Evaluation of Publicly Available Scientific Evidence Regarding Certain Nutrient-Disease Relationships:

9. Lipids and Cardiovascular Disease

December 1991

By
Scott M. Grundy, M.D., Ph.D.

Prepared for
CENTER FOR FOOD SAFETY AND APPLIED NUTRITION
FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20204

under
FDA Contract No. 223-88-2124
Task Order #9

LIFE SCIENCES RESEARCH OFFICE
FEDERATION OF AMERICAN SOCIETIES
FOR EXPERIMENTAL BIOLOGY
9650 Rockville Pike
Bethesda, MD 20814-3998
EVALUATION OF PUBLICLY AVAILABLE
SCIENTIFIC EVIDENCE REGARDING
CERTAIN NUTRIENT–DISEASE RELATIONSHIPS:

9. LIPIDS AND CARDIOVASCULAR DISEASE

December, 1991
By
Scott M. Grundy, M.D., Ph.D.

Prepared for
CENTER FOR FOOD SAFETY AND APPLIED NUTRITION
FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20204

under
FDA Contract No. 223-88-2124
Task Order #9

LIFE SCIENCES RESEARCH OFFICE
FEDERATION OF AMERICAN SOCIETIES
FOR EXPERIMENTAL BIOLOGY
9650 ROCKVILLE PIKE
BETHESDA, MARYLAND 20814
FOREWORD

The Life Sciences Research Office (LSRO), Federation of American Societies for Experimental Biology (FASEB), provides scientific assessments of topics in the biomedical sciences. Reports are based upon literature reviews and the scientific analyses of knowledgeable investigators engaged in work in specific areas of biology and medicine.

This report was developed for the Center for Food Safety and Applied Nutrition, Food and Drug Administration (FDA), in accordance with the provisions of Task Order #9 of Contract No. 223-88-2124. Potential authors and reviewing consultants were identified by the LSRO based on their qualifications, experience, and freedom from conflict of interest, with due consideration for balance and breadth in appropriate disciplines. The author and reviewing consultants were selected with the concurrence of the LSRO Advisory Committee (which consists of representatives of each constituent Society of FASEB).

On March 14, 1991, the FDA requested submission of scientific data and information on the ten specific topics for which health claims might be made (Federal Register 56:12932-12933). The scientific data and information provided in response to this request were considered by LSRO in preparing this report. Copies of the submitted materials are available for public inspection at the Dockets Management Branch, FDA (Docket No. 91N-0096). Copies of documents cited in this report are available for public inspection at LSRO, FASEB.

Scott M. Grundy, M.D., Ph.D., Professor of Internal Medicine and Biochemistry, and Director, Center for Human Nutrition, University of Texas Southwestern Medical Center, Dallas, TX should be cited as the author of this report. The LSRO acknowledges the efforts of Scott M. Grundy, M.D., Ph.D. and also the critical assistance of Richard J. Havel, M.D., Professor Department of Medicine, and Director, Cardiovascular Research Institute, University of California School of Medicine, San Francisco, CA; and Richard B. Shekelle, Ph.D., Professor of Epidemiology, School of Public Health, University of Texas Health Science Center, Houston, TX, who reviewed several drafts of the manuscript. The appendix tables were prepared by the LSRO staff and author and were critically reviewed by the author and reviewers. Subsequently the draft report and tables were revised by the author, edited by the LSRO scientific staff, and received final concurrence from the author and reviewing consultants.

The evaluation of scientific literature, data, and information submitted to the LSRO was made by the author, reviewers, and the LSRO independently of FDA or any other group, governmental or non-governmental. The author and LSRO accept responsibility for the accuracy of the report conclusions and its appendix table(s). This final report was reviewed and approved by members of the LSRO Advisory Committee under authority delegated by the Federation Board. The LSRO Advisory Committee members who reviewed this report were free of conflicts of interest in regard to the subject matter under policies established by the Federation. Upon completion of these review procedures, the report was approved by the Executive Director, FASEB, and transmitted to FDA.

While this is a report of the Federation of American Societies for Experimental Biology, it does not necessarily reflect the opinion of each individual member of the FASEB constituent Societies.

__________________________

Date

Kenneth D. Fisher, Ph.D.
Director
Life Sciences Research Office
TABLE OF CONTENTS

Page

I. INTRODUCTION ......................................................... 1
   A. Background Information ........................................ 1
      2. Objective and scope ........................................... 2

   II. REVIEW OF THE LITERATURE SINCE 1987 ......................... 5
      A. Dietary Cholesterol .......................................... 5
      B. Saturated Fatty Acids ........................................ 8
      C. Obesity and Overnutrition ................................... 14
      D. Omega–6 Polyunsaturates .................................... 15
      E. Omega–3 Polyunsaturates .................................... 19
      F. Cis–Monounsaturated Fatty Acids (Oleic Acid) ............... 21
      G. Trans–Monounsaturated Fatty Acids ......................... 23
      H. Carbohydrates ................................................ 25
      I. Alcohol ....................................................... 27
      J. Coffee ........................................................ 28

   III. BIBLIOGRAPHY ..................................................... 31

APPENDIX TABLES ..................................................... A–1
I. INTRODUCTION

A. BACKGROUND INFORMATION


Atherosclerosis is the principal pathologic process that underlies coronary heart disease (CHD) and other diseases such as peripheral arterial disease and some kinds of stroke. Extensive evidence from epidemiologic, clinical, and laboratory animal studies conducted over the past several years indicates a powerful direct relationship between serum total cholesterol, LDL-cholesterol, and atherogenesis (National Research Council, Committee on Diet and Health [NRC], 1989; U.S. Department of Health and Human Services [USDHHS], 1988). These two reports reviewed and evaluated the extensive literature published up to 1987–1988, and it is on the basis of these major reviews that the following synopsis of the diet–heart relationship can be stated with considerable certainty.

Coronary heart disease is the leading cause of death in the United States and in many western industrialized countries. Elevated blood cholesterol, especially low-density lipoprotein–cholesterol (LDL-cholesterol) is a major cause of coronary atherosclerosis. Lowering elevated levels of LDL-cholesterol slows the progression of coronary atherosclerosis and decreases the risk of coronary heart disease. Populations differ greatly in rates of coronary disease, and these differences are related to a large extent to differences in the average level of LDL-cholesterol. The demonstration of these connections has led to a national program to lower blood cholesterol in the American population.

The principal nutritional factors that affect the level of LDL-cholesterol are the saturated fatty acids with 12 to 16 carbon atoms (i.e., lauric, myristic, and palmitic acids), dietary cholesterol, and nutrition–related obesity. All three can increase the level of LDL-cholesterol. Although individuals differ in their sensitivity to these factors, few are completely insensitive. While many genetic and environmental factors affect the level of LDL-cholesterol in individuals, most of the differences among populations in mean level of LDL-cholesterol appear to be explained by differences in these three dietary factors.

The evidence underlying these statements has led expert groups in many countries to recommend restriction of saturated fatty acids and cholesterol in the diet of adults and children over two years of age. The Committee on Diet and Health of the National Research Council (1989) recommended that intake of saturated fatty acids should be under 10 percent of calories and that intake of cholesterol should be under 300 mg/d. The Committee also noted that reduction of saturated fatty acids to 7 or 8 percent of calories or lower would be likely to lead to even greater health benefits. Although some dietary fats do not raise LDL-cholesterol and increase risk of CHD, several lines of evidence have linked high intakes of fat to increased incidence of certain cancers, e.g., colon and breast. Some evidence suggests that high-fat diets may also contribute to obesity, which itself has been linked to increased risk of cardiovascular and metabolic diseases. For these reasons, the NRC report also recommended that individual intake of total fat generally should not exceed 30 percent of calories. Some evidence has indicated that low-fat diets decrease blood levels of high-density lipoprotein–cholesterol (HDL-cholesterol), the latter being correlated to decreased risk of CHD. Low-fat diets also can increase, at least temporarily, the blood levels of triglycerides, which some investigators believe can contribute to atherosclerosis. It is uncertain whether these changes in blood levels of triglycerides and of HDL-cholesterol have adverse effects on health in the general population, but these concerns have led some investigators to raise the question of whether reduction in intake of saturated fatty acids should be offset by increases mainly in complex carbohydrates or in monounsaturated fatty acids.
In summary, there is substantial agreement among experts that high-fat diets (e.g., over 40 percent of calories from fat) should be avoided by adults in the general U.S. population, but some disagreement exists among individual investigators whether the target value for intake of total fat should be low, e.g., 20 percent of calories or less, or whether it should be in the range of 30–35 percent of calories. There is also substantial agreement among experts that high intakes of dietary cholesterol (e.g., >500 mg/d) should be avoided, and the recommendation for intakes of less than 300 mg/d is widely accepted. Expert opinion expressed in current recommendations is essentially unanimous that intake of saturated fatty acids, particularly lauric, myristic, and palmitic acids, should be kept below 10 percent of calories.

The influence of dietary lipids on plasma lipids and lipoproteins and on atherosclerosis (and other chronic diseases) continues to be an active area of research. Many papers have been published since the release of the 1989 *Diet and Health* report. This monograph reviews the results of studies that have focused on the role of nutrition in cardiovascular disease published since 1987. A majority of these investigations confirm and extend the conclusions reached prior to 1989, and they provide additional insights into relationships between dietary lipids and cardiovascular disease.

2. Objective and scope

This review considers the weight of scientific evidence that relates dietary lipids to the occurrence of serum cholesterol abnormalities, atherosclerosis, and CHD. It reviews and evaluates the literature published since 1987 on these relationships and compares the conclusions reached with those of previously published exemplary reviews. The review focuses on the effects of dietary cholesterol, the various dietary fatty acids, obesity, carbohydrates, alcohol, and coffee. Each topic contains its own conclusions. Animal studies are cited only when they contribute to understanding the mechanisms of lipid effects. The review is a component of a series of reports on the interrelationships of dietary components and nutrients with various human diseases.

Three major dietary factors have been implicated in the causation of coronary heart disease. These are dietary cholesterol, saturated fatty acids, and excess total energy intake, the third being manifested as obesity. Enough evidence has accumulated on these relationships to persuade several agencies concerned with health to recommend that the American public modify its dietary habits to reduce intakes of cholesterol and saturated fatty acids and to eliminate excess body weight. Although these factors predominate in the diet–heart link, other nutrients also affect the metabolism of lipids and lipoproteins, and thus may modify the diet–heart relationship. These include both macronutrients (unsaturated fatty acids, carbohydrate, protein, and fiber) and micronutrients (vitamins and minerals). In this review, the literature from 1988 to 1991 relating diet to lipids and lipoproteins and to CHD will be reviewed. Standard reference searches were made. Each section will be introduced with a short statement of current concepts of the role of each of the nutrients in causation of CHD. These introductory sections, which will not be referenced, are based on recent, extensive, well-documented reviews of each topic (National Cholesterol Education Program [NCEP], 1991; NRC, 1989; USDHHS, 1988). Each summary introduction will be followed by a more detailed consideration of recent publications as they pertain to each of the nutrients; the section will be concluded by a consideration of whether the new findings justify a change in current recommendations about a particular nutrient.

Since dietary recommendations typically are based on data that require years to accumulate, it seems unlikely that a four-year increment of new research, short of the report of a major clinical trial or epidemiologic study, will markedly alter current recommendations. In the period of 1988 to 1991, no large-scale studies or trials of momentous import were published. Nonetheless, there is a growing interest in human nutrition as it relates to CHD, and a relatively large number of smaller and discrete studies were reported. These studies raised new questions, and in some cases, appear to have
answered some previously unresolved issues. This review therefore tries to identify the important, unresolved question being asked in each study and makes an attempt to determine the extent to which the question is answered. As a general rule, most studies included in this review were human investigations, although a few key animal studies were noted. A review of all animal studies would have added greatly to the length and complexity of this report, and it is doubtful that the results would have directly affected current dietary recommendations, although such reviews certainly raise important questions that can be addressed in future human investigations. The studies discussed herein varied in their quality, but they were included in the review if they addressed an important question for the diet–CHD link and if they were designed in a way to provide a meaningful result. Since it is much more difficult to design near "flawless" nutrition trials, compared with drug trials, overly strict criteria were not employed to permit a report to be considered in this review. On the other hand, an attempt was made to critically evaluate the quality of each study and its significance.
II. REVIEW OF THE LITERATURE SINCE 1987

A. DIETARY CHOLESTEROL

High intakes of cholesterol have been implicated in causation of hypercholesterolemia and atherosclerosis since early studies showed that feeding cholesterol to rabbits induced marked elevations of serum cholesterol and cholesterol deposits in the arterial wall. Subsequently, many other species, including nonhuman primates, proved to be responsive to dietary cholesterol by developing hypercholesterolemia. Some species (e.g., dogs and rats), however, are not particularly sensitive to dietary cholesterol, and under normal conditions they display neither a marked rise in serum cholesterol levels nor arterial wall accumulation of cholesterol. For many years, the question of degree of responsiveness of humans to high cholesterol intakes has been subject to debate. Some investigators reported substantial rises in serum cholesterol levels, whereas others found little effect. Nonetheless, when the total database from previous studies is taken into consideration, it can be said that increasing dietary cholesterol by 100 mg/1000 kcal raises the serum total cholesterol on the average by 6 to 10 mg/dL. Most of this rise occurs in the low density lipoprotein (LDL) fraction, although small increments can occur in very low density lipoproteins (VLDL) and high density lipoproteins (HDL).

One characteristic of the human response to dietary cholesterol is variability; some individuals apparently have a rather marked increase in serum cholesterol levels when excess cholesterol is added to the diet, whereas others show little or no increase. It must be noted at the outset that many previous studies on responsivity have been flawed in one way or another, i.e., they did not separate variation in response due to apparently spontaneous "random" fluctuation in plasma cholesterol concentrations from stable interindividual variation. These various studies have led to speculation that some individuals are "high responders" whereas others are "low responders" to dietary cholesterol, and the hypothesis has been put forward that difference between these two types of response has a genetic basis. On the other hand, some workers have questioned whether a significant variability in responsiveness to dietary cholesterol on a genetic basis really exists in humans. This issue remains an open question. The primary mechanism whereby dietary cholesterol raises the serum LDL-cholesterol level is by suppression of the activity of LDL receptors; secondary factors, however, may affect the degree of response. It is through raising LDL-cholesterol concentrations that dietary cholesterol generally is considered to be atherogenic. Nonetheless, when dietary cholesterol is absorbed, it is carried with chylomicrons (and chylomicron remnants), and if the cholesterol transported in postprandial lipoproteins is atherogenic, dietary cholesterol could promote atherosclerosis other than by raising LDL-cholesterol levels.

In recent years the apparent variability of humans in sensitivity to dietary cholesterol has evoked growing interest. The possible reasons for this variability have been examined recently. One possibility is that the apo E isoforms of an individual affect responsiveness. Three major apo E isoforms exist — E2, E3, and E4. Alleles for one isoform are inherited from each parent, so that six possible pairs of isoforms are possible: E2/E2, E2/E3, E2/E4, E3/E3, E3/E4, and E4/E4. It is known that in general apo E4 is associated with higher LDL-cholesterol levels, apo E3 with intermediate levels, and apo E2 with lower levels. The reasons for these differences are not well understood. Previous studies, however, suggest that responsiveness to dietary cholesterol is influenced by the apo E genotype.

Mäntärri et al. (1991) very recently confirmed that the particular apo E isoforms present affect the extent of LDL-cholesterol lowering when hypercholesterolemic Finnish patients are changed from a diet high in saturated fats and cholesterol to a low-fat, low-cholesterol diet. Individuals possessing apo E4 showed the greatest reductions in LDL levels. Although these findings support the concept
that the apo E isoform pattern affects dietary responsiveness, they nonetheless raise another question. Subjects with higher cholesterol levels typically respond to a cholesterol-lowering regime with a greater absolute lowering of serum cholesterol in response than do individuals with lower cholesterol levels; still, when changes are expressed as a percentage, responses tend to be similar. The same relationships may hold for the influence of apo E isoforms. Individuals having the apo E4 isoform may have the greatest absolute change upon dietary modification; yet the percentage change in cholesterol levels may not be greater than for people with other isoforms. This issue remains to be resolved. The influence of apo E4 on response to diet also has been shown for the Finnish population by Tikkanen et al. (1990). Still, it must be pointed out that Finns in general have unusually high cholesterol levels, and the impact of apo E4 may be accentuated in this population compared with other populations. Indeed, almost opposite results were reported by Clifton et al. (1990). These workers examined responsiveness of 56 hypercholesterolemic and normocholesterolemic Australian men and women to dietary cholesterol. They observed that apo E4 was present more often in the diet-insensitive subgroup of this population, but the difference was not significant. Overall, individuals with an E4 allele showed a rise of 0.12±0.36 mmol/L and individuals without an E4 allele, a rise of 0.27±0.37 mmol/L (p>0.05).

Another factor that could influence individual responsiveness to dietary cholesterol is a person's inherent capacity to absorb cholesterol. This possibility was examined by Miettinen and Kesaniemi (1989) in 63 middle-aged Finnish men. They reported that serum levels of total, LDL−, and HDL−cholesterol are possibly correlated with cholesterol absorption. They further noted that a high efficiency cholesterol absorption is accompanied by reduced cholesterol synthesis and increased LDL−cholesterol concentrations. These same workers (Miettinen et al., 1990) further observed a high correlation between serum plant sterols and cholesterol absorption efficiency; thus by measurement of plant sterols, it may be possible to assess the influence of individual variability in cholesterol absorption on LDL−cholesterol concentrations in large populations. These workers provide convincing evidence that individual differences in cholesterol absorption efficiency are an important determinant of differences in responsiveness to dietary cholesterol, at least in Finnish men.

Although the intestine may be important, the liver stands as the major regulator of LDL metabolism. Consequently, once dietary cholesterol enters the liver, it could affect intrahepatic regulatory mechanisms differently among individuals. One indirect way to examine this possibility is to see whether individual responsiveness to dietary cholesterol and saturated fatty acids is congruent. If so, this would suggest that dietary cholesterol probably affects hepatic cholesterol metabolism, since the action of saturated fatty acids to raise LDL−cholesterol most likely occurs in the liver. Katan et al. (1988a) addressed this question in a group of subjects who previously had participated in three or four experiments dealing with the reproducibility of response to dietary cholesterol; the subjects were then fed a diet high in saturated fatty acids, and response was noted. The investigators found a congruence of responsiveness to dietary cholesterol and saturated fatty acids; this observation suggests that the two nutrients act at a common site of regulation, most likely in the liver, and further, this site is variable in its response from one person to another.

The above studies confirm that people respond variably to dietary cholesterol, and several different mechanisms (apo E genotype, absorption efficiency, hepatic responsiveness, and level of obesity) may be involved. This difference in responsiveness could mean that people vary in their susceptibility to the atherogenic potential of dietary cholesterol. A broad question nonetheless remains as to the extent to which a high intake of dietary cholesterol is a "risk factor" for CHD. A widely held belief maintains that dietary cholesterol has a rather small effect on serum cholesterol levels in humans, and consequently it plays little role in the genesis of CHD in the general population. This unresolved issue led Stamler and Shekelle (1988) to reassess available epidemiologic data. They examined results of four prospective, within-population studies reported since 1981. The combined data from these studies strongly suggest that the level of dietary cholesterol relates significantly to long−term CHD

6
risk; this risk imparted by dietary cholesterol appeared to be independent of, and in addition to, serum total cholesterol levels, blood pressure, and cigarette use. On the average, a 200 mg/1000 kcal increment in dietary cholesterol induced a 30 percent higher rate of CHD. Although epidemiologic studies do not prove a causal connection between correlated variables, this finding taken together with other types of evidence definitely supports the concept that dietary cholesterol contributes significantly to CHD risk. Additional evidence to support the same concept was reported more recently by Shekelle and Stamler (1989). They published results of a 25-year follow-up of 1824 middle-aged men. They observed that the relative hazard of death from all cardiovascular diseases combined was positively and significantly associated with cholesterol intake. This relationship was independent of the serum cholesterol level, again suggesting that dietary cholesterol is atherogenic beyond its action to raise the LDL-cholesterol level.

According to Peto (1989), data from observational studies suggest that a 10 percent reduction of total cholesterol over a period of decades would be associated with a 33 percent reduction in the rate of fatal CHD. On the basis of clinical trials, a "rule of thumb" has emerged that for each 1 percent decrease in blood cholesterol an approximate 2 percent reduction in CHD incidence can be expected (NCEP, 1991).

The research of the last three years has been largely directed toward answering important gaps in our knowledge of the relation of dietary cholesterol to (a) serum lipoproteins and (b) CHD. Although some of the variability in responsiveness to dietary cholesterol appears to be an artifact of limited accuracy of methods to assess cholesterol metabolism in humans, significant questions about individual variability remain unanswered. For example: (a) To what extent does variability in diet composition affect the response to dietary cholesterol? (b) How much does the absorption of dietary cholesterol vary from one person to another? and, (c) What metabolic (and genetic) factors besides the apo E genotype, account for the variability in response of serum lipoproteins to dietary cholesterol? Moreover, an extremely important and unresolved issue is whether dietary cholesterol increases risk for CHD beyond its effect to raise the LDL-cholesterol level. If so, the mechanism for this effect, whether through postprandial lipoproteins or reverse cholesterol transport, needs to be determined.

