The Lipid Research Clinics Coronary Primary Prevention Trial Results

I. Reduction in Incidence of Coronary Heart Disease

Lipid Research Clinics Program

• **The Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT), a multicenter, randomized, double-blind study, tested the efficacy of cholesterol lowering in reducing risk of coronary heart disease (CHD) in 3,806 asymptomatic middle-aged men with primary hypercholesterolemia (type II hyperlipoproteinemia). The treatment group received the bile acid sequestrant cholestyramine resin and the control group received a placebo for an average of 7.4 years. Both groups followed a moderate cholesterol-lowering diet. The cholestyramine group experienced average plasma total and low-density lipoprotein cholesterol (LDL-C) reductions of 13.4% and 20.3%, respectively, which were 8.5% and 12.6% greater reductions than those obtained in the placebo group. The cholestyramine group experienced a 19% reduction in risk ($P<.05$) of the primary end point—definite CHD death and/or definite nonfatal myocardial infarction—reflecting a 24% reduction in definite CHD death and a 19% reduction in nonfatal myocardial infarction. The cumulative seven-year incidence of the primary end point was 7% in the cholestyramine group *v* 8.6% in the placebo group. In addition, the incidence rates for new positive exercise tests, angina, and coronary bypass surgery were reduced by 25%, 20%, and 21%, respectively, in the cholestyramine group. The risk of death from all causes was only slightly and not significantly reduced in the cholestyramine group. The magnitude of this decrease (7%) was less than for CHD end points because of a greater number of violent and accidental deaths in the cholestyramine group. The LRC-CPPT findings show that reducing total cholesterol by lowering LDL-C levels can diminish the incidence of CHD morbidity and mortality in men at high risk for CHD because of raised LDL-C levels. This clinical trial provides strong evidence for a causal role for these lipids in the pathogenesis of CHD.**

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CORONARY heart disease (CHD) remains the major cause of death and disability in the United States and in other industrialized countries despite recent declines in CHD mortality rates. It accounts for more deaths annually than any other disease, including all forms of cancer combined.[1] Nationally, more than 1 million heart attacks occur each year and more than a half million people still die as a result. Coronary heart disease ranks first in terms of social security disability, second only to all forms of arthritis for limitation of activity and all forms of cancer combined for total hospital bed days. In direct health care costs, lost wages, and productivity, CHD costs the United States more than $60 billion a year.

This enormous toll has focused attention on the possible prevention of CHD by various means, especially through lowering of the plasma cholesterol level. Observational epidemiologic studies have established that the higher the plasma total or low-density lipoprotein cholesterol (LDL-C) level, the greater the risk that CHD will develop.[2] The view that LDL-C is intimately involved in atherogenesis, the basic pathophysiologic process responsible for most CHD, is sustained by reports from other epidemiologic studies as well as many animal experiments, pathological observations, clinical investigations, and metabolic ward studies.[3]

Plasma total and LDL-C levels may be reduced by diets and drugs. However, before such treatment can be advocated with confidence and before it can be concluded that cholesterol plays a causal role in the pathogenesis of CHD, it is desirable to show that reducing cholesterol levels safely reduces the risk of CHD in man. Many clinical trials of cholesterol lowering have been conducted, but their results, although often encouraging, have been inconclusive.

The most appropriate clinical trial of the efficacy of cholesterol lowering would be a dietary study, because of the links between diets high in saturated fat and cholesterol typical of most industrialized populations, high plasma total and LDL-C levels, and a

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high incidence of CHD. However, the 1971 National Heart and Lung Institute Task Force on Arteriosclerosis recommended against conducting a large-scale, national diet-heart trial in the general population because of concern regarding the blinding of such a study, the large sample size, and the prohibitive cost, then estimated to range from $500 million to more than $1 billion.[4] Accordingly, the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) was initiated in 1973 as an alternative test of the efficacy of reducing cholesterol levels. The choice of hypercholesterolemic men at high risk of CHD events developing reduced the necessary sample size to a feasible level; in this regard, women were not recruited because of their lower risk of CHD.

The use of the drug cholestyramine resin permitted a double-blind design. This drug, previously approved for general use by the Food and Drug Administration, was selected on account of its known effectiveness in reducing total cholesterol and LDL-C levels,[5] the availability of a suitable placebo, its nonabsorbability from the gastrointestinal (GI) tract, its few systemic effects, and its low level of significant toxicity.

Reported herein is the outcome of the study with respect to its major response variables, definite CHD death and/or definite nonfatal myocardial infarction, and related data.

PARTICIPANTS AND METHODS

The design of the LRC-CPPT has been described in detail.[6] Briefly, the LRC-CPPT was a double-blind, placebo-controlled clinical trial that tested the efficacy of lowering cholesterol levels for primary prevention of CHD. Twelve participating Lipid Research Clinics (LRCs) recruited 3,806 middle-aged men with primary hypercholesterolemia (type II hyperlipoproteinemia) free of, but at high risk for, CHD because of elevated LDL-C levels. The men were randomized into two groups that were similar in baseline characteristics. The treatment group received the bile acid sequestrant cholestyramine resin, and the control group received a placebo; both groups followed a moderate cholesterol-lowering diet. To ensure comparability of all data across the 12 clinics over a ten-year period, a common protocol documenting all procedures in detail was strictly adhered to by clinical personnel, who were trained and certified in standardized procedures.[7] All aspects of the conduct of the study were carefully monitored by the Central Patient Registry and Coordinating Center and by the Program Office. The progress of the trial and the possibility of serious side effects were reviewed twice a year by a Safety and Data Monitoring Board. Any protocol violations that were identified were brought to the attention of this board; none were regarded by them to put the trial into jeopardy.

Selection of Participants

The LRCs recruited men aged 35 to 59 years with a plasma cholesterol level of 265 mg/dL or greater (the 95th percentile for 1,364 men aged 40 to 49 years who participated in a previous LRC pilot study) and with an LDL-C level of 190 mg/dL or greater. Men with triglyceride levels averaging greater than 300 mg/dL or with type III hyperlipoproteinemia were excluded.

The numerous sources of the volunteer participants and the techniques of their recruitment have been described.[8,9] Of the approximately 480,000 age-eligible men screened between July 1973 and July 1976, 3,810 were eventually entered into the trial.[10] Four, two in each treatment group, were subsequently removed when they were found to have type III hyperlipoproteinemia, and the results reported are for the 3,806 type II participants. The participants were preponderantly college- or high school-educated whites. Their mean age was 47.8 years. Informed consent was obtained from each participant randomized into the study.

Participants were also excluded if they had any of the following clinical manifestations of CHD: (1) history of definite or suspect myocardial infarction; (2) angina pectoris, as determined by Rose Questionnaire; (3) angina pectoris during exercise electrocardiography; (4) various ECG abnormalities, according to the Minnesota code—left bundle-branch block, tertiary or secondary heart block, two or more consecutive ventricular premature beats, left ventricular hypertrophy, R-on-T-type ventricular premature beats, or atrial flutter or fibrillation; or (5) congestive heart failure. Men with a positive exercise test result in the absence of other manifestations of CHD were not excluded. Only men in good health and free of conditions associated with secondary hyperlipoproteinemia, such as diabetes mellitus, hypothyroidism, nephrotic syndrome, hepatic disease, hyperuricemia, and notable obesity, were selected. Men were excluded if they had hypertension or were receiving antihypertensive medication or had life-limiting or comorbid conditions such as cancer or nonatherosclerotic cardiovascular disease. Men who required long-term use of certain other medications were also excluded.

