Meeting Summary

Workshop on the Impact of Dietary Cholesterol on Plasma Lipoproteins and Atherogenesis

Scott M. Grundy, Elizabeth Barrett-Connor, Lawrence L. Rudel, Tatu Miettinen, and Arthur A. Spector

A workshop entitled The Impact of Dietary Cholesterol on Plasma Lipoproteins and Atherogenesis was held in Bethesda, Maryland on July 1–3, 1986. This workshop was cosponsored by the National Heart, Lung, and Blood Institute and the Agricultural Research Service, United States Department of Agriculture (USDA). Its purpose was to review existing data relating dietary cholesterol to coronary heart disease (CHD) and to define needs for future research on this issue. The topics discussed ranged from basic science to epidemiology and included investigations using both humans and laboratory animals.

A possible relation between dietary cholesterol and atherosclerosis was first brought to light in laboratory animals. The feeding of cholesterol can induce marked hypercholesterolemia and atherosclerosis in many species. This observation and the susceptibility of nonhuman primates to the plasma cholesterol-raising effects of dietary cholesterol has influenced thinking about the role of dietary cholesterol in the genesis of CHD in humans. For many years, however, skeptics have questioned whether findings in laboratory animals can be extended to humans. Clinical investigations have revealed that high intakes of cholesterol in humans do not induce a marked hypercholesterolemia. Thus, some workers have suggested that humans are basically resistant to dietary cholesterol, and they contend that CHD risk is not reduced by restricting dietary cholesterol. This workshop examined the bases for these opposing views by considering the known or potential effects of dietary cholesterol.

Dietary Cholesterol and Plasma Cholesterol

Drs. Henry McGill and Lawrence Rudel reviewed the current status of research in animals noting that many species are susceptible to diet-induced atherosclerosis, especially rabbits, pigeons, chickens, pigs, and some nonhuman primates. Recently, primate models, which are phylogenetically close to humans and have lipoproteins similar to those of humans, have been widely used. Some nonhuman primates are "hyperresponsive" to dietary cholesterol, developing marked hypercholesterolemia on high intakes of cholesterol; others, more resistant to dietary cholesterol, demonstrate modest rises in cholesterol levels. Thus, variability in response of plasma cholesterol to dietary cholesterol is a characteristic of nonhuman primates. Variability is even more pronounced across species lines; for example, rats and dogs on high cholesterol diets (in contrast to rabbits and chickens) demonstrate little or no rise in plasma cholesterol. Because of this variability, the response of humans to dietary cholesterol cannot be predicted from animal responses.

Many studies indicate that humans are more resistant to dietary cholesterol than most nonhuman primates, because humans rarely develop marked hypercholesterolemia even when fed large quantities of cholesterol. Several studies suggest that dietary cholesterol has little effect on plasma cholesterol levels; these studies, reviewed by Dr. Roslyn Alfin-Slater, used outpatients fed ad libitum diets. However, in the carefully controlled, metabolic-ward investigations discussed by Dr. Martijn Katan, raising dietary cholesterol usually increased plasma cholesterol concentrations. Dr. Fred Mattson noted that, although not all investigations have provided identical results, when all data are averaged, the rise in plasma total cholesterol is about 10 mg/dl for every 100 mg of dietary cholesterol per 1000 calories.

Workshop participants considered whether the rise in plasma cholesterol in response to an increment in dietary cholesterol is linear or curvilinear. This question remains unanswered for cholesterol intakes between zero and 500 mg/day. Investigations by Hegsted et al. 1,2 and Mattson et al.3 suggested a linear relationship up to at least 500 mg/day, but Keys et al.4 claimed a curvilinear response. Over the usual range of cholesterol intakes for humans, however, there is little difference in absolute response, regardless of which relationship pertains.5 Most workers agreed that progressively higher intakes exceeding 500 mg/day have only small incremental effects on cholesterol levels. This may explain why adding extra cholesterol to ad libitum diets has generally failed to cause a further rise in plasma cholesterol levels. The critical question to be resolved is whether raising dietary cholesterol from about 250 to 500 mg/day will induce a significant rise in plasma cholesterol concentrations. (This is the range in which most Americans could reduce their cholesterol intakes.)