Conclusions. There has been a tendency on the part of some investigators to dismiss dietary cholesterol as an important cause of elevated serum cholesterol. Instead, saturated fatty acids have been given "first billing" and have been considered the major culprit in dietary atherogenesis. Although saturated fatty acids undoubtedly are important, dietary cholesterol may be a more important dietary risk factor than generally realized. As previously reviewed (NCEP, 1991) there is growing evidence that most people respond to dietary cholesterol with at least some rise in serum cholesterol; the reviewed data indicate that the average increase is 6–10 mg/dL per 100 mg cholesterol per 1000 kcal. This means that every 200 mg/d of dietary cholesterol raises the serum cholesterol level on the average about 8 mg/dL. According to available epidemiologic data, a 1 mg/dL rise in serum cholesterol will increase the risk for CHD by 1 percent. Accordingly, an 8 mg/dL increment in serum cholesterol, due to 200 mg/d of excess dietary cholesterol, should raise CHD risk by 8 percent. Since the American public has traditionally consumed about 200 mg/d cholesterol more than has been generally recommended (See: Current recommendations, p. 8), approximately 8 percent of CHD can be attributed to the effect of dietary cholesterol to raise total cholesterol levels. It should be noted that the cholesterol–raising effect of dietary cholesterol is lifelong because overconsumption of cholesterol begins early in life. Moreover, newer analyses of epidemiologic data suggest that a one mg/dL higher cholesterol level sustained for many years actually increases CHD risk by about 1.5 percent; thus, lifelong consumption of excess dietary cholesterol could account for up to 12 percent of all CHD in the United States. For certain individuals, who are high responders to dietary cholesterol, the danger of a high intake of cholesterol could be even greater than the average. Some people have an unusually high absorption of dietary cholesterol; others cannot downregulate cholesterol synthesis.
in response to cholesterol in the diet, and still others may have a sluggish conversion of cholesterol into bile acids. All of these people should be relatively high responders to dietary cholesterol. The same hyperresponsiveness may occur in people who have apo E4. Since most of these metabolic aberrations cannot be detected short of elaborate metabolic studies, avoidance of high intakes of dietary cholesterol for the whole population is prudent.

And in addition, postprandial lipoproteins enriched with dietary cholesterol may be atherogenic beyond the rise in serum cholesterol that occurs from a high cholesterol intake. Other adverse effects of dietary cholesterol also can be visualized. For example, dietary cholesterol could interfere with reverse cholesterol transport or expand whole body pools of cholesterol, the latter possibly promoting atherogenesis in subtle ways. All of these possibilities are in accord with the risk-raising effect attributed to dietary cholesterol in epidemiologic studies. Indeed, Stamler and Shekelle (1988) presented data suggesting that even more than 12 percent of all CHD can be attributed to excessive consumption of cholesterol. More research is needed to determine whether this "extra" atherogenic effect of dietary cholesterol is real.

The diet need contain no cholesterol for health, and any dietary cholesterol will raise LDL-cholesterol to some extent. Considerations or recommendations thus are based on practicability. Current recommendations restrict dietary cholesterol to less than 300 mg/d for the whole public (children, women, and men). Average intakes of cholesterol in American children and women are not far above this recommendation, whereas current intakes for men average about 425 mg/d. Seemingly, cholesterol consumption has declined over the past three decades, a change that may have contributed to a decrease in average levels of serum cholesterol and to the fall in CHD rates in the United States. It would be desirable if cholesterol intake could be reduced by another 200 mg/d; but in practical terms, this probably is impossible for a majority of adult Americans. Such a change would require a severe reduction in consumption of animal products, a change that may not be acceptable to some persons. Nevertheless, such dietary changes are common in some groups; for example, with few exceptions, vegetarians have lower cholesterol intakes because of the absence of animal products in their diets. Thus, the current less than 300 mg/d recommendation appears reasonable. Little change in cholesterol intake will be required for women and children; on the other hand, American men should substantially reduce their dietary cholesterol by further curtailment of egg yolk, dairy fat (butter, ice cream, cheese, and whole milk), and meat fat (fat on outside of meat and processed meats). The recommendation for less than 300 mg/d for men thus is within reach. Further, as recommended by the National Cholesterol Education Program, people with hypercholesterolemia should reduce their dietary cholesterol to less than 200 mg/d (NCEP, 1991).

At present, recommendations about the dietary cholesterol-CHD link must be based on (a) animal studies, (b) epidemiologic surveys, and (c) metabolic-ward and related studies. A primary prevention trial specifically to test effects of dietary cholesterol on CHD risk is out of the question because of cost and priority. Nonetheless, a strong case based on the first three lines of evidence has been developed to implicate dietary cholesterol in atherogenesis, and available evidence allows for estimates of the magnitude of the effect. These estimates support recommendations to restrict cholesterol intakes. No good reason can be visualized to relax these recommendations; if anything, they should be reinforced through public education, modification of food products by industry, and appropriate food labeling.

B. SATURATED FATTY ACIDS

Many investigators hold the opinion that saturated fatty acids are the "most important" dietary factor related to CHD. Without question, certain saturated fatty acids more consistently raise LDL-cholesterol levels than does dietary cholesterol, and this consistency underlies the view that high intakes of saturated fatty acids constitute an important dietary "risk factor". Many health agencies
thus recommend that consumption of saturated fatty acids be reduced in the American diet (NCEP, 1991; NRC, 1989; USDHHS, 1988). This general recommendation is warranted, as is documented by the rationale sections of these important reports.

In spite of the general recommendation, it must be noted that saturated fatty acids in the American diet consist of a series of fatty acids ranging in chain length from 8 to 18 carbon atoms. Strong evidence from many years ago indicates that those of 8 and 10 carbon atoms (medium-chain fatty acids) almost certainly do not raise the cholesterol level. The longer-chain acids (12, 14, and 16) do raise serum cholesterol levels, but the precise extent to which this occurs with the 12-carbon lauric acid is uncertain. In contrast, the 18-carbon saturated acid, stearic acid, does not raise the cholesterol level. A high content of stearic acid in beef fat and cocoa butter thus explains why these fats do not raise the cholesterol level as much as butter fat, which is rich in myristic acid (14 carbons) and palmitic acid (16 carbons).

One question that is persistently asked, but not adequately answered, is: by what mechanisms do cholesterol-raising saturated fatty acids raise the serum cholesterol level? Clearly, saturated fatty acids increase LDL-cholesterol levels compared with all the other major nutrients -- polyunsaturated and monounsaturated fatty acids and carbohydrates. How can we account for this unique effect? Do saturated fatty acids (a) inhibit clearance of circulating LDL by suppressing the activity of LDL receptors? (b) alter LDL particles to make them poor ligands for LDL receptors? (c) enrich LDL particles with cholesterol? or, (d) increase hepatic secretion of lipoproteins containing apolipoprotein B-100 (apo B)? Since responsiveness to saturated fatty acids and cholesterol was shown to be congruent (Katan et al., 1988a), this finding suggests that saturated fatty acids, like dietary cholesterol, suppress the activity of LDL receptors. Recent studies in laboratory animals (Nicolosi et al., 1990; Spady and Dietschy, 1989) lend support to this mechanism; however, one study in primates failed to find a reduction in mRNA for LDL receptors in primates fed diets high in saturated fatty acids (Sorci-Thomas et al., 1989) in contradistinction to a previous report (Fox et al., 1987). Thus, if saturated fatty acids in fact interfere with uptake of LDL, which they appear to do, the precise mechanism for this action is unclear. Regarding studies in laboratory animals, saturated fatty acids in the absence of dietary cholesterol seem to be much less "hypercholesterolemic" than in man; for instance, in laboratory animals, the feeding of dietary cholesterol appears to be required to bring out the hypercholesterolemic response to saturated fatty acids (Hayes et al., 1991). This observation again supports the concept that saturated fatty acids act at the level of the LDL receptor.

But do saturated fatty acids also enhance the secretion of apo B-containing lipoproteins? Spady and Dietschy (1989) reported that dietary saturated fatty acids fed to hamsters simultaneously reduce clearance of LDL by receptor-mediated pathways and raise production rates for LDL. However, since LDL receptors remove LDL precursors (i.e., VLDL), in addition to LDL, a reduction in receptor activity could lead to enhanced conversion of VLDL to LDL, hence to increased LDL "production". Nonetheless, in a study on secretion of lipoproteins from isolated hepatocytes obtained from hamsters primed with saturated fatty acids, Ohtani et al. (1990) reported an enhancement in secretion of VLDL-cholesterol; this finding raises the possibility that saturated fatty acids stimulate the secretion of VLDL; if so, this could be yet another way whereby saturated fatty acids raise the LDL-cholesterol level.

Even though high intakes of saturated fatty acids consistently raise LDL-cholesterol concentrations in humans, how much variability in this response exists? Are there "high" and "low" responders to saturated fatty acids? In the studies on Finnish men noted above (Mänttäri et al., 1991; Tikkanen et al., 1990), the apo E phenotype appeared to affect the magnitude of response, at least for absolute changes. Individuals with apo E4 manifest the greatest responses. The report of Katan et al. (1988a) indicates variability in responsiveness to saturated fatty acids that is congruent with that of dietary cholesterol. Prior reports pointed out that responsiveness to cholesterol-lowering diets depends on
the initial level of total cholesterol when one is on a diet high in saturated fatty acids. By the same token, switching from a cholesterol-lowering diet to a diet high in saturated fatty acids will raise cholesterol more in some people than others.

Variability in responsiveness depending on the baseline cholesterol level was noted by Boyd et al. (1990) in women in a randomized, controlled dietary trial. These workers reported that changes in serum cholesterol for women were greater than the mean changes predicted by the formulas of Hegsted et al. (1965) and Keys et al. (1965) when initial serum cholesterol values were in the upper tertile of the population; they were not significantly different from those in the middle tertile, and were significantly less than predicted in women in the lower tertile. This observation confirms the principle of variability of response described in the preceding paragraph and it is in accord with the results of earlier findings of Keys et al. (1965) that the response to diet is in proportion to the baseline levels. The finding that women respond quantitatively as predicted by the equations of Hegsted and Keys, which were developed in men, strongly suggests a similarity in response between men and women. This similarity was noted more directly by Katan et al. (1988b) in reanalysis of studies carried out previously in monks and nuns in Dutch and Belgian Trappist monasteries. The average degree of response in these studies was the same for the two sexes.

In the analysis of Katan et al. (1988b), a wide variation was noted in individual responses to dietary modification. Much of this variation, however, was due to seemingly spontaneous, random, within-person fluctuations of serum cholesterol. Even so, systematic differences in responsiveness of subjects to changes in dietary fatty acids were observed. Moreover, very few subjects were entirely nonresponsive to dietary change. These workers believe that pure "hyper- and non-responders" to saturated fatty acids are relatively rare, and whenever cases of apparent extreme susceptibility or resistance to fat-modified diets are encountered in clinical practice, these should be attributed first to chance excursions of serum cholesterol rather than to inherent deviations in metabolic susceptibility to dietary change.

Although men and women seemingly have a similar responsiveness to saturated fatty acids, it can be asked whether all populations have the same propensity to increase serum cholesterol levels by saturated fatty acids. Prewitt et al. (1988) reported similar levels of LDL-cholesterol and saturated fatty acid intakes in black children and white children, which suggests a similar inherent responsiveness. In this comparison, however, blacks tended to have higher levels of HDL-cholesterol and lower levels of VLDL-cholesterol and triglycerides on the same diet. Whether these latter differences represent a racial difference in responsiveness for HDL and triglycerides to saturated fatty acids is not clear. In a recent report by van Horn et al. (1991), intakes of saturated fatty acids were similar for children and adults, whether black or white, and levels of LDL-cholesterol levels were comparable for the two races.

These results are consistent with the concept that saturated fatty acids affect LDL-cholesterol levels similarly in blacks and whites, but a more direct study is required before a definite conclusion can be drawn.

Although without question diets high in saturated fatty acids will raise serum cholesterol levels in metabolic ward studies, and this effect can be readily observed between populations, we might ask whether an influence of dietary saturates can be detected as a determinant of serum cholesterol within populations. If not, such a finding might cause some people to wonder whether variability in intake of saturated fatty acids is a particularly important determinant of the variability in serum cholesterol levels in the general population. Several previous studies, although not all, were able to identify an independent effect of saturated fatty acids on cholesterol levels within certain populations. Moreover, Keys (1988) pointed out that because of large differences in the inherent metabolism of lipoproteins among individuals within the general population, failure to find an effect of a given dietary factor in
no way negates the role played by that factor in the average level of serum cholesterol for that population. One reason for failure to observe a correlation between serum cholesterol concentrations and a particular nutrient intake (e.g., saturated fatty acids) is that the range of intakes within a population may be relatively small. Even so, in some recent cross-sectional studies, a significant relation between diet composition (mainly saturated fatty acids) and serum cholesterol levels has been noted. For example, van Horn et al. (1991) reported that in the Coronary Artery Risk Development in Young Adults (CARDIA) Study the Keys’ score (determined mainly by saturated fatty acids) was significantly correlated with serum total cholesterol and LDL-cholesterol in white men and women. In another survey of 4903 Italian men and women, ages 20 to 59, Trevisan et al. (1990a) found that increased saturated fatty acids in the form of butter was correlated with significantly higher levels of serum cholesterol in men; this same relationship, however, could not be demonstrated for women. These same investigators (Trevisan et al., 1990b) also reported that intake of atherogenic foods (foods high in cholesterol and saturated fatty acids) was accompanied by higher levels of serum cholesterol within the Italian population. This latter finding seemingly was independent of several possible confounding variables — age, adiposity, alcohol intake, and cigarette smoking.

In contrast, in the Lipid Research Clinics (LRC) Prevalence Study (Prewitt et al., 1988), a significant correlation was not found between intakes of saturated fatty acids and LDL-cholesterol in black children and white children. This failure may have been due to the inherent limitations of such comparisons noted above by Keys (1988). On the other hand, in the Dutch Nutrition Surveillance System, Löwik et al. (1991) noted that intakes of saturated fatty acids were positively correlated with serum total cholesterol in elderly women. Although this relation did not reach statistical significance in men, intakes of monounsaturated fatty acids, which were highly correlated with intakes of saturates, also were positively associated with cholesterol levels in men. The authors conclude that elderly people are still sensitive to the cholesterol-raising effects of saturated fatty acids and would benefit from modification of their diets. In addition, in their examination of the relationship between dietary factors and serum cholesterol values in the black population of the South African Cape Peninsula, Steyn et al. (1990) noted that intakes of saturated fatty acids contributed to variations in total cholesterol levels in men. In women, this relation was not statistically significant, but total cholesterol levels were correlated significantly with the inverse of the polyunsaturated/saturated fat ratio. Finally, Thorogood et al. (1990) studied a cross-sectional sample from a large prospective cohort of people eating different diets in Britain and compared diet composition to cholesterol levels; in this study, a positive correlation was found between the Keys score (reflecting primarily intake of saturated fatty acids) and serum total cholesterol levels. Thus, in spite of some early failures to find a relation between dietary saturates and cholesterol levels within populations, and in contrast to a clear correlation between populations, many recent studies of the past three years have demonstrated a positive link within populations; this strengthens the previous conclusion that saturated fatty acids contribute significantly and importantly to raising serum cholesterol levels within high-risk populations and thus are an important atherogenic factor.

Although unanswered questions persist about the action and variability in individual responsiveness to saturated fatty acids, their overall consistency in raising serum LDL-cholesterol levels justifies the general recommendation that their intake be reduced in populations at high risk. Since it does not necessarily follow that this recommendation will be heeded, new questions arise: namely, has the intake of saturated fatty acids declined recently in the United States, and is it possible to intervene in populations to modify intakes of saturated fatty acids and thereby to lower cholesterol levels?

Slattery and Randall (1988) examined trends in nutrient composition of the diet as indicated by changes in national food disappearance data and USDA household survey data between 1909 and 1980. Depending on the methods employed, somewhat different results are obtained. The following general conclusions however were drawn from their survey, although the limitations of the database must be kept in mind. Over the past 40 years consumption of saturated fatty acids in the form of pure fat
(butter and lard) apparently has decreased progressively. At present, the largest contributors to dietary fat are meat, fish, and poultry. The red meat (beef and pork) consumed in the United States unfortunately is unnecessarily high in fat because of the premium paid for a high-fat content. Consumption of red meat increased after 1940, providing higher intakes of saturates. Poultry consumption rose strikingly later in the 1940s, which also has contributed to saturated fatty acids. Intake of saturated fatty acids from red meat over the past two decades has been relatively stable, or perhaps has declined somewhat. On the other hand, consumption of cheese has increased and partially offsets a decline in butter-fat intake. On balance, when all of these changes are considered, there may have been a decreased intake of saturated fatty acids by the American public during the past 30 years, although a longitudinal decline in intake of saturates as percentage of total calories is difficult to document because of limitations of the database. These overall assessments support previous data reviewed in the recent report of the National Research Council (1989) which suggests that intake of saturated fatty acids in the American diet has declined somewhat over the past two decades.

In the attempt to determine whether changes in diet, mainly a reduction in saturated fatty acids, actually correlate with cholesterol levels, investigations in the Minnesota Heart Study (Burke et al., 1991; Graves et al., 1990) compared changes over the past decade. They found a small reduction in intake of saturated fatty acids apparently associated with a decrease in serum cholesterol levels of 5 to 6 mg/dL. All of this change, however, may not have been due to a reduction in saturated fatty acids per se because other factors (weight loss and drug therapy) may have contributed. Murray et al. (1990), investigators of the Minnesota Heart Health Program, indicate that low-intensity interventions in a community may enhance cholesterol lowering.

A final question to be addressed is whether a reduced intake of saturated fatty acids will actually reduce the risk for CHD, as demonstrated by clinical trial. Previous dietary trials have supported such a concept, although a definitive diet–heart trial has not been deemed feasible (U.S. Department of Health, Education and Welfare, 1971). An interesting result was obtained by the recent Lifestyle Heart Trial (Ornish et al. 1990); this latter was a randomized, controlled trial in which 28 patients were assigned to an experimental group (low-fat vegetarian diet, weight reduction, stopping smoking, stress-management training, and moderate exercise) and 20 patients to a usual-care group. Coronary angiography was carried out before and one year after intervention. Significantly more patients in the experimental group had regression of coronary atherosclerosis than did usual-care subjects. Mean body weight and SD of the experimental group at baseline was 91.1 (15.5) kg; at 12 mo it was 81.0 (11.4) kg. This small trial was suggestive that comprehensive lifestyle change may favorably modify coronary atherosclerosis, but it is not possible to say exactly what was the beneficial factor(s), whether a decrease in intake of saturated fatty acids or other factors. Certainly, the question of the specific role of saturated fatty acids must be taken in the light of the multifactorial etiology of CHD, and while it is probable that dietary saturated fatty acids raise the risk for CHD, they are only one of several factors. This explains why it is difficult (if not impossible) to design a clinical trial to test the specific effect of saturated fatty acids on CHD end points.

The safety of public health programs aimed at reducing serum cholesterol levels in whole populations as well as intervention programs in selected groups of subjects has been questioned by some investigators who have noted evidence of disturbing associations between low serum cholesterol levels and survival. Examples include an increased frequency of hemorrhagic stroke in hypertensive subjects with levels <160 mg/dL (Iso et al., 1989), and in men, an increased frequency of cancer, in particular lung cancer, as cholesterol levels drop from ≥254 mg/dL to ≤195 mg/dL (Isles et al., 1989) and lung cancer deaths in men at cholesterol levels under 170 mg/dL (Keys et al., 1985). A recent analysis of total mortality from CHD, cancer, and causes unrelated to illness in six primary prevention trials of cholesterol reduction indicated a protective effect against death from CHD, no consistent association between cholesterol levels and cancer prevalence, no effect on total mortality but a significant increase...
in deaths from accidents, suicides, and violence (Muldoon et al., 1990). However, further analysis of results from the LiRC Coronary Primary Prevention Trial indicated that the excess deaths resulting from accidents, suicide, and violence in that study could not be attributed either to treatment or cholesterol lowering itself and were probably the result of chance (Wysowski and Gross, 1990). Also, the analyses from all randomized controlled trials of cholesterol lowering by Yusuf et al. (1988) indicated that lowering cholesterol was not significantly associated with increased risk of noncardiac–related deaths. The question of possible risks associated with lowering cholesterol was discussed at a National Institutes of Health Conference on Low Blood Cholesterol Levels: Disease Associations, on October 9 and 10, 1990. The conferees concluded that the evidence available at that time did not warrant change in dietary recommendations on intakes of fats and cholesterol. Publication of the conference proceedings is pending.

**Conclusions.** Current recommendations call for less than 10 percent of total calories as saturated fatty acids. This recommendation represents a compromise between two opposing needs: (a) to achieve a maximal reduction in serum cholesterol levels through lowering saturated fatty acids and (b) to maintain a palatable diet that the American public will accept. Certainly a further reduction in intake of saturates to well below 10 percent of calories would lower serum cholesterol levels still more, but extreme recommendations for the general public are not realistic. Thus the current recommendation of less than 10 percent of total calories appears to be a reasonable balance between realistic possibilities and potential benefit. The emphasis for reducing intakes of saturated fatty acids, of course, should be on those with cholesterol–raising potential.

The major sources of saturated fatty acids in the American diet are animal fats. These include meat fat, butter fat, and eggs. The largest portion comes from meat fat, and to achieve the desired intake of saturated fatty acids, it will be necessary to reduce meat–fat consumption, i.e., fat on outside of meat, high–fat cuts such as hamburger, processed meats, and tallow and lard used in cooking and bakery products. A reduction in butter fat consumption (e.g., whole milk, ice cream, cheese, butter) also will further decrease saturated fatty acids. Decreased intake of egg yolk will curtail both saturated fatty acids and cholesterol in the diet. Since reduction in animal fats does not necessarily mean a reduced intake of the nonfat portion of animal products, the latter can be retained in cholesterol–lowering diets. The fat of animal products does not carry any inherent nutritional components other than total energy. The latter quality is of dubious value for most Americans above the age of two, and any extra requirements for energy can be easily filled with other products that do not raise the serum cholesterol level. Plant sources also provide some of the saturated fatty acids in the American diet. The tropical oils (palm oil, coconut oil, and palm kernel oil) are especially rich in serum–cholesterol raisers. Recent attempts by industry to reduce use of tropical oils in their products are laudatory, but their replacement by other oils, relatively high in cholesterol–raising saturates, e.g., cotton seed oil, may have blunted the desired intent. The presence of some saturates in many nutritious vegetable products prevents the complete elimination of saturated fatty acids from the American diet.

Certainly, individuals with high blood cholesterol should make an extra effort to decrease dietary saturates, but even those with borderline–high or desirable cholesterol levels could achieve an additional reduction in cholesterol levels by further restricting saturated fatty acids. All people in the United States public therefore will potentially benefit from a reduction in CHD risk. It can be estimated from metabolic ward studies that lowering intakes of cholesterol–raising saturated fatty acids by 7 percent of total calories will decrease cholesterol levels by approximately 20 mg/dL, which should translate into a CHD risk reduction of about 20 percent. This 20 percent reduction, if true, could represent a substantial reduction in total CHD rates. This estimate, of course, is based on indirect evidence — epidemiologic data, clinical investigation, and prevention trials using drugs. Although several primary prevention trials of the dietary type add support for this approximation, a
definitive diet–heart trial, which features primarily a reduction in saturated fatty acids, has never been carried out. The lack of such a trial makes it impossible to know whether the above estimate would be confirmed precisely in practice, but this should not stand in the way of the general recommendation to decrease intake of saturated fatty acids.