Screening (Prerandomization) Visits

The accrual phase consisted of four screening visits at monthly intervals. Physical examinations, lipid and lipoprotein level determinations, clinical chemistry measurements, medical history ascertainment, and resting and graded exercise ECGs were performed. At the second screening visit, a moderate cholesterol-lowering diet, which aimed to provide 400 mg of cholesterol per day and a polyunsaturated-to-saturated fat ratio of approximately 0.8 and which was designed to lower cholesterol levels 3% to 5%, was prescribed for all potential participants.[6]

A cholesterol-lowering diet was offered to potential participants because, when the LRC-CPPT began, it was the practice of many physicians to recommend such a diet to hypercholesterolemic patients. Although the cholesterol lowering expected from the diet given to both study groups had the potential to diminish the statistical power of the trial by reducing the subsequent incidence of CHD, it was hoped that such a diet, along with a nutritional counseling program, would facilitate recruitment of participants. Moreover, since the diet was introduced before randomization, it was possible to exclude men whose plasma cholesterol levels were highly sensitive to diet. Thus, men whose LDL-C levels fell below 175 mg/dL at the third or fourth screening visit were excluded. The maintenance of both treatment groups on the diet after randomization minimized the opportunity for confounding of the study because of differential dietary intakes. Dietary intake was assessed semiannually by means of a 24-hour dietary recall.[11]

Randomization

At the fifth visit to the clinic, eligible participants were randomly divided by the permuted block method into two treatment groups within eight prognostic strata at each of the 12 clinics. The strata were based on high and low risk of CHD with respect to LDL-C level ($\geq$ or $<$215 mg/dL), ST-segment depression during exercise testing, and a logistic risk function of age, cigarette smoking, and diastolic blood pressure.

Only five of 83 variables compared at baseline showed statistically significant differences (height, weight, and two-hour postchallenge glucose, SGOT, and albumin levels).[10] Because the observed differences were small and the number of statistically significant differences is that expected by chance in comparisons involving a large number of variables, the randomization and stratification process was found to produce two almost identical groups.

Study Medication

Participants were prescribed either the bile acid sequestrant cholestyramine resin at 24 g/day (six packets per day, divided into two to four equal doses) or an equivalent amount of placebo, dispensed in identical sealed packets. Those unable to tolerate six packets per day were prescribed a reduced dosage. Rigorous steps such as unique marking of individual packets and boxes and continuous external auditing of medications were followed to ensure proper drug-allocation assignment. Medication adherence was monitored by means of a packet count (packets issued minus packets returned, divided by the number of days elapsed since the packets were issued).

Postrandomization Visits

Participants attended clinics every two months, at which time the study medication was dispensed, dietary and drug counseling was given, and end points and possible drug side effects, as well as possible confounding variables such as blood pressure and weight, were evaluated. Intervention by LRC-CPPT staff was restricted to prescription of the study medication and the diet. At annual and/or semiannual visits, resting and graded exercise ECGs, 24-hour dietary recalls, and complete physical examinations and medical histories were obtained. All participants initially entered were followed up to the completion of the trial irrespective of their levels of adherence and the frequency of their visits.

Lipid Measurements

Lipid levels were determined with high precision and accuracy. Comparability of the measurements of the 12 LRC laboratories was ensured by a rigorous quality control program especially designed for the LRC Program and maintained by the Lipid Standardization Laboratory. The lipid levels at the second screening (prediet) visit were used as the baseline to calculate the changes in levels of total cholesterol and LDL-C and triglyceride observed at subsequent visits. Since the measurement of HDL-cholesterol (HDL-C) levels at the second screening visit was not performed according to protocol at several clinics, the levels at the first screening visit were used as the baseline to calculate change in HDL-C levels.

End Points

The primary end point for evaluating the treatment was the combination of definite CHD death and/or definite nonfatal myocardial infarction. Appendix A gives the detailed definitions of these events as well as the definition of suspect CHD death and suspect nonfatal myocardial infarction. Other end points included all-cause mortality, the development of an ischemic ECG response to exercise (positive exercise test result), angina pectoris as determined by Rose Questionnaire, atherothrombotic brain infarction, arterial peripheral vascular disease (intermittent claudication as determined by Rose Questionnaire), and transient cerebral ischemic attack. Detailed definitions of these nonprimary end points have been published elsewhere.[6]

The classification of cause of death was based on the examination of death certificates, hospital records, and interviews with physicians, witnesses of the death, and next of kin. The diagnosis of nonfatal myocardial infarction was based on ECGs, blood enzyme levels, and history of chest pain at the time of the clinical event. A physician at the clinic at which the potential end point occurred classified the end point. In addition, each potential end point was classified independently by two members of a blinded verification panel. If the three reviewers agreed, the diagnosis was accepted. If there was disagreement, the case was submitted for definitive classification to the LRC-CPPT Cardiovascular Endpoints Committee.[6] Classification of deaths not caused by CHD was also performed by a blinded panel.

An intraoperative event was classified on the basis of ECG changes occurring during coronary bypass surgery or other cardiac surgery or during the recovery period extending from the time of surgery until discharge from the hospital.

Statistical Methods

The hypothesis of the LRC-CPPT was that lowering cholesterol (or LDL-C) levels would reduce the incidence of end points, and, hence, a one-sided test was used for the main hypothesis. The statistic reported is a stratified (using the eight baseline risk strata) log rank (Mantel-Haenszel) statistic.[12] This statistic compares the life-table survival (or failure) curves in the two groups rather than the proportion of failures. In view of the necessity for periodic review, the data were analyzed many times, and conventional methods of computing statistical significance no longer applied. Several statistical methods were used to monitor the trial. These methods included a modification of the method of O'Brien and Fleming,[13] the two-dimensional rank statistic of Majundar and Sen,[14] and a modification of the method of Breslow and Haug.[15] All of these methods essentially gave the same result, and, in view of its ease of presentation, the modified O'Brien and Fleming method was used for this article. As formulated by O'Brien and Fleming, the data are analyzed k times after an equal number of end points. In practice, the data for this trial were analyzed at 15 equal time intervals, and strictly speaking, the method of determining the critical value proposed by O'Brien and Fleming does not hold. The distribution of the statistic taking into account the actual times when the analyses were conducted was determined by simulation and the critical z value for a one-sided test with $\alpha=0.05$ was found to be 1.87, as compared with the O'Brien-Fleming value of 1.83. The simulated critical value 1.87 is used in this report.

This method for determining significance was used for the primary end point of the study. Other statistical tests reported use the nominal level of significance. The reader is cautioned that interpretation of these nominal P values should include the possibility that some may be significant by chance because of the many comparisons made.

The Kaplan-Meier method was used for construction of the life-table plots.[12] The percentage reduction of end points is reported as $(1-RR)\times100$, where RR is the estimated relative risk of an event in the cholestyramine group, compared with the placebo group. For end points where time of occurrence could be obtained precisely, the relative risk was estimated from the life tables. Where the actual time of occurrence (eg, the onset of angina) could not be precisely determined, the relative risk was estimated from the 2×2 table defined by treatment and the occurrence of an end point. All relative risks were estimated, taking into account the baseline risk strata, unless otherwise noted.