Most agreed on the variability of the response to dietary cholesterol. Some people demonstrate a substantial increment in plasma cholesterol when dietary cholesterol is
increased — perhaps two to three times greater than the average response — while others have little change. In addition, the response varies from time to time. Although these probably are hyperresponders and hyporesponders among humans, Dr. Martijn Katan noted a considerable inconsistency in response in a group of people studied several times over a prolonged period. He suggested that what is seen as response variability may, in fact, be random fluctuations of serum cholesterol that are unrelated to dietary stimulus. It seems unlikely that a simple cholester-0l-loading test that would define a given individual's susceptibility to dietary cholesterol can be devised.

An issue considered by Dr. Gustav Schonfeld was whether the response to dietary cholesterol depends on the amounts and types of fat in the diet. For instance, a rise in cholesterol levels could be greater in response to a given amount of dietary cholesterol if the diet contains more saturated fatty acids, an effect reported by Schonfeld et al. However, it was the view of several participants that this issue remains to be settled. If dietary cholesterol does not raise the plasma cholesterol when intakes of saturates are low (when the diet is low in total fats or high in unsaturated fatty acids) this would have implications for dietary recommendations; for instance, a greater emphasis might be given to reducing intakes of saturated fatty acids than to decreasing cholesterol intakes.

In sum, carefully controlled studies carried out under metabolic-ward conditions leave little doubt that increasing the dietary cholesterol induces a rise in the plasma total cholesterol in many people. The lack of this effect in out-patients may result from other factors: 1) the limited response of plasma cholesterol to dietary cholesterol (approximately 10 mg/dl per 100 mg cholesterol per 1000 calories), 2) the variability in response among individuals, and 3) the diminishing response at higher intakes of cholesterol. Exogenous factors determining the variability of response have not been determined, although amounts and types of dietary fat might be important modulating factors.

**Dietary Cholesterol and Plasma Lipoproteins**

The major effect of dietary cholesterol on plasma lipoproteins is to raise low density lipoproteins (LDL). The mechanism for this action may be twofold. First, dietary cholesterol probably suppresses the synthesis of LDL receptors since, as Goldstein and Brown have demonstrated, the synthesis of LDL receptors by cells depends on their cholesterol content. When cellular cholesterol rises, the synthesis of LDL receptors is suppressed; when cellular cholesterol falls, the synthesis of new receptors is increased. Recent work shows the liver to be the major site for removal of LDL, and since the primary fate of dietary cholesterol is hepatic uptake of chylomicron remnants, it seems likely that high intakes of dietary cholesterol suppress the synthesis of hepatic LDL receptors.

A second mechanism whereby dietary cholesterol might raise LDL levels is by enhancing the cholesterol content of newly secreted lipoproteins. This mechanism was suggested by Nestel et al. who reported that high intakes of dietary cholesterol in humans cause an increased flux of cholesterol through intermediate density lipoproteins. Dr. Lawrence Rudel reviewed the effects of dietary cholesterol on various lipoprotein fractions of nonhuman primates, and he, too, found an enhanced secretion of cholesterol-rich lipoproteins during the feeding of excess cholesterol; this effect may account for the high molecular weight LDL observed in certain nonhuman primates fed cholesterol. Dr. Rudel noted that LDL of responding animals became greatly enriched with cholesterol esters, mostly cholesterol oleate of hepatic origin. Cholesterol oleate is the product of intracellular acyl-CoA:cholesterol acyl transferase, whereas the normally more abundant LDL cholesterol linolate is derived through the action of lecithin cholesterol acyl transferase in plasma. Dr. Rudel noted that, in contrast to nonhuman primates, human LDL does not increase in size on high cholesterol diets; however, the observations by Nestel et al. may indicate that similar underlying mechanisms do exist.

Investigations into the kinetic behavior of lipoproteins in response to dietary cholesterol in humans were reviewed by Dr. Henry Ginsberg. He and his colleagues found no increase in LDL concentrations after raising the cholesterol content of the study diet; consequently, no changes were found in production rates or fractional catabolic rates (FCR) of LDL. In contrast, a study by Packard et al. showed that LDL cholesterol levels rose by 40% when a high cholesterol diet was fed to humans; this increase in LDL cholesterol level apparently resulted from a decrease in FCR plus an increase in production rate for LDL. These two studies differ in the P/S ratio, which was 0.4 in the Ginsberg study and 0.17 in the Packard study. Kesaniemi and Grundy reported the converse: when absorption of cholesterol was inhibited by oral administration of neomycin, the plasma level of LDL cholesterol fell and kinetic parameters for LDL were reversed (production rates for LDL declined and FCR for LDL increased). Changes in FCR for LDL in these latter two investigations could be explained by alterations in receptor-mediated clearance of LDL, but changes in production rates for LDL are more difficult to explain.

