pounds when both are mixed and coadministered. (d) Slightly less of the absorbed radioactive coenzyme is flushed out in the urine by a large parenteral dose of unlabeled compound as compared with radioactive cyanocobalamin. These findings show that coenzyme behaves much like cyanocobalamin in intestinal absorption, quantitatively as well as in mechanism.

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Clinical Studies of Long-Term Estrogen Therapy in Men with Myocardial Infarction. (27531)

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Patients with atherosclerotic heart disease often manifest abnormal blood-fat patterns which most clinicians believe are causally related to the disease(1-5). Previous investigations by the authors and others indicate that administration of certain estrogens, *e.g.*, Lynoral (ethinyl estradiol) and Anvene (mytatrienediol), cause a shift toward normal of these blood-fat patterns(6-20). The present study was designed(1) to determine whether administration of moderate doses of estrogen does in fact prevent subsequent infarctions and thus improve survival in men patients who previously have suffered at least one myocardial infarction, and (2) to evaluate the efficacy of 3 estrogen preparations, Anvene, Lynoral (ethinyl estradiol), and Premarin (mixed, conjugated equine estrogens) for this purpose.

This report summarizes our findings in the first 5 years of this study and calls attention to the unexpected finding that, in the doses used, preparations which correct abnormal blood-fat patterns (*i.e.*, Lynoral and Anvene) apparently do not increase survival in men, whereas Premarin increases survival but has no significant effect on serum lipids.

We have reported elsewhere(21) that Pre-

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marin (mixed, conjugated equine estrogens, NNR) significantly increases survival rate in men with myocardial infarction when given in small, well tolerated doses that cause minor evidences of feminization, chiefly some degree of breast pain or tenderness. This finding is in accord with the suggestive evidence of Stamler, Pick and Katz(22), who used larger and more grossly feminizing doses of this same mixture of natural estrogens. In a recent study using pure, synthetic ethinyl estradiol, Oliver and Boyd(23) failed to note any effect on survival. These studies show that ethinyl estradiol in small doses and Premarin in large doses lower cholesterol levels (22,23). Survival rates in our ethinyl estradiol-treated patients showed no difference from controls.

Although no definite evidence exists that reduction in serum cholesterol increases survival, and cholesterol levels are of little predictive value, the idea is prevalent that reduction of elevated serum cholesterol constitutes *prima facie* evidence of antiatherogenic activity and improves chances for survival. The autopsy finding by Rivin and Dimitroff(24) that atherosclerosis is reduced in men who have been given stilbestrol in treatment of prostatic cancer has been interpreted as supporting the thesis that estrogens may be antiatherogenic. Our clinical studies indicate that the survival effect of Premarin is independent of any effect on serum cholesterol.

Material and methods. Sources of patients were the Los Angeles County Hospital and Cedars of Lebanon Hospital, Los Angeles. All men newly admitted with the diagnosis myocardial infarction, about 1000 per year, were potential candidates for the study. Of these, roughly 50% died during the acute phase of the attack, and an additional 25% were unwilling to attend our clinics regularly. The approximately 250 patients remaining were screened during their first visit to our special atherosclerosis clinics and eligibility for our study determined in accordance with the established protocol.

The presence of myocardial damage was determined by clinical history, electrocardiographic evidence and transaminase tests. Patients accepted for study were ambulatory, cooperative and able to attend the clinics regularly; they were willing to take hormone (estrogen) treatment if prescribed, had not suffered cerebrovascular accidents, and were free of concomitant illnesses threatening survival. Because we intended to study urinary hormone metabolites during therapy, patients also were required to be free from liver or kidney disease and without requirement for hormone therapy other than insulin or thyroid. Complications of atherosclerotic heart disease were acceptable: patients with heart failure, hypertension, myxedema, diabetes and combinations thereof were included if otherwise suitable. Patients with coronary insufficiency (22 cases) were accepted into the study during its initial 7 months upon approval of the cardiology consultant; clinical evidence strongly suggested myocardial infarction in these cases, but as electrocardiographic evidence was lacking, these are classified conservatively as "no infarction."