To conform with the one-sided test of the main hypothesis, 90% confidence intervals for the estimated reduction in risk are reported. The Cox proportional hazards model[17] was used to adjust the treatment comparisons for other variables, such as blood pressure. Tests of interaction in the proportional hazards model were accomplished by including cross-product terms in the model.

Homogeneity of treatment effect over risk strata was assessed by an efficient scores test based on the proportional hazards model and included parameters for treatment and strata.[16] Homogeneity of effect over clinic was similarly assessed.

RESULTS

Follow-up

All men were followed up for a minimum of seven and up to ten years. The average period of follow-up was 7.4 years. Between May 15 and Aug 27, 1983, contact was made with all of the men who were still living, including any who discontinued visits during the course of the trial. Thus, the vital status is known for all men

Table 1.—Median Daily Dietary Intake

	Placebo				Cholestyramine Resin			
	Pre-entry		Postentry		Pre-entry		Postentry	
Dietary Variable	Prediet	On-Diet	1st Year	7th Year	Prediet	On-Diet	1st Year	7th Year
Total calories	2,264	2,023	2,056	2,060	2,278	2,027	2,058	2,086
Cholesterol, mg	309	248	255	284	308	243	251	288
Total fat, g	95	79	83	87	97	80	82	89
Saturated fat, g	33	24	26	28	34	24	26	29
P/S* ratio	0.48	0.73	0.69	0.67	0.47	0.72	0.67	0.66

*Ratio of polyunsaturated fats to saturated fats.

Table 2.—Mean Plasma Lipid and Lipoprotein Cholesterol Concentrations

	Placebo				Cholestyramine Resin			
	Pre-entry		Postentry		Pre-entry		Postentry	
Lipid	Prediet	On-Diet	1st Year	7th Year	Prediet	On-Diet	1st Year	7th Year
Total cholesterol, mg/dL	291.8	279.2	275.4	277.3	291.5	280.4	238.6	257.1
LDL* cholesterol, mg/dL	216.2	204.5	198.8	197.6	215.6	205.3	159.4	174.9
HDL* cholesterol, mg/dL	45.1	44.4	44.5	45.5	45.0	44.4	45.6	46.6
HDL cholesterol/total cholesterol	0.16	0.16	0.16	0.17	0.16	0.16	0.20	0.19
Triglycerides, mg/dL	158.4	153.2	162.0	173.5	159.8	156.3	172.2	182.9

*LDL indicates low-density lipoprotein; HDL, high-density lipoprotein.

originally entered into the study. In addition, every man or a close relative was questioned before and at the end of the study regarding previous hospitalizations for CHD or other reasons.

Adherence to Treatment

During the first year, the mean daily packet count for participants attending clinic was 4.2 in the cholestyramine and 4.9 in the placebo group, falling to 3.8 and 4.6, respectively, by the seventh year. Adherence to the diet as determined by a 24-hour dietary recall conducted at six-month intervals showed no important differences between the two treatment groups (Table 1). A rise of 2 kg in body weight occurred in each group during the seven years of the study.

Maintenance of Blind

No cases of medical emergency required the unblinding of participants or staff and no one asked to be told his treatment assignment.

Lipids and Lipoproteins

When the LRC-CPPT diet was introduced, total cholesterol levels fell 11.1 ± 0.65 (mean $\pm$ SE) mg/dL in the cholestyramine group and 12.6 ± 0.67 mg/dL in the placebo group (Table 2). Corresponding falls of 10.3 ± 0.61 and 11.7 ± 0.63 mg/dL occurred in LDL-C levels. During the first year of follow-up, there were additional falls of 41.8 ± 0.81 mg/dL and 45.9 ± 0.82 mg/dL in total and LDL-C levels in the cholestyramine group and 3.8 ± 0.51 mg/dL and 5.7 ± 0.48 mg/dL in the placebo group. By seven years, the total and LDL-C levels had fallen, from the pre-entry postdiet levels, 23.3 ± 0.99 mg/dL and 30.4 ± 0.99 mg/dL in the cholestyramine group and 1.9 ± 0.75 mg/dL and 6.9 ± 0.70 mg/dL in the placebo group. Almost all of the change in total cholesterol was in the LDL-C fraction. During treatment, the cholestyramine group experienced average plasma total cholesterol and LDL-C reductions of 13.4% and 20.3%, respectively, which were 8.5% and 12.6% greater ($P<.001$) than those obtained in the placebo group. (It should be noted that these percentage changes were computed for each individual and then averaged.) There was a 1.6 ± 0.19-mg/dL increase in HDL-C levels and a larger increase in triglyceride levels attributable to cholestyramine therapy. There also was a rise in triglyceride levels in the placebo group, although not as great as in the cholestyramine group. Additional details are provided in the companion article.[17]

Primary End Point

The cholestyramine group experienced 155 definite CHD deaths and/or definite nonfatal myocardial infarctions, whereas the placebo group had 187 such events (Table 3). When the stratified log rank test was used to take into account the stratification of participants at entry and their differing lengths of follow-up, the incidence rate of CHD was estimated to be 19% lower in the cholestyramine than in the placebo group. The z score for this difference was 1.92 with $P<.05$, after adjustment for multiple looks at the data. Both the fatal and nonfatal categories of the primary end points showed corresponding reductions. Thirty CHD deaths occurred in the cholestyramine group as compared with 38 CHD deaths in the placebo group, representing a reduction in risk of 24%. The cholestyramine group experienced 130 definite nonfatal myocardial infarctions, compared with 158 in the placebo group, with a 19% reduction in risk. The inclusion of the categories of suspect CHD death and suspect nonfatal myocardial infarction resulted in an overall reduction in risk of 15%, with a 30% reduction for fatal events and a 15% reduction for nonfatal events. The z score for this comparison exceeded the nominal 5% threshold (1.65) for statistical significance and

Table 3.—Definite or Suspect Primary End Points and All-Cause Mortality

End Point	Placebo (N=1,900) No.	Placebo (N=1,900) %	Cholestyramine Resin (N=1,906) No.	Cholestyramine Resin (N=1,906) %	% Reduction in Risk*	90% Confidence Interval for % Reduction in Risk		z Score
Definite coronary heart disease (CHD) death and/or definite nonfatal myocardial infarction	187†	9.8	155†	8.1	19	+3	+32	1.92‡
Definite CHD death	38	2.0	30	1.6	24	. . .	. . .	. . .
Definite nonfatal myocardial infarction	158	8.3	130	6.8	19	. . .	. . .	. . .
Definite or suspect CHD death or nonfatal myocardial infarction	256†	13.5	222†	11.6	15	+1	+27	1.80
Definite or suspect CHD death	44	2.3	32	1.7	30	. . .	. . .	. . .
Definite or suspect nonfatal myocardial infarction	225	11.8	195	10.2	15	. . .	. . .	. . .
All-cause mortality	71	3.7	68	3.6	7	−23	+30	0.42

*Percent reduction in risk is defined as $(1-RR)\times 100\%$, where RR is the incidence rate ratio of an event in the cholestyramine group compared with the placebo. Percent reduction in risk and z score are adjusted for follow-up time and stratification.

†A subject experiencing a myocardial infarction and CHD death is counted once in this category. Hence, this line is not the sum of the following two lines.