Another lipoprotein that is affected by dietary cholesterol is the chylomicron. Almost all newly absorbed cholesterol enters the body with chylomicrons. As dietary cholesterol increases, the cholesterol content of chylomicrons increases and consequently, chylomicron remnants are enriched in cholesterol. The spectrum of cholesterol-rich, postprandial lipoproteins in humans has not been thoroughly studied. Dr. Robert Mahley described investigations in which a cholesterol-rich particle isolated from chylomicron-fed animals appeared to be a chylomicron remnant. This lipoprotein contained apolipoprotein B-48 and apo E, and it was cleared from plasma by hepatic apo E receptors. According to Dr. Mahley, clearance of chylomicron remnants by apo E receptors occurs rapidly under normal circumstances, but these remnants accumulate in plasma when the diet contains large quantities of cholesterol.

Moreover, a high intake of cholesterol may affect triglyceride-rich lipoproteins of endogenous origin. Dr. Mahley indicated that dietary cholesterol induces accumulations of cholesterol-rich VLDL (called beta-VLDL) in plasma of
dogs and swine. Beta-VLDL apparently are remnants of VLDL because they contain apolipoprotein B-100 of hepatic origin. They are cleared from the circulation mainly by LDL receptors (B/E receptors) and accumulate in plasma because the activity of LDL receptors is downregulated by excess dietary cholesterol; as beta-VLDL acquire large amounts of cholesterol, their circulation time is slowed. Beta-VLDL from animals resemble the beta-VLDL that accumulate in humans with familial dysbetalipoproteinemia.

VLDL enriched in cholesterol esters might increase in plasma of humans on high-cholesterol diets as they do in many laboratory animals. Scattered reports suggest that dietary cholesterol may raise VLDL cholesterol and IDL cholesterol levels, although the appearance of definite beta-VLDL secondary to increasing dietary cholesterol has not been found in humans.

The influence of dietary cholesterol on the metabolism of high density lipoproteins (HDL) and "reverse cholesterol transport" was discussed by Dr. Alan Tall. Reduced levels of HDL cholesterol are associated with increased risk for CHD. Whether a high level of HDL directly promotes removal of excess cholesterol from the arterial wall or whether a low level of HDL merely reflects the presence of remnant lipoproteins that are highly atherogenic has not been determined. In fact, a reduced level of HDL may indicate both a deficiency of reverse cholesterol transport and an excess of atherogenic remnant lipoproteins. A paradox is that high cholesterol diets may actually raise the level of HDL cholesterol in some people, although it seems unlikely that a high intake of cholesterol will actually protect against atherosclerosis. More investigations will be required to determine the nature of HDL particles that are induced by cholesterol feeding and how these lipoproteins may affect atherogenesis.

Metabolism of Dietary Cholesterol

A critical issue for the clinical significance of dietary cholesterol is how much is absorbed. Findings indicate that dietary cholesterol is incompletely absorbed (perhaps from 25% to 75%), and there is considerable individual variation. However, the validity of these values depends on accurate measurement. Most available techniques use radioactive tracers, and some investigators doubt whether the rate of tracer uptake by intestinal mucosa accurately reflects absorption of cholesterol mass. They claim that luminal cholesterol exchanges with mucosal cholesterol, and thus the rate of disappearance of radioactivity from the lumen overestimates the mass absorption. Other workers, notably Samuel and McNamara, have reported that significant lumenn-mucosal exchange does not occur in humans, and thus, uptake of radioactive cholesterol from the lumen faithfully reflects the mass absorption of dietary cholesterol. This issue needs to be resolved for a better interpretation of absorption data.

One puzzling feature in estimations of cholesterol absorption is that a constant fraction of cholesterol tracer appears to be absorbed regardless of the cholesterol intake. Since absorption of cholesterol is not compete, this finding is contrary to what might be expected, namely, that with increasing cholesterol intake, the percent absorption would decrease, as in other biological systems. This finding could be explained by exchange of radioactive luminal cholesterol with unlabeled mucosal cholesterol; therefore, this observation heightens the need for further evaluation of the exchange question. Even if use of a radioactive tracer does give accurate absorption values, estimates of cholesterol absorption still may not be accurate over a full day. The timing and frequency of administration of tracer relative to dietary intake and biliary secretion of cholesterol must be taken into account.

