THE LINK BETWEEN HYPERLIPIDEMIA AND CORONARY ARTERY DISEASE

David T Nash

600 East Genesee Street
SYRACUSE, N.Y.13

St Joseph's Hospital
Syracuse, New York
University Hospital
Syracuse, New York

David T. Nash, M.D.,
Clinical Professor of Medicine

The link between coronary artery disease and cholesterol was first suggested by Ignatowski, a Russian investigator who demonstrated that he could produce atherosclerosis-like lesions in the rabbit by feeding these vegetarians milk, meat, and eggs. This diet produced plaques in the arterial wall of the rabbits. Since then a series of animals have demonstrated similar changes. In a way, by converting the diet of these animals to a diet similar to that of affluent Americans, investigators have shown that there is a price to be paid for living "high" on the fat and protein of animal products.

A large body of evidence links elevated blood cholesterol levels with coronary artery disease. The evidence comes from a broad variety of investigations. For example, genetic evidence. Children born with homozygous Type II hypercholesterolemia will regularly develop severe coronary artery disease in childhood, even if every other risk factor such as smoking and hypertension is absent.

Other types of evidence include pathologic and epidemiologic studies. The data establish that there is a close relationship between elevated levels of blood cholesterol, particularly of LDL, and the risk of development of premature coronary atherosclerosis.

Recent studies have demonstrated the beneficial aspects of reducing serum cholesterol levels in the prevention of coronary heart disease. (1) Although dietary management is a key element to the reduction of elevated levels of serum cholesterol, the usual tactic of restricting saturated fat and cholesterol intake is usually only modestly effective. In part, this reflects on the limited willingness of many to reduce their intake of animal products, and in part it reflects less than enthusiasm on the part of the medical profession.

The adverse effect of elevated serum lipid levels is also apparent when one examines the relationship of risk factors to the development of atherosclerosis in saphenous vein grafts studied ten years after saphenous vein bypass. (2) These authors examined 82 patients ten years after saphenous vein bypass grafts, and they learned that only 50 of 132 grafts were unaffected after ten years. New lesions developed in 67 of the 82 patients. The levels of VLDL and LDL were higher in those demonstrating progression. Analysis showed that the levels of cholesterol and triglyceride were significantly higher at the time of surgery and at the ten-year examination in those who developed new lesions. High density lipoprotein cholesterol levels (HDL) were lower in those who demonstrated new disease. The levels of HDL and of LDL apoprotein B were the best distinguishing factors for predicting the presence or absence of atherosclerotic change.

A recent trial called the Lipid Research Center Coronary Primary Prevention Trial or LRC-CPPT was designed to answer the question: "Does lowering the blood cholesterol level reduce the risk of heart disease"? (3) In this trial 3,806 men between the ages of 35 and 59 years participated in a dozen centers throughout the United States. Each volunteer had a serum cholesterol above 265 mg% despite an appropriate cholesterol-lowering diet. Individuals with known heart disease, high blood pressure, or serious other illnesses were excluded. The study was of an enormous magnitude: It required 193,000 clinic visits, 72,000 electrocardiograms, and cost over $140,000,000. Each patient was given dietary instruction, and the group was randomly divided into a drug group which took the resin cholestyramine and an equal group which received placebo. Both groups were followed for at least seven years before the double-blind code was broken.

The results were revealing: There was a significant drop in total cholesterol, in LDL, and in cardiac deaths and myocardial infarction in the drug treated group (see Figure 1). This significant reduction was based only on so-called "hard" end points; i.e., cardiac death and proven acute myocardial infarction. The study also demonstrated the value of lowering the serum lipids for such "soft" end points as the development of a positive exercise test, the occurrence of angina pectoris, and/or the need for saphenous vein bypass surgery (see Figure 2).

FIGURE 1

LRC-CPPT

PRIMARY ENDPOINT (DEFINITE CORONARY HEART DISEASE DEATH AND/OR NONFATAL MYOCARDIAL INFARCTION)

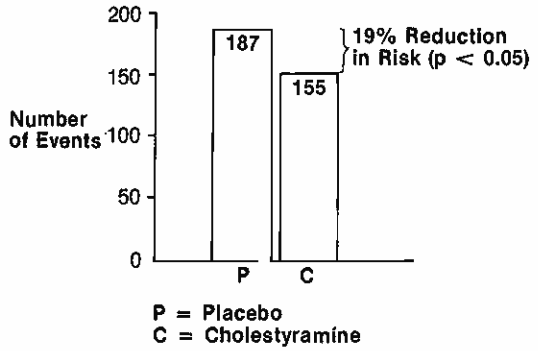


FIGURE 2

LRC-CPPT

OTHER CORONARY HEART DISEASE ENDPOINTS

	Placebo No.	Cholestyramine No.	Reduction in Risk
Positive exercise ECG	345	260	25%
Angina	287	235	20%
Coronary bypass surgery	112	93	21%

One concern of any large study that encompasses hundreds of subjects and multiple years of follow-up is that other risk factor changes, rather than the one under study, might be responsible for the observed results. This was not the case in the LRC-CPPT study because at the end of seven years, the placebo group and the cholestyramine group were similar in weight, smoking behavior, exercise, blood pressure, and alcohol intake. The groups differed only in their lipid levels, and it was this lowering of cholesterol which was responsible for the reduction in cardiac deaths and other cardiac events.