Finally, it must be remembered that the saturated fatty acids in the American diet consist of a series of fatty acids ranging in chain length from 8 to 18 carbon atoms and only those with 12, 14, and 16 carbon atoms raise cholesterol levels. The variability in cholesterol-raise raising potential for different saturated fatty acids opens new opportunities for manufacture of foods containing lesser amounts of cholesterol-raising saturates and replacement by other saturates that are not cholesterol raisers, i.e., medium-chain fatty acids and stearic acid. To achieve this exchange, current food labeling practices with respect to saturated fatty acids will have to be modified; the potential to raise cholesterol levels and not the category of saturates in general will have to be noted.

C. OBESITY AND OVERNUTRITION

An intake of total calories exceeding energy expenditure, and resulting in obesity, is another dietary factor influencing the serum lipoproteins. It has been known for many years that obese people have higher triglyceride levels and lower HDL-cholesterol concentrations than nonobese individuals. That obesity is accompanied by higher levels of LDL, however, has not been certain. This latter question is of considerable importance for diet recommendations, and it can be reviewed in the light of recent reports on the relation of nutritional status, energy intake, and obesity to serum lipids and lipoproteins.

In Western populations, the serum cholesterol level (including LDL-cholesterol) increases with age, but the reasons for this rise are not well understood. One possibility is that increasing obesity with age is a contributing factor. To examine whether a rise in body weight with age can account in part for the increase in cholesterol levels, Berns et al. (1988) did a longitudinal study of 99 men and 70 women between the ages of 20 and 30. Regression analysis of their data showed that in men a change in body mass index (BMI) partially explained changes in cholesterol levels; this same effect, however, was not observed in women. There was no correlation between changes in diet composition and cholesterol levels. The authors therefore concluded that the rise of serum cholesterol levels between the ages of 20 and 30 is not the result of changes in food composition but can be explained in part to increasing obesity. In a preliminary report, Denke et al. (1991) noted that increasing body mass indexes with age in the NHANES II survey were associated with higher levels of total and LDL-cholesterol, and lower HDL-cholesterol.

Several cross-sectional studies within populations have been carried out to compare body weight parameters to cholesterol levels. In a survey of 7188 whites in South Africa, Steenkamp et al. (1990) noted that serum total cholesterol levels are correlated with the degree of obesity. In young-adult, Dutch men, Berns et al. (1990) reported that estimated body fat content was positively correlated with serum cholesterol concentrations. These workers concluded that obesity almost certainly is a major determinant of serum lipoprotein levels within populations. In the CARDIA study (Van Horn et al., 1991), which included black and white men and women, ages 18 to 30 years at baseline, multiple linear regression analysis showed that the body mass index was positively and significantly correlated with total-cholesterol and LDL-cholesterol levels and inversely correlated with HDL-cholesterol across all race-sex groups. The BMI indeed was more strongly and consistently associated with higher total cholesterol in this age group than any other factor examined. In the black population of the South African Cape Peninsula, the BMI likewise was positively correlated with total cholesterol levels (Steyn et al., 1990). Thus, recent data from several sources provide strong supporting evidence that obesity is a cause of increased levels of total cholesterol and probably LDL-cholesterol.
Conclusions. The detrimental effects of obesity on health are well recognized. The complications of obesity include various dyslipidemias (high triglycerides and low HDL−cholesterol), hypertension, diabetes mellitus, gallstones, and possibly even cancer (Grundy and Barnett, 1990). The recognition of these detrimental effects has led to many recommendations that achievement and maintenance of ideal body weight are desirable. On the other hand, the extent to which being overweight raises the total cholesterol and LDL−cholesterol has not been entirely clear in the past, and the primary emphasis has been put on changes in diet composition (saturated fatty acids and cholesterol) in most dietary recommendations. Still, in recent years, the evidence implicating obesity in the causation of diet−induced hypercholesterolemia has been growing rapidly. This evidence provides a stronger reason to emphasize weight reduction for obese people as a major element in the management of high serum cholesterol.

One of the characteristics of obesity is that the increase in serum total cholesterol is distributed between both LDL and very low density lipoproteins (VLDL), whereas saturated fatty acids and cholesterol in the diet raise mainly LDL−cholesterol. Since the National Cholesterol Education Program (1988) identified high serum LDL−cholesterol as the primary target for cholesterol lowering, this leaves open the question of significance of the obesity−induced increase in VLDL−cholesterol (versus LDL−cholesterol) for CHD risk. Whether VLDL particles are as atherogenic as LDL has been a question of dispute, although there is a growing body of data that VLDL as well as LDL, has atherogenic potential; if so, the increase in VLDL−cholesterol levels that accompany obesity must be considered in addition to LDL in the atherogenic equation. A recent report (Vega and Grundy, 1990) indicated that the (VLDL+LDL) cholesterol level is highly predictive of serum total apolipoprotein B levels, another putative risk factor for CHD. Obesity thus appears to raise the apolipoprotein B levels more than LDL−cholesterol levels, and its influence on apolipoprotein B concentrations may be another way to view its adverse influence on the total spectrum of atherogenic lipoproteins.

Since obesity is a major cause of dyslipidemia in the American population, the causes underlying the obese state are important to understand if effective means are to be instituted to reduce body weight in overweight people. Unfortunately, the causes of obesity are poorly understood. Americans in general are more overweight than many other populations that on the average consume more total energy. This fact leads some workers to believe that lack of exercise, and not total energy consumption, is the predominant cause of obesity in the United States. Other investigators however consider high−fat intakes to be a major cause of obesity in Americans. This latter view provides one justification for lowering total fat intake. On the other hand, other factors in the causation of obesity cannot be ignored. These include genetics, family and cultural attitudes, socioeconomic status, inherent metabolic and hormonal regulation, and psychological factors. The causation of obesity undoubtedly is a complex issue, and simple solutions will not be immediately forthcoming. Nonetheless, a major research effort to identify and modify these causes appears justified, and if successful, this could have a significant impact on reducing CHD risk through elimination of the metabolic consequences of excess body weight.

D. OMEGA−6 POLYUNSATURATES

The major fatty acids of the diet in quantitative terms are the unsaturated fatty acids. This category of fatty acids includes four major groups: (a) ω−6 polyunsaturates, (b) ω−3 polyunsaturates, (c) cis monounsaturates, and (d) trans monounsaturates. All four categories have different effects on the metabolism of lipids and lipoproteins, and beyond this, they could have independent effects on the atherogenic process. And finally, they may influence other metabolic processes and thus affect the development of other diseases. Recent reports on each of these categories of unsaturated fatty acids therefore will be reviewed. This section will examine the ω−6 polyunsaturates.
The predominant fatty acid in this class is linoleic acid (18:2 ω6). It has 18 carbons, and 2 double bonds, the last being 6 carbons removed from the terminal methyl group. When the literature refers to "polyunsaturates", unless otherwise indicated, this usually means linoleic acid. This fatty acid is found in plant products, and it cannot be synthesized by animals. When present in animal foods, it has been derived from the animals' diet. Since the 1950s, linoleic acid has been thought to have unique serum cholesterol-lowering properties. In the equations developed by Keys and coworkers (1965), and Hegsted and coworkers (1965), saturated fatty acids were indicated to raise the serum total cholesterol levels relative to carbohydrates, which were considered to be "neutral" with respect to cholesterol levels. According to these equations, saturates increase cholesterol levels twice as much as linoleic acid lowers them, both relative to carbohydrates. These equations have had a great influence on nutrition education and the food industry, and recommendations to reduce dietary saturated fatty acids and to increase linoleic acid have been widespread. The food industry has responded to this recommendation by increasing production of linoleate-rich oils, and the consumption of linoleic acid in the United States has increased by several percent of total calories over the past 40 years. The idea that polyunsaturates (linoleic acid) lower cholesterol levels whereas saturates raise the levels has led to describing diets in terms of the polyunsaturated/saturated (P/S) ratio, accordingly the higher the P/S ratio of the diet, the better. In addition to lowering cholesterol levels, other beneficial effects have been attributed to linoleic acid on the basis of limited experimental and epidemiologic data. For example, it has been reported that high intakes of linoleic acid will (a) lower the blood pressure, (b) protect against cardiac arrhythmias, and (c) independently protect against development of coronary atherosclerosis and CHD.

In spite of widespread enthusiasm for increasing dietary linoleic acid over the past 40 years, several issues have been raised during the past 15 years that call this concept into question. For example, no large populations have ever consumed large quantities of linoleic acid (over 10 percent of calories) for long periods with proven safety; indeed, there are few epidemiologic data on intakes greater than 7 percent. In laboratory animals, moreover, high intakes of linoleic acid can suppress the immune system and promote development of cancer. Human studies furthermore have demonstrated that consumption of large amounts of linoleic acid (over 10 percent of calories) lowers HDL-cholesterol and may predispose to cholesterol gallstones. Finally, there is growing interest in the process of lipid peroxidation in the pathogenesis of several diseases (e.g., cancer and atherosclerosis), and since linoleic acid is highly susceptible to oxidation, enrichment of lipoproteins and body tissues with this fatty acid is worrisome. The recent literature, therefore, can be examined for the pros and cons of recommending moderately high amounts of linoleic acid in the American diet.

Rose (1989) recently reviewed available epidemiologic evidence as it relates to effects of dietary linoleic acid on trends of CHD in different countries. He noted that "in the United States and Australia the changing balance of polyunsaturated to saturated fatty acids correlates better with the fall in CHD than do changes in total fat or saturated fat intake". A similar trend was noted in the United Kingdom (UK); the P/S ratio in the UK apparently rose from 0.24 in 1980 to 0.35 in 1985, and this change coincided with a fall in CHD. In contrast, in the USSR, the P/S ratio fell from 0.5 to 0.3 between 1965 and 1977, and recently there has been an alarming increase in CHD mortality. Rose thus believes that "the P/S ratio is probably one of the most potent determinants of CHD rates and trends and that its practical importance should be emphasized accordingly". At the same time, he acknowledges that the concept of the P/S ratio is a gross oversimplification because it does not take into account several issues: (a) different types of saturated fatty acids that may vary in their ability to raise the cholesterol level, (b) ω-6 vs ω-3 polyunsaturates, (c) evidence from the Seven Country Study (Keys et al., 1966) showing low rates of CHD in populations consuming large amounts of monounsaturates (olive oil) and low intakes of saturated fatty acids, and (d) the unresolved issue of biological effects of hydrogenation of polyunsaturated vegetable oils. Further, a change in the P/S ratio fails to indicate whether the predominant change resides with saturated or polyunsaturated fatty acids. For example, if intake of
saturates in the American diet should fall from 14 percent of energy intake to 7 percent, the P/S ratio would increase from 0.5 to 1.0 without any change in consumption of polyunsaturates.

In another review, Oliver (1989) examined the evidence for benefit of dietary linoleic acid for the prevention of CHD, and he noted that populations with a high prevalence of CHD, such as Scots and Finns, have a low percentage of linoleic acid in adipose tissue. In these populations, moreover, patients with CHD have a lower linoleic acid content of adipose tissue than nonCHD people. This difference might have two explanations: first, linoleic acid may have a direct protective effect; but second, cigarette smoking may be a confounding variable because smokers in general have been found to be relatively deficient in tissue levels of linoleic acid. The mechanism for the latter effect is not well understood. Oliver (1989) nonetheless concludes that a case can be made for recommending higher intakes of linoleic acid to protect against CHD.

In the past, several clinical trials have been carried out to determine whether a change in diet will reduce the risk for CHD. In most of these trials, the major comparison has been between diets high in saturates and diets high in linoleic acid. In general, the results of these trials have been equivocal. Several have been suggestive of a benefit of a high-linoleic diet, but not definitive. A similar result was reported in 1989 by Frantz et al. (1989) for the Minnesota Coronary Survey. This study was a 4.5-year, open-enrollment, single end-time, double-blind, randomized clinical trial conducted in 6 Minnesota state mental hospitals and one nursing home. It involved 4393 institutionalized men and 4664 women. The trial compared a diet high in saturated fatty acids (39 percent fat energy, 18 percent saturates, 5 percent polyunsaturates, 16 percent monounsaturates, 446 mg/d cholesterol) with a diet high in polyunsaturates (38 percent fat, 9 percent saturates, 15 percent polyunsaturates, 14 percent monounsaturates, and 116 mg/d cholesterol). The mean level of serum cholesterol in the treatment group was 175 mg/dL, and it was 203 mg/dL in the control group; therefore a major difference in cholesterol levels was obtained. For the entire study population, no differences were observed between the two groups for cardiovascular events, cardiovascular deaths, or total mortality; even so, a favorable trend for all of these end points occurred in the younger age group. Thus, this study, like previous dietary trials, was suggestive that replacement of saturated fatty acids with linoleic acid leads to a reduction in coronary risk, but because of limitations in number of participants and duration of study, a definitive result was not obtained.

Another potential benefit of dietary linoleic acid is that high intakes might lower the blood pressure. Claims to this effect have been made previously, although not all studies have produced consistent results. However, Iacono et al. (1989, 1990) have recently reiterated this claim. These workers summarized previous dietary studies carried out in the United States, Finland, and Italy. In their studies, consumption of 3 percent of energy as linoleic acid was compared to 10 percent. Although they speculated that the increase in dietary linoleic acid was primarily responsible for lower blood pressures on the 10 percent linoleic-acid diet, they could not rule out other possible factors (e.g., lower total fat). Indeed, Kestin et al. (1989) have reported that blood pressure is lower on a low-fat diet without an increase in polyunsaturated fatty acids.

On the negative side for linoleic acid, there is the concern that a high intake may increase the risk for developing cancer. Although this effect has been demonstrated repeatedly in experimental animals, the epidemiologic evidence has been thought to be minimal. Still, Prentice and Sheppard (1990) have recently reviewed all available epidemiologic data, and their analysis showed a positive and significant correlation between intake of polyunsaturates (mostly linoleic acid) and the incidence of certain types of human cancer (breast, colon, and prostate). Certainly, significant epidemiologic correlations do not constitute proof, but this analysis is suggestive and reinforces the recent recommendation that intake of linoleic acid should not exceed 10 percent of calories in the United States, i.e., an average intake should remain at the current level of about 7 percent of total calories (NRC, 1989).
Another concern about dietary linoleic acid is that it could promote the oxidation of LDL in the arterial wall. The latter process has been implicated as a significant factor in atherogenesis (Steinberg et al., 1989). If this mechanism pertains, factors that promote the oxidation of LDL might be atherogenic. One of these might be polyunsaturated fatty acids which are highly susceptible to free-radical oxidation, and their presence in LDL particles theoretically could render LDL particles more prone to oxidation. Indeed, two recent studies support this concept. Parthasarathy et al. (1990) reported that feeding of linoleic acid to rabbits made their LDL more susceptible to oxidation, compared with a diet high in monounsaturates. In addition, Berry et al. (1991) have reported similar results for humans. In their study, when 24 students were randomized to diets high in linoleic acid or oleic acid, those on the high-linoleic diet had LDL that were more easily oxidized than those on the high-oleate diet. If oxidation of LDL in the arterial wall thus proves to be a clinically important contributor to atherogenesis, concern about overenrichment of LDL particles with dietary linoleic acid naturally would exist.

Finally, Renaud and DeLorgeril (1989) have raised the possibility that a high consumption of linoleic acid may promote coronary thrombosis, a crucial event in the development of acute myocardial infarction. These investigators pointed out that in most clinical trials in which linoleic acid has been given in large amounts, the occurrence of CHD has not been reduced. They speculate that a high intake of linoleic acid may enhance formation of prostaglandins which can cause platelet aggregation and myocardial infarction. In their view, any protective effect of linoleic acid probably would be expressed at lower intakes, and higher intakes could be dangerous.

Conclusions. Current recommendations for ω-6 polyunsaturates, i.e., linoleic acid, are ambiguous. These recommendations generally fall under the heading of "polyunsaturates" but evidently are intended to include almost exclusively linoleic acid. Even with this said, there is some hedging on the recommendation for intake for the U.S. public. The American Heart Association recommends that consumption of polyunsaturates by Americans should be up to 10 percent of total calories. The National Cholesterol Education Program (1991) indicates that for the general public, polyunsaturated fat can provide up to, but no more than, 10 percent of total calories. The Program's recommendation further states that the average intake of ω-6 polyunsaturates in the American diet currently is about 7 percent of total calories, which is an acceptable intake. The National Research Council (1989) has indicated somewhat more forcefully that the U.S. public should not raise intakes of linoleic acid above current levels because of concern for increased cancer risk.

It is clear from the reports of the past three years that the desirable level of linoleic acid in the diet remains an open question. Higher intakes may slightly reduce LDL-cholesterol, perhaps decrease blood pressure by a small amount, and in other unknown ways possibly retard atherogenesis. On the other hand, a higher consumption may increase risk for some cancers, promote LDL oxidation within the arterial wall, and possibly raise the risk for coronary thrombosis. Clearly, more research is needed on this complex issue, but a reasonable recommendation may be to avoid both excessively low intakes of linoleic acid (below 4 percent of calories) and higher intakes (above 7 percent of calories). Within this range, the potential benefits may be available without the dangers of higher intakes.

The concept has emerged that linoleic acid is a metabolically active nutrient. This property apparently contrasts with several other nutrients, like monounsaturated fatty acids and carbohydrates, which are considered "neutral"; beyond the property of the latter to provide energy, they do not significantly modify metabolic processes, either positively or negatively. Linoleic acid, on the other hand, appears to be a biologically active molecule, being a precursor of prostinoids, enhancing membrane fluidity, and having susceptibility to oxidation. These various properties give it potential to be beneficial, detrimental, or both. Clearly, much more information is needed before the net balance of benefit versus risk can be assessed accurately for any given level of intake. For example, if high intakes of
linoleic acid lower LDL levels but make LDL more susceptible to oxidative modification, what is the net effect — benefit or harm? Do the actions of linoleic acid to promote membrane fluidity or to provide arachidonic acid to platelets retard or promote coronary thrombosis? Obviously, the gaps in our knowledge about the consequences of enriching the body's lipids with linoleic acid are enormous, and they deserve much more research. Until a better assessment has been made of the balance between harm and benefit, prudence suggests that intakes of linoleic acid not exceed current levels in the American diet.

E. OMEGA-3 POLYUNSATURATES

It is recognized that one of the expert reviews of diet-disease relationships in this series is on the topic, omega-3 fatty acids and heart disease. Nevertheless, for the sake of completeness of this review of dietary lipids and cardiovascular disease, the omega-3 polyunsaturates are briefly reviewed in the following.

The parent ω-3 polyunsaturated is linolenic acid (18:3 ω3). This fatty acid occurs in certain vegetable oils, particularly soybean oil, rapeseed oil, and linseed oil. The oils from ocean fish contain unusually large amounts of very-long-chain, ω-3 polyunsaturates that have their origins from linolenic acid of plant sources. The major fatty acids of this class are eicosapentaenoic acid (EPA) (20:5 ω-3) and docosahexaenoic acid (DHA) (22:6 ω-3). These two acids together constitute about 26 percent of fish oil fatty acids. Previous data suggest that linolenic acid and other ω-3 fatty acids (EPA and DHA) have about the same effect on LDL-cholesterol levels as linoleic acid. However, EPA and DHA in the diet have a greater influence on triglyceride metabolism than does dietary linoleic acid. High intakes of EPA and DHA actively lower triglycerides, especially in patients with hypertriglyceridemia. These fatty acids may have other actions whereby they reduce risk for CHD. For example, they interfere with platelet aggregation, which may reduce risk for coronary thrombosis, and some workers have speculated that they may modify cellular responses in the arterial wall to directly prevent atherogenesis. This article will review recent reports on the effects of ω-3 polyunsaturates. A critical review of effects of ω-3 polyunsaturates on plasma lipid and lipoprotein metabolism has been written by Harris (1989). Another valuable review on the same topic has been provided by Nestel (1990). Further, Cave (1991) has recently reviewed the effects of ω-3 polyunsaturates on animal tumorigenesis. In the latter review, Cave (1991) concluded that in most tumor models, high intakes of linoleic acid have promoted tumorigenesis, whereas ω-3 fatty acids have diminished this response.

One question that has not been answered fully is whether ω-3 and ω-6 polyunsaturates have similar (or different) effects on total and LDL-cholesterol levels in subjects without hypertriglyceridemia. Friday et al. (1991) have addressed this question in patients with heterozygous familial hypercholesterolemia (FH) and in normal control subjects. Diets high in ω-3 and ω-6 polyunsaturates were compared to a diet high in saturates, the latter in the form of butter. FH subjects lowered levels of total cholesterol by 36 percent and 26 percent on ω-3 and ω-6 diets, respectively, compared with the butter diet. LDL-cholesterol declined 31 percent and 29 percent and apo B levels decreased 28 percent and 27 percent on ω-3 and ω-6 diets, respectively. The normal subjects responded similarly. Thus, the authors conclude that subjects without hypertriglyceridemia respond in a similar fashion to diets low in saturated fatty acids and high in ω-3 and ω-6 polyunsaturates, with decreased LDL-cholesterol and LDL-apo B levels. Although the triglyceride-lowering effect of ω-3 fatty acids is well-established, some questions remain to be answered. For example, the effects of prolonged use of very low doses of ω-3 fatty acids on lipids and lipoproteins have not been defined. This prompted Radack et al. (1990) to study the effects of very-low, clinically practical doses of ω-3 polyunsaturates in patients with hypertriglyceridemia. Ten subjects received 2.2 g/d of ω-3 polyunsaturates and 7 others received 1.1 g/d. Eight received olive oil capsules as a control. Intakes of ω-3 acids produced no significant reductions in triglyceride levels, and in fact, concentrations of LDL-cholesterol and LDL
apo B actually rose on the ω-3 polyunsaturates. The authors thus concluded that relatively small doses of ω-3 fatty acids are of no benefit in hypertriglyceridemic patients, and may in fact be detrimental.