In spite of methodological problems, abundant data indicate that absorption is variable from one person to another. Therefore, it can be asked whether fractional absorption rates for individuals affect their plasma level of cholesterol, a question that was reviewed by Dr. Donald McNamara. In recent investigations, he measured the percentage absorption of dietary cholesterol in a sizable group of men with a range of plasma cholesterol levels and found no correlation between percentage absorption and plasma cholesterol concentration. Dr. Tatu Miettinen reported a different result. Dr. Miettinen and his co-workers divided a group of middle-aged Finnish men into three subgroups — those with high, moderate, or low levels of LDL cholesterol — and determined the percentage absorption of cholesterol in all subjects. Those with the highest levels of LDL cholesterol had the highest percentage absorption of cholesterol, while those with the lowest levels had the lowest percentage absorption. Dr. Miettinen therefore proposed that the percentage absorption of cholesterol can have a significant effect on cholesterol synthesis within a given population. Limited data from studies in different populations appear to support this view; some populations, such as American Indians, seem to have both a low level of plasma cholesterol and a low percentage absorption of dietary cholesterol. Nonetheless, the relation between cholesterol absorption rates and plasma cholesterol concentrations has not been fully resolved.

Still another question concerning dietary cholesterol is whether an increment in absorption of cholesterol produces a corresponding feedback inhibition on the synthesis of cholesterol. Dr. Peter Edwards reviewed the regulation of cholesterol synthesis as influenced by the activity of several key enzymes. If feedback inhibition were to balance exactly the increment in absorption, the net change in body pools of cholesterol would be zero and dietary cholesterol would not raise the plasma cholesterol level. The fact that increasing amounts of dietary cholesterol does raise the plasma cholesterol in some people indicates that the feedback system is not perfectly regulated. Dr. McNamara examined the variability of cholesterol synthesis in mononuclear cells from patients loaded with an excess of dietary cholesterol. Most of his patients did not show a detectable rise in plasma cholesterol, and he concluded that such patients efficiently suppress cholesterol synthesis. About 20% of the patients did respond with higher plasma cholesterol levels, suggesting a lack of an efficient feedback mechanism. Dr. McNamara thus hypothesized that some people have an insensitive feedback mechanism, and these individuals will likely respond to dietary cholesterol with a rise in plasma cholesterol levels.

Finally, feedback inhibition of cholesterol synthesis is
not the only mechanism preventing hypercholesterolemia after high intakes of cholesterol. For example, Quintao et al.\textsuperscript{14} demonstrated that a portion of newly absorbed cholesterol is resecreted into bile. This leads to an increase in biliary cholesterol during feeding of cholesterol and serves to rid the body of a fraction of excess dietary cholesterol. Another theoretical, protective mechanism is increased conversion of cholesterol into bile acids. This serves to prevent hypercholesterolemia in cholesterol-fed rats and dogs, but in humans, enhanced formation of bile acids in response to dietary cholesterol has not been consistently shown.\textsuperscript{14} Dr. DeWitt Goodman stated that although it has not been proven that high intakes of cholesterol cause an expansion of whole-body pools of cholesterol, the mass of total body exchangeable cholesterol does rise with increasing concentrations of plasma cholesterol. To the extent that high cholesterol intake increases the plasma cholesterol level, whole-body pools of cholesterol can be expected to increase.

**Dietary Cholesterol and Risk for Coronary Heart Disease**

**Epidemiological Evidence**

Dr. Richard Shekelle reviewed four published studies with reliable assessments of cholesterol intakes in which adjustments were made for variation in caloric intake: the Chicago Western Electric, the Zutphen, the Boston-Irish, and the Honolulu Studies. All four investigations found a positive association between the cholesterol intake and subsequent rates of CHD, and in some studies, this association appeared to be independent of plasma cholesterol concentrations. Dr. Shekelle emphasized the limitations of population-based studies in assessing any nutrient, dietary cholesterol in particular: 1) miscalculation of true intake tends to reduce the size of any association and may obscure it entirely, 2) most Western populations consume a diet so high in cholesterol and saturated fatty acids that there is no low risk group for comparison, and 3) the use of clinical endpoints leads to inaccuracies in quantifying atherosclerosis, the disease of interest. Postmortem studies show that coronary atherosclerosis is common in middle-aged men even when they do not have clinical CHD. Dr. Shekelle noted that these four epidemiological studies revealed a positive correlation between dietary cholesterol and development of CHD despite such problems.

