The Lipid Research Clinics Coronary Primary Prevention Trial Results

II. The Relationship of Reduction in Incidence of Coronary Heart Disease to Cholesterol Lowering

Lipid Research Clinics Program

• In the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT), a 19% lower incidence of coronary heart disease (CHD) in cholestyramine-treated men was accompanied by mean falls of 8% and 12% in plasma total (TOTAL-C) and low-density lipoprotein (LDL-C) cholesterol levels relative to levels in placebo-treated men. When the cholestyramine treatment group was analyzed separately, a 19% reduction in CHD risk was also associated with each decrement of 8% in TOTAL-C or 11% in LDL-C levels ($P<.001$). Moreover, CHD incidence in men sustaining a fall of 25% in TOTAL-C or 35% in LDL-C levels, typical responses to the prescribed dosage (24 g/day) of cholestyramine resin, was half that of men who remained at pretreatment levels. Adherence to medication was associated with reduced incidence of CHD only when accompanied by falls in TOTAL-C and LDL-C levels. Small increases in high-density lipoprotein cholesterol levels, which accompanied cholestyramine treatment, independently accounted for a 2% reduction in CHD risk. Thus, the reduction of CHD incidence in the cholestyramine group seems to have been mediated chiefly by reduction of TOTAL-C and LDL-C levels.

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THE ASSOCIATION of total plasma cholesterol levels (TOTAL-C) with incidence of coronary heart disease (CHD) is well established.[1,2] The low-density lipoprotein cholesterol (LDL-C) subfraction is the main contributor to this relationship, while high-density lipoprotein cholesterol (HDL-C) levels are inversely related to CHD incidence.[3,4] Whether levels of very low-density lipoprotein cholesterol or triglyceride (TG) are independently related to CHD incidence is uncertain.[5]

Although TOTAL-C and LDL-C are potent risk factors for CHD, observational studies cannot prove that lowering these cholesterol levels by diet or drugs or both will reduce the subsequent incidence of CHD. The Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT),[6,7] the results of which are reported in part I,[8] was designed to test this hypothesis. In the LRC-CPPT, despite only a moderate difference in mean TOTAL-C and LDL-C levels between the two treatment groups, the incidence of CHD (defined as definite CHD death and/or definite nonfatal myocardial infarction[6,8]) was 19% lower among men assigned to active treatment ($P<.05$). Trends toward lower incidence of CHD in treated subjects have also been observed in many other randomized trials,[9-17] although no single one of these studies is convincing.[18-22]

In this article, the LRC-CPPT results are considered critically with respect to the quantitative impact of cholesterol lowering on CHD incidence. Specifically, the wide range of reductions in TOTAL-C and in LDL-C levels attained by persons treated with cholestyramine resin is used to relate the degree of cholesterol reduction to incidence of CHD. The relationship of changes in TG, HDL-C, and HDL-C/TOTAL-C levels to incidence of CHD is also examined. Such analyses, because they are not based on comparison of the randomly assigned treatment groups, may be influenced by extraneous factors related to adherence to medication. Nevertheless, these analyses may complement and illuminate the rigorous demonstration of treatment benefit presented in the accompanying article[8] by addressing the following specific questions: (1) Was CHD incidence within the cholestyramine group related to the degree of reduction in TOTAL-C and LDL-C levels? (2) Did differences in CHD incidence among men with differing degrees of cholesterol reduction arise from an underlying "dose-response" relationship or from self-selection? (3) Might cholestyramine resin also have modified CHD risk by its effect on HDL-C or TG levels? (4) Are the LRC-CPPT results internally consistent? (5) Are the LRC-CPPT results consistent with those of observational studies and other clinical trials of cholesterol lowering?

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METHODS

The Study Design

In the LRC-CPPT, the incidence of CHD (definite CHD death and/or definite nonfatal myocardial infarction) in hypercholesterolemic men treated with cholestyramine resin and diet was compared with that in similar men treated with placebo and diet. The trial, its participants, and its main findings are described elsewhere in detail.[6-8]

Estimation of Adherence to Medication

Cholestyramine resin was dispensed in sealed packets, each containing 4 g of the active medication. Placebo was dispensed in similar packets. Adherence to the prescribed dosage (six packets per day) was estimated from the number of packets returned by each participant at bimonthly visits (the packet count).[8]

Measurement of Plasma Lipid and Lipoprotein Levels

Fasting plasma levels of TOTAL-C, TG, and HDL-C were measured at each clinic on a bimonthly basis.[23] Posttreatment levels were expressed as percent changes (%Δ) from the participant's baseline (prediet) level.[8]

Missing Data

Complete bimonthly data were required for packet count, TOTAL-C, LDL-C, HDL-C, and TG for every participant up to the occurrence of a primary end point or the end of follow-up, whichever came first. Because of the occasional failure of participants to attend clinic, return unused packets of medication, or fast for 12 hours, as well as infrequent laboratory problems, this information was sometimes incomplete. Missing values of these variables were, therefore, imputed by methods described in the "Appendix". Because this imputation assumed that protracted absences from clinic implied nonadherence to medication and return to baseline lipid levels, the estimates of mean adherence, %ΔTOTAL-C, %ΔLDL-C, %ΔHDL-C, and %ΔTG reported herein are slightly smaller than those reported in the companion article, in which no imputation was done.[8]

Statistical Methods

Year-by-Year Descriptive Tabulation.—The 155 men in the cholestyramine group who had a primary CHD end point were subdivided into cohorts according to the year of follow-up that included their final scheduled clinic visit before their respective CHD events (see "Appendix"). The mean %ΔLDL-C for each cohort of cases was compared with that of men without a primary CHD end point for the concurrent and each prior follow-up year. For example, first-year cases were compared with noncases only in the first year of follow-up, while seventh-year cases were compared with noncases in each of the first seven years of follow-up. To control for potentially confounding baseline inequalities in CHD risk factors between cases and noncases, the mean %ΔLDL-C for each cohort was covariance adjusted[24] for baseline measures of LDL-C, HDL-C, TG, age, systolic blood pressure, cigarettes smoked daily, and exercise test outcome. Separate computations were performed for each follow-up year.