‡The .05-level, one-sided critical value of the z score adjusted for multiple looks at the data is 1.87.

was close to the modified O'Brien-Fleming threshold of 1.87 (see "Participants and Methods" section). Thus, the conclusion that treatment was beneficial is not essentially altered by the inclusion of suspect events. The separate category of intraoperative myocardial infarction (Table 4) also showed more cases in the placebo group (7 *v* 5), although the difference is not statistically significant. (One of the four type III participants excluded after the randomization experienced a nonfatal myocardial infarction; he was in the placebo group.)

Table 4.—Other Cardiovascular Events*

End Point	Placebo (N=1,900) No.	Placebo (N=1,900) %	Cholestyramine Resin (N=1,906) No.	Cholestyramine Resin (N=1,906) %	% Reduction in Risk
Coronary disease					
Positive exercise test	345	19.8†	260	14.9†	25‡
Angina (Rose Questionnaire)	287	15.1†	235	12.4†	20‡
Coronary bypass surgery	112	5.9	93	4.9	21‡
Congestive heart failure	11	0.6	8	0.4	28
Intraoperative myocardial infarction	7	0.4	5	0.3	29
Resuscitated coronary collapse	5	0.3	3	0.2	40
Cerebrovascular disease					
Definite or suspect transient cerebral ischemic attack	22	1.2	18	0.9	18
Definite or suspect atherothrombotic brain infarction	14	0.7	17	0.9	−21
Peripheral vascular disease					
Intermittent claudication (Rose Questionnaire)	84	4.4†	72	3.8†	15‡

*Counts all events for each individual, including events occurring after a nonfatal myocardial infarction.

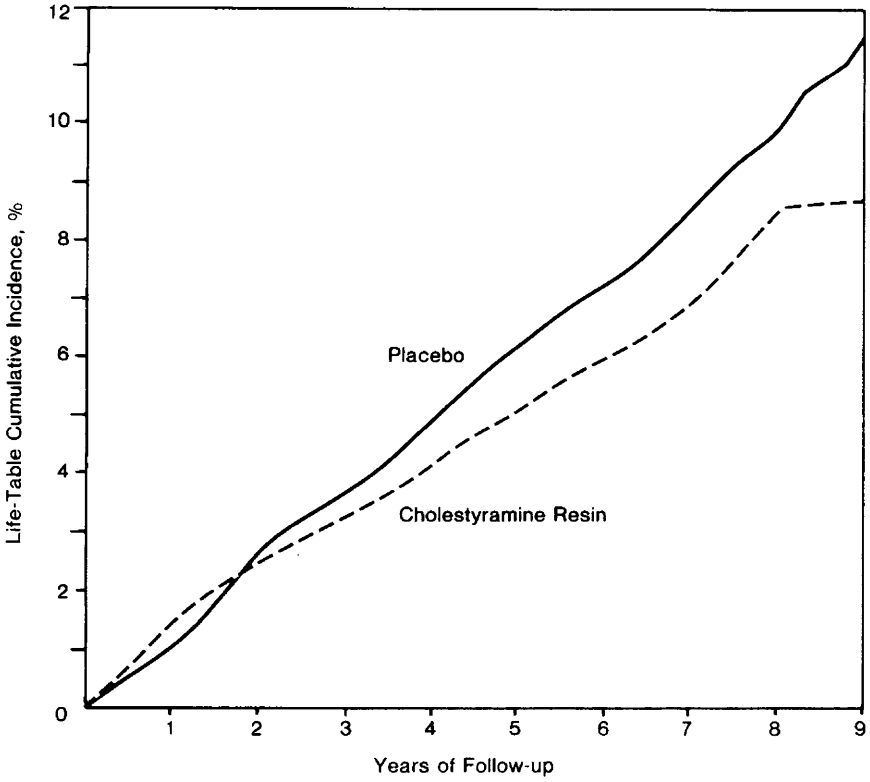
†Percent of those without condition at baseline.

‡Percent reduction in risk is adjusted for stratification.

The life-table failure rates in the two groups are plotted in the Figure. Very early in the follow-up period, the number of CHD events was higher in the cholestyramine group, but by two years the two curves were identical. Thereafter, there was a steady divergence of the two sets of event rates, and at seven years of follow-up the event rate was 8.6% in the placebo group and 7.0% in the cholestyramine group, a reduction of 19%.

The primary end points were examined within the risk strata defined at randomization. The hypothesis of homogeneity of effect across these strata was not rejected. Thus, although differences were observed in the estimated relative risk among the strata, there was insufficient statistical evidence to claim that the treatment was more beneficial in one stratum than in another. The cholestyramine-treated group at seven clinics had at least 18% fewer primary end points than placebo-treated men. At four clinics there was essentially no treatment difference; only one clinic showed an excess of events in the drug group. The statistical hypothesis of homogeneity of effect among clinics also was not rejected; thus, the benefit of cholestyramine resin treatment cannot be attributed to effects in only a small number of clinics.

This stratified analysis provided an estimate of treatment benefit adjusted for baseline strata of what were considered to be the most important CHD risk factors when the study began. Adjustment for a more extensive list of baseline characteristics, including LDL-C, HDL-C, triglyceride, age, cigarette smoking, and systolic blood pressure, each considered as a continuous variable, as well as exercise test outcome, was performed by Cox proportional hazards analysis. The adjusted estimates of treatment effect (20.0% risk reduction) and z score (2.05) were slightly greater than those obtained in the stratified analysis. There was no significant interaction of the treatment effect with any of the seven baseline characteristics. Thus, the proportional hazards and stratified analyses both indicate that it is highly unlikely that the treatment benefit could have arisen from inequality of the two treatment groups with respect to CHD risk at baseline or from a par-



N=3,806 3,753 3,701 3,659 3,615 3,564 3,520 3,466 1,816 302

Life-table cumulative incidence of primary end point (definite coronary heart disease death and/or definite nonfatal myocardial infarction) in treatment groups, computed by Kaplan-Meier method. N equals total number of Lipid Research Clinics Coronary Primary Prevention Trial participants at risk for their first primary end point, followed at each time point.

ticular subgroup of LRC-CPPT participants.

Other Cardiovascular End Points

The frequency of other cardiovascular end points in the two treatment groups is reported in Table 4. Each of the CHD categories having a large number of events showed a reduction in incidence similar to the 19% reduction in the primary end point. Thus, the cholestyramine group showed reductions of 20% ($P<.01$) in the incidence of the development of angina ascertained by the Rose Questionnaire, 25% ($P<.001$) in the development of a new positive exercise test result, and 21% ($P=.06$) in incidence of coronary bypass surgery. The two cerebrovascular disease categories did not provide a consistent or significant pattern of benefit, but the numbers were small. For peripheral vascular disease there was a 15% ($P>.1$) reduction in new intermittent claudication in the cholestyramine group. None of the other differences in Table 4 were statistically significant, possibly because of the small numbers.

All-Cause Mortality

Although the incidence of definite and of definite and suspect CHD death was reduced by 24% and 30%, respectively, in the cholestyramine group, that of all-cause mortality was reduced by only 7% (Table 3), reflecting an increase in deaths not caused by CHD. Table 5, patterned after a similar table reported in the World Health Organization Clofibrate Trial,[18] breaks down the all-cause mortality into major categories. None of the differences are statistically significant. More details are provided in Appendix B. The only noteworthy difference ($P=.08$) was 11 deaths from accidents and violence in the cholestyramine group, compared with four in the placebo group. Of these, five in the cholestyramine and two in the placebo group were homicides or suicides, and six in the cholestyramine and two in the placebo group were accidents, mainly automobile. Each of the other major categories, including malignant neoplasms, differed only by one or two cases.