Among the four studies, only the Western Electric Study showed an association between dietary cholesterol and cardiovascular risk independent of dietary saturated fat. Investigators of the Honolulu Heart Study felt that the fact that persons eating high cholesterol diets also tend to eat high saturated fat diets (multicollinearity) precluded meaningful multivariate analysis. The issue of independence was not addressed in the Zutphen or the Boston-Irish Studies.

Dr. Lewis Kuller suggested that observational investigations are potentially valuable experiments of nature. He defined three types of studies: 1) comparison of different populations, 2) time trends of food intake versus trends in mortality, and 3) migration studies. He concluded that all three are appropriate for evaluation of a common source epidemic.

There has always been great interest in unique populations, but Dr. Kuller noted that the problem of confounding variables makes drawing definite conclusions difficult. Populations with unique dietary habits usually differ from comparison populations in several other ways; for instance, unique populations of interest are a Nigerian group that consumes a diet high in saturated fatty acids yet eats little animal fat or cholesterol and ovovegetarians (compared with so-called pure vegetarians). Comparisons of plasma cholesterol levels and rates of CHD in these populations might help to differentiate between the influence of saturated fatty acids and dietary cholesterol on plasma cholesterol levels.

Turning to trend analysis, Dr. Kuller noted the problems of confounding variables; changes in diet may coincide with other changes. For instance, during the period of declining mortality from CHD in the United States, there were remarkable changes in cigarette smoking, blood pressure control, and treatment of myocardial infarction. All these make it difficult to know the contribution of each factor.

Concerning migrant studies, Dr. Kuller cited the Ni-Hon-San Study of Japanese men as one of the best. In this study, intakes of dietary cholesterol, levels of plasma cholesterol, and mortality from heart disease increased progressively for men who remained in Japan, moved to Hawaii, or went to San Francisco. This study strongly implicates dietary factors in atherogenesis, although many other changes in lifestyles occurred with migration.

Dr. Eleanor Pao made available USDA data on recent food consumption in the United States that was based on a one-day, food-recall method. Although this survey was based on small samples in a limited age range, it suggests that almost one-half of the cholesterol eaten by American adults comes from meat, poultry, and fish. Another one-third is from milk products and eggs. A broad category that includes pastries and cheese pastas provides the remainder. Eggs are no longer the primary source of dietary cholesterol in the United States; only 15% to 18% of total dietary cholesterol comes from eggs. If the USDA survey findings are confirmed, the American diet may have changed enough for investigators to distinguish between the effect of dietary cholesterol and that of dietary fat on plasma cholesterol levels (eggs contribute the major part of cholesterol intake but only a small part of total fat intake). Nonetheless, interpretation might be complicated by other factors, such as changes in the amounts and types of fat and fiber in the diet.

If the cholesterol intake of Americans has declined in recent years, has the change produced a corresponding fall in plasma cholesterol? And if so, has this fall contributed to the decline in CHD mortality in the United States? Dr. Richard Havlik discussed the problems associated with extrapolating between alterations in diet and changes in rates of heart disease. He indicated that since about 1967, the American population has experienced a 40% decline in CHD death rates, too large a decline to be explained by methodological phenomena. Dr. Havlik further noted that decreasing death rates from CHD have been found in both blacks and whites, but recently there is a slowdown in the rate of decline for all but white men. Data from the National Health and Nutrition Examination Survey (1960 to 1980)
Predicted Coronary Heart Disease Risk from Plasma Cholesterol Changes

Another way to estimate the impact of dietary cholesterol on CHD is to extrapolate from the known relationship between plasma cholesterol and risk for CHD. Epidemiological investigations such as the Framingham Heart Study indicate that for every 1 mg/dl rise in plasma cholesterol, the risk for CHD increases by approximately 1%. This relationship has been remarkably constant among other surveys. Furthermore, in the recent Lipid Research Clinics Coronary Primary Prevention Trial, the relationship was found to hold in reverse; for every 1 mg/dl fall in plasma cholesterol levels during treatment with cholestyramine, the rate of CHD fell by about 1%. This connection, of course, represents an average for a large population and does not necessarily hold for individuals. One nevertheless might speculate about the impact of dietary cholesterol on risk for CHD.