Proportional Hazards Models.—The proportional hazards model of Cox[25] was used to quantify the parameters relating changes in lipid levels to incidence of CHD within each treatment group. In this method, CHD events are first ordered by the time of occurrence during follow-up. At the time of each successive event, a pre-event characteristic of the CHD case (eg, his %ΔLDL-C) is compared with those of all men in his treatment group known to be free of CHD at the same follow-up time. A standard statistical package was used to fit each model.[26] Adjustment for pretreatment inequalities between men who did and did not have a CHD event was accomplished by including covariance terms for baseline measures of LDL-C, HDL-C, TG, age, systolic blood pressure, cigarettes smoked daily, and exercise test outcome in each model. Since it is unlikely that modifying plasma lipid levels alters CHD risk instantaneously, the models reported in this article were based on averages of %ΔTOTAL-C, %ΔLDL-C, etc, for the two years immediately preceding the CHD event. Similar models, based on averages taken over two months, six months, one year, three years, and five years, gave equivalent results and are not reported herein.

Computation of Percent Risk Reduction for Strata of %ΔLDL-C

To examine the dependence of CHD incidence on the two-year average of %ΔLDL-C without assuming a specific mathematical model, the risk of CHD within strata of %ΔLDL-C was estimated and compared with a common reference level of risk. These strata were based on the distribution for all participants in each treatment group of the two-year average of %ΔLDL-C, evaluated at visits selected at random, one per participant, such that sampling probability was uniform over follow-up time. The distributions were divided into 5% intervals of %ΔLDL-C; the tails of each distribution, defined so as to contain at least 100 men, were each considered as single strata. Cases were placed within these strata according to their %ΔLDL-C averaged over the two years preceding their CHD events. The estimated CHD risk for each %ΔLDL-C stratum (ie, the number of cases divided by the number of men in the stratum) was compared with that of a hypothetical man in the cholestyramine group who experienced no change in LDL-C level. This latter reference level of risk was estimated by multiplying the risk of CHD in the cholestyramine group as a whole (155/1,906) by $\exp(-\beta \times \overline{\%\Delta\text{LDL-C}})$, where β and $\overline{\%\Delta\text{LDL-C}}$ are the proportional hazards coefficient and mean value, respectively, for %ΔLDL-C in the cholestyramine group. Covariance adjustment for baseline measures of LDL-C, HDL-C, TG, age, systolic blood pressure, cigarettes smoked daily, and exercise test outcome was used to eliminate potentially confounding inequalities between CHD cases and other participants.

Comparison With the Results of Other Clinical Trials of Cholesterol Lowering

Since life-table-based statistics were not reported for all studies and individual follow-up times were not available, percent reduction of CHD incidence (CHD death and/or myocardial infarction) in the active treatment group was defined as $100\% \times (1-ad/bc)$, where a equals the number of incident CHD cases in the actively treated group, b equals the number of actively treated participants remaining free of CHD, c equals the number of incident CHD cases in the control group, and d equals the number of control participants remaining free of CHD. Treatment differentials in cholesterol levels were obtained by averaging annual mean levels in each treatment group over the years of follow-up. Since most studies did not measure lipoprotein levels, only TOTAL-C was considered. No correction was made for selection bias resulting from missing values of TOTAL-C for some participants. Methodological differences in cholesterol determination were also ignored.

RESULTS

Effect of Cholestyramine Resin on Plasma Lipid and Lipoprotein Levels

The response of plasma lipid and lipoprotein levels to treatment is summarized in Fig 1. The initial dietary intervention was associated in both groups with a 3.4% fall in TOTAL-C, a 3.8% fall in LDL-C, a 0.4% fall in HDL-C, and a 1% rise in TG levels as well as a 3.7% rise in HDL-C/TOTAL-C ratio. The introduction of cholestyramine resin was accompanied by additional falls of 14% in TOTAL-C and 21% in LDL-C levels during the first year of follow-

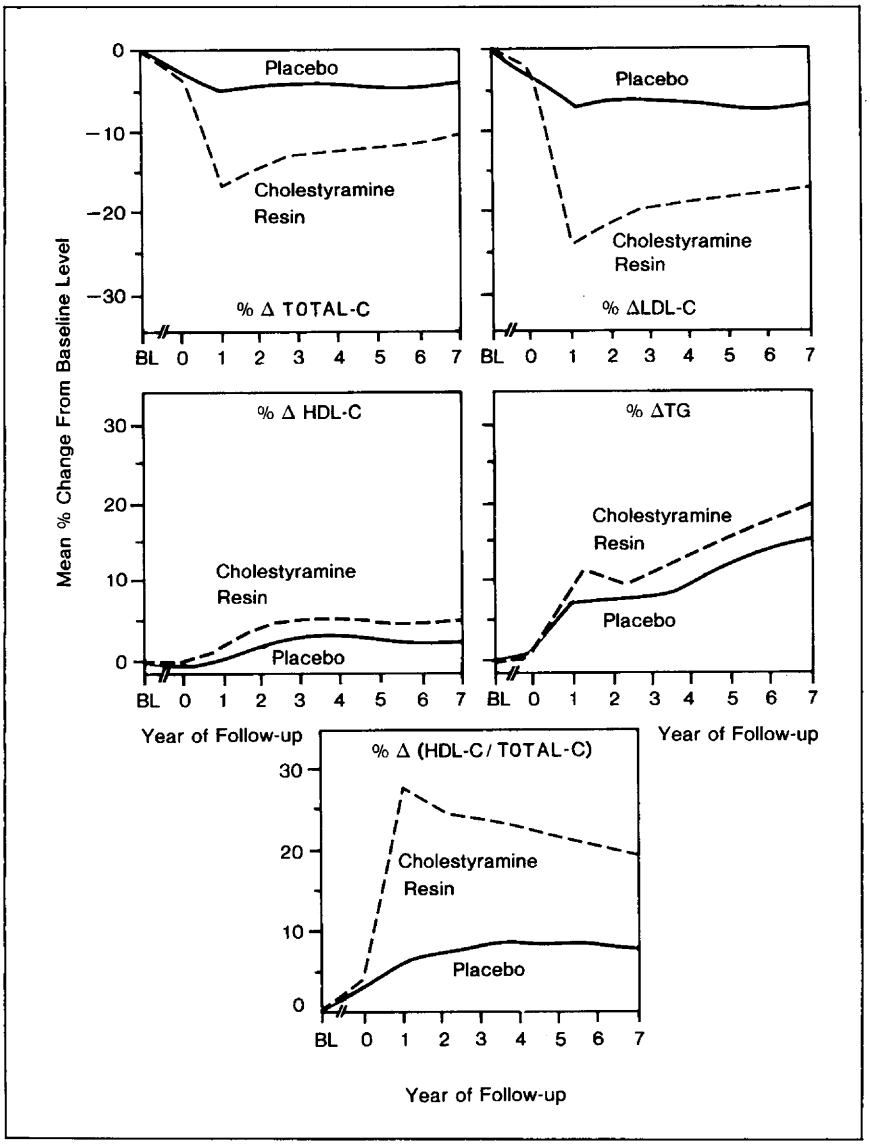

Fig 1.—Mean yearly plasma lipid levels for cholestyramine- and placebo-treated men. On abscissa, BL represents baseline (prediet) period and 0 years represents three-month interval between initiation of Lipid Research Clinics diet and study medication. Year 1 is average of visits 7 through 13, and each year thereafter represents average of six visits (see "Appendix"). Δ indicates change from baseline level; TOTAL-C, plasma total cholesterol levels; LDL-C, low-density lipoprotein cholesterol levels; TG, triglyceride levels; and HDL-C, high-density lipoprotein cholesterol.