Roughly 125 patients per year were admissible to the study using the aforementioned criteria.

These studies were initiated in Sept. 1956, when patients were randomly assigned to either Lynoral (ethinyl estradiol) or to placebo therapy. Three months thereafter Anvene was added as a third treatment, and 6 months later Premarin was added. All patients entering the study after April 1957 were randomly assigned to one of the 4 treatments. Numbers of patients in the 4 treatment groups reflect this difference in starting dates.

To insure initial comparability of the 4 groups, the randomized allocation was stratified by age, number of previous myocardial infarctions (1,2 or more), cardiac failure requiring digitalization, hypertension, myxedema, and diabetes (Tables I and II). Although total numbers of patients in the 4 treatment samples differ, the proportions by age and by complication are equivalent.

Most of the patients were middle aged or older, primarily of the laboring class, with limited education and low income. About 10% were native American Negroes, 11% were Jews, 5% were Mexicans, and the re-

mainder native Americans of miscellaneous European origins.

Patients first were seen in the clinics about 6 weeks after hospital discharge, at which time the best standard care for patients convalescent from myocardial infarction was instituted. Anticoagulants were not prescribed and special diets were not imposed. With the exception of estrogen or placebo therapy, the care of experimental and control patients was similar.

Estrogen or placebo therapy was usually begun within 3 months after the myocardial injury. No effort was made, as was done in other studies(15), to adjust dose to obtain predetermined serum lipid effects. In the current study estrogen dose initially administered was roughly equivalent in physical response to .05 mg Lynoral (ethinyl estradiol). Thereafter doses were increased in equal multiples at each 6-week visit until signs of minor intolerance (usually breast tenderness) were observed.

Estrogen or placebo was supplied orally in the following dosages:

	Placebo	Lynoral	Anvene	Premarin
		mg		
Initial daily dose	One tablet	.01-.10	5-10	.625
Usual maintenance dose, per day	"	.05-.15	10-15	1.25-2.5

Once the maximum tolerated dose was reached, the patient was maintained on that dose. Usually, any early physical signs or symptoms, such as breast tenderness, disappeared or became less marked with continuation of this dose, but in a few instances it was necessary to reduce the dose. Changes in libido were rarely noted. Clinic physicians were informed as to which treatment each patient was receiving. This was done to insure safety of the patients, because so little was known about the effects of these hormones in patients with heart disease. A double-blind, randomized study comparing the effects of 2 small, fixed doses of Premarin with the effects of a placebo is now under way.

Early studies(17,19,25) showed that lipid changes resulting from estrogen (Lynoral or Anvene) treatment in men (a) occur with small or very moderate doses, (b) precede the appearance of breast tenderness and other symptoms, (c) reach a maximum within the first 3 months of treatment, (d) persist at the new levels with continued treatment with no "escape," and (e) can be attained and maintained with clinically tolerable doses.

After a patient was assigned to one of the treatment regimens, his clinic physician provided him with the number of tablets needed until the next visit, plus an additional number of extra tablets. The patient was instructed to return with the box of tablets at that time, and count of the remaining tablets provided a partial check on patient adherence to the prescribed dosage.

Patients were seen by the physician assigned at 6- to 10-week intervals. Failure to keep an appointment set in motion immediate efforts to trace the patients. Patient retention was very high, only 14 out of 432 (3%) being lost in 5 years of follow-up.

During the patient's first 2 visits to our clinic, a complete history and work-up were obtained. Check-sheets for subsequent visits insured completeness of check-ups and provided data for later analyses. Laboratory studies were made prior to therapy, at 6 weeks, at 3 months, and at 3-month periods thereafter.

Urine samples for concurrent analysis of hormone metabolites were collected at 3- to 6-month intervals. These analyses provided a further check on dose adherence, as total estrogen excretion generally was compatible with the prescribed treatment.

