thesis of Vit. C in the rat. The protective effect of high levels of dietary protein may be interpreted as the effect of excess protein *per se* on the biosynthetic mechanisms or on the precursors or indirectly on the microflora. Further experiments are in progress to test these hypotheses.

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Effect of Premarin on Survival in Men with Myocardial Infarction.* (26196)

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Considerable epidemiological and experimental evidence suggests that estrogens may be antiatherogenic(1-11). However, only 2 clinical trials of the effect of estrogens on survival in men with myocardial infarction have been reported. Oliver and Boyd(12) failed to observe any effect of ethinyl estradiol on survival but Stamler, Pick and Katz in an interim report(13) found suggestive evidence that mixed, conjugated estrogens (Premarin) increased survival. The latter used doses causing manifest feminization and the results lacked statistical significance.

This paper reports results of a continuing study of Premarin in men using small, well tolerated doses, in which survival in the Premarin group is significantly higher than in the controls.

Material and methods. Clinical material consists of men who had recovered from a myocardial infarction in the Los Angeles County General Hospital or the Cedars of Lebanon Hospital, who were ambulatory, cooperative and considered able to attend our clinics regularly, who were willing to take estrogen if prescribed, who had no requirement for hormone therapy (other than insulin or thyroid), and who were free of concomitant illness threatening survival. Acceptability was determined during the first few visits to the clinic, which was staffed entirely by project personnel. Upon acceptance, patients were randomly allocated to control or treatment with Premarin or one of 2 other estrogens (results with these being reported elsewhere(14)). In those receiving Premarin, dosage was regulated solely by tolerance of the individual and in most cases was 1.25 to 2.5 mg daily. These doses usually gave rise, after some months, to minor breast changes that were not objectionable to the patient. In the event of objectionable side effects, dosage was reduced to the point of ready tolerance.

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Reduced libido was an infrequent complaint (15).

Patients were seen in the special atherosclerosis research clinics at 3 to 6-week intervals, usually by the same physician. Autopsies were secured in about 40% of the fatalities and copies of the death certificate in almost all. Since this study is directed to atherosclerosis alone, we have removed from the series all deaths except those reportedly due to arteriosclerotic heart disease. Furthermore, since we have no reason to expect that very brief treatment with these small doses might be effective, we have confined our analysis to those treated with Premarin or placebo a minimum of 75 days.

Life table analyses were utilized(16). It is important to note that a number of patients, after being treated 75 days or more, subsequently left the clinic and discontinued therapy. Some of these were truly lost (Table I) and were dropped at that point from the analysis. Others, however, remained in contact with the study though no longer under treatment: these individuals, having had at least 75 days of treatment, continue to be counted. Finally, it should be noted that this is an analysis of a continuing study. Thus, a follow-up is now possible through the 39th month on those first admitted to the project. A patient beginning treatment Jan. 1, 1960, however, can enter into the analysis for only the first 6 months, the date of analysis being June 1, 1960. At each interval of time, therefore, there are a number of patients whose period of observation has not yet exceeded that period, although they were still alive, and this number must be taken into account under some heading such as "withdrawn alive." It is clear that these individuals have been "withdrawn" simply because their period of observation has not yet passed the stated interval, rather than for any medical reason.

Results. Table I shows the period in months from beginning of treatment, number of patients alive and at risk at beginning of the period, number of deaths due to arteriosclerotic heart disease during the period, percentage surviving through the period, number "lost" to all follow-up, and number "withdrawn alive" at end of the period. The percentage surviving (Fig. 1) is of course a cumulative figure.†

TABLE I. Survival Rates in Men with Myocardial Infarction Receiving No Estrogen or Treated with Premarin for at Least 75 Days, Showing (1) No. of Months from Beginning Treatment, (2) No. at Risk (*i.e.*, Alive) at Beginning of Each Period, (3) No. of Deaths Due to Arteriosclerotic Heart Disease in the Period, (4) % Surviving through Period, (5) No. with Whom All Contact Became Lost in the Period, and (6) No. "Withdrawn Alive" in the Period Because They Had Been under Observation Only This Long as of June 1, 1960.