up; slight falls were also observed in the placebo group during this year. Mean TOTAL-C and LDL-C levels rose slowly in the actively treated men in succeeding years, and the treatment differential gradually diminished to 6.5% in TOTAL-C and 9.6% in LDL-C by year 7. Mean HDL-C levels were consistently 3% higher in the cholestyramine group than in the placebo group (which also sustained a slight rise). Mean TG levels steadily increased over the course of the trial in both treatment groups and were consistently 2% to 4.5% higher in the cholestyramine group. A similar tendency of cholestyramine resin to raise TG levels has been reported by others.[27] Cholestyramine therapy accounted for a 21% increment in HDL-C/TOTAL-C ratio in the first year of treatment and a 12% increment in the seventh year of treatment. Except in the case of TG, the differences between treatment groups in each year of treatment were significant ($P<.001$). Significant ($P<.05$)-differences for TG were seen only for the first and fourth years.

Mean reported packet counts were relatively stable over the course of the trial. During the first year, the average daily packet count was 4.1 in the cholestyramine group and 4.7 in the placebo group; these values fell to 3.6 and 4.4 packets per day, respectively, in year 7. The relationships of plasma lipid changes to packet count, averaged over seven years, are displayed in Table 1. With the exception of HDL-C, there was a clear dose-response relationship of each lipid and lipoprotein change to reported intake of cholestyramine resin. However, the relationship of %ΔTOTAL-C and %ΔLDL-C to packet count was not constant throughout the study. Men who attended clinic during the first year of treatment and reported an intake of at least 20 g of cholestyramine resin (five packets) daily showed mean falls of 23% in TOTAL-C and 33% in LDL-C levels from their (prediet) baseline levels. The same reported packet count was accompanied on the average by only a 17% fall in TOTAL-C and a 26% fall in LDL-C levels in the seventh year. These trends may indicate either that the drug lost some efficacy over time or that the packet count provided a progressively less reliable measure of drug intake.

Relationship of Lipid Changes and Adherence to CHD Incidence

Descriptive Tabulation.—The cholestyramine and placebo groups differed by 8.2% in mean %ΔTOTAL-C and by 12.0% in mean %ΔLDL-C, averaged over the entire trial. However, many participants in the cholestyramine group, especially those who took five or more packets of medication daily, sustained levels of TOTAL-C and LDL-C at least 25% and 35% below their respective baseline levels, while many others who adhered less well had little or no change. This wide range of decreases in TOTAL-C and LDL-C levels within the cholestyramine group provided an opportunity to study the relation between the degree of cholesterol lowering and the incidence of CHD. Furthermore, analysis of the placebo group, which contained adherent and nonadherent participants who differed little from each other with respect to changes in TOTAL-C and LDL-C levels, made it possible to investigate whether self-selection influenced this relationship.

Since the mean reduction of TOTAL-C and LDL-C levels tended to diminish with time in the cholestyramine group (Fig 1), it was appro-

Table 1.—Dose-Response Relationships of Lipid Level Changes to Packet Count*

Mean Daily Packet Count	N	%ΔTOTAL-C†	%ΔLDL-C†	%ΔHDL-C†	$\%\Delta\left(\frac{\text{HDL-C}}{\text{TOTAL-C}}\right)$	%ΔTG†
Cholestyramine Resin						
0-1	294	−3.9	−6.6	+5.2	+10.8	+10.7
1-2	145	−5.4	−8.7	+2.3	+10.1	+12.7
2-3	135	−8.2	−13.1	+5.5	+17.2	+12.9
3-4	156	−11.1	−16.5	+6.0	+22.3	+14.2
4-5	205	−14.0	−20.9	+3.8	+23.5	+15.5
≥5	965	−19.0	−28.3	+4.3	+32.3	+17.1
Placebo						
0-1	133	−3.2	−4.8	+2.8	+7.5	+8.9
1-2	79	−1.7	−3.6	+5.4	+8.5	+7.9
2-3	88	−4.0	−6.9	+5.4	+11.3	+9.7
3-4	105	−3.5	−6.3	+3.8	+8.4	+9.0
4-5	214	−4.1	−6.0	+1.8	+7.2	+11.3
≥5	1,274	−5.4	−8.4	+1.2	+8.2	+11.7

*As calculated until the occurrence of (1) death, (2) definite myocardial infarction, or (3) the completion of the seventh year of follow-up. Only those clinic visits at which packet counts and plasma lipid measurements were obtained were included in the computation; there was no imputation of missing data. Six cholestyramine-treated and seven placebo-treated participants did not attend clinic after the first month of follow-up and were not included in this tabulation.

†Δ indicates change from baseline level; TOTAL-C, plasma total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; and TG, triglyceride.

Table 2.—Mean Percent Change in LDL-C in Cholestyramine Resin-Treated Men With and Without a Primary Coronary Heart Disease (CHD) End Point*

Year of Visit Before CHD Event†	No. of Men	Year of Follow-up 1	2	3	4	5	6	7	+8
No CHD event‡	1,751	−24.9	−21.0	−19.9	−18.9	−18.4	−17.9	−16.9	−15.8
Year 1	32	−26.6	...	...	...	...	...	...	...
Year 2	19	−22.7	−16.9	...	...	...	...	...	...
Year 3	14	−14.2	−13.4	−12.9	...	...	...	...	...
Year 4	21	−12.7	−11.3	−7.7	−7.1	...	...	...	...
Year 5	17	−21.8	−14.7	−15.0	−15.7	−12.2	...	...	...
Year 6	12	−27.2	−23.7	−22.1	−19.1	−18.3	−18.5	...	...
Year 7	25	−21.2	−18.5	−17.0	−15.5	−14.6	−14.1	−10.1	...
Year 8+	13	−19.8	−12.0	−10.9	−13.2	−12.4	−10.9	−10.0	−5.8

*Adjusted for low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol, triglyceride, age, systolic blood pressure, cigarette smoking, and exercise test outcome at baseline (see "Methods" section).