The possibility that a CHD event could have been the underlying cause of a violent or accidental death was examined. All of these deaths had been evaluated by the Cardiovascular Endpoints Committee without knowledge of treatment group, and none had met the study criteria of a CHD death. Furthermore, none had any clinical evidence suggestive of myocardial ischemia. Subsequent to the conclusion of the study, all of these deaths were carefully scrutinized for the possibility of a CHD event. Seven were due to homicide or suicide, and in none of these was there any reason to doubt the diagnosis. Autopsy information was available for seven of the eight accidental deaths; seven of these deaths were due to automobile or motorcycle accidents. None showed evidence of new coronary thrombosis or acute myocardial infarction. Half had high blood alcohol levels. In four, this information and the circumstances of death made it virtually certain that CHD was not an underlying cause of death. In the other four, although the circumstances of death did not completely rule it out, a CHD episode was regarded as highly unlikely.

Possible Confounders

The results described previously show that the cholestyramine-treated group had a reduced rate of CHD. If during the course of the LRC-CPPT there were changes in CHD risk factors other than total cholesterol or LDL-C levels that were not the same in the two groups, this could pose an alternative explanation of the observed treatment benefit. Table 6 gives the pre-entry, first-year, and seventh-year mean values for selected variables that include the major known risk factors for CHD. For all of these major risk factors, the change from baseline was similar in the two groups, and, thus, they do not explain the treatment benefit. In addition, very similar percentages of participants in both groups (eg, placebo, 37%, *v* cholestyramine, 38%, at year 7) reported taking at least one aspirin in the previous week. Slightly more placebo- than cholestyramine-treated participants reported the use of β-blockers at the end of the trial.

Side Effects and Toxicity

Many possible side effects to treatment were monitored throughout the

Table 5.—Deaths in the Lipid Research Clinics Coronary Primary Prevention Trial

Cause of Death	Placebo	Cholestyramine Resin
Coronary heart disease (CHD)	44	32
Other vascular	3	5
Malignant neoplasm	15	16
Other medical causes	5	4
Accidents and violence	4	11
Total, all causes other than CHD	**27**	**36**
All causes other than CHD, other vascular, and accidents and violence	20	20
Total, all causes	**71**	**68**

Table 6.—Selected Variables Before and During Treatment

	Placebo			Cholestyramine Resin		
Variable	Pre-entry	1st Year	7th Year	Pre-entry	1st Year	7th Year
Mean systolic blood pressure, mm Hg	121	120	122	121	120	122
Mean diastolic blood pressure, mm Hg	80	79	78	80	78	78
Mean Quetelet index, g/sq cm	2.6	2.6	2.7	2.6	2.6	2.7
Mean weight, kg	81	81	83	80	80	82
% current smokers	37	35	26	38	36	27
Mean cigarettes per day for current smokers	25	24	25	26	25	26
% regular exercisers	30	...*	27	31	...*	28
Median alcohol consumption, g/wk	61	58	51	64	57	53

*No assessment of exercise was done in the first year.

trial. There were no noteworthy differences in non-GI side effects between the groups. Gastrointestinal side effects occurred frequently in the placebo- and cholestyramine-treated participants, especially the latter (Table 7). In the first year, 68% of the cholestyramine group experienced at least one GI side effect, compared with 43% of the placebo group. These diminished in frequency so that by the seventh year, approximately equal percentages of cholestyramine and placebo participants (29% *v* 26%) were so affected. Constipation and heartburn, especially, were more frequent in the cholestyramine group, which also reported more abdominal pain, belching or bloating, gas, and nausea. The side effects were usually not severe and could be dealt with by standard clinical means.

Little or no differences were seen between the two treatment groups for most of the clinical chemical tests monitored during the study (Appendix C). During the first year, serum alkaline phosphatase levels, iron binding capacity, SGOT levels, and the WBC count were higher in the cholestyramine group, while carotene and uric acid levels were lower (Table 8). These differences were generally less apparent by the seventh year; none was associated with clinically apparent disease.

The number of participants hospitalized for conditions other than CHD was monitored. The hospitalizations were classified, using the H-ICDA code, eighth revision,[19] according to the primary diagnosis on the hospital discharge form. In particular, hospitalizations for GI tract disease were monitored (Appendix D). Of the many categories, the only difference with nominal statistical significance, using a test of comparison of proportions, was the primary diagnosis of deviated nasal septum, with more (16 *v* 6) cases in the cholestyramine group. Similar monitoring of all noncardiac operations or procedures was conducted. The only significant difference was a greater number in the cholestyramine group (40 *v* 23) of operations or procedures involving the nervous system. This excess mainly reflected more operations or procedures in the cholestyramine group for spinal disease (23 *v* 10), especially lumbar (19 *v* 9), and for decompression of the carpal tunnel (7 *v* 1).

Diagnoses and procedures involving the gallbladder were scrutinized in view of the ability of certain lipid-lowering drugs to produce gallstones and gallbladder disease. A few more hospitalized participants in the cholestyramine group had, as their main diagnosis, gallstones (16 *v* 11) and more cholestyramine-treated participants had an operation involving the gallbladder (36 *v* 25), but the differences were not significant. Gallstones, not necessarily as the main diagnosis, were reported in the cholestyramine group slightly more frequently than in the placebo group (31 *v* 30), as were other gallbladder and biliary tract diseases (28 *v* 23). No death attributable to gallbladder disease was recorded.

Appendix E indicates that the numbers of incident and fatal cases of malignant neoplasms were similar in the two groups: 57 incident cases in the placebo group, of which 15 were fatal; and 57 incident cases in the cholestyramine group, of which 16 were fatal. The cholestyramine group had a few more malignant neoplasms in some categories (eg, buccal cavity and pharynx) and less in others (eg, respiratory system) than the placebo group, but the numbers were small. When the various categories of GI tract cancers (buccal cavity-pharynx, esophagus, stomach, colon, rectum, and pancreas) were considered together, there were 11 incident cases and one fatal case in the placebo group and 21 incident and eight fatal cases in the cholestyramine group. The total number of incident colon cancers was identical.