The mechanism of lowering triglycerides by ω-3 polyunsaturates is thought to be through inhibition of synthesis of VLDL triglycerides in the liver. However, several previous studies also are consistent with another mechanism, namely, an increased clearance of VLDL triglycerides. Therefore, Nozaki et al. (1991) examined the postheparin lipolytic activity response to ω-3 polyunsaturates in patients with primary hypertriglyceridemia. In this study, lowering of triglycerides by ω-3 fatty acids was not accompanied by an increase in postheparin lipoprotein lipase or hepatic triglyceride lipase; this observation is consistent with the general hypothesis that ω-3 fatty acids lower serum triglyceride levels by inhibiting the formation of VLDL triglycerides and not by promoting their clearance.

In another study on hyperlipidemic patients, Failor et al. (1988) examined whether ω-3 fatty acids are beneficial in patients with familial combined hyperlipidemia. Even though ω-3 polyunsaturates lowered serum triglyceride concentrations in these patients, total cholesterol and total apo B levels were not lowered by ω-3 fatty acids, and LDL-cholesterol and LDL apo B levels showed an upward trend. Thus, patients with familial combined hyperlipidemia apparently do not have a favorable response to ω-3 polyunsaturates. Similar results have been obtained in patients with diabetes mellitus, both insulin-dependent types (Mori et al. 1988) and noninsulin-dependent types (Schectman et al., 1988).

The question whether ω-3 polyunsaturates might have a beneficial effect on prevention of CHD has been examined in a review by Kromhout (1989). He concludes that the available data suggest that a low level of consumption of fish oil, taken with fish, may potentially be of benefit in the primary prevention of CHD. If this were the case, what might be the mechanism? Will fish oils reduce platelet aggregation and thereby prevent coronary thrombosis? Or would they directly inhibit atherogenesis at the vessel wall level? A few studies in laboratory animals raise the possibility of the latter, but not all studies are in accord; more importantly, no human data are available.

Let us next inquire whether ω-3 fatty acids might be useful in secondary prevention of CHD, that is, in preventing recurrence of cardiovascular complications after myocardial infarction. This question was addressed in the Diet and Reinfarction Trial (DART) (Burr et al., 1989), which was a randomized, controlled trial in 2033 men who had previous myocardial infarction. Patients entered four groups: (a) reduction in fat intake, (b) increase in ratio of linoleic acid to saturated fat, (c) increase in fatty fish intake, and (d) increase in fiber intake. Only the group that consumed fatty fish had a reduction in overall mortality. This group had a 29 percent decrease in 2-year, all-cause mortality, a result that was statistically significant, and the significance persisted after adjusting for 10 potentially confounding variables. The beneficial effect occurred almost immediately after starting fish consumption. It should be noted, however, that only 10 percent of patients in this trial took aspirin, and it is possible that the fish oil inhibited platelet aggregation and thereby prevented recurrence of coronary thrombosis. A more realistic trial therefore might be one in which fish oil is given in addition to aspirin, since in the United States most patients take aspirin indefinitely after myocardial infarction.

Another potential use of ω-3 fatty acids is after percutaneous transluminal coronary angioplasty (PTCA). This procedure is being used commonly in patients with coronary artery disease. In the majority of patients, the procedure successfully restores blood flow through the coronary arteries for prolonged periods; however, in 25 percent to 40 percent of patients, the treated vessels restenose during the first six months after PTCA. Some investigators have speculated that ω-3 polyunsaturates might prevent restenosis after PTCA. In fact, one strongly positive result from fish-oil therapy after PTCA was reported by Dehmer et al. (1988). These workers dilated 103 coronary lesions in 82 men,
and they were divided into control and treatment groups, the latter receiving 3.2 g/d EPA besides conventional antiplatelet therapy. All patients were subjected to repeat angiograms after 3–4 mo of therapy. The incidence of early vessel restenosis was 36 percent in the control group, but only 16 percent in the EPA group (p = 0.026). A similar finding was reported by Milner et al. (1989), who studied 194 patients. The control group of this study received standard antiplatelet therapy, and the treatment group the same with 4.5 g/d of EPA. For those who maintained EPA treatment, reocclusion rate was 19 percent, whereas it was 35 percent in the control group.

In another study, however, Reis et al. (1989) did not obtain these good results. They carried out a double-blind, randomized trial in 204 patients. Both the treatment group (6 g/d ω-3 fatty acid) and the control group (placebo) received PTCA. Restenosis was confirmed in most patients by repeat coronary angiogram six months later. In this trial, the incidence of restenosis was actually higher in the ω-3 group (34 percent) compared with control (23 percent). Therefore, it is unclear whether ω-3 polyunsaturates confer any benefit in prevention of restenosis after PTCA, and further trials will be required to give a final answer.

Conclusions. Current recommendations about ω-3 polyunsaturates are especially vague because little is known about their true benefit or harm. Even more than linoleic acid, the ω-3 polyunsaturates are biologically active molecules, the consequences of which are not fully understood. For example, they apparently interfere with platelet aggregation, which may reduce the risk of coronary thrombosis, but at the same time may predispose to gastrointestinal or cerebral hemorrhage in some people. They may suppress tumorigenesis under certain circumstances, but they also are highly susceptible to oxidation, and consequently, they theoretically could promote atherogenesis, carcinogenesis, and aging. Thus, recommendations for increasing ω-3 fatty acids for the purpose of preventing common chronic diseases must be made with caution and only after more conclusive data are available. The possibility that small amounts of these fatty acids are necessary in the diet for normal function of the nervous system and retina certainly deserves more research, but this issue should be separated from the use of ω-3 polyunsaturates to prevent or treat chronic disease. Since these fatty acids are biologically active, they deserve intensive investigation but not premature recommendation for their consumption by the general public.

F. CIS-MONOUNSATURATED FATTY ACIDS (Oleic Acid)

Oleic acid (cis 18:1 ω9) is the major monounsaturated fatty acid of the diet. It is synthesized both by plants and animals. Olive oil, canola oil, and high-oleic forms of sunflower oil and safflower oil are particularly rich in oleic acid. Previous studies have shown that oleic acid neither raises nor lowers the serum total cholesterol level relative to carbohydrates, and thus oleic acid has been called "neutral" in its action on serum cholesterol. It should be noted, however, that dietary carbohydrates tend to raise triglyceride levels and lower HDL-cholesterol levels relative to oleic acid. One potential advantage of oleic acid is that it has been consumed in large amounts for centuries in the Mediterranean region in the form of olive oil, and there is no evidence that it is harmful. Further, rates of CHD are relatively low in this region suggesting that it may have a "protective" effect against CHD. Whether this effect is an independent action of olive oil or is simply the result of its replacement of saturated fatty acids is not certain.

If oleic acid and carbohydrates similarly affect total cholesterol levels, and if oleic acid more favorably influences triglycerides and HDL, is it necessary to consume a low-fat (high-carbohydrate) diet to obtain a satisfactory lipid profile? Would not replacement of saturated fatty acids with oleic acid be sufficient? These questions were addressed by Ginsberg et al. (1990) in a randomized, double-blind trial involving 36 healthy young men. These workers evaluated the effects of both an American Heart
Association (Step 1 diet) (in which 30 percent of energy was supplied as fat: 10 percent saturated, 10 percent oleic acid, and 10 percent linoleic acid, 250 mg/d cholesterol) and an oleic acid–enriched diet (with 38 percent of energy as fat: 10 percent saturated, 18 percent oleic acid, and 10 percent linoleic acid, 250 mg/d cholesterol). These two diets were then compared to a more typical American diet (38 percent total fat, 18 percent saturated, 10 percent oleic acid, and 10 percent linoleic acid, with 500 mg/d cholesterol). Compared with baseline and the typical American diet, both the low-fat (Step 1) diet and the high–oleic acid diet produced equal lowering of plasma total cholesterol levels and LDL–cholesterol levels. The authors concluded that enrichment of the Step 1 diet with oleic acid does not alter the beneficial effects of the Step 1 diet on plasma lipid concentrations. From the viewpoint of cholesterol lowering, therefore, no advantage can be ascribed to a lower fat diet. Of course, there might be other benefits to a low–fat diet. For example, such a diet might facilitate weight reduction in obese people. It also might lower the risk for cancer, although in analysis of available epidemiologic data, Prentice and Sheppard (1990) found no evidence that monounsaturated fatty acids are linked to various cancers, different than what was found for saturated and polyunsaturated fatty acids.

Since dietary oleic acid does not lower HDL–cholesterol, whereas high–carbohydrate diets do, Mensink et al. (1989) raised the question of within which fraction of HDL does the lowering of HDL by dietary carbohydrates occur? At the same time they asked whether oleic acid retains the "coronary protective" HDL–2 fraction. Finally, they examined what happens to apo A–I levels during consumption of a low–fat (high–carbohydrate) diet compared to a diet high in oleic acid. In this study, they found that while the Keys' formula (which predicts no change in total cholesterol levels when carbohydrate is replaced by oleic acid) holds for LDL. It does not hold for VL LDL and HDL. These latter two lipoproteins change in opposite directions on high–oleate and low–fat diets. They further found that apo A–I levels decreased by 10.2 mg/dL in the high–carbohydrate group and rose by 2.6 mg/dL in the high–oleate group. The low–fat diet produced a lowering of both HDL–2 and HDL–3, whereas the diet high in oleic acid caused equal percentage lowering in HDL–2 and LDL, but HDL–3 rose slightly on the high–oleate diet.

Still another question about oleic acid is whether the equations of Keys and Hegsted are correct, namely, whether linoleic acid and oleic acid have different effects on total cholesterol, and by inference, LDL–cholesterol levels. In a recent review, Grundy and Denke (1990) detailed available data on this question. Although early studies certainly suggested that linoleic acid lowers cholesterol levels more than does oleic acid compared with saturated fatty acids, more recent investigations have thrown this concept into doubt, especially as it pertains to LDL–cholesterol. Several additional studies have addressed this issue in the past three years. In an important study, Mensink and Katan (1989) investigated outpatients using a solid–food diet to compare oleic acid and linoleic acid. Their findings indicated that total cholesterol and LDL–cholesterol lowering actions were identical for the two forms of unsaturated fatty acids. Similar results have been obtained in three other comparison studies (McDonald et al., 1989; Dreon et al., 1990; Wardlaw and Snook 1990), although these investigations were not of the size and rigor of that of Mensink and Katan (1989). In a more recent investigation, Berry et al. (1991) observed that a high–linoleate diet reduced total plasma cholesterol by 16 percent compared with 10 percent for a high–oleic acid diet. However, there was no significant difference in LDL–cholesterol lowering between the two diets. Thus, while it now appears that there is very little difference between linoleic acid and oleic acid in their quantitative effect on LDL–cholesterol levels, it remains possible that a large study might find a slightly greater LDL–lowering effect of linoleic acid, although this is by no means certain. In any case, in practical terms for LDL lowering, evidence for a substantial difference between oleic acid and linoleic acid in the diet is not strong.

When linoleic acid is fed in large amounts (10 to 20 percent of energy), there is a reduction in HDL–cholesterol levels compared with saturated fatty acids; this effect is not observed with diets containing a similar high percentage of oleic acid. The question has been raised whether lesser increases of
linoleic acid, say from 5 to 10 percent of energy consumption, will produce a detectable decrease in HDL–cholesterol levels, as compared to a diet high in oleic acid. Several studies (Dreon et al., 1990; McDonald et al., 1989; Mensink and Katan, 1989; Wardlaw and Snook, 1990) indicate that a significant lowering of HDL–cholesterol cannot be detected when intakes of linoleic acid are increased within this range.

**Conclusions.** In recent years, the recommendations about use of oleic acid in the diet have become more liberal. When the first recommendations for a 30 percent fat diet were made, the proposed intake of oleic acid was at a level of 10 percent of calories. More recently, the recommendation has increased from 10 percent to 15 percent of total energy intake from oleic acid. This more liberal range seems to reflect (a) the desire to lower intakes of saturates still more, (b) to avoid the possible dangers of higher intakes of polyunsaturated fatty acids, and yet (c) to allow total fat to comprise 30 percent of energy intake. The studies of the past three years are consistent with the concept that oleic acid can be safely substituted for saturated fatty acids in the diet, and so far there is no evidence that a high consumption of oleic acid promotes the development of other diseases. Oleic acid thus appears to have certain potential advantages over linoleic acid, and it can be substituted for saturates in the place of carbohydrates without detrimental effects on lipoprotein metabolism. The only potential disadvantage of a diet very high in oleic acid, i.e., 20 percent to 25 percent of total calories, is that it could promote the development of obesity if this level of consumption leads to an excessive intake of total energy. Current recommendations, however, do not call for such a high consumption of oleic acid.

It might be noted that oleic acid generally is not considered to be a "biologically active" fatty acid in the same sense that polyunsaturated fatty acids are. Oleic acid is not an important contributor to formation of active prostinoids, nor is it highly prone to oxidation. For these reasons, it may have less potential for some of the long–term adverse effects that could occur with polyunsaturated fatty acids.

G. **TRANS-MONOUNSATURATED FATTY ACIDS**

Another category of monounsaturated fatty acids are the trans isomers, which like cis monounsaturated fatty acids, have 18 carbons and 1 double bond. The most common trans isomer is elaidic acid, which has its double bond in the ω–9 position. Other trans isomers also occur, which have their double bond displaced up and down the chain on both sides of the ω–9 position. The physical structures of cis and trans monounsaturates differ significantly. The cis double bond causes the carbon chain to be bent; this bend interferes with packing of the molecules and thus lowers the temperature of crystallization. Oils rich in cis monounsaturates thus are typically liquid at room temperature. The trans double bond, in contrast, straightens out the carbon chain and makes it more rigid, like a saturated fatty acid. This rigidity promotes packing of fatty acid molecules and raises the temperature of crystallization, so that fats rich in trans monounsaturates usually are solids at room temperature (Mensink and Katan, 1990; Senti, 1985). The presence of trans monounsaturates explains why hydrogenation of polyunsaturated vegetable oils produces margarines and shortenings. In the process of hydrogenation, one double bond of linoleic acid is reduced, and the other double bond is randomized into either cis or trans configurations. Also, the remaining double bond can migrate up and down the carbon chain. Therefore, several trans isomers are present in hydrogenated vegetable oils. Trans fatty acids also are found in small amounts in fats of ruminants; about four to eight percent of the fatty acids in butter fat are of the trans variety. In some countries, margarines are produced by hydrogenation of marine oils, and since these oils are rich in EPA and DHA, the products are more complex and contain trans isomers of fatty acids with 20– and 22–carbon atoms (Mensink and Katan, 1990; Senti, 1985).
The "average" American consumes six to eight grams of trans fatty acids daily. This amount corresponds to about three percent of total calorie intake. Since trans fatty acids are not "natural", except when present in butter fat, the question naturally arises as to whether they are safe. Several issues might be raised. What is their fate in the body? Do they raise the serum cholesterol level, like saturated fatty acids, or are they neutral on cholesterol levels, like oleic acid? Finally, does long-term ingestion of trans fatty acids lead to side effects, such as promotion of carcinogenesis? The latter question is extremely difficult, if not impossible to answer. It should be much easier to determine whether trans fatty acids raise the serum cholesterol. Still, there is divided opinion about the answer to this question. Several studies have been carried out in the past to assess the effects of fats rich in trans fatty acids on cholesterol levels. The findings have been mixed. Some prior studies indicated that trans monounsaturated fatty acids raise the cholesterol level, like saturated fatty acids, whereas others have been unable to confirm a cholesterol-raising action (Senti, 1985).

To address this question further, Mensink and Katan (1990) recently compared an oil rich in trans fatty acids with one high in oleic acid in a study in 34 young women and 25 young men. Three mixed, solid-food diets were compared, and the diets were identical in composition except that they differed in 10 percent of their calories as fatty acids. In one, the comparison fatty acid was oleic acid, in another, it was trans monounsaturates, and in a third, it was saturated fatty acids. The source of the high-oleic fat was high-oleic sunflower seed oil. The high-trans oil was obtained by chemical randomization of the cis double bond of oleic acid in the high-oleic sunflower oil. The fat high in saturated fatty acid was contained in a special kind of margarine and shortening, this one being high in lauric and palmitic acid. The results of this study showed that the high-trans oil raises the serum total cholesterol level, compared with the high-oleic oil, but only about half as much as the high-saturated oil. However, the high-trans oil raised the LDL-cholesterol level almost as much as the high-saturated oil. The reason why the high-trans oil did not increase total cholesterol as much as the high-saturated oil is because the former reduced HDL-cholesterol levels, as compared with the high-oleic oil. Thus, the overall effect of trans monounsaturates on the lipoprotein profile appeared to be disadvantageous, i.e., it raised LDL-cholesterol and lowered HDL-cholesterol. Further, both saturated fatty acids and trans fatty acids caused a small, but statistically significant increase in triglycerides, compared with oleic acid.

The results of the study of Mensink and Katan (1990) raise the strong possibility that trans-monounsaturated fatty acids are LDL-raising fatty acids and thus have atherogenic potential. The apparent HDL-lowering effect of these fatty acids also is of concern since a low HDL-cholesterol is a well-established risk factor for coronary heart disease.

Certainly, the question must be raised whether the results of Mensink and Katan (1990) are generalizable to all sources of trans fatty acids, and in fact, whether they can be reproduced. Although further study clearly is needed to address these questions, it must be recognized that this study included a large number of subjects of both sexes; it was a well-designed study; it was executed under rigorous conditions; and the results are highly consistent. If future studies are not carried out with the same rigor and if different results are obtained, such results must be viewed with some skepticism. This is not to say that additional well-designed studies would not be valuable, but poorly designed studies could muddy the waters and do more harm than good.

Fortunately, the intake of trans fatty acids in the American diet on the average is relatively low (about 3 percent of total calories), although many individuals may consume a considerably higher percentage. Let us consider the impact of trans fatty acids on cholesterol levels among Americans as it relates to cholesterol-raising fatty acids. If the average intake of saturated fatty acids in the United States is 14 percent of total calories, and if trans fatty acids are added to this total, at first glance this would appear to bring cholesterol-raising fatty acids to about 17 percent of total calories. This, however, is not entirely true, since about 3 percent of saturates are not cholesterol raisers, i.e., they are stearic.
acid. As a result, therefore, adding trans fatty acids to saturated cholesterol raisers will bring the total of cholesterol raisers to 15 percent to 14 percent of calories. Current recommendations for saturated fatty acids are for less than 10 percent of total calories. Since this recommendation does not exclude stearic acid, which does not raise the cholesterol, then the unstated recommendation for cholesterol-raising saturated fatty acids is for an intake of 7 percent (or less) of total calories. If trans fatty acids are added to cholesterol-raising saturated fatty acids, this means that the United States public is now consuming twice the unstated but implied recommended intake for cholesterol raisers, i.e., 14 percent vs 7 percent of calories. Although current recommendations do not single out cholesterol-raising fatty acids, this certainly is the intention when referring to saturated fatty acids. If the recommendations are going to persist with the concept of saturated fatty acids, instead of cholesterol-raising fatty acids, then it may be appropriate to add trans fatty acids to the category of "saturates," which will raise the average American consumption of "saturates" to 16 percent to 17 percent of total calories. The recommended reduction of "saturates" to less than 10 percent of total calories then would have the desirable effect of lowering cholesterol-raising fatty acids by more than 7 percent of calories. For the purpose of food labeling, the alternatives, therefore, appear to be to add trans fatty acids to the saturated fatty acid category, or to create a new category of nutrient called "cholesterol-raising fatty acids." The latter would have the advantage of defining food composition according to the intended effect, and it would allow for increases in stearic acid at the expense of cholesterol-raising fatty acids, both saturated and trans fatty acids.

If the results of the recent study (Mensink and Katan, 1990) can be taken at face value, then it would be reasonable to ask the food industry to seek alternatives to trans fatty acids in their products. Since it will not be easy to develop alternatives on a large scale, it is not reasonable to ask for a reduction in trans fatty acids overnight. Nonetheless, a gradual reduction in their intake seems prudent. The major sources of trans fatty acids are margarines and shortenings, but it should be noted that a great many processed foods contain hydrogenated vegetable oils, all of which contain some trans fatty acids.

Finally, the question remains whether trans monounsaturates have any adverse effects other than modifying the lipoprotein levels (raising LDL and lowering HDL). Certainly, this possibility has been raised in speculation (Booyens et al., 1988), but no "hard" data support such a concept. Still, since the American diet undoubtedly will contain trans fatty acids for many years, additional studies on other metabolic effects of these fatty acids should be carried out, at least in animals.

Conclusions. Until recently there was the general belief that transmonounsaturates are "neutral" with respect to serum cholesterol levels. However, the recent findings of Mensink and Katan (1990) strongly suggest that these fatty acids have an adverse effect on serum lipoprotein levels, especially raising LDL-cholesterol levels. Still, it hardly seems prudent to alter general dietary recommendations on the basis of a single study, albeit an excellent piece of investigation. Further carefully controlled studies thus appear to be in order before definitive recommendations can be made about trans fatty acids for the American diet.

H. CARBOHYDRATES

Carbohydrates can be considered in two categories: absorbable and nonabsorbable. The former consists of monosaccharides, disaccharides, and polysaccharides (starches). The nonabsorbable carbohydrates comprise the fibers. This article will examine the influence of absorbable carbohydrates; dietary fiber will be considered elsewhere. Since the early 1960s, carbohydrates generally have been considered to be "neutral" on cholesterol levels, neither raising nor lowering the levels. In this way they resemble oleic acid. Their neutrality, however, does not extend to all lipids. For example, more recent studies indicate that, compared with fats, carbohydrates raise serum triglycerides and
reduce HDL-cholesterol levels in many subjects. These changes are potentially detrimental, but since populations that consume low-fat diets often have low rates of CHD, many workers hold the view that the actions of carbohydrates to raise triglycerides and to lower HDL are not harmful.