The study also showed that there was a greater drop in cholesterol and in LDL with every increment in the total dosage of cholestyramine taken over the seven-year period; but this was not true of the response to placebo, which was essentially flat. In the 50% of the drug treated patients who took the recommended dosage of five or six packets, there was a 19% reduction in cholesterol and a 39% reduction in coronary heart disease.

The LRC-CPPT demonstrated conclusively that reduction in cholesterol resulted in a lowered incidence of heart attack and death in asymptomatic hyper-cholesterolemic men who were followed for more than seven years. There was a similar reduction in cardiac events for equivalent reductions in cholesterol even when the reductions were due entirely to diet. When the cholesterol is reduced by a full 25% as is possible with diet and drug therapy, there was a 50% reduction in coronary heart attack rates, results far superior to any reported in most series even after open-heart surgery. Yet total cholesterol is an imperfect tool in measuring the risk of coronary heart disease. Generally the level of the HDL or high density lipoprotein cholesterol is a better measure of the risk of heart disease. The level of HDL bears an inverse relationship to the risk of heart disease so that the higher the level of HDL, the lower the risk of heart disease. Recently new drugs have been developed which lower the total cholesterol and yet raise the HDL level. Foremost amongst drugs which have the ability to increase the level of HDL is gemfibrozil (Lopid). It reduces the level of VLDL and TLDL while raising HDL.

I had the opportunity to study gemfibrozil in a group of hyperlipidemic subjects in Syracuse, N.Y. Responders were defined as those who demonstrated at least a 20% reduction in triglyceride levels after therapy. Figure 3 demonstrates that there were significant reductions in triglyceride levels as well as in total cholesterol, VLDL, and LDL levels. The HDL rose by more than 50% in this group of responders.

Some patients are easier to manage than others. Figure 4 reveals the data on a young college professor

FIGURE 3

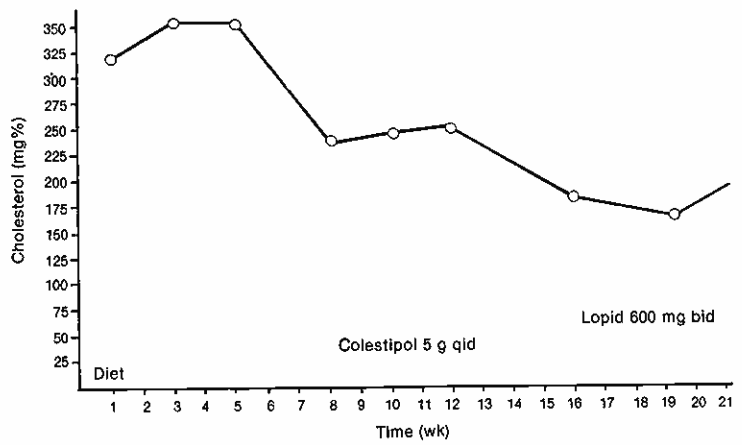
Gemfibrozil Responders (10/16)
Percent Change

	TG	Chol	HDL	LDL	VLDL	LDL/HDL
Average	−54	−19	+52	−18	−50	−40

Nash *Angiology* 1982

FIGURE 4

Effect of Diet, Colestipol and Lopid on Cholesterol Levels



who had severe Type IIa hypercholesterolemia unresponsive to diet. The use of tolerable dosages of resin and gemfibrozil completely normalized his total cholesterol and LDL levels.

I recently studied 57 patients with significant coronary atherosclerotic narrowing proven by arteriography. Each patient had a serum cholesterol level greater than 250mg% after the maximum effects of a low cholesterol diet, and a coronary artery narrowing of 75% or greater. Each patient was followed for two years on either placebo or colestipol, and then a second coronary arteriogram was carried out and the two studies compared by arteriographers who were blinded to treatment.

Figure 5 reveals that the two groups did not differ significantly in gender, age, smoking behavior, hypertension, family history, Type A behavior, diabetes, or the presence of previous open-heart surgery. Thirty-six subjects received resin and 21 received placebo. Figure 6 reveals that the resin treated group experienced a 21% reduction in total cholesterol, whereas the placebo group remained essentially unchanged.