†Grouped according to follow-up year of final clinic visit before CHD event (see "Methods" section). Two men with primary CHD end points in the first month of follow-up are not included in the tabulation.

‡Men who had no primary CHD event during the trial. Their number diminished slightly in successive follow-up years because of non-CHD death; 1,728 survived to the seventh year. Although the minimum length of follow-up was seven years, 1,437 participants were followed up for longer periods; 13 had CHD events.

priate to compare participants in whom CHD developed only with others who were at risk *at the same point of follow-up.* In Table 2, the 155 cholestyramine-treated men who had a primary CHD end point at some point in the trial were subdivided into cohorts according to the follow-up time at which their end point occurred (see "Methods" section). Each row in the Table (except the first) represents one such cohort. The mean levels of %ΔLDL-C (adjusted for seven baseline CHD risk factors, see "Methods" section) for each cohort during each year of follow-up before their CHD event were then compared with the yearly averages of %ΔLDL-C for the cohort of men without a primary CHD end point. Note that, with the exception of the first-year and sixth-year cases, the CHD cases showed substantially smaller mean falls in LDL-C levels than did the men without CHD at every point of follow-up. By examining the diagonals of this table (upper left to lower right), one may note that these differences were often greatest during the one to two years immediately preceding each group of events. The absence of any effect for the first-year cases is not surprising, since one would not necessarily expect an immediate reduction of CHD risk when the LDL-C level is lowered. The similarity of the sixth-year cases to CHD-free men with respect to %ΔLDL-C may be due to chance, since there were only 12 cases in this group. A similar tabulation of %ΔTOTAL-C (not shown) gave essentially the same results. (This tabulation and similar ones for packet count and other lipids and lipoproteins in both treatment groups are available on request. All were consistent with the more concise analyses of two-year pre-event averages presented in the next section.)

Proportional Hazards Analysis.—To quantify more concisely how these variables are related to CHD and to assess more readily the statistical significance of these relationships, Cox proportional hazards models of two-year averages of packet count, %ΔTOTAL-C, %ΔLDL-C, %ΔHDL-C, %Δ(HDL-C/TOTAL-C), and %ΔTG were computed (Table 3). A positive regression coefficient implies that a decrease in the posttreatment variable is associated with lower CHD incidence; a negative coefficient implies an inverse relationship to CHD incidence. Adherence to cholestyramine resin but not to placebo, as measured by mean daily packet count, was associated with lower incidence of CHD. The relationships of decreases in TOTAL-C and LDL-C levels to reduction of CHD incidence in the cholestyramine group were both significant ($P<.001$). When terms for the two-year average of packet count and either %ΔTOTAL-C or %ΔLDL-C were included simultaneously in the same model, the term for either cholesterol change remained significant ($P<.001$) while the term for packet count was noncontributory ($P>.85$). Thus, there was no evidence for an effect of packet count on CHD incidence in the cholestyramine group other than that from the cholesterol-lowering effect of the drug.

The analysis also showed a relationship ($z=-1.81$) of increases in HDL-C levels to reduced incidence of CHD in the active drug group. When the coefficient for %ΔHDL-C was adjusted by including a term for %ΔLDL-C (or %ΔTOTAL-C) in the same model, neither coefficient changed appreciably. Thus, changes in LDL-C and HDL-C levels were related independently to incidence of CHD in the active drug group.

Reflecting the independent associations of %ΔHDL-C and %ΔTOTAL-C (or %ΔLDL-C) with CHD incidence, increases in HDL-C/TOTAL-C ratio were also strongly predictive of reduced incidence of CHD.

No association of lipid or lipoprotein changes with CHD was demonstrated in the placebo group. This result may reflect the inability of this type of analysis to detect an effect when changes in levels of TOTAL-C, LDL-C, etc, are not distributed over a sufficiently broad range. Although the regression coefficients for these variables in the placebo group were all smaller than their counterparts in the drug group, the differences between the corresponding drug and placebo coefficients were not statistically significant. Thus, there is insufficient evidence to demonstrate that %ΔLDL-C, for example, was related differently to CHD when it was produced by diet alone (placebo group) rather than the combination of diet and cholestyramine resin.

In Fig 2, the reduction in CHD risk estimated for strata based on 5% intervals of %ΔLDL-C (see "Methods" section) is compared with that predicted by the proportional hazards model. In view of the variability of the data points about the line representing the proportional hazards model in the cholestyramine group, the possibility of nonlinear (quadratic or cubic or both) effects was assessed; only the linear effect was significant. This finding tends to confirm the model's assumption of a log-linear relationship between CHD risk and %ΔLDL-C. In the range of %ΔLDL-C where sufficient data were available, similar reductions in CHD risk were observed in both treatment groups. However, since decreases of more than 25% in LDL-C levels were observed in only 3% of the placebo group (*v* 32% of the cholestyramine group), a linear trend is not readily demonstrable when the placebo group is considered alone. In the cholestyramine group, a 64% reduction in CHD risk was observed in the strata with decreases of more than 25% in LDL-C levels. The proportional hazards model for the cholestyramine group predicts a 49% reduction in CHD risk for a 35% decrease in LDL-C levels.

Application to Comparison of Treatment Groups

One may use the proportional hazards models to compare the observed 18.8% reduction in CHD incidence in the cholestyramine relative to the placebo group,[8] with the reduction one would expect based on the mean difference in TOTAL-C and LDL-C levels between the two treatment groups. In the models for the cholestyramine group, an 18.8% reduction in CHD incidence corresponds to a 7.9% decrease in TOTAL-C and a 10.8% decrease in LDL-C levels. The actual mean differences between the cholestyramine and placebo groups were 7.2% in TOTAL-C and 10.4% in LDL-C levels (based on two-year averages).

