SD* 0.9) months of treatment between the 2 Rorschach testings, whereas those on placebo averaged 8.9 (*SD* 2.5) months, a significantly longer period ($p<.001$). Spearman rank correlation coefficients were computed to determine whether the length of time between the first and second Rorschach testing was related to improvement in mental functioning. For cerebral patients on Premarin the coefficient between time on treatment and decrease in impairment was .13, $p>.20$; for cardiac patients on Premarin, −.03, $p>.20$; for cerebral patients on placebo it was −.07, $p>.20$;

and for cardiac placebo patients, –30, $p > .10$. Thus no relationship was seen between time on treatment (after 6 months) and amount of improvement, and the slightly longer treatment period for the cardiac patients on placebo was considered inconsequential. The changes observed following treatment were assumed to have occurred within the first 6 months.

In addition to the 101 patients herein reported who received both a first and second Rorschach, 20 other patients were given the Rorschach once but were unavailable for retesting because of refusal, illness, death, or withdrawal from clinic attendance. Analysis of these patients revealed no differences between those on Premarin and those on placebo in any parameter which might bias the comparison in the 101 patients available for the second testing.

Because the Rorschach impairment scale yields scores which are not truly numerical, nonparametric techniques were used in the analysis. Significance levels of differences between groups were calculated by means of the Mann-Whitney *U* test, which requires only that scores be ranked. Spearman rank correlation coefficients were computed where the data permitted; otherwise contingency coefficients were used.

Results. Rorschach impairment scores from the initial testing ranged from 1 to 44 with a median of 19 for the cerebral patients, and from 1 to 32 with a median of 10 for the cardiac patients. There was no difference in in initial impairment score between the Premarin and placebo patients in either the cerebral ($p > .26$) or cardiac group ($p > .21$), so that Premarin and placebo patients started from essentially the same baseline before treatment. Scores from the second testing ranged from 2 to 38 with a median of 20 in the cerebral group, and 0 to 29 with a median of 11 in the cardiac patients. Difference scores denoting change following treatment, listed in Table I, were derived by subtracting each patient's Rorschach impairment score on the second testing from his initial impairment score, *i.e.*, minus scores in Table I indicate decreased impairment, and plus scores represent increased mental impairment.

TABLE I. Change in Number of Rorschach Indications of Impaired Thinking upon Retest.*

Cerebral thrombosis		Myocardial infarction	
Premarin N = 23	Placebo N = 28	Premarin N = 25	Placebo N = 25
–23	–17	–14	–6
–18	–12	– 8	–5
–11	–11	– 8	–4
–10	–11	– 8	–1
–10	– 6	– 6	–1
– 9	– 6	– 6	–1
– 8	– 5	– 5	–1
– 7	– 4	– 4	0
– 7	– 3	– 4	1
– 6	– 3	– 3	1
– 5	– 2	– 3	1
– 5	– 2	– 1	1
– 5	– 1	– 1	1
– 5	0	– 1	2
– 3	2	0	2
– 1	5	0	3
0	6	1	5
0	6	2	5
4	8	3	6
5	8	3	6
7	10	4	7
7	10	6	7
16	12	7	7
	12	8	8
	13	11	10
	15		
	15		
	20		

* Minus scores indicate a decrease in signs of impairment; plus scores represent an increase.

There was great overlap in scores for the Premarin and placebo patients. Furthermore, the intellectual improvement was not great for individual patients. From all those on Premarin the median improvement was 3 points on the Rorschach scale, while for the patients on placebo there was a median decline of 2 points, an overall median difference of 5 points between the two groups.

As a group the cerebral patients given Premarin showed more positive change in their thinking than did similar patients on placebo treatment (Table II). Myocardial infarction patients on Premarin also improved more than those on placebo. Contingency coefficients between change in impairment score and form of treatment indicated a positive relationship between Premarin therapy and improvement in mental functioning for the cerebral patients, for the cardiac patients, and for both combined (Table II).