When patients were readmitted to the hospital for any reason medical supervision was continued on the hospital ward by clinic physicians. Upon discharge the patient was returned to the atherosclerosis clinic.

Death certificates were obtained for all deaths. Autopsies were performed on approximately 40%. Exact causes of sudden deaths occurring outside the hospital were obtained from the county coroner's office.

Five years after beginning the study, as of June 1961, 432 men patients have been

TABLE I. Distribution of 432 Male Patients in Study by Age, Complications and Treatment.*
(All patients treated at least 3 mo.)

	Placebo	Ethinyl estradiol	Anvene	Premarin	Total
Total patients	*147*	*120*	*85*	*80*	*432*
No complicating factors	*76*	*68*	*48*	*43*	*235*
Ages—Under 50	24	18	16	11	69
50-69	42	39	28	25	134
70+	10	11	4	7	32
Initial complicating factors	*71*	*52*	*37*	*37*	*197*
Ages—Under 50	12	7	0	8	27
50-69	43	35	32	18	128
70+	16	10	5	11	42

* Eleven of these patients are not included in the analysis of deaths because their deaths resulted from causes totally unrelated to cardiovascular disease, *i.e.: Placebo-treated, 3 cases:* 1) gunshot wound, 2) skull fracture, 3) prostatic carcinoma. *Ethinyl estradiol, 6 cases:* 1) gunshot wound, 2) bronchopneumonia, 3) fractured pelvis and abdominal hemorrhage, 4) hemopericardium and dissecting aneurysm of aorta, 5) massive upper GI bleeding, 6) thrombosis of common iliacs and aortic bifurcation. *Premarin, 2 cases:* 1) pulmonary infarction, 2) GI hemorrhage.

TABLE II. Nature of Complications in Each Treatment Group.*
(All patients treated at least 3 mo.)

Nature of initial complicating factors	Placebo	Ethinyl estradiol	Anvene	Premarin	Total
Failure	29	19	16	10	74
Diabetes	6	5	3	5	19
Hypertension	19	16	9	7	51
Myxedema	0	0	0	1	1
More than 1 of above	17	12	9	14	52
None	76	68	48	43	235
Total	147	120	85	80	432*

* Eleven of these patients are not included in analysis of deaths because their deaths resulted from causes totally unrelated to cardiovascular disease. (See footnote, Table I.)

under treatment in our clinics for at least 3 months. Eleven of the patients are not included in this analysis because they died from causes totally unrelated to cardiovascular disease (Footnote, Table I). The 421 patients upon whom this analysis is based include: 144 placebo-treated patients, 114 treated with Lynoral (ethinyl estradiol), 85 with Anvene, and 78 with Premarin.† The 53 patients first included in the study have received 60 months of continuous treatment with Lynoral (ethinyl estradiol).

Results. Inasmuch as some time is required for adjustment to clinic routine and daily estrogen intake, and our experience has indicated that clinical and laboratory changes attendant on estrogen therapy are maximal within a 3-month period, analysis of our data is restricted to patients treated for a minimum of 3 months.

Mortality and survival analysis. Survival curves developed by the standard life table method(26) are illustrated in Fig. 1. All deaths, from whatever cause, are included. Cumulative survivals are shown in detail through the period 33-36 months, beyond which numbers at risk are too small for fruitful analysis. Survival curves for Anvene and Lynoral (ethinyl estradiol) are generally similar to the curves for patients on placebo. Contrariwise, *a substantial difference in favor of Premarin is obvious after 12 months of treatment: only one Premarin-treated patient per 100 has died, whereas 7 deaths per 100 have occurred among patients receiving place-*

† Approximately the same number of women are the subject of a separate study running in the same clinics.