If a change in cholesterol intake of 100 mg/1000 calories will raise the plasma cholesterol by about 10 mg/dl, what then should be the impact of reducing the cholesterol intake from 500 mg/day, which was typical of middle-aged American men about 15 years ago, to the commonly recommended 300 mg/day? For a caloric intake of 2000 to 2500 cal/day, this change in cholesterol intake should cause a reduction in plasma total cholesterol of about 8 to 10 mg/dl. Based on epidemiological studies relating plasma cholesterol levels to CHD risk, a decrease in cholesterol levels of 10 mg/dl should reduce coronary risk by about 10%. Apparently the plasma cholesterol of Americans has fallen by about 6 to 10 mg/dl over the past 20 years, and some have speculated that this change in cholesterol level has been due to a decreased intake of dietary cholesterol. Goldman and Cook have recently argued that the modest decrease in plasma cholesterol levels among Americans has contributed significantly to the decline in overall CHD mortality. A reduction in cholesterol intake, along with changes in the quantity and quality of dietary fat, may be partially responsible for falling levels of plasma total cholesterol; these dietary modifications thus could be one of many factors contributing to the decline in death rates for CHD.

According to the data of Keys et al., a decrement in plasma cholesterol resulting from a decline in cholesterol intake from 500 to 300 mg/day would be somewhat less than 8 to 10 mg/dl, perhaps only 5 to 6 mg/dl. If so, a 200 mg/day reduction in cholesterol intake would reduce coronary risk by only about 5%. Even this relatively small change, however, is not trivial when applied to a whole population. Still, if CHD risk rises only 5% to 10% as a result of cholesterol intakes of 500 mg/day, compared with less than 300 mg/day, this strongly suggests that dietary cholesterol is not the major dietary factor affecting coronary risk. For example, according to the same equations of Keys et al., a decrease in the dietary saturated fatty acids from 17% to 10% of total calories would reduce total cholesterol levels by an average of 19 mg/dl, and hence coronary risk by about 19%.

Another question for which there are few answers is whether long-term ingestion of high cholesterol diets, over decades for example, will produce a slow, but progressive, rise in the plasma cholesterol. This is not the case in non-human primates, in whom long-term feeding of excess cholesterol induces an "adaptation" to dietary cholesterol that blunts the initial hypercholesterolemic response. On the other hand, humans in high risk cultures demonstrate a progressive rise of plasma cholesterol until about age 45 and an increase that might be related to gradual accumulation of cholesterol in body pools secondary to ingestion of high cholesterol diets.

"Independent" Effect of Dietary Cholesterol on Coronary Risk

There has been a persistent concern that dietary cholesterol may have an atherogenic action independent of its effect to raise the fasting level of LDL. The possibility that postprandial lipoproteins containing dietary cholesterol are atherogenic was first suggested by Zilversmit. More recently, with increasing evidence from animal work and in vitro studies suggesting that remnants of triglyceride-rich lipoproteins could be atherogenic, several investigators have continued to speculate that induction of cholesterol-rich chylomicron remnants by dietary cholesterol may be an atherogenic factor that is independent of fasting cholesterol levels. Studies have been inconclusive because of insufficient knowledge of the lipoprotein system and lack of techniques to specifically detect postprandial lipoproteins. Researchers currently know what to look for and are obtaining the analytical tools for critical measurements. Drs. Sandra Gianturco and Robert Mahley pointed out that present data indicate that increasing the intake of dietary cholesterol will increase the cholesterol content of chylomicrons and hence chylomicron remnants. This high cholesterol content should enhance their atherogenicity. Dietary cholesterol likewise may increase the cholesterol content of VLDL remnants or reduce their clearance by the liver, changes that could enhance their atherogenic potential as well. Although this concept does not seem radical, the clinical implications may be profound. For instance, further investigations could lead to a change in the practice of measuring plasma lipids only in the fasting state. New information about postprandial lipoproteins might explain the epidemiological linkage between dietary cholesterol and CHD.

Recommended Research

From the presentations, no single question that was of overriding importance or that could be definitively answered by one study emerged. Instead, five important areas deserving thorough investigation were identified.