Although high-carbohydrate diets have been shown many times to increase serum triglycerides in short-term, metabolic-ward studies, the claim has been made that this response is transitory. For example, the argument has been set forth that populations around the world that consume low-fat diets do not have elevated triglyceride levels. To determine whether this latter argument is valid, West et al. (1990) studied 719 boys from different populations throughout the world. These populations had marked differences in long-term intake of carbohydrate. The boys ranged in age from 8 to 9 years, and came from 12 different countries (8 in Europe, 3 in Africa, and 1 in Asia). Boys from populations in which the diet was higher in carbohydrate and lower in fat had lower levels of LDL-cholesterol but higher fasting serum triglycerides and lower HDL-cholesterol levels than boys having higher-fat, lower-carbohydrate diets. The results of this study thus indicate that long-term ingestion of higher-carbohydrate diets leads to higher triglyceride (and lower HDL-cholesterol) levels and suggest that at least part of the triglyceridemia is permanent. However, some investigators still regard the actions of a high-carbohydrate diet on triglyceride and HDL levels as transitory. Other confounding variables such as types of fats consumed and intakes of protein and micronutrients were not reported in the studies.

The influence of dietary carbohydrate on lipid metabolism is not fully understood. Important questions remain to be answered; for example, how do carbohydrates (a) raise triglycerides?, (b) lower LDL-cholesterol (relative to saturated fatty acids)?, and (c) lower HDL-cholesterol levels? The mechanisms whereby carbohydrates raise triglycerides and lower LDL-cholesterol were recently addressed by Abbott et al. (1990). These workers examined the kinetics of VLDL, intermediate density lipoprotein (IDL), and LDL apo B and VLDL triglycerides in nondiabetic and noninsulin-dependent diabetes mellitus (NIDDM) patients during the feeding of high-fat and high-carbohydrate diets. The high-fat diet was rich in saturated fatty acids. The high-carbohydrate diet led to a decrease in LDL-cholesterol. Changes in triglyceride levels were variable, some patients showing an increase, and others little change. The major action of the high-carbohydrate diet appeared to be to decrease the conversion of VLDL to LDL, possibly by interfering with the normal catabolism of VLDL triglycerides. Although it is generally believed that the rise in triglycerides on low-fat, high-carbohydrate diets is due to increased production of VLDL triglycerides (which probably is a factor); a second effect may be a decreased lipolytic capacity for triglycerides, possibly by reducing synthesis of lipoprotein lipase. Furthermore, this study did not rule out the possibility that substitution of carbohydrates for saturated fats leads to an increase in LDL-receptor activity, although the lipoprotein kinetic data did not reveal such a change.

In an effort to determine why a low-fat, high-carbohydrate diet decreases HDL-cholesterol levels, Brinton et al. (1990) determined the fractional catabolic rates for apolipoprotein A-I (apo A-I) in individuals fed two diets, one being low-fat and high carbohydrate and the other being high-fat and low-carbohydrate. The decrease in HDL-cholesterol levels and apo A-I levels on the high-carbohydrate diet was highly correlated with a decrease in production rates for apo A-I. The authors concluded that the carbohydrate-induced reduction in HDL-cholesterol levels probably is the result of a decreased secretion (and probably synthesis) of apo A-I. The authors speculated that the mechanisms for carbohydrate lowering of HDL-cholesterol levels may differ from mechanisms for low HDL-cholesterol levels in populations that consume high-fat diets. Therefore, they hypothesize that it may be inappropriate to conclude that carbohydrate-induced lowering of HDL has the same pathogenetic significance with regard to CHD risk as other forms of low HDL. Whether this is actually true, of course, must await further investigation.
Current recommendations call for reduction in fat intake in the American diet, with an increase in carbohydrate. The current intake of carbohydrate is about 48 percent of total calories, and the recommendations are for an increase to 55 percent. The major reasons for favoring carbohydrate over unsaturated fat as a replacement of saturated fatty acids in the diet are threefold: (a) epidemiologic evidence that populations that consume low-fat, high-carbohydrate diets usually have a relatively low incidence of CHD, (b) low-fat diets may promote weight reduction in obese individuals, and (c) low-fat diets may be associated with a lower risk for some kinds of cancer than high-fat diets.

However, it is remarkable that so much emphasis is placed on carbohydrate as a replacement of saturated fatty acids in the American diet when so little is known about the effects of carbohydrate on metabolism of lipids and lipoproteins. Far fewer investigations have been carried out on the effects of carbohydrates than of fatty acids in the diet. For example, the mechanisms whereby carbohydrates increase triglyceride levels and lower HDL levels have not been studied extensively. Although recommendations about dietary carbohydrates may be rationalized from epidemiologic data, they cannot be entirely justified from their effects on lipoprotein metabolism. Clearly, the unsaturated fatty acids produce a better overall lipoprotein profile than carbohydrates. Further, many Americans who are obese have relatively high triglycerides and low HDL-cholesterol levels. However, because carbohydrates replace fats as energy sources in high-carbohydrate diets, the associated influence of low-fat on obesity is an important consideration. Some recent reports provide additional evidence that dietary fat intake is an important determinant of weight gain (Kendall et al., 1991; Tremblay et al., 1991). Nevertheless, it may be questioned whether accentuation of high triglycerides and low HDL-cholesterol with a high-carbohydrate diet is beneficial.

Thus, much more research is needed to define the range of response to high-carbohydrate diets in Americans in general. These diets probably are safe in thin people. We can recommend that obesity is undesirable and, if possible, should be avoided. But this is not reality, and more research is needed on the influence of high-carbohydrate diets in overweight people who do not (or cannot) lose weight.

Conclusions. Current recommendations to reduce total fat consumption to less than 30 percent of total calories, primarily by reducing cholesterol-raising fatty acids, still are prudent. This means that the percentage carbohydrate in the diet will be increased. To achieve weight reduction in obese individuals, however, total caloric intake must be reduced so that absolute carbohydrate intake should not be increased. If weight loss is achieved this way, there should be less likelihood of a fall in HDL-cholesterol or a rise in triglycerides. Individuals who are not overweight may have greater choice in selecting diets in which cholesterol-raising fatty acids are replaced by carbohydrate or oleic acid.

I. ALCOHOL

The relation between alcohol consumption and CHD risk continues to be a perplexing issue. There is epidemiologic evidence that populations that have unusually high consumptions of alcohol have relatively low rates of CHD. In addition, alcohol consumption leads to an increase in HDL-cholesterol levels, which may be accompanied by a decreased risk for CHD. Epidemiologic data were recently reviewed by Hegsted and Ausman (1988). They reviewed dietary and alcohol consumption from 18 countries. They found simple correlations between CHD and intakes of saturated fatty acids ($r = +0.71$), polyunsaturated fatty acids ($-0.34$), and total alcohol consumption ($r = -0.58$). They concluded that alcohol intake was an important dietary "determinant" of CHD. It must be noted that these correlations do not necessarily denote causation, and there might be confounding variables. The apparent inverse association between alcohol intake and CHD rates, nonetheless, is suggestive and certainly deserves further investigation.
More recently, Castelli (1990) examined the effects of alcohol on CHD risk in participants of the Framingham Heart Study. Alcohol consumption seemingly lowered CHD risk in the Framingham cohort. This "protective" effect of alcohol was associated with higher HDL-cholesterol levels. The apparent beneficial effect of alcohol, however, was limited to moderate ingestion. When consumption exceeded two drinks per day, mortality was increased, apparently due to increased blood pressure, stroke, and cancer.

**Conclusions.** The inverse association between alcohol intake and CHD, observed both within and between populations, is an interesting observation. Even so, too many questions remain to be answered before moderate intake of alcohol can be recommended for dietary prevention of CHD. For example, is the association truly causative? If so, what is the mechanism? Can the association be explained by an increase in HDL-cholesterol? And most importantly, does a "cardioprotective" action of alcohol outweigh the detrimental effects of increased alcohol consumption, i.e., social consequences, accidents, liver disease, pancreatitis, hypertension, stroke, and cancer? Before alcohol can be advocated for prevention of CHD, all of these questions must be addressed and favorably resolved. For most individuals who restrict themselves to modest intakes of alcohol, no adverse cardiovascular effects should occur. An exception are those who have severe hypertriglyceridemias and who are unusually sensitive to alcohol.

**J. COFFEE**

For many years it has been uncertain whether the high consumption of coffee in the United States has contributed to a high prevalence of CHD. Several epidemiologic studies have been carried out, but the results are inconsistent. Both case-control studies and prospective studies have been carried out, but with no definitive or even consistent findings. When a positive association exists, it usually has been noted for individuals who consume large amounts daily. A few reports suggest that large intakes increase the serum cholesterol level, which could be one mechanism. Also, coffee ingestion could raise the blood pressure, or induce cardiac arrhythmias. Regarding an effect on blood cholesterol, the type of coffee consumed has been implicated with the suggestion that boiled coffee has the greatest cholesterol-raising action.

Recently Rosenberg et al. (1988) examined the relation between coffee consumption and risk of first, nonfatal myocardial infarction in men under the age of 55 years in a hospital-based, case-control study. After taking into account other major risk factors for CHD, recent consumption of caffeine-containing coffee increased risk for CHD in proportion to the average daily intake. This positive association held in both smokers and nonsmokers. The evidence also was suggestive that intake of decaffeinated coffee was accompanied by increased risk. In summary, the data of this study suggested that men who drink at least five cups of coffee per day have a twofold increase in CHD risk.

More recently, Grobbee et al. (1990) prospectively examined the link between risk for CHD (myocardial infarction, coronary artery surgery, or coronary angioplasty) and risk for stroke in 45,589 American men. The men of this study were 40 to 75-years-old in 1986, and they had no history of CHD. During a 2-year follow-up, 357 men developed CHD and 54 had strokes. No correlation was found between coffee consumption and either CHD or stroke. A high consumption of decaffeinated coffee, however, was associated with a marginally increased risk for CHD. Overall nonetheless, the findings of this study did not support the concept that consumption of coffee is associated with increased risk for CHD or stroke.

For the issue of effects of coffee on cholesterol levels, Rosmarin et al. (1990) carried out a prospective, randomized crossover clinical trial in 21 healthy men who consumed an average of 3.6 cups of filter-
brewed coffee per day. In this study, coffee consumption was not found to affect total cholesterol, LDL-cholesterol, HDL-cholesterol, or apo B levels. It thus appeared that filtered coffee has no adverse influence on serum lipids and lipoproteins. Further, van Dusseldorp et al. (1990) reported that decaffeinated coffee at a level of five cups per day had no detectable effect on serum total cholesterol, HDL-cholesterol, or triglycerides when substituted for regular coffee. Also, Bak and Grobbee (1989) noted that there was little difference in serum total cholesterol or HDL-cholesterol between persons who drank filtered coffee and those who drank none.

In contrast, boiled coffee may produce an increase in cholesterol levels. For example, Pietinen et al. (1990) examined the link between coffee consumption and serum-cholesterol concentration in a cross-sectional study of 5704 men and women in Finland. In this study a weak association was noted between consumption of filtered coffee and serum-cholesterol levels, but the connection was much stronger for boiled coffee. A significant dose-dependent correlation was noted between intake of boiled coffee and serum-cholesterol levels both for men and women. Boiled coffee seemingly is consumed commonly in Scandinavia. To determine the mechanism for this effect, Zock et al. (1990) obtained a lipid-enriched fraction from boiled coffee and gave it to 10 volunteers for 6 weeks. Serum-cholesterol levels rose significantly in all subjects. The increase in cholesterol levels was found both in LDL and VLDL fractions. HDL-cholesterol levels were unchanged. Thus, on the basis of the above studies boiled coffee seemingly contains a lipid that raises serum-cholesterol levels. This evidence has been substantiated by van Dusseldorp et al. (1991), who found that coffee contains a factor that raises LDL-cholesterol, and this factor is not found in filtered coffee.

Conclusions. Recent studies indicate that coffee contains substances that will raise the serum cholesterol. These substances are most potent in boiled coffee, but seemingly, are manifest minimally in filtered or decaffeinated coffee. Since boiling is not a procedure commonly used in the United States, this cholesterol-raising substance apparently is present only in small concentrations in American-brewed coffee. Although several studies suggest that high intakes of filtered coffee and decaffeinated coffee may cause a modest elevation of cholesterol levels, this is not well substantiated. More studies are needed to define precisely whether American coffee has a cholesterol-raising potential; certainly, at present, the possibility of a minor effect should not be dismissed. High intakes of coffee may increase the cholesterol level to a small extent, and, if this effect is confirmed, a recommendation to avoid large amounts of coffee may be justified. Still, the available data appear to be insufficient to make such a recommendation at the present time.

Epidemiologic data about the association between coffee consumption and CHD risk are still inconclusive. If such a definite connection can be shown epidemiologically, it seems doubtful that a significant effect could be detected from the small effect of coffee on cholesterol levels. If future investigations do show a significant association, additional mechanisms must be sought.
III. BIBLIOGRAPHY


* This bibliography contains all reference citations that are either in the text or the appendix table, or both.


38
APPENDIX

CRITERIA FOR INCLUSION OF ARTICLES IN APPENDIX TABLES

Articles in peer-reviewed journals related to the topic of this review were selected primarily on the basis of date and content. In general, papers appearing in 1988 or thereafter were included, provided that they presented original data from studies in humans. Certain items tabulated for the sake of completeness may not have been cited in the body of the text if their weight or relevance did not add significantly to development of the author's argument. Reviews have not been listed except as they included new data or useful meta-analyses.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Objective</th>
<th>Study Design</th>
<th>Subjects</th>
<th>Duration</th>
<th>Test Materials</th>
<th>Dose</th>
<th>Base Diet</th>
<th>Results</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott et al., 1990</td>
<td>To examine the effects of high-fat and high-CHO diets on blood lipids</td>
<td>A prospective, self-controlled dietary trial</td>
<td>7 non-diabetic Pima Indians (6 f, 1 m, avg age 32±4 yr) and 7 Pima Indians with uncomplicated NIDDM (4 f and 2 m, avg age 39±4 yr)</td>
<td>High-fat diet 5 wk</td>
<td>Low-fat, high-CHO diet 5–7 wk</td>
<td>Readily available foods</td>
<td>High-CHO low-SF diet resulted in reduced LDL-chol. No differences between non-diabetic and diabetic subjects in apo B and TG kinetics. Did not induce hypertriglyceridemia. No increase in production rate of VLDL, apo B, or VLDL TG.</td>
<td>Adjusted to maintain body weight</td>
<td>The authors suggested 3 mechanisms contributed to the decreased LDL concentrations. A carefully performed study, but with a marginal number of subjects</td>
</tr>
<tr>
<td>Berns et al., 1988</td>
<td>To investigate the increase of serum cholesterol with age over a period of 6–10 yr in relation to changes in BMI and habitual food intake</td>
<td>A non-randomized, self-controlled cohort study plus a limited dietary intervention trial Baseline data collected for chol in 1974 and for chol, TGs, body fatness, and habitual diet in 1975–1979 Follow-up measurements Dec 1984–Feb 1985</td>
<td>Baseline 1974–1979: 339 (187 f, avg age 22 yr; 152 m, avg age 21.4 yr) Follow-up in winter 1985: 189 (96 f, 70 m) &quot;back to the seventies&quot; dietary intervention group: 34 f and 9 whose change in BMI was &lt;2 kg/m².</td>
<td>Intermittent, 1974–1989 including time for data analyses and report preparation</td>
<td>Habitual diets: 3-wk dietary intervention (Apr–May 1985) Habitual diets consumed by the subjects in the 1970s</td>
<td>Ad lib</td>
<td>See Test Materials</td>
<td>At follow-up, serum chol increased 14% in f and 7% in m. BMI increased by 0.9 kg/m² in f and 0.5 kg/m² in m, which partly explained the increase in serum chol in m but not in f. Serum chol declined 0.1 mmol/L in the intervention trial, thus not abolishing the age-associated increase.</td>
<td>Authors concluded the increase in serum chol between ages 20 and 30 was not caused by changes in food intake and, in these subjects, only a small proportion of the increase is related to changes in BMI. The data were unique for the age group and populations of subjects. The validity of results of the dietary intervention may have been influenced by the relatively small n and short duration.</td>
</tr>
<tr>
<td>Berns et al., 1999</td>
<td>To establish strength of association between diet and serum lipids and lipoproteins in a free-living population</td>
<td>Cohort study</td>
<td>f 28–29 yr</td>
<td>1 wk (approx)</td>
<td>Usual dietary fats and chol estimated from diet hx, food frequency questionnaire, and dietary lipid score</td>
<td>N/A</td>
<td>Usual diet</td>
<td>Association of Keys score with total serum chol, LDL-chol, and HDL total chol ratio was weak but significant. Alcohol intake strongly associated with total and HDL-chol and body fat strongly associated with all serum lipids and lipoproteins</td>
<td>Authors conclude the contribution of dietary differences to differences in serum lipids and lipoproteins is real but small. Validity of dietary intake data can be questioned because of method.</td>
</tr>
</tbody>
</table>
## APPENDIX TABLE. DIETARY LIPIDS AND CARDIOVASCULAR DISEASE

<table>
<thead>
<tr>
<th>Reference</th>
<th>Objective</th>
<th>Study Design</th>
<th>Subjects</th>
<th>Duration</th>
<th>Test Materials</th>
<th>Dose</th>
<th>Base Diet</th>
<th>Results</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berry et al., 1991</td>
<td>To compare effects on lipoprotein structure and function of a high-MUFA, low-PUFA diet with those of a high-PUFA, low-MUFA diet</td>
<td>A randomized, crossover dietary intervention study</td>
<td>26 healthy college students (26 completed first experiment period; 22 completed second period)</td>
<td>32 wk (12 wk on each test diet)</td>
<td>Natural, common foods, 2600 kcal/d—98 g F, 100 g F, 325 g CHO, 300 mg chol MUFA and PUFA diets rich in MUFA and PUFA respectively</td>
<td>See preceding column</td>
<td>See Test Materials</td>
<td>Total plasma chol ↓ 10% and ↓ 16% on MUFA and PUFA diets respectively; No sig change in HDL—chol; LDL—chol ↓ in both diets; Plasma TG response variable Higher tendency toward lipid peroxidation on the PUFA—rich diet</td>
<td>Authors note their data support concept that MUFA may serve as substitute for SFAs in optimizing plasma lipid concentrations and a MUFA—rich diet may reduce susceptibility of LDL to oxidative stress. A careful, useful study; however, results are not necessarily generalizable to other populations and women.</td>
</tr>
<tr>
<td>Boyd et al., 1990</td>
<td>To quantitate relationship between changes in nutrient intake and changes in serum chol</td>
<td>A PRCT of the effect of low-fat, high—CHO diet on serum chol concentrations</td>
<td>239 G with ≥ 50% breast dysplasia; mean age 44 ± 7.9 yr.</td>
<td>12 mo</td>
<td>Intervention group: low-fat (target: 15% of calories) diet; fat replaced by complex CHO Controls: usual diet, with advice on a healthy diet</td>
<td>See previous column</td>
<td>See previous column</td>
<td>Average total fat intake ↓ from 37% to 21% of calories Changes in serum chol levels reflected baseline levels: overall 1 serum chol 8%, 6%, and 4% at 4, 8, and 12 mo respectively.</td>
<td>Results add new data on predictability of equations of Hegsted and Keys; suggests that G and σ respond similarly to low—fat diet. There was some uncertainty on compliance because intake estimates were based on food records provided by participants; results are not necessarily generalizable to other age groups.</td>
</tr>
<tr>
<td>Brinton et al., 1990</td>
<td>To examine mechanisms of HDL—chol lowering, by low—fat, high—CHO diets</td>
<td>A prospective, self—controlled dietary trial</td>
<td>6 σ and 8 σ with fasting HDL—chol levels &gt;30 mg/dL and TG levels below 90th age—sex percentile while on a high—fat diet</td>
<td>8 wk (two 4—wk test diets) plus about 4 wk for diet equilibration, etc.</td>
<td>Natural, commonly available foods formulated for high—fat, low—CHO diets</td>
<td>Intakes adjusted to estimated caloric requirements</td>
<td>Not specified</td>
<td>HDL—chol decreased 29% after change from high to low intake of SF and chol Decreased HDL—chol and apo A—I levels on high—CHO diet correlated well with decreased production of apo A—I.</td>
<td>A carefully conducted study No information on base diets</td>
</tr>
<tr>
<td>Reference</td>
<td>Objective</td>
<td>Study Design</td>
<td>Subjects</td>
<td>Duration</td>
<td>Test Materials</td>
<td>Dose</td>
<td>Base Diet</td>
<td>Results</td>
<td>Comment</td>
</tr>
<tr>
<td>-----------</td>
<td>-----------</td>
<td>--------------</td>
<td>----------</td>
<td>----------</td>
<td>----------------</td>
<td>------</td>
<td>-----------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Burke et al., 1991</td>
<td>To examine trends in mean serum cholesterol levels, prevalence of hypercholesterolemia, cholesterol awareness, and treatment patterns in an urban population in the early to the mid-1980s</td>
<td>A randomized series of surveys of $\sigma$ and $\tau$ in Minneapolis-St. Paul, 1980-1982 and 1985-1987</td>
<td>1588 $\sigma$ and 1777 $\tau$, age range 25-74 yr</td>
<td>Approximatively 11 yr including field work, data analysis, and report preparation</td>
<td>Low-fat diets were commonly prescribed for pts with hypercholesterolemia.</td>
<td>N/A</td>
<td>Not described</td>
<td>Mean serum chol decreased ($p&lt;0.01$) from 1980-82 to 1985-87 in $\sigma$ (from 5.3 mmol/L to 5.16 mmol/L) and $\tau$ (from 5.19 mmol/L to 5.04 mmol/L). Prevalence of hypercholesterolemia decreased ($p&lt;0.05$) in $\sigma$ (17.8% to 15.1%) and $\tau$ (17.1% to 13.6%). Total chol:HDL-chol ratio unchanged. Cholesterol awareness, treatment, and control of cholesterolemia increased and changes occurred in types of treatment.</td>
<td>The authors concluded the decline in prevalence of hypercholesterolemia may be attributed to changes in lifestyle such as diet and exercise, and to more aggressive clinical intervention with lipid-lowering drugs. The surveys and analyses were carefully done, with statistically meaningful numbers of subjects.</td>
</tr>
<tr>
<td>Burr et al., 1989</td>
<td>To determine whether dietary advice on fat, fish, or fiber is beneficial in the secondary prevention of MI</td>
<td>A randomized, controlled dietary intervention trial</td>
<td>2033 $\sigma&lt;70$ yr who had previous MI (excluded pts with diabetes, heart surgery, and those on intervention diets)</td>
<td>2 yr</td>
<td>Three diets: 1 fat, 1 PUFA:SFA ratio 1 fatty fish intake 1 cereal fiber intake</td>
<td>Cereal fiber 18 g/d compared with 9 g/d for subjects not given fiber advice</td>
<td>Usual diet modified as noted</td>
<td>Sig i in 2-yr all-cause mortality in fish-consuming group.</td>
<td>Data for the fish-consuming group appear convincing; however, other data may be questionable because of methods imposed in this large, hard-to-control study population; there were some compliance difficulties; some controls shifted to an intervention diet. Results are not necessarily generalizable to a healthy population.</td>
</tr>
</tbody>
</table>
### APPENDIX TABLE. DIETARY LIPIDS AND CARDIOVASCULAR DISEASE