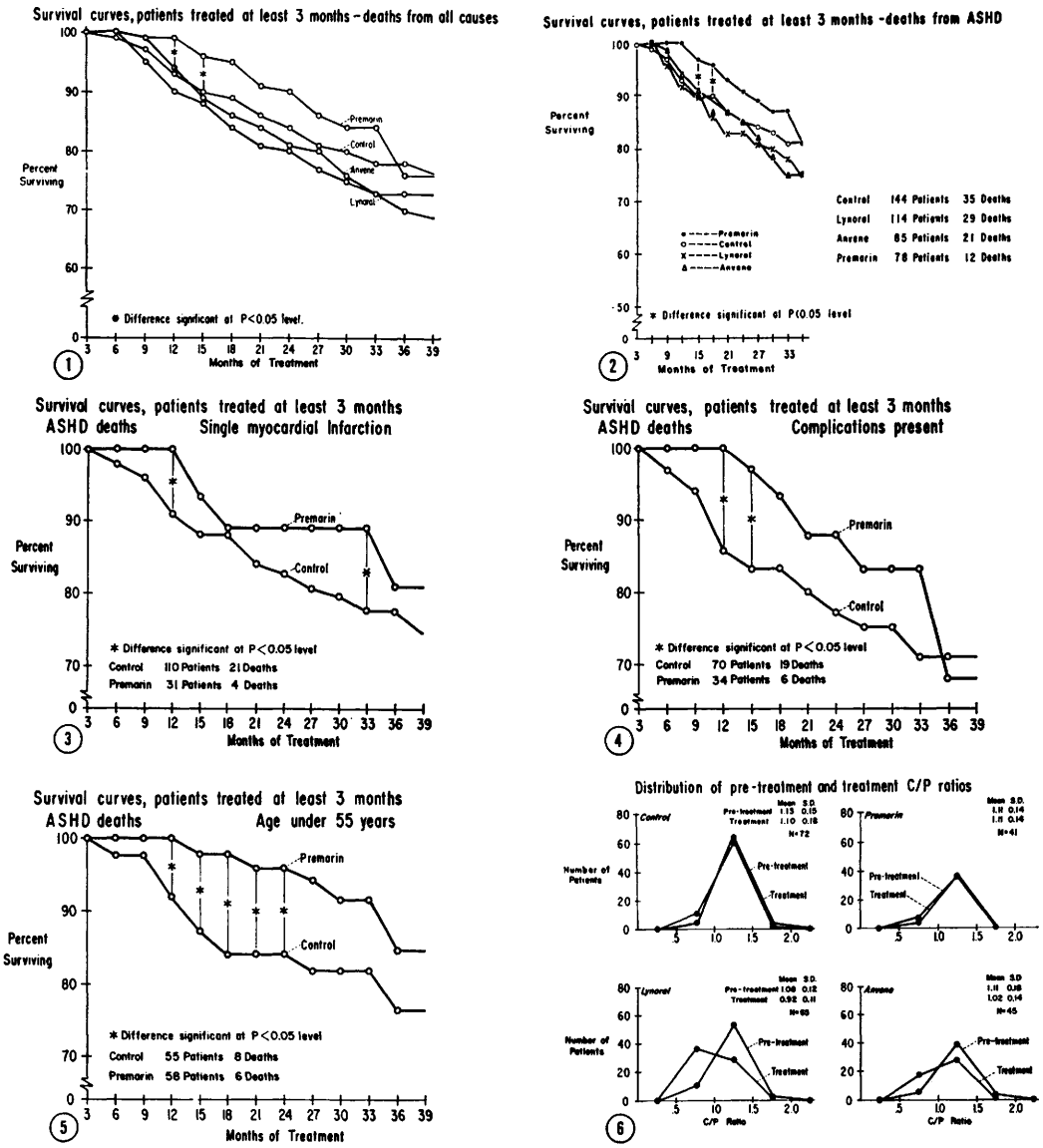

FIG. 1-6.

bo; again, after 15 months of treatment, 4 patients per 100 in the Premarin-treated series have died, as contrasted with 10 per 100 among patients receiving placebo. These differences (at 12 and 15 months of treatment) are statistically significant in that $P<0.05$. A substantial and almost constant difference continues in favor of Premarin-treated patients through the thirty-third month.