Figure 7 reveals the results of the comparison of the two coronary arteriograms, before and after a treatment period of two years. Those patients treated with placebo and diet had a 48% progression rate, whereas the drug treated patients experienced a progression rate of 17% after two years of cholesterol lowering therapy. The differences are significant; and interestingly enough, the $P < .02$ value is the same as found in an NIH study of the effects of cholestyramine in the treatment of Type II subjects with known coronary artery lesions who were followed for 5 years.

A Consensus Development conference met recently in Washington at the National Institutes of Health. This distinguished panel examined the evidence supporting the so-called lipid hypothesis and felt it was convincing. They also examined the question of what level of blood cholesterol required treatment either by diet or drugs (Figure 8).

FIGURE 5

Description of patients

by baseline characteristics

	NUMBER OF PATIENTS	MEAN AGE	SEX		RISK FACTORS						PREVIOUS OPEN HEART SURGERY
			M	F	SMOKES	FAMILY HIST*	HYPER-TENSION	OBESITY	DIAB. MELL	TYPE A**	
DRUG TREATED	36	54.3	34	2	20	30	18	8	3	13	15
PLACEBO	21	52 9	17	4	15	17	9	8	2	8	9
TOTAL	57	53.8	51	6	35	47	27	16	5	21	24

*1 patient in drug treated adopted, thus no family history.
**1 patient in placebo did not have personality typed.

FIGURE 6

Mean serum cholesterol levels before and after treatment

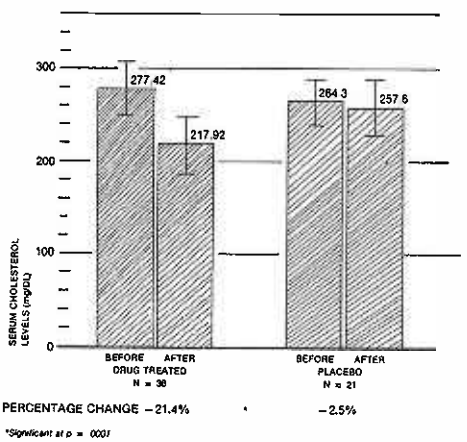


FIGURE 7

Arteriographic status of drug treated and placebo treated patients

	ARTERIOGRAPHIC STATUS				TOTAL	
	STABLE		PROGRESSION			
	NUMBER	PERCENT	NUMBER	PERCENT	NUMBER	PERCENT
DRUG TREATED	30	83.3	6	16.7	36	100.0
PLACEBO	11	52.4	10	47.6	21	100.0
TOTAL	41	71.9	16	28.1	57	100.0

$X^2 = 6.29 \quad d.f = 1.0 \quad p < .02$

FIGURE 8

Under what circumstances and at what level of blood cholesterol should dietary or drug treatment be started?

Values above 200-230 mg/dL represent an increased risk of developing coronary heart disease.

High risk comprises values above the 90th percentile. Moderate risk, values between the 75th and 90th percentiles.

The panel determined that moderate risk was defined as values between the 75th and 90th percentiles (Figure 9).

High risk blood cholesterol was defined as at the 90th percentile. The panel specified that the most aggressive treatment is required. In a significant, additional decision, the panel agreed that withholding treatment from these individuals subjects them to unnecessary risks (Figure 10).

Using the data collected by the Lipid Research Clinics, the panel provided blood cholesterol values for selecting men and women at moderate and high risk requiring treatment (Figure 11).

We now have the knowledge to do something important in the prevention of coronary heart disease. We have the required diagnostic tools to determine who is ill and who is at risk. We have potent dietary and pharmacologic agents which have proven effectiveness. What we require is the will and the determination to carry out what we already know will reduce the progression of the worldwide problem of coronary artery disease.

There is an old saying: "We are not required to complete the task at hand — neither are we free from making a start."

FIGURE 9

Moderate-Risk Blood Cholesterol (Moderate Hypercholesterolemia)

This is defined as values approximately between the 75th to 90th percentiles (See table for guidelines.)

This category includes people with elevated blood cholesterol due, in part, to their diets.

The intensity of treatment is guided by clinical and family history and presence of other risk factors predisposing to coronary heart disease.

FIGURE 10

High-Risk Blood Cholesterol (Severe Hypercholesterolemia)

This is defined as values at approximately the 90th percentile as determined by the Lipid Research Clinics Prevalence Study (See table for guidelines.)

This category includes individuals with hereditary forms of high blood cholesterol.

The most aggressive treatment is required.

Withholding treatment subjects these individuals to unnecessary risk.

FIGURE 11

Values for Selecting Men and Women at Moderate and High Risk Requiring Treatment

Age	Moderate Risk	High Risk
2-19	> 170 mg/dL	>185 mg/dL
20-29	> 200 mg/dL	>220 mg/dL
30-39	> 220 mg/dL	>240 mg/dL
40 and over	> 240 mg/dL	>260 mg/dL

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