Effects of Dietary Cholesterol on Fasting Plasma Lipoproteins

Several carefully controlled studies on metabolic wards have proven that addition of cholesterol to the diet will
increase the plasma total cholesterol, but the effects of dietary cholesterol on cholesterol concentrations in the different lipoprotein fractions — VLDL, IDL, LDL, and HDL — need to be defined. If an increase occurs in HDL cholesterol, it seems of particular importance to learn in which fraction of HDL this occurs — HDL₃, HDL₂, or apo E-rich HDL. Particular attention should be given to effects of dietary cholesterol on IDL, a lipoprotein that may have heightened atherogenecity. The average response for any given lipoprotein species within a group of people fails to convey a picture of the true variability, and the range of response for each species also needs to be better defined.

Because it has been difficult to show a consistent effect of dietary cholesterol in free-living populations, a study in noninstitutionalized individuals that minimizes the likelihood of a false-negative result would be a valuable guide for public health recommendations. Furthermore, in the view of some, but not all, investigators at the workshop, the anticipated results of this type of trial were not deemed to be of such overriding importance that it should be given significantly higher priority than other studies. The limitations of such a study should not be overlooked. A definitely positive study would support public health recommendations to reduce dietary cholesterol. However, a negative trial would not support the opposite recommendation because of two factors: 1) increasing evidence that postprandial lipoproteins may be atherogenic, and 2) the possibility that dietary cholesterol may have a long-term effect not detectable in a short-term study.

Effects of Dietary Cholesterol on Postprandial Lipoproteins

In what follows, the discussion is structured to focus on postprandial lipoproteins because these lipoprotein species have been most widely studied in relation to dietary cholesterol and because these lipoproteins have the potential to increase the plasma total cholesterol, but the effects of dietary cholesterol on cholesterol concentrations in the different lipoprotein fractions — VLDL, IDL, LDL, and HDL — need to be defined. If an increase occurs in HDL cholesterol, it seems of particular importance to learn in which fraction of HDL this occurs — HDL₃, HDL₂, or apo E-rich HDL. Particular attention should be given to effects of dietary cholesterol on IDL, a lipoprotein that may have heightened atherogenecity. The average response for any given lipoprotein species within a group of people fails to convey a picture of the true variability, and the range of response for each species also needs to be better defined.

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Effects of Dietary Cholesterol on Cholesterol Metabolism In Humans

Further investigation is needed on the influence of dietary cholesterol: 1) the absorption of cholesterol, 2) whole-body synthesis of cholesterol, 3) conversion of cholesterol to bile acids, 4) biliary secretion of cholesterol, 5) the activity of LDL receptors, 6) the accumulation of cholesterol in various tissues, 7) reverse cholesterol transport, and 8) accumulation of cholesterol in body pools, which could be atherogenic without raising the plasma cholesterol level.

Because the response of plasma cholesterol to dietary cholesterol shows considerable individual variability, the cause of this variability and the range of variability needs further exploration.

Interactions of Postprandial Lipoproteins and Lipoprotein Remnants with Cells

The different types of remnants that may be generated by high cholesterol diets need to be isolated. These remnants may be found in all lipoprotein fractions — chylomicrons, VLDL, IDL, LDL, and HDL. They could have various types of actions on cells that may be involved in the atherogenic process. These include cytotoxicity, interactions with different types of receptors, formation of foam cells, direct transfer of cholesterol from lipoproteins to cells, and interference with the release of cholesterol from cells. Many of these processes may be intimately involved in atherogenesis, and each requires further investigation. Since different types of remnants may be involved in these processes, a study of remnant-cell interactions is important.

Effects of Dietary Cholesterol In Experimental Animals

An appropriate selection of animal models and experimental design should be used to learn about the effects of dietary cholesterol on metabolism of cholesterol and lipoproteins in animals. Investigations on types of postprandial lipoproteins and studies on primates would be useful. More investigation in laboratory animals is needed to identify and characterize postprandial lipoproteins; other experiments might discover the fate of dietary cholesterol, the effects of dietary cholesterol in the diet on HDL metabolism and reverse cholesterol transport, the influence of dietary cholesterol on cholesterol metabolism, and the mechanisms of atherogenesis that respond to cholesterol-induced lipoproteins. The advantage of using laboratory animals is that a direct assessment of the relative atherogenicity of any dietary cholesterol-induced change in plasma lipoproteins can be made.

References

Index Terms: cholesterol • lipoproteins • metabolism • epidemiology • coronary disease • diet
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doi: 10.1161/01.ATV.8.1.95

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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