Qualitatively, as compared with placebo-

TABLE II. Significance of Differences Between Premarin and Placebo Patients in Improvement in Mental Functioning,* and Correlation Coefficients Between Improvement and Form of Treatment.

		N	Mann-Whitney *U* test		Contingency coefficients†		
			z	*p*	*C*	X^2	*p*
Cerebral thrombosis	Premarin	23	2.31	.01	.25	3.30	<.05
	Placebo	28					
Myocardial infarction	Premarin	25	2.11	<.02	.27	3.93	.02
	Placebo	25					
CT and MI combined	Premarin	48	3.13	<.001	.22	5.23	<.02
	Placebo	53					
Total female patients	Premarin	10	2.16	<.02	.27	1.93	<.10
	Placebo	15					
Total male patients	Premarin	38	2.64	.004	.25	5.27	<.02
	Placebo	38					

* In all comparisons the Premarin-treated group improved more.
† Corrected for continuity.

treated patients, the changes in those on Premarin may be described as follows: Their thinking became less concrete and less stereotyped, and they were more flexible and more focused in dealing with the test material. They showed greater memory recovery, became more confident of their abilities, better able to make fine distinctions, and especially became more accurate in their perceptions.

No relationship was found between age and improvement on Premarin therapy. For cerebral patients on Premarin the Spearman rank correlation between age and decreased impairment was −.10, $p>.20$; for cardiac patients it was .27, $p>.10$; for cerebral patients on placebo treatment the coefficient was −.14, $p>.20$; and for cardiac patients, −.17, $p>.20$.

There was no association apparent between sex and increased mental capability with therapy; both men and women on Premarin improved more than those given placebo treatment (Table II).

A positive relationship was noted between degree of initial impairment and improvement after therapy. For all patients on Premarin the Spearman rank coefficient between initial impairment and improvement on retest was .56, $p<.001$. For placebo-treated patients the Spearman was .29, $p<.05$. For all patients combined, both Premarin and placebo, a correlation of .37, $p<.001$, was found. In other words, the greater the initial impairment, the more the improvement after treatment, whether Premarin or placebo. Of course, the more severe the deficit, the more latitude there is for recovery. Improvement was generally greater in those on Premarin, nevertheless.

Test-retest Rorschach scores were available for 10 patients (5 cerebral, 5 cardiac) who had been given ethinyl estradiol (Lynoral), a synthetic estrogenic preparation. In comparison with the 53 placebo patients, those on Lynoral showed decreased mental impairment (p .04) similar to the patients on Premarin reported herein.

Test-retest scores were also available on several other psychological tests for small numbers of cerebral and cardiac patients combined (from 6 to 10 on either Premarin or Lynoral and from 10 to 20 on placebo). The following changes were noted in the estrogen-treated patients as compared with those on plcaebo: No difference in visual-motor functioning as measured by either the Draw-A-Man test (p .35) or the Bender-Gestalt (p .34); slight improvement in abstract thinking as gauged by Proverb Interpretations (p .21); increased immediate memory as tested by the Digit Span subtest of the Wechsler Adult Intelligence Scale ($p<.07$); greater improvement in abstract thinking as measured by Raven's Coloured Progressive Matrices test ($p<.004$); and decreased impairment in thinking as assessed with the Rorschach (p .002).

Discussion. Inasmuch as there was consid-

erable overlap in scores for the Premarin and placebo patients, and the gains were relatively small for individual patients, the results must be viewed with caution. They were consistent and statistically significant, however, and deserve further investigation.