Mo of therapy	No. at risk	No. of deaths	% surviving	No. lost	No. withdrawn alive
		Control group			
3- 6	123	6	95	1	5
6- 9	111	4	91	1	5
9-12	101	4	88	0	3
12-15	94	1	87	0	4
15-18	89	2	85	1	7
18-21	79	3	81	0	7
21-24	69	3	78	0	8
24-27	58	2	75	0	4
27-30	52	1	73	3	2
30-33	46	1	72	1	4
33-36	40	2	68	2	2
36-39	34	0	68	0	8
		Premarin group			
3- 6	62	0	100	1	7
6- 9	54	0	100	0	4
9-12	50	1	98	1	2
12-15	46	1	96	0	5
15-18	40	1	93	0	6
18-21	33	1	90	0	8
21-24	24	0	90	0	6
24-27	18	0	90	0	1
27-30	17	1	84	0	2
30-33	14	0	84	0	4
33-36	10	0	84	0	4
36-39	6	0	84	0	3

At each 3-month interval from the 3rd thru the 15th month, p value for the difference in survival rates in the 2 groups was .05, except at the 9th month interval where p value was .01. Beyond 15 months, the numbers of cases which have been currently followed for these long periods is not yet sufficient to lend the differences statistical significance. However, the available data tend to suggest that the significant differences found in the first

† Thus, if 80% have survived through period i-1 and if 10% of these survivors die in period i, then 10% of 80% die in period i (or 8%) and 80-8% (or 72%) survive thru period i.

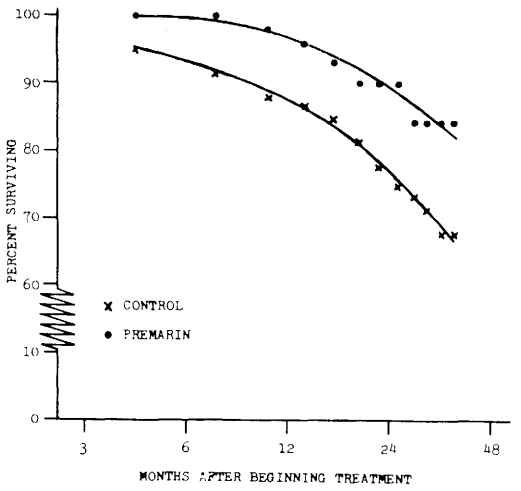

FIG. 1. Graphic representation of percentage survival rates shown in Table I.

15 months may continue or increase thereafter.

Discussion. This is the first demonstration, to our knowledge, of a significant effect of any medical agent on incidence of deaths due to arteriosclerotic heart disease in man. It is of interest that this result was obtained with a mixture of natural estrogens, presumably including a variety of female hormones and their metabolites, administered in doses that failed to cause objectionable evidences of feminization in men. Much of the data (1-10) suggesting that estrogens may be antiatherogenic is based on the epidemiology of coronary artery disease or on the experimental use of Premarin. Our findings are also in accord with the interim report of Stamler, Pick and Katz(13) who used comparatively large doses of Premarin. Our results with this mixture of natural estrogens fail to agree with the negative findings of Oliver and Boyd(12) who used considerable doses of the pure compound, ethinyl estradiol.

Since both Premarin and ethinyl estradiol in sufficient dosage are potent feminizing agents, since one affects survival while the other does not appear to do so, and since our survival effects were obtained with doses that caused only minor breast changes, it seems entirely possible that the beneficial effects of Premarin on survival may be mediated by constituents whose protective activity greatly exceeds their feminizing potency.

Conclusion. The incidence of deaths due to arteriosclerotic heart disease is being compared in men recovered from myocardial infarction and treated 75 days or more with either Premarin or no estrogen (control), allocation of treatments being randomized. Survival rate in those receiving Premarin is significantly higher than in controls.

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