One may also use the proportional hazards models to analyze the separate contributions of changes in lipid levels and the lipoprotein cholesterol components to the observed treatment benefit (Table 4). The models for the cholestyramine group predict that the observed treatment differences of 7.2% in %ΔTOTAL-C and 10.4% in %ΔLDL-C should have brought about reductions of 17.1% and 18.1%, respectively, in CHD incidence in the cholestyramine *v* the placebo group. The 2.8% mean treatment difference in HDL-C levels, con-

Table 3.—Cox Proportional Hazards Models for Incidence of Coronary Heart Disease*

Postrandomization Variable	Cholestyramine Resin (155 Cases)		Placebo (187 Cases)	
	Regression Coefficient	*z* Score†	Regression Coefficient	*z* Score†
Mean daily packet count	−0.069	−1.79	−0.021	−0.53
ΔTOTAL-C‡	2.63	3.47	0.67	0.71
ΔLDL-C	1.92	3.37	0.70	0.93
ΔHDL-C	−1.15	−1.81	−0.25	−0.44
Δ(HDL-C/TOTAL-C)	−1.46	−3.64	−0.35	−0.78
ΔTG	0.14	0.63	0.06	0.24

*Each model contains a single postrandomization variable, averaged over the two years preceding each case's coronary heart disease event (see "Appendix"). Lipid changes (Δ) are expressed as proportions of baseline levels. Each model also contained terms for each of the following baseline covariates: low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), age, systolic blood pressure, cigarettes smoked daily, and exercise test outcome.

†The ratio of the regression coefficient and its SE. The one-sided and two-sided thresholds for statistical significance ($P<.05$) are $|z| \geq 1.65$ and 1.96, respectively.

‡TOTAL-C indicates plasma total cholesterol.

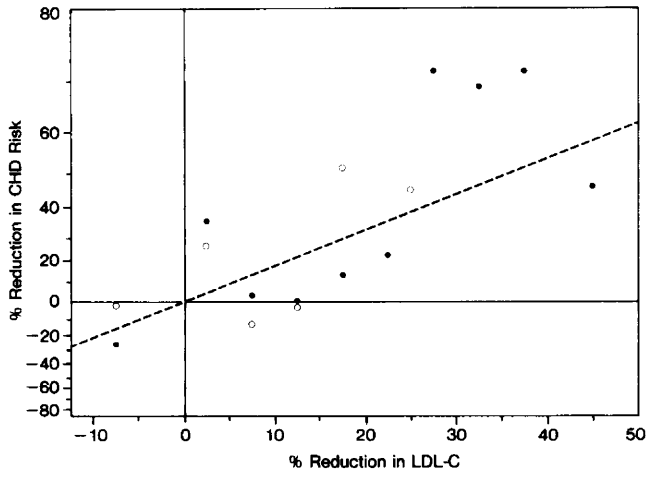

Fig 2.—Relationship of reduction in low-density lipoprotein cholesterol (LDL-C) levels to reduction in coronary heart disease (CHD) risk (logarithmic scale). Risk reduction was estimated by comparing distribution of percent change in LDL-C levels among CHD cases to that among all participants in same treatment group (see "Methods" section). Dashed line represents reduction in CHD risk predicted by proportional hazards model for given decrease in LDL-C level in cholestyramine group. Estimates of percent reduction in CHD risk for men in cholestyramine group (solid circles) and placebo (open circles) group with differing degrees of LDL-C level reduction are compared with this line. Each point (except those at either extreme) is plotted at center of 5% interval of percent change in LDL-C levels that it represents. Points for open-ended strata at extremes are plotted at their approximate median values of percent change in LDL-C levels.

Table 4.—Estimated Risk Reduction Predicted by Cox Proportional Hazards Models for Lipid Level Change

Model	Change From Baseline, %* Cholestyramine Resin	Change From Baseline, %* Placebo	Cox Regression Coefficient†	Estimated Risk Reduction, %
Single Response Variable				
%ΔTOTAL-C‡	−11.0	−3.8	2.63	17.1
%ΔLDL-C‡	−16.4	−6.0	1.92	18.1
%ΔHDL-C‡	+4.0	+1.2	−1.15	3.2
%ΔTG‡	+10.9	+8.8	0.14	−0.3
Combined Response Variable				
%Δ(HDL-C/TOTAL-C)	+20.1	+6.3	−1.46	18.2
%ΔHDL-C	+4.0	+1.2	−1.07	20.2
%ΔLDL-C	−16.4	−6.0	1.88	

*Means of two-year averages calculated at a single randomly selected visit for each participant.
†For cholestyramine group.
‡Δ indicates change from baseline level; TOTAL-C, plasma total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride.

sidered alone, could explain only a 3.2% reduction in CHD risk in the cholestyramine group. When one examines the incremental effect of changes in HDL-C levels (above that of changes in LDL-C levels) by simultaneously including terms for %ΔHDL-C and %ΔLDL-C in the same model (Table 4, %ΔHDL-C and %ΔLDL-C under "Combined Response Variables"), the estimated reduction in CHD risk is 2.1% greater than when %ΔLDL-C is considered alone. The observed 13.8% treatment difference of %Δ(HDL-C/TOTAL-C) accounted for an 18.2% reduction in CHD incidence, about the same as that accounted for by the 10.4% difference in %ΔLDL-C. The observed 2.1% increase in TG levels in the cholestyramine *v* the placebo group had no apparent effect on CHD incidence.

COMMENT

The most important finding in this report is the strong and consistent association between intake of cholestyramine resin, lowering of plasma total and LDL cholesterol levels, and reduction of CHD risk. These results extend those that were reported in the companion article[8] by indicating that the reduced incidence of CHD in the cholestyramine group was mediated chiefly by cholesterol lowering.

Influence of Self-selection

Although the LRC-CPPT was a randomized experiment, the results reported herein are based on comparisons of men with differing levels of adherence and response to treatment within the cholestyramine group. Because these levels were determined by the participant's behavior rather than the experimental design, these analyses could be vulnerable to the biases that may occur in any observational study. In the Coronary Drug Project, for example, a significant inverse relationship between mortality and adherence *to placebo* was reported.[28] This relationship, which the authors attributed to self-selection, was just as strong as that between mortality and adherence to an active drug (clofibrate) in their study.

Nevertheless, the relationship of changes in TOTAL-C and LDL-C levels to incidence of CHD among cholestyramine-treated men in the LRC-CPPT seems genuine for the following reasons.

1. No significant association was demonstrated between adherence to placebo and incidence of CHD.

2. When terms for packet count and %ΔTOTAL-C or %ΔLDL-C were included in the same proportional hazards model of CHD incidence, the coefficient for packet count was almost zero. This result implies that participants in the cholestyramine group who had high packet counts but little change in TOTAL-C or LDL-C levels had essentially the same incidence of CHD as those who did not take the drug at all.

3. All analyses were adjusted for baseline levels of the known major CHD risk factors. Thus, it is unlikely that the relationship reported herein could have arisen from differences in these risk factors between good and poor adherers that were present before treatment began.