<table>
<thead>
<tr>
<th>Reference</th>
<th>Objective</th>
<th>Study Design</th>
<th>Subjects</th>
<th>Duration</th>
<th>Test Materials</th>
<th>Dose</th>
<th>Base Diet</th>
<th>Results</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clifton et al., 1990</td>
<td>To examine the relationships between sensitivity to dietary fat and chl and whether responsiveness to these dietary constituents is inherited</td>
<td>A double-blind, prospective, crossover trial of the effect of 700 mg egg yolk chl on plasma chl, LDL, HDL, and plasma TGs</td>
<td>56 otherwise healthy, hypercholesterolemic or normochole-esterolic, free-living, and 7-year old, hypercholesterolemic group; 54±10 yr; of normocholesterolemic group; 42±9 yr. Hypercholesterol- emic subjects divided into diet-sensitive and insensitive.</td>
<td>4 wk on background diet then 4 wk on 1 of 2 liquid supplements, 1 containing egg yolk, 1 a cholesterol-free fat mixture</td>
<td>See also Duration Background diet was 25 en% P (P&lt;1).</td>
<td>Egg yolk supplement provided 700 mg chl/d; followed by 4-wk crossover</td>
<td>After 4 wk the egg yolk supplement resulted in 0.23 mmol/L in plasma chl, 0.19 mmol/L in LDL chl, and 0.07 mmol/L in HDL chl, 1.07 mmol/L in plasma TGs. Normocholesterolemic subjects had nonsignificant changes in total, LDL and HDL chl; diet-sensitive, hypercholesterolemic subjects were more responsive to dietary chl than diet-insensitive subjects.</td>
<td>Authors concluded that hypercholesterolemic persons who are clearly responsive to a low-SF, low-chl diet should avoid dietary chl. Whether less responsive, normocholesterolemic persons should avoid dietary chl based on the hypothesis that dietary chl may be atherogenic even when plasma chl levels are not elevated, has not been determined.</td>
<td></td>
</tr>
<tr>
<td>Dehmer et al., 1988</td>
<td>To determine the safety and benefit of n-3 fatty acid therapy to prevent restenosis after coronary angioplasty</td>
<td>A prospective, randomized, controlled clinical trial. Control group received an anti-platelet regimen (325 mg aspirin and 225 mg dipyridamole/d). Treatment group received the same plus 3.2 g/d eicosapentaenoic acid.</td>
<td>82 div, avg age 56 yr, who had successful angioplasty and subsequently underwent follow-up coronary arteriography. Treated group = 43. Controls = 39</td>
<td>6 mo, starting 7 d before angioplasty</td>
<td>MaxEPA given t.i.d., providing a total dose of 3.2 g eicosapentaenoic acid and 2.2 g docosahexaenoic acid/d</td>
<td>See Test Materials</td>
<td>Not described</td>
<td>At 3-4 mo after angioplasty, the frequency of restenosis was 30% in the controls, 18% in the treatment group (P=0.026). Rate of restenosis per patient was lower in the treatment group (46% vs 18%).</td>
<td>The results suggest a dietary supplement of n-3 fatty acids given 7 d before and for 6 mo after coronary angioplasty is safe and reduces the occurrence of postoperative restenosis. The results appear valid and are consistent with those of Milner et al., 1989.</td>
</tr>
<tr>
<td>Reference</td>
<td>Objective</td>
<td>Study Design</td>
<td>Subjects</td>
<td>Duration</td>
<td>Test Materials</td>
<td>Dose</td>
<td>Base Diet</td>
<td>Results</td>
<td>Comment</td>
</tr>
<tr>
<td>----------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>-------------------------------</td>
<td>-----------------------------------------------</td>
<td>----------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-------------------------------</td>
<td>---------------------------------</td>
<td>-----------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Dreon et al., 1990</td>
<td>To investigate whether results obtained with formula diets in metabolic ward studies can be generalized to a free-living population who eat solid foods</td>
<td>A prospective, randomized, crossover, dietary intervention trial 2 wk of dietary stabilization, 12 wk on poly diet, 12 wk on mono diet</td>
<td>39 volunteers (19♂, 20♀) avg age 48.5 ± 7.1 yr</td>
<td>30 wk</td>
<td>Stabilization diet to standardize fat intake to 30 en%, poly diet; mono diet The PUFA were mainly safflower and corn oil-enriched. MUFA diets were primarily enriched with olive and peanut oils. Composition CHO = 55%, and chole = 24 mg/100kJ</td>
<td>Ad lib</td>
<td>See Test Materials</td>
<td>No significant changes in mean plasma LDL-cholesterol and LDL total mass and HDL-cholesterol and HDL mass HDL₃-cholesterol was 50% higher and HDL₃-cholesterol 7% lower for PUFA compared with MUFA Mean total mass of HDL₃ was 23.5% higher and apo B 5.4% lower on switching to the poly diet.</td>
<td>Authors found no advantage of MUFA over PUFA with respect to plasma HDL-cholesterol levels in subjects on reduced-fat, solid-food diets. In this study population, exchanging unsaturated fats within NCEP guidelines in reduced-fat diets does not affect total cholesterol or LDL-cholesterol levels. Potentially important data that should be replicated in additional studies. Statistical validity of data on LDL-cholesterol has been questioned because of small n and wide confidence intervals.</td>
</tr>
<tr>
<td>Failor et al., 1988</td>
<td>To test the effects of ω-6 and ω-3 fatty acid feeding upon lipid, lipoprotein, and apolipoprotein levels in subjects with FCHL</td>
<td>Crossover randomized dietary intervention</td>
<td>4♂ with FCHL and 4 normolipidemic ♂, age range 33–67 yr</td>
<td>Approx 15 wk</td>
<td>3 diets of natural foods, similar except for source of fatty acids—basal (butter), ω-6 (safflower oil), ω-3 (salmon and salmon oil) Intakes adjusted to individual energy requirements</td>
<td>See Test Materials</td>
<td></td>
<td>ω-3 diet lowered TG levels in FCHL pts but not total cholesterol and total apo B levels. Upward trend of LDL-cholesterol and LDL apo B levels</td>
<td>Pts with FCHL apparently do not respond favorably to ω-3 fatty acids. Data are suggestive only.</td>
</tr>
<tr>
<td>Frantz et al., 1989</td>
<td>To test the effect of lipid lowering by diet on cardiovascular risk</td>
<td>A prospective, randomized, double-blind clinical trial</td>
<td>4383 institutionalized ♂ and 4660 institutionalized ♀</td>
<td>Mean time on diets: 384 d (1568 subjects on diet for &gt; 2 yr)</td>
<td>Usual institutional foods, constituted for a 39% fat control diet (18% SFA, 5% PUFA, 16% MUFA, 446 mg chole/d) or a 38% fat treatment diet (9% SFA, 15% PUFA, 14% MUFA, 166 mg chole/d)</td>
<td>Ad lib (assumed)</td>
<td>See Test Materials</td>
<td>Mean serum chole: treatment group: 175 mg/dl, control group: 203 mg/dl; no differences between groups for cardiovascular events, cardiovascular deaths, or total mortality. Favorable trend for these end points in younger participants</td>
<td>Limitations in number of participants and duration of study precluded a definitive result in the age range most likely to benefit from the treatment diet.</td>
</tr>
</tbody>
</table>
## APPENDIX TABLE. DIETARY LIPIDS AND CARDIOVASCULAR DISEASE

<table>
<thead>
<tr>
<th>Reference</th>
<th>Objective</th>
<th>Study Design</th>
<th>Subjects</th>
<th>Duration</th>
<th>Test Materials</th>
<th>Dose</th>
<th>Base Diet</th>
<th>Results</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Friday et al., 1991</td>
<td>To test the effects of ω-3 and ω-6 FA enriched diets on plasma lipoproteins and apolipoproteins in FH</td>
<td>A prospective, crossover, dietary intervention trial</td>
<td>3 σ and 2 § with FH; Controls: 4 σ and 1 §</td>
<td>Approx 15 wk</td>
<td>3 diets of natural foods, similar except for source of FAs: basal (butter) ω-6 (safflower oil) ω-3 (salmon oil)</td>
<td>Food intakes adjusted to meet caloric requirements Each subject consumed each diet for 3 wk followed by 3 wk washout period</td>
<td>See preceding column</td>
<td>FH pts—total plasma chol 1 by 34% and 26% on ω-3 and ω-6 diets respectively compared with butter diet LDL-cholesterol 31% and 29% and apo B 1 28% and 27% during ω-3 and ω-6 diets, respectively Normal controls responded similarly Total plasma TG and HDL 1 significantly during ω-3 diet in normal and FH subjects</td>
<td>Small n, but careful study with useful data FH and normal subjects respond in similar fashion to diets low in SFA and rich in ω-3 and ω-6 PUFA</td>
</tr>
<tr>
<td>Ginsberg et al., 1990</td>
<td>To test the effects on plasma levels of lipids and lipoproteins in normal σ of 2 fat-modified diets</td>
<td>A prospective, randomized clinical trial</td>
<td>36 healthy σ 22–32 yr with nonfasting plasma chol between 30th and 80th percentiles</td>
<td>20 wk (included 10 wk on average American diet before test diets)</td>
<td>Commonly consumed foods modified to match AHA Step 1 diet (30% total calories as fat) and a Step 1 diet enriched in MUFA (38% of total calories as fat)</td>
<td>Food intake adjusted to meet individual caloric requirements</td>
<td>See Test Materials</td>
<td>Compared with baseline and typical American diet, both the Step-1 and the high-oleic acid diets produced equal 1 of plasma total chol and LDL-cholesterol Addition of monounsaturates did not add substantially to chol-lowering effect of Step 1 diet.</td>
<td>A careful study with useful data; however, small n clouds interpretation of small changes in HDL-cholesterol levels</td>
</tr>
</tbody>
</table>
### APPENDIX TABLE. DIETARY LIPIDS AND CARDIOVASCULAR DISEASE

<table>
<thead>
<tr>
<th>Reference</th>
<th>Objective</th>
<th>Study Design</th>
<th>Subjects</th>
<th>Duration</th>
<th>Test Materials</th>
<th>Dose</th>
<th>Base Diet</th>
<th>Results</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grobee et al., 1990</td>
<td>To examine the relation of coffee, caffeine, and tea intake to the incidence of CAD and cerebrovascular disease</td>
<td>A prospective cohort study (part of the Health Professionals Follow-up Study of Risk Factors for Cardiovascular Disease and Cancer). Study end points: risk of MI, need for coronary artery bypass or angioplasty, and risk of stroke</td>
<td>45,589 $\sigma$ and $\varphi$, age range 40–75 yr, with no hx of CVD</td>
<td>2 yr</td>
<td>Caffeinated and decaffeinated coffee and tea</td>
<td>Intakes estimated by semi-quantitative food-frequency questionnaire (validity tested in a subgroup of 127 participants)</td>
<td>Habitual diet</td>
<td>Total coffee consumption was not associated with increased risk of CHD or stroke, nor were increasing levels of consumption of decaffeinated coffee. Higher consumption of decaffeinated coffee was associated with marginally significant increased risk of CHD (RR = 1.63; 95% CI 1.02 to 2.60). There was no apparent association between consumption of tea and risk of any cardiovascular end point.</td>
<td>Important data from a carefully designed and conducted study</td>
</tr>
<tr>
<td>Iacono et al., 1990</td>
<td>To analyze and summarize results of 10 dietary intervention studies conducted by the authors and their colleagues in the U.S., Finland, and Italy</td>
<td>10 prospective dietary intervention and observational studies using crossover, switchback and cross-sectional epidemiologic designs</td>
<td>Free-living $\sigma$ and $\varphi$ as well as subjects in metabolic wards</td>
<td>Varied between 6 wk and 17 wk</td>
<td>Usual western urban and rural diets modified to 1 SFA (butter eliminated, lean meats only, etc.) and to 1 P/S to approximately 1</td>
<td>Basal diet 2500 kcal Intakes adjusted to meet caloric requirements</td>
<td>See preceding columns</td>
<td>The fat-modified diets lowered systolic and diastolic blood pressures as well as blood lipid levels</td>
<td>A series of well conducted studies Data support hypothesis of antihypertensive effect of linoleic acid; however, 1 intake of SFAs and altered intakes of other nutrients may contribute to antihypertensive effect.</td>
</tr>
<tr>
<td>Isles et al., 1989</td>
<td>To examine the relationships between plasma chol concentrations and CHD and cancer in a general population of middle-aged $\sigma$ and $\varphi$</td>
<td>A statistical analysis of deaths from CHD and cancer in relation to previously surveyed total plasma chol levels and other parameters</td>
<td>15,262 western Scotland $\sigma$ and $\varphi$ aged 45–64 yr, followed for average 12 yr, yielding 975 deaths from CHD (653 $\sigma$, 322 $\varphi$)</td>
<td>Approx 12 yr</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Subjects in top fifth of the chol distribution had approx 1.5 excess risk of CHD compared with those in bottom fifth.</td>
<td>A careful study yielding data that support the lipid hypothesis of CHD; however, accuracy of cause-of-death diagnosis could not be established in some cases.</td>
</tr>
</tbody>
</table>
**APPENDIX TABLE. DIETARY LIPIDS AND CARDIOVASCULAR DISEASE**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Objective</th>
<th>Study Design</th>
<th>Subjects</th>
<th>Duration</th>
<th>Test Materials</th>
<th>Dose</th>
<th>Base Diet</th>
<th>Results</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnson and Greenland, 1980</td>
<td>To investigate the effects of changing dietary chol intake on plasma lipids in normolipidemic healthy σ when exercising regularly and consuming a fat-restricted, low-SP diet</td>
<td>A PRCT, crossover, blind</td>
<td>10 free-living, healthy, athletie, normolipidemic σ, avg age 27 ± 5 yr</td>
<td>Two 4-wk test diet periods</td>
<td>Regular food selections of the Clinical Research Center, with 15% as F, 55% as CHO, 30% as F. Test diets identical except one was low-chol (200 mg/d), the other high (600 mg/d); P/S was 1.5.</td>
<td>See preceding column</td>
<td>See preceding column</td>
<td>LDL-chol and apo B ↑ 10% and 15% respectively after 600 mg/d chol diet compared with 200 mg/d chol diet. Individual responses varied; mean plasma TGs, HDL 2 and 3 and apo A-1 unchanged. Authors suggest restriction of dietary chol may be justifiable even when other lifestyle and dietary measures to minimize blood chol are undertaken.</td>
<td>Relatively small n and brief diet periods. Data may be inappropriate for generalization. Data support findings of other studies showing wide variation in human response to dietary chol.</td>
</tr>
<tr>
<td>Katan et al., 1988a</td>
<td>To examine whether hyperresponders to dietary chol are also hyperresponders to dietary saturated fat</td>
<td>A prospective, controlled, cross-over dietary trial</td>
<td>47 healthy, normolipidemic σ and δ volunteers; avg age of NORM- EGG group (n=23): 34±13 yr; HAB- EGG group (n=24): 54±13 yr; NORM- EGG had &quot;normal dietary habits.&quot; HAB- EGG, high egg intake.</td>
<td>Test diets, 42 d (3 wk per diet)</td>
<td>Mixed natural diets high in PUFA, low in SFA (high P/S diet) or low in PUFA and high in SFA (Low P/S diet)</td>
<td>Intakes adjusted to individual energy needs</td>
<td>See Test Materials</td>
<td>Serum chol higher on low P/S diet than vice versa (avg 23% higher in NORM- EGG and 18% higher in HAB- EGG). Correlation coefficients between each subject's response to dietary chol and dietary fat: 0.62 for NORM- EGG (p &lt;0.01), 0.16 for HAB- EGG.</td>
<td>A well-designed and executed study. Authors concluded that modest differences exist in human serum chol responses to SF and in people with normal chol intake. Responses to dietary chol and SF tend to be congruent. Periods on test diets were relatively short.</td>
</tr>
<tr>
<td>Katan et al., 1988b</td>
<td>To evaluate data from multiple trials on the influence of fat-modified diets on serum chol responses</td>
<td>A reanalysis of previously reported data. Study emphasized reproducibility of response and quantification of differences in responsiveness.</td>
<td>82 monks and 48 nuns, all healthy, mean ages in 1963: monks 53.1±12.8 yr, nuns 43.4±18.4 yr</td>
<td>1963-1974</td>
<td>All subjects participated in 2 or more dietary trials</td>
<td>56 different lipid formulas diets with 20-50% energy as F (vag F, oils, synthetic TGs), with range of FA composition</td>
<td>Ad lib</td>
<td>Lacto-vegetarian</td>
<td>Avg serum chol response: 0.57 mmol/l, on average, σ and δ were equally responsive to dietary FA modification; within-person variance was 4.X greater than between-person variance.</td>
</tr>
<tr>
<td>Reference</td>
<td>Objective</td>
<td>Study Design</td>
<td>Subjects</td>
<td>Duration</td>
<td>Test Materials</td>
<td>Dose</td>
<td>Base Diet</td>
<td>Results</td>
<td>Comment</td>
</tr>
<tr>
<td>-----------------</td>
<td>---------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>------------------------------------------------------</td>
<td>--------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>---------------------</td>
<td>----------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Kestin et al., 1989</td>
<td>To compare the effects on CVD risk when meat protein is substituted for veg protein in a vegetarian diet</td>
<td>A prospective, randomized, open-block-design dietary trial; each subject completed 2 dietary treatments out of 6 possible combinations</td>
<td>26 ε, avg age 44±10 yr, all basically healthy</td>
<td>12 wk (two 6-wk diet periods)</td>
<td>A high-fat diet, a fat modified lactoovegov diet (LOV) and a diet with 60% of plant protein replaced with lean meat (LM).</td>
<td>4 energy levels, 2100-3000 kcal/d, to meet estimated individual energy requirements</td>
<td>Usual Australian diet</td>
<td>Compared with high-fat diet, LOV and LM lowered BP, total chol and LDL-chol but raised serum TGs; chol lowering greater with LOV.</td>
<td>Authors concluded the LM diet did not negate overall CVD risk-lowering effect of the LOV diet. Among remaining uncertainties is whether the source of protein or the amino acid content influences plasma chol concentrations.</td>
</tr>
<tr>
<td>Löwik et al., 1991</td>
<td>To determine whether dietary factors modulate serum chol levels in the elderly and to identify the factors</td>
<td>A clinical laboratory evaluation and diet history study</td>
<td>196 ε and 180 ε, aged 65-70 yr Subjects apparently healthy, non-diabetic, and not on diets</td>
<td>1984-1985</td>
<td>Usual diets of commonly available foods; dietary chol estimated by dietitians</td>
<td>N/A</td>
<td>See Test Materials</td>
<td>In ε, BMI, intake of MUFA, and alcohol were positively correlated with serum total chol; in women, intake of alcohol and SF was positively associated and intake of polysaccharides, inversely associated with serum total chol. Authors concluded the effect of dietary factors on serum chol levels is probably not age-limited and the elderly may benefit from weight reduction, moderate alcohol intake, and avoidance of “too much” dietary fat.</td>
<td>Useful data from a careful study, however, the validity of the dietary intake data may be questioned because of the method.</td>
</tr>
<tr>
<td>Mänttäri et al., 1991</td>
<td>To examine the relationship between apo E polymorphism and changes in lipoprotein levels to determine whether the plasma chol response after diet counseling and gemfibrozil treatment is associated with genetic variation at the apo E locus</td>
<td>A prospective, randomized, double-blind clinical trial</td>
<td>230 dyslipidemic Finnish ε, 40-55 yr</td>
<td>The first 15 mo of the Helsinki Heart Study</td>
<td>Common, readily available foods: subjects were repeatedly counseled to reduce fats from 37-40% to 30-35% of total calories, to increase P/S, and avoid high-chol foods.</td>
<td>Intakes adjusted to individual energy requirements</td>
<td>See Test Materials</td>
<td>In the dietary advice group, subjects with ε4 allele had greater serum chol decreases (p&lt;0.01) and LDL-chol decreases (p&lt;0.02) than those without the ε4 allele. No such association for HDL-chol or TGs. ε4 status did not influence gemfibrozil-induced lipids changes.</td>
<td>Uncertainties exist about dietary compliance. Careful study with useful data Relative significance of decrease in dietary SF and chol response is uncertain.</td>
</tr>
</tbody>
</table>
### APPENDIX TABLE. DIETARY LIPIDS AND CARDIOVASCULAR DISEASE