COMMENT

Previous Trials of Cholesterol Lowering

The LRC-CPPT demonstrated that treatment with cholestyramine resin reduced the incidence of CHD. This result is in agreement with those of previous clinical trials of cholesterol lowering, which have shown a general trend of efficacy for selected CHD end points. However, the earlier trials have not been regarded as conclusive because of such factors as inadequate sample size, absence of a double-blind, failure to achieve identical treatment groups, inadequate cholesterol lowering, or questionable statis-

Table 7.—Percent of Participants Reporting Moderate or Severe Side Effects

Side Effect	Placebo			Cholestyramine Resin		
	Pre-entry	1st Year	7th Year	Pre-entry	1st Year	7th Year
Abdominal pain	5	11	7	5	15	7
Belching or bloating	10	16	6	10	27	9
Constipation	3	10	4	4	39	8
Diarrhea	6	11	8	5	10	4
Gas	22	26	12	22	32	12
Heartburn	10	10	7	10	27	12
Nausea	4	8	4	3	16	3
Vomiting	2	5	3	2	6	2
At least 1 gastrointestinal side effect	34	43	26	34	68	29

Table 8.—Mean Laboratory Values Influenced by Cholestyramine Resin

Laboratory Value	Placebo			Cholestyramine Resin		
	Pre-entry	1st Year	7th Year	Pre-entry	1st Year	7th Year
Alkaline phosphatase, IU/L of serum	71	70	71	71	82	74
Carotene, μg/dL of serum	150	146	149	149	111	132
Iron-binding capacity, μg/dL of serum	355	355	324	357	371	334
SGOT, units/L of serum	30	31	35	30	34	36
Uric acid, mg/dL of serum	6.3	6.1	6.3	6.2	5.8	6.1
WBC count, per cu mm	6,205	6,178	6,043	6,327	6,443	6,299

tical procedures.[20,21]

Several major primary prevention trials of diet have reported encouraging, although not always significant, reductions in CHD incidence. They include the New York Anti-Coronary Club Study,[22] the Los Angeles Veterans Administration Study,[23] and the Finnish Mental Hospital Study.[24] The interpretation of the results of these studies, as well as secondary prevention studies using diet, is clouded by the ascertainment bias that may result from a nonblinded design. Because of this and other shortcomings, these trials have also been regarded as inconclusive.[21] Primary prevention of CHD by diet has been evaluated during concurrent reduction of other CHD risk factors. A 47% lower CHD incidence was observed in the hypercholesterolemic participants in the Oslo Study who were treated with a cholesterol-lowering diet and counseled to reduce their cigarette smoking.[25] The investigators attributed most of the lower CHD incidence to the cholesterol reduction. The Multiple Risk Factor Intervention Trial (MRFIT) achieved too small an overall difference (2%) between the cholesterol levels of its two treatment groups to assess the effect of cholesterol lowering.[26]

One major primary prevention trial of a lipid-lowering drug has been reported: the WHO Clofibrate Study obtained a 9% fall in serum cholesterol levels and a significant 20% reduction in the overall incidence of major ischemic heart disease events, similar in magnitude to the LRC-CPPT findings.[18] However, unlike the LRC-CPPT, this decline was confined to nonfatal myocardial infarction, whereas the incidence of fatal heart attack was similar in both treatment and control groups. Of concern in this study was the increased incidence in all-cause mortality in the clofibrate group, which became more significant during a four-year posttrial follow-up.[18,27]

The Coronary Drug Project (CDP) was a major secondary prevention trial of several lipid-lowering drugs. Three of its groups (high-dose estrogen, low-dose estrogen, and d-thyroxine) had to be discontinued prematurely because of evidence of toxicity.[28-30] The nicotinic acid group, in which a 9.9% fall in cholesterol levels occurred, showed a 27% lower incidence of nonfatal myocardial infarction but little difference in fatal CHD.[31] The clofibrate group, in which a 6.5% reduction in cholesterol levels occurred, had a 9% lower incidence of fatal and nonfatal CHD, but statistical significance was not attained.[31] Two trials of clofibrate, the Newcastle Study[32] and the Scottish Society of Physicians Study,[33] had previously reported a suggestion of benefit, especially in subjects with pre-existing angina, but the post hoc use of subgroups and discordance in placebo group events has led to questioning of the conclusions from these two studies.[34]

The results of these various studies of lipid-lowering drugs for the prevention of CHD indicate that even though some evidence of reduction of CHD has attended their use, noteworthy and sometimes serious toxicity has occurred for each drug.

Side Effects and Clinical Chemistry Analyses

The use of cholestyramine resin resulted in several GI side effects, although these were also common in the placebo group. They were most evident in the initial stages of the study and could usually be handled by symptom-specific treatment, but sometimes they were the basis for cessation of, or reduction in, the drug dose. These side effects, which have been previously noted for cholestyramine resin, reflect the properties of a drug that is not metabolized in, or absorbed from, the GI tract. The monitoring of hospitalizations showed that the two treatment groups were similar for almost all of the large number of primary diagnoses and procedures. Of special interest is the absence of a significant increase in gallstones or cholecystectomy. This contrasts with clofibrate, which, unlike cholestyramine resin, is known to alter the lithogenicity of bile and has been associated in the WHO and CDP trials with an increased incidence of gallbladder disease.[18,31] The results of a systematic radiological study for gallstones in participants at two LRCs before and after the LRC-CPPT will be published.

A greater incidence of respiratory system hospitalizations and of operations and procedures on the nervous system was observed in the cholestyramine group. However, examination of the individual diagnoses or proce-

dures within these categories failed to reveal any disorder for which there was a plausible explanation of an effect that could be attributed to cholestyramine resin. In view of the more than 60 diagnoses and procedures assessed, the two categories in which significant differences were found may represent chance occurrences.

Cholestyramine treatment altered results of several clinical chemistry studies, especially alkaline phosphatase, SGOT, and carotene. Such changes have been previously reported for cholestyramine use and, as in the present study, have not been associated with clinical disease.[5]

Malignant Neoplasms

The total incidence of fatal and nonfatal malignant neoplasms was similar in both treatment groups. When the many different categories are examined, various GI tract cancers were somewhat more prevalent in the cholestyramine group. Other cancers (eg, lung and prostate) were more frequent in the placebo group. The small numbers and the multiple categories prevent conclusions being drawn. However, in view of the fact that cholestyramine resin is confined to the GI tract and not absorbed and of animal experiments in which cholestyramine resin has been found to be a promoter of colon cancer when a cancer-inducing agent was also fed orally,[35] further follow-up of the LRC-CPPT participants is planned for cause-specific mortality and cancer morbidity.

CHD End Points

The LRC-CPPT shows that treatment with cholestyramine resin results in a significantly lower incidence of CHD as measured by the primary end point of the study. The benefit of treatment was not concentrated in any one subgroup or in a few clinics but was widespread. Inspection of the life-table curves shows that benefit became apparent two years after initial treatment. This benefit was reflected in both categories of primary end points. The findings were not essentially altered when the men classified as having a "suspect" primary event were added to the definite CHD category, nor were they altered by the inclusion of the small number of intraoperative events in the primary end-point category. The possibility was considered that some deaths attributed to violence or accidents were precipitated by a CHD event, especially since more of them occurred in the cholestyramine group. As described, an extensive review of autopsy and clinical evidence was convincing that it was extremely unlikely that an underlying CHD event had occurred in any of the accidental or violent deaths.

The evidence of reduction of CHD incidence is further strongly supported by the analysis of other CHD end points for which a sufficient number occurred. Other studies have reported that angina and a positive exercise test result identify subjects at increased risk for CHD. In the LRC-CPPT, angina at entry was an exclusion. A positive exercise test result at entry, in the absence of chest pain, was a significant independent predictor of a subsequent primary end point, using proportional hazards analysis (to be published). Thus, the development of angina or new positive exercise test results, although not primary study end points, seem to be valid indicators of CHD risk status. Incident cases of the development of angina or of a new positive exercise test result were substantially lower by 20% and 25%, respectively, in the cholestyramine group. A corresponding 21% reduction was observed in the number of participants progressing to coronary bypass surgery. Also of interest is the 15% reduction in intermittent claudication.