4. These relationships are quantitatively consistent with the observed difference (18.8%) in incidence of CHD between randomized treatment groups, given the differences that were obtained in TOTAL-C and in LDL-C levels. This latter result cannot be attributed to selection bias, since it was derived by comparing the treatment groups *as initially, randomly assigned.*

Internal Consistency of LRC-CPPT Results

The internal consistency of the LRC-CPPT results is illustrated by considering three ways of estimating the reduction in CHD risk associated with a 22.3-mg/dL (10.4%) decrement in LDL-C levels, the mean treatment differential (based on two-year averages) actually attained in the LRC-CPPT (Table 5). (1) When the relationship of baseline LDL-C level to subsequent CHD was examined in the placebo group, a 22.3-mg/dL decrement predicted a 16.0% reduction in incidence of CHD. (2) Within the cholestyramine group, a 22.3-mg/dL fall in LDL-C level during treatment was associated with a 17.2% reduction in incidence of CHD. (3) A mean 22.3-mg/dL difference in %ΔLDL-C between the cholestyramine- and placebo-treatment groups was associated with an 18.8% difference in their incidence of CHD.

The consistency of these three distinct estimates is impressive.

External Consistency: Observational Studies

The quantitative estimate of the reduction in CHD incidence for a given decrement in baseline TOTAL-C levels in the LRC-CPPT placebo group is also consistent with the findings of observational studies of men in the same age range. In Table 6, the findings of the five component studies of the Pooling Project examined by the Framingham investigators[29] and of the Seven Countries Study[2] are compared with the LRC-CPPT placebo group. Six of the studies predict an 11% to 19% reduction in CHD incidence for a 20.7-mg/dL decrement in TOTAL-C levels, with the LRC-CPPT, at 15.1%, falling in the middle of this range. Only the results of the two smallest studies, the Chica-

Table 5.—Internal Consistency of Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) Results

LRC-CPPT Treatment Group	LDL-C* Determination	Study Design	Reduction in CHD* Incidence per 22.3 mg/dL Decrement in LDL-C Levels, %
Placebo	Baseline	Observational	16.0†
Cholestyramine resin	Change from baseline (two-year average)	Observational	17.2†
Both (cholestyramine resin *v* placebo)	Treatment difference (two-year average)	Experiment (comparison of randomized treatment groups)	18.8‡

*LDL-C indicates low-density lipoprotein cholesterol; CHD, coronary heart disease.

†Based on proportional hazards models containing terms for LDL-C, high-density lipoprotein cholesterol, triglyceride, age, systolic blood pressure, cigarette smoking, and exercise stress test outcome at baseline. The model for cholestyramine resin also contained a term for the two-year average of change (in milligrams per deciliter) of LDL-C from its baseline level.

‡Based on stratified life-table analysis.[8]

Table 6.—Multiple Logistic Coefficients* for a Single Determination of Total Cholesterol as Predictor of First Myocardial Infarction or Coronary Heart Disease (CHD) Death (Males)

Study	N	Mean Years of Follow-up	Age, yr	Mean TOTAL-C	Regression Coefficient	Reduction in CHD Incidence per 20.7-mg/dL Decrement in TOTAL-C, %†
Framingham[29]	1,089	11.5	40-54	226.5	0.0068	13.1
Albany[29]	1,675	9.9	40-54	229.1	0.0080	15.2
Chicago (Gas)[29]	934	9.7	40-54	237.5	0.0048	9.4
Chicago (Western Electric)[29]	1,806	8.5	40-54	247.7	0.0057	11.1
Tecumseh[29]	563	8.0	40-54	230.5	0.0197	33.5
US railroad (Seven Countries)[2]	2,404	5.0	40-59	239.3	0.009	17.0
Europe (Seven Countries)[2]	8,728	5.0	40-59	211.4	0.010	18.7
LRC-CPPT (placebo)	1,900	7.4	35-59	293.7	0.0079	15.1

*The coefficients of all eight studies were covariance adjusted for systolic blood pressure and cigarette smoking. Those for the Seven Countries populations were also adjusted for age and body mass index. The coefficient for the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) was based on a proportional hazards rather than a logistic model and was adjusted for age, high-density lipoprotein cholesterol, triglyceride, and exercise test outcome at baseline, as well as smoking and systolic blood pressure.

†The mean difference in plasma total cholesterol (TOTAL-C) levels (two-year average) between the LRC-CPPT cholestyramine and placebo group.

go Gas and Tecumseh studies, fall outside this range.

External Consistency: Other Clinical Trials

Many other trials of cholesterol lowering have been reported since the early 1960s.[9-17] It is difficult to compare or summarize their results because of differences in their design (eg, sample size and composition, primary *v* secondary prevention, treatment modality, assignment to treatment groups, end point, and length and completeness of follow-up) and in how they reported their findings. However, one can make a meaningful assessment of the consistency of the LRC-CPPT with other studies sharing at least the following features: (1) Subjects were assigned randomly to either an active treatment or control group. (2) Results for the combined end point CHD death and/or nonfatal myocardial infarction were reported. (3) Posttreatment mean TOTAL-C levels were reported. (4) The study protocol incorporated no co-intervention with respect to potential nonlipid CHD risk factors, such as smoking, blood pressure, exercise, and sex hormone levels. (5) At least 100 subjects were assigned to each treatment group. (6) The study was planned to last at least three years, so as to allow a reasonable time for the hypothesized benefit of lipid lowering to take effect. (7) The CHD status of all (or almost all) randomized subjects was known at the end of the study.

Some important studies that did not meet one or more of these criteria (given in parentheses for each study) and were therefore excluded from further analysis herein are the estrogen trials of Stamler et al[30] and the Coronary Drug Project[31,32] (No. 3 and 4), the Upjohn colestipol study[33] (No. 6 and 7), the Finnish Mental Hospital study[34] (No. 1), the nicotinic acid–clofibrate combined therapy report of Rosenhamer and Carlson[35] (No. 7), the Oslo study of diet and smoking cessation[36] (No. 4), the Multiple Risk Factor Intervention Trial[37] (No. 2 and 4), and the National Heart, Lung, and Blood Institute (NHLBI) Type II Coronary Intervention Study[38] (No. 2 and 5).

The studies (including the LRC-CPPT) that did meet all seven criteria are summarized in Table 7 (see "Methods" section). Note that eight were secondary prevention studies, while three were essentially primary prevention studies. Seven studies employed cholesterol-lowering drugs, while four used only diet. Two studies included a small proportion (~20%) of women among their participants;[11,12] the remainder were restricted to men. Most of these trials did not report a statistically "significant" treatment benefit with respect to their predefined primary end point. However, the calculated reductions in CHD incidence demonstrate beneficial trends in nine of the 11 studies.