This gross mortality picture strongly suggests the superiority of Premarin treatment: to investigate the degree of superiority and types of patients which benefit most from Premarin administration, more refined analysis is necessary.

When only deaths due to arteriosclerotic heart disease are included, as in Fig. 2, the superiority of Premarin treatment over the other medications is more noticeable: a statistically significant advantage is observed at 15 months and at 18 months ($P<0.05$), and a

TABLE III. Survival Table: Patients Treated More Than 3 Months. Deaths from ASHD 6/1/61.

Months of treatment	No. patients at beginning of period	Died in period	Lost to follow-up	Withdrawn alive	Cumulative proportion surviving
		Control patients			
3- 6	144	2	0	0	.99
6- 9	142	2	1	0	.97
9-12	139	6	0	3	.93
12-15	130	4	0	7	.90
15-18	119	1	0	3	.89
18-21	115	4	0	1	.86
21-24	110	3	0	6	.84
24-27	101	3	0	3	.81
27-30	95	1	0	4	.80
30-33	90	3	0	3	.78
33-36	84	0	0	4	.78
		Lynoral patients			
3- 6	114	0	0	0	1.00
6- 9	114	6	0	0	.95
9-12	108	5	0	1	.90
12-15	102	2	0	7	.88
15-18	93	5	0	5	.84
18-21	83	3	1	0	.81
21-24	79	1	0	3	.80
24-27	75	2	0	3	.77
27-30	70	2	1	2	.75
30-33	65	2	0	5	.73
33-36	58	2	0	6	.70
		Anvene patients			
3- 6	85	0	0	0	1.00
6- 9	85	1	0	0	.99
9-12	84	4	0	0	.94
12-15	80	4	0	1	.89
15-18	75	3	0	7	.86
18-21	65	1	0	4	.84
21-24	60	2	1	3	.81
24-27	54	1	0	4	.80
27-30	49	2	0	4	.76
30-33	43	2	0	5	.73
33-36	36	0	0	1	.73
		Premarin patients			
3- 6	78	0	0	0	1.00
6- 9	78	1	1	0	.99
9-12	76	0	0	1	.99*
12-15	75	2	0	5	.96*
15-18	68	1	0	4	.95
18-21	63	2	0	7	.91
21-24	54	1	0	3	.90
24-27	50	2	0	3	.86
27-30	45	1	0	5	.84
30-33	39	0	0	5	.84
33-36	34	3	0	7	.76

* Premarin - control difference significant at P = .05 level.

decided advantage continues through the thirty-third month of therapy (Table III).

We have compared the mortality of patients receiving Premarin with the mortality in the total placebo-treated series, and again with the more limited group of controls who have entered the study since April 1957, when Premarin therapy was introduced. In Table IV survival information is presented for (a) all patients dying of arteriosclerotic heart disease and its sequelae; and according to (b) number of previous infarctions, single or multiple, (c) age, whether under 55, or 55 and over, and (d) whether or not complications were present at time of inclusion in the study. Insofar as the deaths attributable to arteriosclerotic heart disease are concerned, the advantage of Premarin treatment is unmistakable: the difference in survival very nearly reaches statistical significance at 6-9 months of treatment ($P<0.09$), and is statistically significant for the periods 9-12 months ($P<0.01$) and 12-15 months ($P<0.05$). A sizable difference (6%) persists to 30 months: by this time patient samples at risk are rather small (90 on placebo, 39 on Premarin), and the curves become too unstable for confident interpretation.

Tally of deaths specifically due to myocardial infarction produces similar survival curves, with a definite advantage of approximately 6% in favor of the Premarin-treated group throughout 12-27 months of treatment.

Previous infarctions. Review of survival of all patients who have had at least one previous infarction in addition to the current episode indicates a continuing advantage in favor of Premarin during the early months of treatment. This advantage is pronounced during the fifteenth through the eighteenth month but disappears by the twenty-fourth month.