After the planning and execution of this investigation 2 other similar studies were noted. Lifshitz and Kline(15) examined the effects of estrogen treatment in 63 men between 55 and 75 years of age with diagnosis of psychosis with cerebral atherosclerosis or senile psychosis. Mental functioning was assessed by means of psychiatric interview, ward personnel ratings, a formalized mental status evaluation, and 5 subtests of the Wechsler Adult Intelligence Scale. An evaluation after 6 months of therapy showed a trend toward improved mental functioning in patients on estrogen. The trend was reversed, however, upon assessment at 12 and at 18 months (when only 31 patients remained) so that there was no difference. Although these patients were similar in age to those in the present study, the fact that they were psychotic introduced an important difference. The means of judging change were also quite different. In the present investigation a pilot study indicated that formal tests of intelligence, such as those used by Lifshitz and Kline, were less sensitive than the Rorschach to the kind of impairment prevalent in older patients with atherosclerosis. The Rorschach was also considered preferable in that it is comprehensive in scope, less reminiscent of school, less affected by education, and less culture bound(8). In line with Lifshitz and Kline's negative results, it might be noted that no differences in mental functioning between Premarin and placebo patients were noticed by the residents in neurology and cardiology who examined the present patients at 6-week intervals, although no systematic evaluation was made. Apparently the changes are of such a nature or magnitude as to be detected only by a sensitive instrument.

Caldwell and Watson(16,17) studied the psychological effects of estrogen treatment in 28 postmenopausal women ranging in age from 54 to 88 years. They used a wide variety of techniques aimed at measuring a number of abilities and attitudes. Several trends were noted favoring improved performance in the estrogen-treated patients, but there was also great overlap in scores between those on estrogen and those on placebo. Among 69 comparisons, not all of which were independent, one showed greater improvement in the control patients (general information), and 6 showed more improvement in those given estrogen (judgment, memory, accuracy of Rorschach perceptions, "intellectual energy," positive feelings toward other people, appropriateness of behavior during testing). The authors concluded that perhaps only one basic factor was involved, intellectual functioning. Remarkably similar results were obtained in the present study using the Rorschach alone. Caldwell and Watson also used that test, but in a limited way. They reported only 9 formal scoring categories, whereas those aspects of the Rorschach records plus a great many others were included in the Rorschach impairment scale in the present investigation. A standard intelligence test, as in the Lifshitz and Kline study, was found to have limited usefulness.

Although the mechanisms by which changes occur under Premarin are unknown, it would appear that improvement in mental functioning in patients who have had cerebral thrombosis depends upon factors other than changes in neural lesions. That is supported by the observation of improvement in cardiac patients who had no objective neurologic findings as tested by traditional clinical techniques.

The results of the use of anticoagulants in treatment of cerebral thrombosis patients have been equivocal and such treatment has inherent dangers(18). Surgery of the extracranial vessels is another approach, but that is not applicable to intracranial occlusive disease. Clot lysis using enzymes is a new and unproved technique. Premarin offers some promise of effecting a decrease in certain features of mental impairment among older people with atherosclerosis. With further study and refinement of methods it may be possible to determine which kinds of patients

can be expected to benefit most from Premarin.

Summary. It is hypothesized that mental impairment decreases in patients with atherosclerosis treated with Premarin. One hundred and one patients were studied, 51 who had had cerebral thrombosis and 50 who had recovered from an acute myocardial infarction. The Rorschach test was first administered when the patients began either Premarin or placebo therapy, and was repeated after 6 to 16 months of treatment. The tests were assessed for indications of impairment in thinking, and each patient received a score denoting amount of increase or decrease in impairment after treatment. There was considerable overlap in scores between Premarin and placebo patients, and gains were relatively small for individual patients. Nevertheless, improved mental functioning was found in both cerebral and cardiac patients treated with Premarin in comparison with those on placebo, and a positive association was observed between Premarin therapy and decreased mental impairment.

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Isolating the Total Coronary Artery Inflow for Administering Pharmacologic Agents: New Method Without Coronary Dissection.* (28467)

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One means of studying the pharmacology and physiology of the heart is to administer pharmacologic agents to anesthetized open-chest dogs while directly measuring cardiac performance. Drugs injected intravenously affect the entire cardiovascular system and its regulating mechanisms, while those injected into a single coronary artery affect only the part of the heart supplied by that particular vessel. Cannulating both coronary arteries to inject drugs into the total coronary artery inflow is difficult, especially when direct measurement of left ventricular output is also desired. The method herein reported is a relatively simple technique for injecting pharmacologic agents into the iso-

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