The overall consistency of these studies with respect to the effect of TOTAL-C on incidence of CHD, despite their methodological differences, may be illustrated graphically[21] by adopting the approach of Peto (Fig 3). The results of eight of the 11 studies in Table 7 (including the LRC-CPPT) fit the regression line based on proportional hazards analysis of CHD incidence *within the LRC-CPPT cholestyramine group.* This regression line, in turn, agrees closely with Peto's regression lines, which project 15.3% (for diet) and 20.9% (for drug) reductions in CHD incidence per 10% decrement in TOTAL-C level. Only the dextrothyroxine arm of the Coronary Drug Project,[14] in which the adverse trend was attributed by the investigators to drug-specific cardiotoxic effects; the Newcastle clofibrate trial,[11] in which the incidence of CHD in the placebo group was unusually high; and the London Medical Research Council Low Fat Diet Study,[15] which because of small sample size

Table 7.—Randomized Trials of Cholesterol Lowering and Coronary Heart Disease (CHD)

Trial	Mode of Intervention	Years of Follow-up*	Treatment Group N	Treatment Group Mean TOTAL-C†	Treatment Group No. of CHD Cases‡	Control Group N	Control Group Mean TOTAL-C†	Control Group No. of CHD Cases‡	Reduction in CHD Incidence, %§
Primary prevention									
A. LRC-CPPT[9]‖	Cholestyramine resin	7	1,906	251	155	1,900	276	187	18.9
B. World Health Organization[9]	Clofibrate	5	5,331	224¶	167	5,296	244¶	208	20.9
C. Los Angeles Veterans Administration[10]#	Diet	8	424	195	52	422	226	65	23.2
Secondary prevention									
D. Newcastle[11]	Clofibrate	5	244	227	54	253	253	85	43.8
E. Edinburgh[12]	Clofibrate	6	350	227	59	367	263	79	26.1
F. Coronary Drug Project (CDP)—clofibrate[13]	Clofibrate	5	1,103	235	309	2,789	251	839	9.5
G. CDP—nicotinic acid[13]	Nicotinic acid	5	1,119	226	287	2,789	251	839	19.8
H. CDP—dextrothyroxine[14]	Dextrothyroxine	5	1,083	226	197	2,715	255	449	−12.2
I. London Medical Research Council (MRC) Low-Fat Diet[15]	Diet	3	123	219	46	129	240	48	−0.8
J. London MRC—soya bean oil[16]	Diet	4	199	224	45	194	258	51	18.1
K. Oslo Diet—heart[17]	Diet	5	206	240	61	206	284	81	35.1

*Length of follow-up specified in study design. Because of the finite time required for recruitment, not every surviving participant was followed up for the specified times. Study H was halted after approximately three years, two years before the planned termination, because of evidence that treatment may have had adverse effects. For studies I and J, mean follow-up time is listed since the authors did not state how long they initially intended to follow up their participants.

†Average of annual posttreatment levels for participants attending clinic. TOTAL-C indicates plasma total cholesterol.

‡Definite nonfatal myocardial infarction or CHD death.

§Obtained by subtracting the odds ratio from unity and multiplying by 100% (see "Methods" section).

‖LRC-CPPT indicates Lipid Research Clinics Coronary Primary Prevention Trial.

¶Adjusted to the Edinburgh laboratory by use of conversion factors published by investigators.[14]

#Since 7.1% of its subjects had a prior myocardial infarction, this was not a pure primary prevention trial.

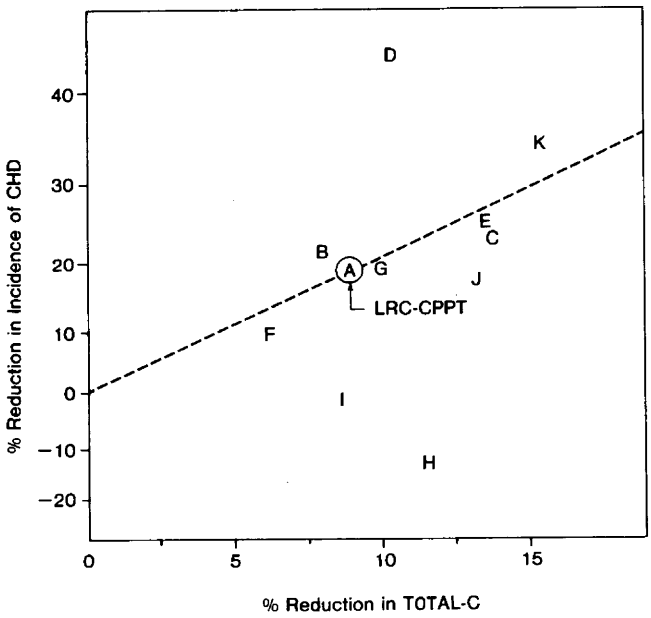

Fig 3.—Comparison of results of 11 cholesterol-lowering trials (indexed in Table 7) with experience of Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) cholestyramine group. Percent reduction in coronary heart disease (CHD) incidence (logarithmic scale) observed between actively treated and control group in each trial is plotted *v* mean difference in plasma total cholesterol (TOTAL-C) levels (expressed as percent of mean level for control group) resulting from treatment (see "Methods" section). Reduction in CHD incidence predicted by proportional hazards model for given decrease in TOTAL-C levels within LRC-CPPT cholestyramine group is indicated by dashed line. Slope of this line has been adjusted by factor 7.14/8.99 to compensate for imputation procedure used in computing two-year averages (see "Appendix"). Numerator and denominator of this adjustment factor are mean percent differences in TOTAL-C levels between LRC-CPPT treatment groups estimated with and without imputation, respectively.

and short follow-up time had little statistical power, were outliers. The observed difference in CHD incidence between the two LRC-CPPT treatment groups is in close accord both with the regression line derived for the cholestyramine group (internal consistency) and with the mainstream of the results of comparable studies (external consistency).