The effect of previous myocardial infarctions on post-infarction survival also is summarized in Table IV. Within the first 24 months patients who have suffered multiple infarctions derive greater benefits from Premarin therapy than do patients who have had but a single infarction. Of the Premarin-treated series, at 18 months, every one of the patients with multiple infarctions has survived, whereas one patient in 10 of those with a single infarction has died. However, as control patients also fare better if they have survived multiple myocardial infarctions, the contrast between Premarin-treated patients

TABLE IV. Condensed Survival Table Summary: Arteriosclerotic Heart Disease Deaths. Premarin vs control (placebo) treatment.†

	Cumulative fraction surviving															
	All ASHD deaths		No. of myocardial infarctions				Complications				Age					
			Single		Multiple		None		Present		< 55				55 and over	
	C	P	C	P	C	P	C	P	C	P	C	P			C	P
At 6 mo	.99	1.00	.98	1.00	1.00	1.00	1.00	1.00	.97	1.00	.98	1.00			.99	1.00
12	.93 *	1.00	.91 *	1.00	.97	1.00	1.00	1.00	.86 *	1.00	.92 *	1.00			.92 *	1.00
18	.90 *	.96	.88	.89	.94	1.00	.97	.98	.83	.93	.84 *	.98			.89	.89
24	.85	.91	.83	.89	.91	.92	.94	.92	.77	.88	.84 *	.96			.83	.74
30	.83	.87	.80	.89	.87	.85	.90	.88	.75	.83	.82	.91			.79	.74
36	.81	.81	.78	.81	.87	.81	.90	.88	.71	.68	.76	.84			.77	.74
No. started	144	78	110	31	34	47	74	44	70	34	55	58			89	20
Deaths in 36 mo	25	9	21	4	4	6	8	4	19	6	10	6			17	4
At risk 36 mo	109	43	82	15	27	29	57	25	53	19	39	35			71	9

* A Premarin - control difference significant at $P < .05$ level when comparison is made between Premarin and Premarin-contemporary controls.
† Total control group was used in preparing table.

with single infarctions and the placebo-treated group is significant only at 12 months, at which time all of the Premarin-treated series are living, but only 91% of their controls (Fig. 3).

It is interesting that at the close of the first 36 months of treatment whereas 19% of the placebo-treated, single infarction group have died, only 13% of the Premarin-treated in this same category have died.

Complications. Comparison of survival of Premarin-treated patients with complications and their placebo-treated controls indicates a statistically significant difference ($P<0.05$) at 12 months of therapy (Fig. 4). This difference is still significant at 15 months, and a somewhat lesser difference continues throughout the thirty-third month of therapy. Whereas 27% of the placebo-treated patients with complications have died by the close of the thirty-sixth month of therapy only 18% of the Premarin-treated in this sub-group have died, an advantage of 9% in favor of Premarin treatment.

Age. In the group of older men, over 55 years of age at admission to the study, the advantage conferred by Premarin is relatively short-lived: although statistically significant at 12 months of therapy, the advantage has disappeared by the eighteenth month.

Benefits of Premarin are most marked in the younger men patients, under 55 at time of admission to the study (Fig. 5). For these patients Premarin confers an advantage which continues throughout the 36 months. This difference reaches statistical significance at the twelfth month of treatment and still is significant at 24 months. After 36 months of therapy, in the placebo-treated group 18% have died, whereas in the Premarin group, deaths have been only 10%.

Effects on serum lipids. Serum cholesterol, phospholipid and cholesterol/phospholipid ratios (C/P) were measured prior to treatment, at 6 weeks, at 3 months, and at 3-month intervals thereafter. Cholesterol was determined by the method of Pearson *et al.*(27) using alcohol acetone extracts of serum. Lipid phosphorus was estimated by the method of Lowry *et al.*(28).