All-Cause Mortality

There was only a 7% reduction of all-cause mortality in the cholestyramine group, reflecting a larger number of violent and accidental deaths. Several other primary prevention trials have reported higher noncardiovascular mortality in their active treatment groups, resulting from a variety of medical causes.[36] Excess mortality in the LRC-CPPT cholestyramine group was confined to violent and accidental deaths. Since no plausible connection could be established between cholestyramine treatment and violent or accidental death, it is difficult to conclude that this could be anything but a chance occurrence.

Confounding

The lower incidence in CHD events seen in the cholestyramine group does not seem to be attributable to changes in CHD risk factors other than cholesterol. The use of randomization and stratification procedures produced two treatment groups that, at entry, were similar with respect to all the major CHD risk factors, other minor or possible risk factors, and a variety of other measurements. The levels of CHD risk factors such as cigarette smoking, systolic and diastolic blood pressure, body weight, and reported levels of physical activity continued to be similar throughout the study. Both groups reported similar nutrient intakes and alcohol consumption.

Maintenance of Double-Blind

Many steps were taken to ensure that neither participants nor clinic staff knew to which treatment group participants had been assigned.[7] No need arose during the study to identify a participant's treatment group to him or to clinical staff. The higher incidence of GI effects in the cholestyramine group, mainly in the first year, made it possible that some loss of the double-blind might have occurred, although the high prevalence of such side effects in the placebo group makes this less likely. A survey at the end of the study showed that approximately equal numbers of participants (cholestyramine group, 56.0% *v* placebo group, 54.6%) or clinic staff (cholestyramine group, 55.2% *v* placebo group, 52.9%) could correctly identify treatment assignments.

Implementation of Study Design

The extent to which the LRC-CPPT was able to implement its original design objectives[6] is noteworthy (Table 9). The study exceeded its original sample size goal of 3,550 and successfully randomized 3,806 participants into two similar treatment groups. Participants were followed up for an average of 7.4 years. Consistent with the initial study parameters, a 4.8% reduction in plasma total cholesterol levels attributed to diet was obtained in the placebo group. In the seventh year, men taking cholestyramine resin maintained a mean plasma total

cholesterol level reduction of 13.9%, attributable to the combination of drug and diet. Thus, the additional reduction in cholesterol levels attributable to cholestyramine resin was only 9.1%, well below the desired 24%. Although the 27% of participants who were taking no drug by seven years was lower than the predicted 35%, a number of participants were not taking the full dose of six packets. Difficulties in adherence related to the bulk, texture, and side effects of the drug seem to explain much of the shortfall in cholesterol lowering. It can be effectively argued that additional deterrents to taking the drug were the participants' lack of knowledge, for seven to ten years, as to which treatment group they were in as well as of their cholesterol levels during treatment. Better cholesterol lowering with cholestyramine resin could be expected when it is used in a routine clinical context. In addition, knowledge that treatment with cholestyramine resin prevents CHD can be expected to motivate adherence.

The seven-year incidence of the combined primary end points in the LRC-CPPT placebo group, 8.6%, was almost identical to the 8.7% predicted in the original study design based on data derived from the Framingham Study.[37] However, the actual incidence of definite CHD death was well below the predicted rate, whereas the rate of definite nonfatal myocardial infarction was increased above the predicted rate. A lower-than-predicted CHD death rate has been a feature of several clinical trials, including the recent MRFIT study.[26] Possible explanations include the stringent selection processes employed, resulting in an atypically healthier study population, better health monitoring and management during the course of the study, and the concurrent national decline in CHD mortality.

Implications of the LRC-CPPT

Caution should be exercised before extrapolating the CPPT findings to cholesterol-lowering drugs other than bile acid sequestrants. It has been shown that bile acid sequestration leads to a substantial reduction in plasma total and LDL-C levels by increasing the removal of LDL from the blood through increased activity of specific cell-surface LDL receptors.[38] This mode of action is conceptually attractive inasmuch as it represents the enhancement of a physiological mechanism for the control of LDL levels. The mode of action, cholesterol-lowering potency, and possible toxicity of other cholesterol-lowering drugs must be taken into account before their use is advocated for the prevention of CHD.

The LRC-CPPT was not designed to assess directly whether cholesterol lowering by diet prevents CHD. Nevertheless, its findings, taken in conjunction with the large volume of evidence relating diet, plasma cholesterol levels, and CHD, support the view that cholesterol lowering by diet also would be beneficial. The findings of the LRC-CPPT take on additional significance if it is acknowledged that it is unlikely that a conclusive study of dietary-induced cholesterol lowering for the prevention of CHD can be designed or implemented.

The consistency of the reductions in CHD manifestations observed with cholestyramine resin in this controlled trial, which extend from the softer end points of angina, a positive exercise test result, and coronary bypass surgery to the hard end points of nonfatal myocardial infarction and CHD death, leaves little doubt of the benefit of cholestyramine therapy. These results could be narrowly interpreted to apply only to the use of bile acid sequestrants in middle-aged men with cholesterol levels above 265 mg/dL (perhaps 1 to 2 million Americans). The trial's implications, however, could and should be extended to other age groups and women and, since cholesterol levels and CHD risk are continuous variables, to others with more modest elevations of cholesterol levels. The benefits that could be expected from cholestyramine treatment are considerable. In the LRC-CPPT, treatment was associated with an average cholesterol fall of 8.5% beyond diet, and an average 19% reduction in CHD risk. Moreover, a companion article[17] that looks at cholesterol reduction and CHD more closely indicates that a 49% reduction in CHD incidence would be predicted for subjects who obtained a 25% fall in plasma cholesterol levels or a 35% fall in LDL-C levels, which are typical responses to 24 g of cholestyramine resin daily.

Table 9.—Comparison of LRC-CPPT* Design Goals and Actual Experience

Design Feature	Goal	Experience
Sample size	3,550	3,806†
Duration of follow-up, yr	7	7-10
Lost to follow-up	0	0
Reduction of plasma total cholesterol levels in placebo group	4%	4.8%
Nonadherers‡ at yr 7	35%	27%
Reduction of plasma total cholesterol levels in men adhering‡ to cholestyramine resin treatment	28%	13.9%§
7-yr incidence of primary end point in placebo group	8.7%	8.6%
Reduction in primary end point	36%	19%

*LRC-CPPT indicates Lipid Research Clinics Coronary Primary Prevention Trial.
†After removal of four type III participants.
‡A nonadherer is someone averaging less than half a packet of cholestyramine resin per day.
§Computed for seventh year.

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Appendix A.—Definition of Primary End Points

Primary End Points

I. Definite atherosclerotic coronary heart disease death—either or both of the following categories:
   - A. Death certificate with consistent underlying or immediate cause plus either of the following:
     1. Preterminal hospitalization with definite or suspect myocardial infarction (see below).
     2. Previous definite angina or suspect or definite myocardial infarction when no cause other than atherosclerotic coronary heart disease could be ascribed as the cause of death.
   - B. Sudden and unexpected death (requires all three characteristics):
     1. Deaths occurring within one hour after the onset of severe symptoms or having last been seen without them.
     2. No known nonatherosclerotic acute or chronic process or event that could have been potentially lethal.
     3. An "unexpected" death occurs only in a person who is not confined to his home, hospital, or other institution because of illness within 24 hours before death.

II. Criteria for definite nonfatal myocardial infarction—any one or more of the following categories using the stated definitions:
   - A. Diagnostic ECG at the time of the event.
   - B. Ischemic cardiac pain and diagnostic enzymes.
   - C. Ischemic cardiac pain and equivocal enzymes and equivocal ECG.
   - D. A routine Lipid Research Clinics ECG is diagnostic for myocardial infarction while the previous one was not.