Changes in HDL-C and CHD Incidence

Increases in HDL-C levels among cholestyramine-treated participants were associated with an additional reduction of CHD risk beyond that arising from reduction in LDL-C levels. This result is qualitatively similar to the findings of the NHLBI Type II Coronary Intervention Study, a secondary prevention trial that used the same drug but a somewhat more rigid diet and a different outcome measure (angiographic assessment of change in coronary artery disease) and that also reported a treatment benefit.[38] Changes in HDL-C levels seemed to be responsible for a larger portion of the treatment benefit in

the latter study than in the LRC-CPPT, wherein the average treatment differential in HDL-C level was less than 3%. However, both studies found that the combination of changes in HDL-C and LDL-C levels, expressed as a ratio of HDL-C to TOTAL-C or LDL-C, was sufficient to explain the observed benefit of cholestyramine treatment.

Clinical Implications

Although the average CHD risk reduction observed in the LRC-CPPT may seem relatively modest, this reduction was attained with a mean treatment differential of only 8% in TOTAL-C and 12% in LDL-C levels. However, LDL-C levels typically fell by 35% in LRC-CPPT participants taking the prescribed 24 g of cholestyramine resin daily. If such a response were sustained, a 49% reduction of CHD incidence would be predicted (Fig 2). The inability of randomized long-term trials, especially those that were blinded, to maintain overall response at such levels over a period of years does not imply that this degree of cholesterol change cannot be maintained when a patient and his or her physician know posttreatment lipid levels and are able to modify treatment and dosage accordingly. The LRC-CPPT results and those of similar trials thus suggest that the risk of an initial CHD episode in hypercholesterolemic middle-aged men can be reduced by half with currently available appropriate cholesterol-lowering agents and diets.

CONCLUSIONS

The LRC-CPPT results give a clear and consistent picture of the relationship of its primary end point, CHD incidence, to changes in cholesterol levels. Whether one (1) examines baseline data prospectively, (2) relates posttreatment cholesterol change, or (3) compares the cholestyramine and placebo groups as randomly assigned, the result is the same: a decrement of 22.3 mg/dL (10.4%) in LDL-C levels is associated with a 16% to 19% reduction in CHD risk (internal consistency). The results of observational studies and other trials of cholesterol lowering, including those of secondary as well as primary prevention of CHD and those of diet as well as drugs, are consistent with this finding (external consistency). The predicted and observed CHD incidence in men maintaining a 25% fall in TOTAL-C or a 35% fall in LDL-C levels, responses often achieved by men taking 24 g of cholestyramine resin daily, was about half that of men with no cholesterol lowering. Thus, the benefit of effective cholesterol-lowering therapy in men with type II hyperlipoproteinemia with regard to incidence of CHD is of great potential clinical as well as statistical significance.

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APPENDIX

Computation of Posttreatment Averages of Packet Count and Lipid Level Change

Since this article deals specifically with the relation of treatment and its effects on plasma lipid levels to incidence of coronary heart disease (CHD), two issues that are commonly not considered systematically in the descriptions of adherence and lipid levels in most clinical trials required explicit attention: (1) the handling of missing data and (2) the definition of the time frame over which one considers these variables. The mechanisms that were devised to deal with these issues are described as follows.

Missing Data.—After successfully completing five pretreatment evaluations, Lipid Research Clinics Coronary Primary Prevention Trial participants were scheduled for clinic visits at two weeks (visit 6) and four weeks (visit 7) after randomization and at bimonthly intervals thereafter. For a typical bimonthly visit, 80% to 95% of participants attended, returned their unused packets of medication, and had valid plasma lipid measurements performed. Perhaps half of the men with incomplete or missing data for a given visit were chronic absentees who were known not to take the study medication. Others simply missed an occasional visit or forgot to return their unused medication while adhering at their customary level. A small number of participants, who moved some distance away from the nearest lipid research clinic but continued to participate in the study, attended clinic at annual or semiannual intervals. To accommodate these different situations as well as possible, missing packet count and lipid data were imputed as follows.

1. When a sequence of five or fewer missed visits or visits with missing values of a particular variable was followed by a visit in which a measurement of that variable was recorded, that measured value was imputed for the entire sequence of missing values.

2. When a sequence of six or more missed visits or visits with such missing values was followed by a visit with a recorded value, that recorded value was imputed for the last five visits in the sequence. The variable was affixed at its baseline level (zero for packet count) for all previous visits in the sequence.

3. Baseline values were imputed for all open-ended sequences of at least two missed visits. When only the final visit was missed, the value of each variable for the next-to-last visits was imputed.

Thus, packet counts and plasma lipid levels obtained after absences of less than one year were assumed to represent the entire interval since the last clinic visit attended, while longer absences were assumed to contain periods of nonadherence. When this imputation process was complete, every participant had an unbroken sequence of packet counts and plasma lipid and lipoprotein values representing two-month intervals until he died, suffered a myocardial infarction, or completed his close-out visit in mid-1983.

Computation of Averages Over Time.—Although each clinic visit was supposed to occur within a fixed range of follow-up times, visits occasionally were completed well outside their target intervals. Computational considerations required that each clinic visit be specified to occur at exactly the same follow-up time for each participant. The median time was used for each visit—31 days for visit 7, 92 days for visit 8, etc, increasing by 61-day increments for successive visits. This approximation occasionally led to minor incongruities, such as not using visit 8 data for a man who died on day 91 even if he completed visit 8 on day 87 of follow-up. Since the full dosage of medication often was not prescribed immediately, packet count and lipid data obtained at visit 6 (two weeks after randomization) were not used.

Three kinds of averages were computed in this article.

1. For descriptive purposes (Fig 1, Table 2), one-year blocks of data were averaged. The first follow-up year (which actually contained 13 months) consisted of visits 7 through 13; visit 7, which represented only a month of follow-up, was given half weight. All other years contained six equally weighted bimonthly visits. Data for the final (partial) year of follow-up for participants who were followed up for a nonintegral number of years were included in these presentations.

2. In Table 1, averages were computed over a variable length of follow-up beginning with visit 7. All visits in the defined interval were averaged, with visit 7 again given half weight.

3. Elsewhere in this article, averages representing a constant period, usually two years, measured backward in time from a defined point of follow-up, such as the occurrence of a CHD event, were computed. In this averaging process, the three months between the introduction of the lipid research clinic diet and randomization were represented by the average of visits 3 through 5. Prediet baseline levels (see "Methods" section) were used when it was necessary to extrapolate back further than visit 2. For example, a man with TOTAL-C equaling 300 mg/dL at visit 2, 280 mg/dL at visits 3 through 5, and 240 mg/dL at visits 7 through 10, would have a two-year average TOTAL-C= $\frac{240\times7+280\times3+300\times14}{24\text{ mo}}=280$ mg/dL at visit 10. Packet counts before randomization were, of course, affixed at zero.