Complete cholesterol and phospholipid de-

terminations prior to and during treatment are available for 223 patients. In each treatment group C/P ratios prior to treatment were "average" (0.9 to 1.1) for about half of the patients, "low" (below 0.9) in a very few instances, and "elevated" (above 1.1) in the remainder. With placebo therapy the C/P ratio increased in 11%, decreased in 24%, and remained unchanged in 65%. With Premarin treatment the C/P ratio increased, decreased or remained unchanged with about equal frequency, whereas with Anvene and Lynoral (ethinyl estradiol) the ratios showed definite decreases: lipids became "normalized", *i.e.*, lipids initially high were reduced, and lipids unusually low tended to rise.

With small to moderate doses of Lynoral (ethinyl estradiol) or Anvene, lipid changes reach a maximum within 3 months of therapy. The data reported here compare serum lipid levels prior to treatment with levels observed after 6 months of uninterrupted treatment.

Shift in C/P ratios with treatment is shown in Fig. 6: In groups of patients receiving either Anvene or Lynoral (ethinyl estradiol), the mean C/P ratio is reduced, whereas C/P ratios of patients receiving Premarin or placebo remain virtually identical with pre-treatment values, further evidence that in the doses used in our study Premarin does not affect serum lipids.

Relationships between cholesterol and phospholipids were explored further in a companion study(29), in which serum lipids of "well controls" and hospitalized "sick controls" who had not suffered myocardial infarction were compared with serum lipids of patients with cerebrovascular disease or myocardial infarction. Highly significant differences were found between either of the 2 control groups and the 2 groups suffering from sequelae of atherosclerosis: in the atherosclerotic groups, a lower phospholipid concentration tended to be associated with a fixed level of cholesterol. This altered cholesterol-phospholipid balance was found at every level of cholesterol. Comparison between lipid levels of "well controls" and "sick controls" disclosed that although serum lipids are substantially reduced in debilitating illness, interlipid relationships remain relatively undisturbed.

Comment. Most of the advantage of Premarin treatment appears to be achieved in the first 2 years of treatment. At the peak of Premarin's effect, at 15 to 18 months of therapy, total deaths from arteriosclerotic heart disease and its sequelae have been only 5%, as compared with 11% in the comparable controls. Premarin may thus be said to afford better than 50% protection overall: *i.e.*, death is postponed in about half of the patients who otherwise might die in the first 18 months.

Of particular interest is the independence of lipid and survival effects. It may be, of course, that reduction of an elevated C/P ratio or of hypercholesterolemia is desirable in its own right. It also is possible that an agent may be developed which will bring about these lipid changes and also improve survival. From our findings, however, it now is reasonably evident that the occurrence or nonoccurrence of lipid changes is not necessarily a reliable predicter of effects on survival.

Conclusions and summary. 1. In a clinical trial men with coronary artery disease who had recovered from a frank myocardial infarction were randomly treated with Lynoral (ethinyl estradiol), Anvene, Premarin, or a placebo. The 3 estrogen preparations were used in small well-tolerated doses of comparable potency as indicated by mild breast tenderness. 2. No untoward effects of the treatment were observed in up to 60 months of continuous treatment. Changes in libido were rarely noted. 3. Premarin therapy significantly improved survival, particularly in the first 2 years of treatment. Lynoral (ethinyl estradiol) and Anvene had no effect on survival as compared with placebo treatment. 4. Subclasses of patients most likely to benefit from Premarin therapy were those with relatively poor initial prognosis: men under age 55, who had had a first myocardial infarction, and with complications of arteriosclerotic heart disease present. 5. Lynoral (ethinyl estradiol) and Anvene significantly lowered the cholesterol-phospholipid ratio. Premarin had no such effect. 6. There is no necessary correlation between physical response (*e.g.*, breast tenderness), serum lipid

and survival effects of estrogen preparations in the male recovering from myocardial infarction: altering of the serum lipids does not necessarily improve survival, and survival may be improved without altering of the serum lipids.

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