III. Suspect atherosclerotic coronary heart disease death—one or both of the following categories:
   - A. Death certificate with consistent underlying or immediate cause but neither adequate preterminal documentation of the event nor previous atherosclerotic coronary heart disease diagnosis.
   - B. Rapid and unexpected death (requires all three characteristics):
     1. Death occurring between one and 24 hours after the onset of severe symptoms or having last been seen without them.
     2. No known nonatherosclerotic acute or chronic process or event that could have been potentially lethal.
     3. An "unexpected death" occurs only in a person who is not confined to his home, hospital, or other institution because of illness within 24 hours before death.

IV. Suspect myocardial infarction—any one or more of the following categories using the stated definitions:
   - A. Ischemic cardiac pain.
   - B. Diagnostic enzymes.
   - C. Equivocal ECG and equivocal enzymes.
   - D. Equivocal ECG alone, provided that it is not based on ST or T-wave changes only.

(Continued on page 363.)

Appendix A.—Definition of Primary End Points (cont)

Glossary

I. Ischemic cardiac pain—severe substernal pain having a deep or visceral quality and lasting for half an hour or more.

II. ECG (classified by Minnesota Code)[39]

A. Diagnostic—either of the following must be present:

1. Unequivocal Q or QS pattern (code 1-1).
2. Q or QS pattern (codes 1-2-1 to 1-2-7), plus any T-wave item (codes 5-1 to 5-3).

Only the first criterion applies in the presence of ventricular conduction defects.

B. Equivocal—any of the following must be present:

1. Q or QS pattern (codes 1-2-1 to 1-2-7).
2. ST junction and segment depression (codes 4-1 to 4-3).
3. T-wave item (codes 5-1 to 5-2).
4. Left bundle-branch block (code 7-1).

III. Enzymes

A. Diagnostic enzymes—all of the following conditions:

1. Creatine kinase, SGOT, or lactic dehydrogenase values determined coexistent with the event.
2. The upper limit of normal for the local laboratory is recorded.
3. The determined value for one or more enzymes is at least twice the upper limit of the local laboratory but does not exceed 15 times that value.

B. Equivocal enzymes—all of the following conditions:

1. Creatine kinase, SGOT, or lactic dehydrogenase values determined coexistent with the event.
2. The upper limit of normal for the local laboratory is recorded.
3. The determined value for one or more enzymes is elevated but does not fulfill criteria for diagnostic enzymes.

Appendix B.—Deaths Not Attributed to Coronary Heart Disease

Cause of Death	Placebo	Cholestyramine Resin
Cardiovascular (non-coronary heart disease)	3	5
Cerebrovascular	2	2
Peripheral vascular with gangrene	0	1
Surgical complications*	1	2
Malignant neoplasm†	15	16
Other illnesses	5	4
Infectious diseases‡	3	2
Chronic obstructive pulmonary disease	1	1
Alcoholism	1	1
Trauma	4	11
Accidents	2	6
Homicide	0	1
Suicide	2	4
Total	27	36

*One placebo participant died while undergoing cardiac catheterization. Two cholestyramine resin participants died of complications ensuing from mitral valve replacement and from carotid endarterectomy.

†Listed by site in Appendix E.

‡Three deaths (two in the placebo group) caused by pneumonia, one placebo death caused by staphylococcal septicemia, and one cholestyramine resin death resulting from an undetermined infectious cause.

Appendix C.—Mean Laboratory Values Not Influenced by Cholestyramine Resin

Laboratory Value	Placebo			Cholestyramine Resin		
	Pre-entry	1st Year	7th Year	Pre-entry	1st Year	7th Year
Albumin, g/dL of serum	4.3	4.2	4.2	4.3	4.2	4.2
Bilirubin, direct, mg/dL of serum	0.04	0.04	0.04	0.04	0.05	0.04
Bilirubin, total, mg/dL of serum	0.52	0.52	0.61	0.52	0.54	0.62
Calcium, mEq/L of serum	4.8	4.8	4.7	4.9	4.8	4.6
Chloride, mEq/L of serum	103	104	103	103	105	103
Creatinine, mg/dL of serum	1.03	1.02	0.98	1.03	1.01	0.98
Globulin, g/dL of serum	2.9	3.0	3.0	2.9	3.0	3.0
Glucose, mg/dL of serum	98	96	101	98	94	100
Hematocrit, %	46	45	45	46	45	45
Iron, μg/dL of serum	114	113	103	113	114	103
Phosphorus, mg/dL of serum	3.1	3.0	3.0	3.1	3.0	3.0
Potassium, mEq/L of serum	4.5	4.5	4.4	4.5	4.5	4.4
Sodium, mEq/L of serum	140	141	141	140	140	141
Thyroxine, μg of T_4-I/dL of serum	4.1	4.0	4.3	4.1	4.1	4.3
Total protein, g/dL of serum	7.2	7.2	7.3	7.2	7.2	7.3
Vitamin A, IU/dL of serum	228	234	267	229	236	270

Appendix D.—Hospitalizations With a Primary Diagnosis* of Gastrointestinal Tract Disease

Primary Diagnosis†	Placebo	Cholestyramine Resin
Intestinal infectious diseases	13	9
Neoplasm		
Benign	11	12
Malignant	11	15
Unspecified	0	1
Diseases of esophagus	5	6
Ulcer	20	30
Gastritis	5	12
Functional and other disorders of stomach	3	0
Appendicitis	4	11
Hernia	100	97
Intestinal obstruction	5	4
Enteritis and colitis	2	1
Diverticular disease of intestine	9	10
Anal fissure and fistula	9	5
Abscess of anal and rectal region	5	5
Peritonitis	0	1
Functional and other diseases of intestine	3	6
Liver disease	2	3
Gallstones	11	16
Other gallbladder and biliary tract disease	19	22
Pancreas	0	3
Hemorrhoids	27	29
Signs, symptoms, and ill-defined conditions	23	16

*Participants are counted only once within each category.
†By H-ICDA code, eighth revision, 1973.

Appendix E.—Incident Malignant Neoplasms

Primary Site	Placebo (N=1,900)		Cholestyramine Resin (N=1,906)	
	All Cases	Deaths*	All Cases	Deaths*
Buccal cavity-pharynx	0	0	6	0
Esophagus	1	0	2	2
Stomach	2	1	0	0
Colon	6	0	6	2
Rectum	2	0	4	1
Pancreas	0	0	3	3
Larynx	3	0	1	0
Lung	10	8	6	3
Leiomyosarcoma	1	1	0	0
Melanoma	5	1	0	0
Other skin	5	0	3	0
Prostate	11	1	7	1
Urinary bladder	3	0	7	0
Kidney	1	0	2	0
Brain	1	1	3	3
Thyroid	1	1	0	0
Thymus	0	0	1	0
Lymphatic tissue	1	0	4	1
Hematopoietic tissue	3	1	2	0
Unknown	1	0	1	0
Total	57	15	57†	16

*Four men with malignant neoplasms (two in each treatment group) died of nonneoplastic causes. They are counted among the incident cases but not among the deaths in this Table.
†One cholestyramine group participant, who survived to the end of the study, had both a prostate carcinoma and a lymphoma; he is counted only once in the total.