<table>
<thead>
<tr>
<th>Reference</th>
<th>Objective</th>
<th>Study Design</th>
<th>Subjects</th>
<th>Duration</th>
<th>Test Materials</th>
<th>Dose</th>
<th>Base Diet</th>
<th>Results</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>McDonald et al., 1989</td>
<td>To examine the effects of different dietary fats on plasma lipids and lipoproteins in healthy volunteers</td>
<td>A prospective, randomized, self-controlled crossover dietary intervention trial</td>
<td>8 healthy volunteer σ, 19–32 yr</td>
<td>48 d (6-d pre-experiment period, two 18-d interventions, 6-d postexperiment period)</td>
<td>Canola oil (CO) (59% oleic acid, 10% linoleic acid) or sunflower oil (SO) (14% oleic acid, 73% linoleic acid)</td>
<td>~28% of 3000 kcal daily energy intake (14.5% from P, 36% from F, 49.5% from CHO)</td>
<td>Western type mixed fat (MF) diet</td>
<td>The CO and SO diets resulted in similar decreases in plasma total− (20% and 15% respectively) and LDL− (25% and 21% respectively) chol, but no changes in HDL and TGs. Bleeding times increased and prostacyclin production increased on CO compared with MF diets. CO and SO diets were equal in hypcholesterolemic and antithrombotic effects.</td>
<td>A careful study. Data confirm other reports of a hypcholesterolemic response to oleic acid in high−fat diets.</td>
</tr>
<tr>
<td>Mensink and Katan, 1989</td>
<td>To compare the chol lowering effects of diets enriched in MUFA or PUFA in healthy σ and σ</td>
<td>Prospective, randomized, controlled dietary trial</td>
<td>Healthy σ (27, 10–48 yr) and σ (81, 19–65 yr)</td>
<td>17 d on high−SFA control diet, 36 d on test diets</td>
<td>MUFA diet (12.9% SFA, 15.1% MUFA, 7.9% PUFA—mixed olive oil and sunflower oils)</td>
<td>Adjusted to estimated daily energy requirement</td>
<td>Conventional, solid foods</td>
<td>Serum LDL chol 1 17.9% in MUFA and 12.9% in PUFA groups In σ, HDL chol slightly on both diets</td>
<td>Careful study. Authors conclude a mixed diet rich in MUFA was as effective as one rich in (n−6) PUFA in lowering LDL chol.</td>
</tr>
<tr>
<td>Mensink and Katan, 1990</td>
<td>To determine the effect of dietary trans−FAs on HDL and LDL chol in healthy subjects</td>
<td>A prospective, randomized, dietary trial of 3 diets</td>
<td>25 healthy σ, 19–25 yr, and 34 healthy σ, 19–57 yr 8 σ on contraceptives, 1 on a beta blocker</td>
<td>63 wk (3 contiguous 21−d test diet periods)</td>
<td>3 similar diets made from conventional solid foods except 10% of total energy was from oleic acid, trans isomers of oleic acid, or SFA</td>
<td>Adjusted to estimated energy requirement</td>
<td>See Test Materials</td>
<td>Trans−FAs decreased HDL chol significantly. LDL chol was lower on oleic acid, and total chol levels were similar on all 3 regimens; apo B levels higher on trans−FA but lower on oleic acid diets. Both trans−FA and SFA diets resulted in higher serum TG levels compared with the oleic acid diet.</td>
<td>Careful study. Trans−FA raise LDL−chol and lower HDL−chol. Authors considered the effect at least as adverse as with chol−raising SFA.</td>
</tr>
<tr>
<td>Reference</td>
<td>Objective</td>
<td>Study Design</td>
<td>Subjects</td>
<td>Duration</td>
<td>Test Materials</td>
<td>Dose</td>
<td>Base Diet</td>
<td>Results</td>
<td>Comment</td>
</tr>
<tr>
<td>--------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------</td>
<td>----------</td>
<td>---------------------------------</td>
<td>---------------------</td>
<td>---------------------------</td>
<td>--------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Mensink et al., 1989</td>
<td>To differentiate the effects of MUFAs and complex CHO's on human serum lipoproteins and apoproteins</td>
<td>A prospective, randomized, controlled, dietary intervention trial: 17 d on high-SFA control diet, 36 d on high complex CHO (24 subjects) or high-F, olive oil-rich diet (24 subjects)</td>
<td>48 healthy, normolipidemic, free-living subjects (24♂, 24♀, avg age 27 yr)</td>
<td>See Study Design</td>
<td>High CHO, high-fiber or high-fat, olive oil-rich diets</td>
<td>Mean daily energy intake: 13.62 MJ for ♂, 12 MJ for ♀</td>
<td>Conventional solid foods</td>
<td>Both test diets lowered serum total chol. On high-F olive oil diet, VLDL and apo B declined; HDL₃ apo A-1, and apo A-I/apoB increased. On the high CHO diet, LDL, HDL₃, apo A-1 and apo A-I/apo B declined while VLDL and apo B increased. HDL₃ declined equally on both diets.</td>
<td>Careful study Subjects on olive oil-rich diet had lipoprotein patterns consistent with lower CHD risk; however, whether such a diet would continue to yield a favorable risk profile when continued for prolonged periods by free-living, coronary-prone populations is unknown.</td>
</tr>
<tr>
<td>Miettinen and Kesaniemi, 1989</td>
<td>To examine relationships between chol absorption, synthesis, and elimination in healthy human subjects</td>
<td>A prospective cohort study of clinical laboratory results and dietary intake estimates: (1) estimated intakes of F and chol, (2) analysis of serum lipids, (3) estimated chol absorption, and (4) calculation of chol synthesis, total intestinal flux, and chol absorption</td>
<td>63 randomly selected, 50-yr-old, free-living, mostly healthy ♂</td>
<td>1 wk for clinical test manipulations</td>
<td>Ordinary diet</td>
<td>Intakes of dietary chol and lipids computerized from 7-d food recall</td>
<td>Usual Finnish diet</td>
<td>Absorbed dietary chol I linearly with intake Rates of biliary secretion, fecal elimination, and chol synthesis varied directly with high chol absorption.</td>
<td>Authors concluded chol absorption efficiency and absorbed dietary chol regulate chol synthesis and elimination and are key determinants of within-population variation of total, LDL-, and HDL-chol.</td>
</tr>
<tr>
<td>Reference</td>
<td>Objective</td>
<td>Study Design</td>
<td>Subjects</td>
<td>Duration</td>
<td>Test Materials</td>
<td>Dose</td>
<td>Base Diet</td>
<td>Results</td>
<td>Comment</td>
</tr>
<tr>
<td>--------------------</td>
<td>----------------------------------------------------------------------------</td>
<td>-----------------------------------</td>
<td>-------------------------------------------------------</td>
<td>----------</td>
<td>----------------</td>
<td>----------------------------------------</td>
<td>------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Miettinen et al., 1990</td>
<td>To examine regulation of serum plant sterols and chol precursor sterols and determine whether these sterols can be used to indicate chol absorption efficiency and overall synthesis in population studies</td>
<td>Essentially the same as in Miettinen and Kasaniemi, 1989</td>
<td>As in Miettinen and Kasaniemi, 1989</td>
<td>As in Miettinen and Kasaniemi, 1989</td>
<td>As in Miettinen and Kasaniemi, 1989</td>
<td>As in Miettinen and Kasaniemi, 1989</td>
<td>(Qualitative only; see source paper for quantitative data) Dietary plant sterol serum levels were positively associated with chol absorption and negatively with chol synthesis and biliary and fecal excretion. Serum contents of chol precursor sterols were positively related to chol synthesis.</td>
<td>Data seem to offer advantageous methodology for population studies. Authors concluded the determination of serum levels of dietary plant sterols can be used as an indicator of chol absorption efficiency.</td>
<td></td>
</tr>
<tr>
<td>Milner et al., 1989</td>
<td>To evaluate the effects of ω-3 FA dietary supplement on coronary artery restenosis</td>
<td>A prospective, randomized clinical trial</td>
<td>194 &amp; 7, mean age 60 yr, with recent percutaneous transluminal coronary angioplasty</td>
<td>6 mo</td>
<td>Promega capsules</td>
<td>9 capsules daily (3150 mg eicosapentaenoic acid, 1350 mg docosahexaenoic acid)</td>
<td>Pts counseled to use fat-modified diet low in chol and SFA</td>
<td>Dietary supplements with ω-3 FA appear to decrease recurrent anginal symptoms substantially; absence of restenosis confirmed by angiography in 7% of treated group and estimated in 84% of treated group by freedom from signs and symptoms.</td>
<td>All pts received aspirin and calcium antagonist. These are potentially very important data that need further validation.</td>
</tr>
<tr>
<td>Mori et al., 1986</td>
<td>To determine the effects of fish oil on serum lipids in subjects with IDDM and in healthy controls</td>
<td>A prospective, nonrandomized control trial of the influence of a daily fish oil supplement on serum lipids and platelet FAs</td>
<td>10 normolipidemic insulin-dependent diabetic &amp; mean age 33.4 yr; 10 &quot;normal healthy&quot; volunteer &amp; mean age 35.6 yr; no subject had hypertension, peripheral vascular disease or renal impairment.</td>
<td>3 wk treatment 6 wk washout</td>
<td>Commercial fish oil capsules</td>
<td>Daily intake of 2.7 g EPA, 1.7 g DHA</td>
<td>Usual diets</td>
<td>Total chol, LDL-chol, and HDL-chol increased; these changes were greater in diabetic subjects. TGs decreased in all subjects; platelet EPA increased, platelet AA decreased in all subjects. Rise in HDL was mainly in HDL-2.</td>
<td>Authors speculate the possible adverse potential of increased total chol may be offset by the accompanying increase in HDL-2-chol. The data do not clearly support the notion of benefit by fish oils in pts with IDDM.</td>
</tr>
</tbody>
</table>
## APPENDIX TABLE. DIETARY LIPIDS AND CARDIOVASCULAR DISEASE

<table>
<thead>
<tr>
<th>Reference</th>
<th>Objective</th>
<th>Study Design</th>
<th>Subjects</th>
<th>Duration</th>
<th>Test Materials</th>
<th>Dose</th>
<th>Base Diet</th>
<th>Results</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ng et al., 1991</td>
<td>To compare the effects on serum lipid levels of diets enriched with palm or corn oil in coconut oil–based diets</td>
<td>A prospective, randomized, double-blind dietary trial with 3 regimens: (1) coconut–palm–coconut (2) coconut–corn–coconut (3) coconut (control group)</td>
<td>80 healthy, normolipidemic σ (n = 55) and ι (n = 22), age range 22.6–24.8 yr, randomly assigned to the 3 test groups</td>
<td>15 wk</td>
<td>Refined, blanched, deodorized (RBD) palm olein, RBD corn or RBD coconut oil as cooking oil in customary Malaysian diets</td>
<td>60 g/d (24 en%)</td>
<td>Usual diet based on individual preferences</td>
<td>Compared with baseline values, coconut oil ↑ serum total chol &gt;10% in all 3 groups; palm olein or corn oil, respectively, ↑ total chol (~19% and ~36%), LDL–chol (~20% and ~42%), HDL–chol (~20% and ~33%); LDL:IDL ratio ±8% by palm olein, ±25% by corn oil</td>
<td>Dietary compliance reported as good. Authors conclude palm olein does not raise serum chol in healthy, young, free-living Malaysians. However, not reported were baseline dietary data, actual intakes and body weight changes, adjustment in data analysis for male–female differences in measures and effects of stratification factors. Without baseline dietary data, it is difficult to determine whether this intervention was a metabolic adaptation to a different dietary regimen.</td>
</tr>
<tr>
<td>Nicolosi et al., 1990</td>
<td>To examine the effects of dietary fat saturation at levels of dietary chol equivalent to human consumption of 550 mg/d, on receptor- and nonreceptor–mediated catabolism of LDL</td>
<td>A prospective dietary study in Cebus monkeys, 5–10 yr old, kept in cages and trained for 8 hr metabolic chair restraint</td>
<td>20 Cebus monkeys</td>
<td>3–10 yr</td>
<td>Corn oil, cholesterol, and coconut oil as components of semipurified diets</td>
<td>The dietary oils comprised 12.5 g/100 g anhydrous diet mix (31 en%); chol 0.8 en%. Dietary intakes consistent with each animal’s estimated energy requirement</td>
<td>Semi–purified, nutritionally complete</td>
<td>(Qualitative only; for quantitative data, see source paper.) Authors concluded the degree of dietary FA saturation induced greater changes in plasma lipoprotein levels and LDL–chol metabolism than did dietary chol and that, at concentrations of dietary chol that approximate human consumption, the degree of fat saturation may be more important than chol in regulating LDL metabolism.</td>
<td>Understanding this study is somewhat impeded by lack of data on temporal aspects (when and how often were metabolic measures made?), details of feeding procedures, and the health, morbidity, and mortality of the animals during the 3–10 yr period.</td>
</tr>
</tbody>
</table>
**APPENDIX TABLE. DIETARY LIPIDS AND CARDIOVASCULAR DISEASE**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Objective</th>
<th>Study Design</th>
<th>Subjects</th>
<th>Duration</th>
<th>Test Materials</th>
<th>Dose</th>
<th>Base Diet</th>
<th>Results</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nozaki et al., 1991</td>
<td>To examine changes in plasma postheparin LPL and HL during feeding of ω-3 PUFA in pts with primary hypertriglyceridemia and to relate changes in lipolytic activity to changes in plasma lipoproteins</td>
<td>A prospective dietary inter- vention trial</td>
<td>12 pts, age range 45–70 yr, whose fasting plasma TG were &gt;2.8 mmol/L 7 pts had CAD but no recent MI</td>
<td>Approx. 28 d</td>
<td>Capsules of commercially available fish oil concen- trate</td>
<td>Natural food- based Step I, NCEP diet</td>
<td>Fish oil substituted isocalorically for usual fats, providing 10 g/d ω-3 PUFA</td>
<td>ω-3 PUFA resulted in 53% and 61% plasma TG and VLDL-chol respectively, but LDL-chol ↑ 28%. Postheparin activities of lipoproteinlipase and hepatic lipase remained the same.</td>
<td>Results do not support hy- pothesis that fish oils may secondarily ↑ postheparin LPL and HL. Authors con- clude the mechanism for ↑ of plasma TG by ω-3 polyunsaturates seems related to enhanced activity of LPL or HL but appears to be modu- lated by ↑ in hepatic secre- tion of VLDL triglycerides. A useful contribution</td>
</tr>
</tbody>
</table>

| Ornish et al., 1990 | To determine whether comprehensive lifestyle changes affect coronary atherosclerosis after 1 yr | A PRCT of free-living pts with angiographically identified CAD; expl group were prescribed a low-fat, vegetarian diet, aerobic exercises, stress mgmt, no smoking, and group support. Control group had usual clinical care. Coronary arteries assessed at baseline and after about 1 yr | Total 41, age range 35–75 yr; treated group 22 (21 m, 1 f) mean age 56.1 yr; control group 19 (15 m, 4 f) mean age 59.8 yr | Approx. 1 yr | A low-fat, vegetarian diet of fruits, veg, grains, legumes, soybean prod- ucts; fat ≈ 10% of cal P/S >1; no animal prod- ucts except egg white and 1 cup/d nonfat milk or yoghurt; chol intake ≤ 5 mg/d or less No caffeine, alcohol <2 units/d if desired | Ad lib | N/A | An overall regression of coronary atherosclerosis determined by quantitative coronary angiography, compared with controls, who showed an overall progression Mean body weight and SD of experimental group at baseline: 41.1 (15–5) kg, at 12 mo: 81.0 (11–4) kg | An unusual and valuable study despite small n. Results suggest low-fat, veg diet contributed to the beneficial effect, but this study was not designed to separate the effects of each component of the protocol. |
### APPENDIX TABLE: DIETARY LIPIDS AND CARDIOVASCULAR DISEASE

<table>
<thead>
<tr>
<th>Reference</th>
<th>Objective</th>
<th>Study Design</th>
<th>Subjects</th>
<th>Duration</th>
<th>Test Materials</th>
<th>Dose</th>
<th>Base Diet</th>
<th>Results</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pekkanen et al., 1990</td>
<td>To examine relationships between lipid levels and mortality from CHD or CVD over a 10-yr period in those with and without evidence of CVD at baseline</td>
<td>A prospective cohort follow-up study of subjects from the Lipid Research Clinics Program Prevalence Study (Williams et al., 1986)</td>
<td>2541 free-living Baltimore males who were 40-69 yr old at visit #2 of LRCPPS #3 had hx of MI; 235 had abnormal exercise test; 135 had other manifestations of CVD; 150 had no CVD at baseline, and 130 were &quot;unclassifiable&quot;.</td>
<td>Approx. 10 yr</td>
<td>N/A</td>
<td>N/A</td>
<td>Not specified</td>
<td>Of subjects with CVD at baseline, those with total cholesterol &gt;6.19 mmol/L had 3.45 times greater risk of death from CVD than those with total cholesterol &lt;5.16 mmol/L. Corresponding RRs were calculated for LDL-cholesterol, total cholesterol and LDL-cholesterol also predicted death in subjects who were without CVD at baseline but at a lower level of absolute risk of death.</td>
<td>A valuable data set derived by careful analysis</td>
</tr>
<tr>
<td>Pietinen et al., 1990</td>
<td>To examine the influence of the method of coffee brewing on the association between coffee consumption and serum cholesterol in Finland</td>
<td>A cross-sectional, epidemiologic study of a random age-stratified population sample in which blood samples, dietary, and lifestyle factors were evaluated</td>
<td>5704 free-living subjects (2728 males, 2976 females), age range 25-66 yr, who were part of the second Finnish cardiovascular risk factor survey in 1987 and who answered detailed questionnaires on diet and lifestyle.</td>
<td>The risk factor surveys occur every 5 yr, Time required to conduct the coffee brewing/lifestyle data acquisition not specified.</td>
<td>Widely available types of coffee for filtering, boiling, or instant uses</td>
<td>Est mean consumption of boiled coffee in cups/d = 6.2; filtered coffee = 5.7, filtered and boiled = 7.5, instant = 4.7</td>
<td>Usual diet</td>
<td>24% of subjects consumed boiled coffee. Mean serum cholesterol values were significantly higher (69% of subjects) than those of filtered coffee drinkers: in males 6.37 versus 6.02 mmol/L and in females 5.22 versus 5.34 mmol/L. (after adjusting for age, BMI, smoking, serum gamma glutamyl transferase, index of saturated fat intake, and physical activity).</td>
<td>The study confirms other reports that consumption of boiled coffee raises serum cholesterol levels. The authors suggest that the downward trend in consumption of boiled coffee may have contributed to the 10% reduction of serum cholesterol in the Finnish population.</td>
</tr>
</tbody>
</table>
## APPENDIX TABLE. DIETARY LIPIDS AND CARDIOVASCULAR DISEASE

| Reference          | Objective                                                                 | Study Design                                                                 | Subjects                                      | Duration | Test Materials | Dose | Base Diet | Results                                      | Comment                                                                                                                                                                                                 |
|--------------------|---------------------------------------------------------------------------|------------------------------------------------------------------------------|-----------------------------------------------|----------|---------------|------|-----------|-----------------------------------------------|                                                                                                                                                                                                                                                                 |
| Prewitt et al., 1988 | To examine differences in nutrient intake and in lipids and lipoprotein chol between black children and white children | Data obtained from 2 examinations of the Lipid Research Clinics Program Prevalence Study (Williams et al., 1986) combined with nutrient intake and blood lipids data of children in Cincinnati and Houston were the basis for this analysis. | 259 black children (129 , 130 ?) and 811 white children (424 , 387 ?), age range 5–19 yr | N/A      | N/A           | N/A | Usual diets | Total energy intakes*, calories per kg bw*, TGs and VLDL-chol were lower in blacks than in whites*; total chol and HDL-chol were higher in blacks; there were no sig diffs in chol intakes and in LDL-chol. *Consistent difference in ; less consistent but lower in black than white ? | Race seems to be a major independent variable for lipid and lipoprotein chol levels. A possible weakness in this study was reliance on the 24-hr dietary recall to estimate intakes; however, since the study was retrospective, there was no alternative. |
## APPENDIX TABLE. DIETARY LIPIDS AND CARDIOVASCULAR DISEASE

<table>
<thead>
<tr>
<th>Reference</th>
<th>Objective</th>
<th>Study Design</th>
<th>Subjects</th>
<th>Duration</th>
<th>Test Materials</th>
<th>Dose</th>
<th>Base Diet</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radack et al., 1990</td>
<td>To examine the effects of prolonged consumption of low doses of ω-3 FAs on lipids, lipoproteins, and apolipoproteins in hypertriglyceridemic subjects</td>
<td>A randomized, placebo-controlled, dietary intervention trial conducted in 3 phases: 6-wk stabilization period, 20-wk treatment period, a 4-wk washout period</td>
<td>25 free-living male and female, age range 21-85 yr, with non-severe hypertriglyceridemia</td>
<td>Approx 30 wk</td>
<td>Commercially supplied fish or olive oil capsules</td>
<td>Group 1: 2.2 g/d total ω-3 FAs (1.1 g fish oil capsules plus 1 g olive oil capsule i.d.); Group 2: 1.1 g/d total ω-3 FAs (1 fish oil capsule plus 2 olive oil capsules i.d.); Group 3 (control group): placebo (3 capsules of olive oil, i.d.)</td>
<td>A.H.A. Step I diet started for all subjects at initiation of study</td>
<td>Group 1: LDL–cholesterol and LDL–apo B ↑ 28% and 23% respectively, compared with placebo group. The ↑ apo B in both fish oil groups was statistically and clinically significant; only minor changes in TG levels occurred.</td>
</tr>
</tbody>
</table>
## APPENDIX TABLE. DIETARY LIPIDS AND CARDIOVASCULAR DISEASE

<table>
<thead>
<tr>
<th>Reference</th>
<th>Objective</th>
<th>Study Design</th>
<th>Subjects</th>
<th>Duration</th>
<th>Test Materials</th>
<th>Dose</th>
<th>Base Diet</th>
<th>Results</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosenberg et al., 1988</td>
<td>To examine the risk of first, nonfatal MI in relation to coffee consumption in males under 55 yr old</td>
<td>A hospital-based, case-control study of MI pts and noncardiac control pts in which data on coffee and tea consumption and other possible lifestyle cardiovascular risk factors were collected and analyzed</td>
<td>1873 males aged 25-54 yr, hospitalized for first MI and 1161 males 25-54 yr, admitted for conditions unrelated to coffee consumption and with no hx of MI or chest pain</td>
<td>Data were gathered from 1980 to 1983.</td>
<td>Both regular and decaffeinated coffee and tea</td>
<td>Estimated cups/d during mo before hospital, plus yr of consumption</td>
<td>Usual diet</td>
<td>After adjusting for other major risk factors, recent consumption of caffeine-containing coffee led to a higher risk of CHD in proportion to average daily intake, e.g., about 2X 1 in risk in males consuming 5 or more cups/d. Limited data also suggested that males who had consumed at least 5 cups of decaffeinated coffee/d for less than 8 yr had an 1 risk of CHD.</td>
<td>The authors critique their own study in terms of possible biases but conclude that there is sufficient evidence from this and other studies to suggest coffee drinking increases risk of MI but insufficient to establish a causal relationship.</td>
</tr>
<tr>
<td>Rosmarin et al., 1990</td>
<td>To determine the effect of consuming 3 or more cups of filter-brewed coffee/d on serum lipid levels</td>
<td>A prospective, randomized, crossover clinical trial Group A drank 3 or more cups of coffee/d for 2 mo, then crossed over to coffee abstinence for 2 mo; Group B was on the opposite schedule.</td>
<td>21 free-living, healthy white males, age range 22-45 yr</td>
<td>4 mo</td>
<td>Drip-grind coffee (other sources of caffeine were excluded)</td>
<td>Avg 3.6 cups/d</td>
<td>Usual diet</td>
<td>No effect of coffee consumption was found on serum total chol, HDL-chol, LDL-chol, or apo B.</td>
<td>Filtered coffee appears to have no adverse effect on serum lipids and lipoproteins; however, the study results are not necessarily generalizable to the population at large.</td>
</tr>
<tr>
<td>Reference</td>
<td>Objective</td>
<td>Study Design</td>
<td>Subjects</td>
<td>Duration</td>
<td>Test Materials</td>
<td>Dose</td>
<td>Base Diet</td>
<td>Results</td>
<td>Comment</td>
</tr>
<tr>
<td>-----------</td>
<td>-----------</td>
<td>--------------</td>
<td>----------</td>
<td>----------</td>
<td>----------------</td>
<td>------</td>
<td>-----------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Schectman et al., 1988</td>
<td>To examine the effect of fish oil supplements on VLDL and LDL levels and composition in NIDDM pts</td>
<td>A prospective, randomized, placebo-controlled, single-blind, crossover trial</td>
<td>13 free-living NIDDM pts (9 m, 4 f), mean age 54±4 yr</td>
<td>Approx 16 wk</td>
<td>Commercial fish oil or safflower oil (placebo) capsules</td>
<td>12 g/d safflower oil in both arms of crossover; 12 g/d fish oil in first crossover arm, 15 g/d in 2nd arm, providing respectively, 4.0 and 7.5 g/d ω-3 fatty acids</td>
<td>Standard diabetic diet</td>
<td>Compared with safflower oil, fish oil supplementation resulted in decreased total plasma TGs of 24% at the 4 g dose and 39% at the 7.5 g dose. These decreases were associated with similar reductions in VLDL TGs; LDL chol &quot;mildly elevated;&quot; LDL apo B increased 20% at the 7.5 g dose; fasting glucose and glycohemoglobin levels increased 20% and 12% respectively.</td>
<td>Authors noted that the increase in LDL apo B levels and the signs of deterioration of glycemic control raise doubts about the advisability of fish oil supplementation in diabetic pts; however, this study was inconclusive in this respect.</td>
</tr>
<tr>
<td>Shekelle and Stamler, 1989</td>
<td>To investigate the hypothesis that intake of dietary cholesterol affects the risk of ischemic heart disease (IHD) independently of the total serum chol level</td>
<td>A longitudinal cohort study of associations between dietary chol intake and risk of death from IHD, other CVD combined, and from all causes combined. Vital status of participants was determined on 25th anniversary of the first examination in the Western Electric Study (Shekelle et al., 1981).</td>
<td>1843 middle-aged f followed for 25 yr</td>
<td>Intermittent for about 31 yr including initial examination and data collection, data analysis, and report preparation</td>
<td>Dietary cholesterol estimated from original dietary records of the Western Electric Study</td>
<td>Mean intake 240 mg/1000 kcal (SD 68) or 775 mg/d (SD 276)</td>
<td>Habitual diet (except for 283 participants who reported following special diets for various clinical disorders)</td>
<td>663 f (36.3%) died during the 25 yr follow-up: 307 from IHD, 89 from other CVD, 119 from malignancies, 90 from other causes. The RR of death from all CVD combined, associated with the difference between the mean of the first and fifth quintiles of chol intake was 1.46 (95% CI 1.10–1.94). Stratification of decedents by estimated total serum chol levels showed an inverse relationship with risk of death from all CVD combined.</td>
<td>Authors noted the results are further evidence that dietary chol is atherogenic in man and that the effect is partly independent of total serum chol. An important study Whether results may be generalizable to f in other age groups and to m is unknown.</td>
</tr>
</tbody>
</table>
## APPENDIX TABLE. DIETARY LIPIDS AND CARDIOVASCULAR DISEASE

<table>
<thead>
<tr>
<th>Reference</th>
<th>Objective</th>
<th>Study Design</th>
<th>Subjects</th>
<th>Duration</th>
<th>Test Materials</th>
<th>Dose</th>
<th>Base Diet</th>
<th>Results</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slattery and Randall, 1988</td>
<td>To examine trends in food consumption and CHD mortality in the United States between 1909 and 1980</td>
<td>An ecologic comparison of data and trends in CHD mortality and food consumption and fatty acid composition of the diet</td>
<td>Pts who died from CHD and samples of the population who were subjects in food consumption surveys</td>
<td>Data span 71 yr</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>A decline in mortality from ischemic heart disease in €45–64 yr has been documented since the mid-1960s. Changes in food consumption occurred 10–15 yr before the decline in CHD. Food pattern changes trended toward diets lower in SFAs; however, cheese consumption has increased.</td>
<td>Although difficult to document, intake of SFAs by the public during the past 30 yr may have declined, but whether this has contributed to the age-adjusted decline in CHD rates is uncertain.</td>
</tr>
<tr>
<td>Sorci-Thomas et al., 1989</td>
<td>To compare the effects of modified dietary fat and chol diets on apo B48 gene expression and the LDL receptor in nonhuman primates</td>
<td>Prospective dietary trial and tissue analysis</td>
<td>African green monkeys: about 19 adult € for the modified fat diets; number not stated for the separate liver perfusion study</td>
<td>5 yr for the 19 € animals; at least 2 yr for the separate liver perfusion group</td>
<td>Diets containing low (0.03 mg/kcal) or moderate (0.8 mg/kcal) chol concentrations and 40 en% of calories as PUPA or SFA</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Plasma total chol, LDL–chol, and apo B concentrations were generally high in animals fed chol at 0.8 mg/kcal and in animals fed SFA. No dietary chol or fat effects on liver apo b mRNA abundance; animals fed chol at 0.8 mg/kcal had 50% lower hepatic LDL receptor mRNA. Liver perfused animals showed no dietary fat effect on apo B secretion rate. No relationship existed between plasma LDL–chol level and rate of hepatic apo B production. Intestinal apo B mRNA level was approx. 30% higher in animals fed chol at 0.03 mg/kcal.</td>
<td>This study does not support the concept that the mechanism for elevation of LDL–chol levels by SFAs is suppression of LDL receptor activity.</td>
</tr>
</tbody>
</table>
## APPENDIX TABLE. DIETARY LIPIDS AND CARDIOVASCULAR DISEASE

<table>
<thead>
<tr>
<th>Reference</th>
<th>Objective</th>
<th>Study Design</th>
<th>Subjects</th>
<th>Duration</th>
<th>Test Materials</th>
<th>Dose</th>
<th>Base Diet</th>
<th>Results</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spady and Dietsch, 1989</td>
<td>To examine the effect of aging on LDL metabolism in an animal model</td>
<td>Dietary intervention, LDL metabolic study</td>
<td>6 Golden Syrian hamsters, age range 1 mo to 24 mo</td>
<td>Up to 24 mo</td>
<td>(1) Purina Rodent Laboratory Chow® (0.02% chol, 4.5% TG (w/w); (2) Purina Rodent Chow® enriched with 0.06% chol and 20% saturated TGs (w/w)</td>
<td>Ad lib</td>
<td>See Test Materials</td>
<td>On diet (1), rates of LDL tissue transport and plasma LDL concentrations were constant over all experimental periods (1 mo to 24 mo). Rates of de novo chol synthesis decreased 50-97% during transition from rapid body growth to stable adult size. In animals on diet (2), LDL production rates increased, total body LDL receptor activity decreased, plasma LDL-chol levels increased.</td>
<td>Authors concluded that aging per se had no effect on LDL transport by the liver and other tissues in this model.</td>
</tr>
<tr>
<td>Steenkamp et al., 1990</td>
<td>To relate the prevalence of hypercholesterolemia, other CHD risk factors, treatment status, and HDL-chol levels in a rural South African population</td>
<td>Data acquisition by laboratory, medical exam, personal and dietary histories; included 1 nonfasting blood sample. Subjects stratified by age and sex</td>
<td>7188 white 6 and 6, 15-64 yr, who participated in the Coronary Risk Factor Study High- and low-risk groups defined by serum total chol levels</td>
<td>N/A</td>
<td>Energy, macronutrients, and fiber in usual diets or chol-lowering diets</td>
<td>Dietary intakes estimated for high- and low-risk sub-samples of the study population</td>
<td>See Test Materials</td>
<td>Serum chol levels were correlated with degree of obesity, personal/family hx of CHD, hypertension, smoking, and hyperuricemia. No differences between high- and low-risk groups in intakes of dietary fats and chol; high-risk subjects ate more animal protein and less dietary fiber than low-risk subjects.</td>
<td>Although absolute accuracy of some of the data (e.g., dietary intakes, chol level based on a single determination) cannot be assured, this study appears to have been carefully conducted, and it produced useful data.</td>
</tr>
<tr>
<td>Steyn et al., 1990</td>
<td>To examine associations of nutrient intake, BMI, and age with serum total chol</td>
<td>A cross-sectional analysis of data from clinical lab, medical hx, and exam, and dietary intake estimates</td>
<td>An age- and sex-stratified random sample of 976 6 and 6, 15-64 yr, from the black population of Cape Peninsula, South Africa</td>
<td>N/A</td>
<td>Energy, macronutrients, and fiber in usual diets including prudent diets</td>
<td>Dietary intakes estimated for the full study sample and for high- and low-CHD risk sub-samples</td>
<td>See Test Materials</td>
<td>About 68% of the 6 and 73% of the 6 consumed typical Western-style diets high in fats and protein, P/S ratio &lt;0.85. Saturated fat intake and Keys score correlated independently with serum total chol levels. LDL-chol values significantly higher for subjects on a typical Western diet than those on a prudent diet.</td>
<td>The data suggest a valid need for an intervention program for this population group, with a prudent diet as a key element.</td>
</tr>
</tbody>
</table>
### APPENDIX TABLE. DIETARY LIPIDS AND CARDIOVASCULAR DISEASE

<table>
<thead>
<tr>
<th>Reference</th>
<th>Objective</th>
<th>Study Design</th>
<th>Subjects</th>
<th>Duration</th>
<th>Test Materials</th>
<th>Dose</th>
<th>Base Diet</th>
<th>Results</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thorogood et al., 1990</td>
<td>To reexamine the relation between diet and plasma lipids in selected population groups</td>
<td>Collection and analysis of blood samples and diet records of a cross-sectional sample of a large prospective, controlled cohort study of people eating different diets</td>
<td>208 British volunteer ♀ and ♂, 24–69 yr</td>
<td>Part of long-term Oxford Vegetarian Study; single blood sample 1984–1986; 4–d diet records 1985–1986</td>
<td>Four diets groups: vegans, vegetarians, fish eaters who did not eat meat, and meat eaters 52 subjects for each group</td>
<td>Al lib (however, most subjects were &quot;health conscious&quot;).</td>
<td>See Test Materials</td>
<td>A positive correlation of 0.37 (p&lt;0.001) was found between Keys score (reflecting mainly intake of SFAs) and serum chol levels. Mean intake of SF was low; of PUFA, higher. High fiber intake was not associated with high CHO intake. HDL−chol values were not associated with any measure of fat intake.</td>
<td>Authors concluded the nature of dietary fat rather than its quantity is an important determinant of chol concentrations. Validity of dietary estimates appears above average; however, the significance of a single serum chol determination is uncertain.</td>
</tr>
<tr>
<td>Tikkanen et al., 1990</td>
<td>To test the hypothesis that apo E isof orm-related differences in plasma and LDL chol result from differential responses to dietary lipids</td>
<td>Collection and analysis of fresh blood samples and reanalysis by apo E phenotype of original results of previously conducted dietary interventions in Finland</td>
<td>110 ♀ and ♂ from original study population, 30–50 yr at start, phenotyped for apo E, and who were in the original low-fat, low-chol, P/S ratio 1 dietary intervention group</td>
<td>Not specified</td>
<td>Baseline diets were high-fat, high chol. Intervention diet was low-fat, low-chol.</td>
<td>Ad lib</td>
<td>Usual Western-style diet</td>
<td>During high-fat, high-chol diet, plasma chol levels were higher for individuals with apo E4/4 and lowest for those with apo E3/3 phenotypes. This apparent effect declined during the low−fat, low−chol diet.</td>
<td>The apo E phenotype appeared to affect the magnitude of the plasma and LDL−chol responses to high versus low intakes of SFs. These suggestive data require further confirmation.</td>
</tr>
<tr>
<td>Reference</td>
<td>Objective</td>
<td>Study Design</td>
<td>Subjects</td>
<td>Duration</td>
<td>Test Materials</td>
<td>Dose</td>
<td>Base Diet</td>
<td>Results</td>
<td>Comment</td>
</tr>
<tr>
<td>-----------</td>
<td>-----------</td>
<td>--------------</td>
<td>----------</td>
<td>----------</td>
<td>----------------</td>
<td>------</td>
<td>-----------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Trevisan et al., 1990a</td>
<td>To examine associations between various dietary lipids and CHD risk factors</td>
<td>Part of the Italian Nine Communities Study of risk factors for atherosclerosis, a prospective, randomized health and nutrition screening survey. Cross-sectional analytic model for the present study included age, BMI, smoking, atherogenic diet index, and fat consumption score.</td>
<td>2365 ♂, mean age 49.8±11.3 yr and 2538 ♀, mean age 49.9±10.9 yr.</td>
<td>N/A</td>
<td>Intakes of 11 dietary fat sources were estimated such as butter, olive oil, corn oil, margarine, etc.</td>
<td>Ad lib</td>
<td>Usual diet</td>
<td>Increased consumption of butter was associated with higher BP, serum chol, and glucose levels in ♂ in women, only higher glucose levels were significant. In both sexes, intake of olive oil and vegetable oil was inversely associated with chol and glucose levels and systolic BP.</td>
<td>Authors noted the data suggest that consumption of butter may adversely affect coronary risk factors, while PUFA and MUFA may be associated with a lower coronary disease risk profile. Although this seems to be a carefully designed and executed investigation, the limitations of dietary intake estimates method and one-time blood biochemical determinations should be kept in mind.</td>
</tr>
<tr>
<td>Reference</td>
<td>Objective</td>
<td>Study Design</td>
<td>Subjects</td>
<td>Duration</td>
<td>Test Materials</td>
<td>Dose</td>
<td>Base Diet</td>
<td>Results</td>
<td>Comment</td>
</tr>
<tr>
<td>--------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
<td>----------</td>
<td>----------------</td>
<td>--------</td>
<td>----------------</td>
<td>--------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Trevisan et al.,</td>
<td>To examine associations between consumption of foods rich in saturated</td>
<td>Part of the Italian Nine Communities Study (see Trevisan et al., 1990 a).</td>
<td>2,377♂, 40.7±11.3 yr, and 2,540 ♀, 40.9±9 yr.</td>
<td>N/A</td>
<td>Foods designated as atherogenic (high in chol and SFAs) contained in the usual diets of the participants</td>
<td>Ad lib</td>
<td>See Test Materials</td>
<td>In both sexes, systolic BP, serum glucose, and serum chol levels increased with higher consumption of atherogenic foods.</td>
<td>Authors note the findings were independent of possible confounding factors such as age, adiposity, alcohol, and cigarettes. Potential limitations of this study are the same as in Trevisan et al., 1990a.</td>
</tr>
<tr>
<td>1990b</td>
<td>fats and cholesterol and a series of CHD risk factors</td>
<td>Cross-sectional analysis focused on frequency of consumption of atherogenic foods and each CHD risk factor selected by the investigators.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van Horn et al.,</td>
<td>To examine differences and associations among sex, age, education, and</td>
<td>Statistical analyses of data from the Coronary Artery Risk Development in Young Adults (CARDIA) study</td>
<td>5111 white and black ♂ and ♀ in 4 large U.S. cities, age range 18-30 yr at baseline (1985-1986)</td>
<td>Usual diets</td>
<td>Dietary intakes estimated by interviewer-administered diet history covering the past 30 d</td>
<td>See Test Materials</td>
<td>Keys score correlated with plasma chol in older white ♂ and ♀ and positively associated with total and LDL-chol in white ♂ and women. BMI positively associated with total and LDL-chol and inversely with HDL-chol in all race-sex groups. Education was associated with HDL-chol in black and white ♂ and white ♀. The study demonstrated expected relations among Keys score, dietary chol, and blood lipids for white, but not black participants.</td>
<td>Authors discussed possible problems in dietary intakes methodology and noted possible need for improvements to ensure valid data collection from black participants.</td>
<td></td>
</tr>
</tbody>
</table>
### APPENDIX TABLE. DIETARY LIPIDS AND CARDIOVASCULAR DISEASE

<table>
<thead>
<tr>
<th>Reference</th>
<th>Objective</th>
<th>Study Design</th>
<th>Subjects</th>
<th>Duration</th>
<th>Test Materials</th>
<th>Dose</th>
<th>Base Diet</th>
<th>Results</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wardlaw and Snook, 1990</td>
<td>To reexamine the effect of PUFA and MUFA on HDL–cholesterol and to document the effects on serum lipids of high–oleic acid sunflower oil</td>
<td>A prospective, randomized, blind, crossover dietary trial</td>
<td>20 volunteer σs, average age 34.7±1.5 yr, with serum cholesterol values between 5.5 and about 6.2 mmol/L</td>
<td>150 d</td>
<td>Butter–based diet 2 wk; corn oil (Poly) diet or high–oleic acid sunflower oil (Mono) diet, 5 wk; washout period, 7 wk; then crossover repeat of entire sequence</td>
<td>Intakes adjusted to maintain body weight Basic diet provided 40 en% as fat (range 37–43%).</td>
<td>See Test Materials</td>
<td>Compared with butter–based diet, the two veg oil diets reduced serum total cholesterol by 16–21% (p&lt;0.001), LDL–cholesterol by 21–26% (p&lt;0.001), TGs by 10–21% (p&lt;0.01 for the higher value) and apo B–100 by 22–29% (p&lt;0.001). No changes in HDL–cholesterol or apo A–1</td>
<td>Authors conclusion: the data suggest that σ on a high SF diet reduce their SF intake, many can experience a significant lowering of serum total cholesterol. This study was carefully designed, controlled, and executed. Results are not necessarily generalizable to σ in other age groups or to σ.</td>
</tr>
<tr>
<td>West et al., 1990</td>
<td>To examine the question whether hypertriglyceridemia associated with high–CHO diets is transient or permanent</td>
<td>A prospective, international collaborative cohort study</td>
<td>A total of 719 healthy boys, 7.6–10.5 yr, from 12 countries including Europe, Africa, and Asia (Study included published values from USA Lipid Research Clinics Prevention Study, Lipid Research Clinics Program, 1980, 1982).</td>
<td>1984–1989</td>
<td>High–CHO or high–fat diets typical of the populations sampled</td>
<td>Dietary intakes were ad lib. Mean values of dietary lipids intakes and CHO intakes were determined by dietary surveys.</td>
<td>See Test Materials</td>
<td>Fasting serum TG levels were highest in boys in the 4 developing countries of Africa and Asia where diets were low in fat (12–22 en%) and high in CHO (68–75 en%) as compared with boys in more affluent countries. LDL– and HDL–cholesterol were also lower in boys consuming high–CHO, low–fat diets. Data suggest at least part of the CHO–induced triglyceridemia is permanent.</td>
<td>The results are in accord with results of controlled dietary trials and epidemiologic studies. Despite logistic and other factors such as a global investigation, great care was used to eliminate the possible sources of bias. However, the influence of certain possible confounders such as population–related genetic factors cannot be ruled out.</td>
</tr>
</tbody>
</table>
**APPENDIX TABLE. DIETARY LIPIDS AND CARDIOVASCULAR DISEASE**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Objective</th>
<th>Study Design</th>
<th>Subjects</th>
<th>Duration</th>
<th>Test Materials</th>
<th>Dose</th>
<th>Base Diet</th>
<th>Results</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zock et al., 1990</td>
<td>To examine whether the cholesterol-raising effect of boiled coffee results from its lipid content</td>
<td>A prospective dietary trial</td>
<td>10 healthy volunteers (6 male, 4 female); mean age 28±6 yr</td>
<td>17 wk (pretreatment 1 wk; dietary trial 6 wk; posttrial 10 wk)</td>
<td>Lipid–enriched fraction from boiled coffee</td>
<td>1.3 g lipid and 1.6 g other solvents</td>
<td>Usual diet but with regular desserts replaced by expl desserts made from 80 g of the lipid–rich boiled coffee supernatant and 200 g custard</td>
<td>Serum total chol increased in all subjects (mean rise at 6 wk was 23%); LDL–chol rose by 29%, and TGs by 55%. HDL–chol was unchanged. At the end of the post–trial period (wk 17), these values had returned to pretreatment levels.</td>
<td>These results need validation in a PRCT with larger n and placebo controls.</td>
</tr>
</tbody>
</table>

**Abbreviations:**

- A.H.A. American Heart Association
- apo apolipoprotein
- AA arachidonic acid
- BP blood pressure
- BMI body mass index
- CAD coronary artery disease
- CHD coronary heart disease
- CHO carbohydrate
- CVD cardiovascular disease
- DHA docosahexaenoic acid
- en% percent energy intake
- EPA eicosapentaenoic acid
- F fat
- FCHL familial combined hyperlipidemia
- FH familial hypercholesterolemia
- HDL high density lipoprotein
- HL hepatic lipase
- hx history
- IDDM insulin–dependent diabetes mellitus
- LDL low density lipoprotein
- LPL lipoprotein lipase
- MI myocardial infarction
- MJ megajoules
- MUFA monounsaturated fatty acid
- N/A not applicable
- NCEP National Cholesterol Education Program
- NIDDM noninsulin–dependent diabetes mellitus
- P protein
- pts patients
- PRCT prospective, randomized control trial
- PUFA polyunsaturated fatty acid
- SF saturated fatty acid
- SFA saturated fat
- TG triglyceride
- VLDL very low density lipoprotein
- trans–FA Trans fatty acid