THE FEASIBILITY OF UNDERTAKING
A COMPREHENSIVE REVIEW
OF
RELATIONSHIPS AMONG DIETARY FATS,
CHOLESTEROL, CORONARY HEART
DISEASE, AND CANCER

March 1987

Prepared for
NATIONAL DAIRY COUNCIL
ROSEMONT, ILLINOIS 60018
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NATIONAL DAIRY COUNCIL
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edited by
John M. Talbot, M.D.

LIFE SCIENCES RESEARCH OFFICE
FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY
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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 on literature reviews and the scientific opinions of knowledgeable investigators engaged in work in relevant areas of biology and medicine.

This report was developed for the National Dairy Council, 6300 North River Road, Rosemont, Illinois 60018, in accordance with the provisions of a memorandum of agreement between LSRO/FASEB and the National Dairy Council for a feasibility study entitled, "The Relationship of Dietary Fat and Cholesterol to Coronary Heart Disease and Cancer." It was compiled and edited by John M. Talbot, M.D., Senior Medical Consultant, LSRO, FASEB.

The LSRO acknowledges the contributions of the investigators and consultants who assisted in this study. The report reflects the opinions expressed by members of an ad hoc Working Group who met at the Federation on October 24, 1986 and by other consultants. The study participants reviewed a draft of the report and their various viewpoints are incorporated. They and the LSRO accept responsibility for the accuracy of the report; however, the listing of their names in Chapter VII does not imply that they endorse each study conclusion.

The report was reviewed and approved by the LSRO Advisory Committee (which consists of representatives of each constituent Society of FASEB) under authority delegated by the Executive Committee of the Federation Board. Upon completion of these review procedures, the report was approved and transmitted to the National Dairy Council by the Executive Director, FASEB.

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.

March 21, 1987

Kenneth D. Fisher, Ph.D.
Director
Life Sciences Research Office
SUMMARY

This report addresses the feasibility of conducting a comprehensive review and analysis of available data on the role of foods containing dietary fats and cholesterol in the etiology of coronary heart disease (CHD) and cancer in the same population. It covers the possible need for a comprehensive review, the availability and strength of scientific evidence necessary to conduct such a review, and the probability of success in undertaking the review. The report is based on the opinions of expert scientists who participated in the feasibility study and on a limited overview of published scientific literature.

The study participants agreed that the evidence supporting the lipid hypothesis of atherosclerosis and CHD is widely accepted as definitive. They noted that the data are sufficiently strong to warrant consideration of public health measures that would lead to reduction of serum cholesterol concentrations in the general population. However, they also pointed out that concurrence on the postulated relationships between diet and CHD is not unanimous within the scientific community because some studies do not support public health recommendations to reduce dietary fats to 30% of caloric intake.

With regard to the etiology of cancer, they concluded that the role of dietary fats and cholesterol is less well established. None of the participants considered the available evidence sufficient to document a causal relationship between human cancer and consumption of dietary fats and cholesterol. A majority agreed that available epidemiological data do not provide justification for public health recommendations for reducing consumption of dietary fats and cholesterol as a means to prevent or reduce the risk of cancer.

The study participants also concluded that there is a need for a better understanding of the relationships of dietary fats and cholesterol to the etiology of atherosclerosis and cancer. They expressed concern as to whether currently available data on the combined endpoints, CHD and cancer, in relation to estimated dietary intakes of fats and cholesterol in common study populations are sufficient for a meaningful comprehensive review. Although some participants considered it probable that the amounts of available data are sufficient for such a review, none supported undertaking such a comprehensive study. Rather, most participants favored the conduct of reviews of more limited scope as an approach to improved understanding of available data and for identifying needed research.

The study participants suggested that a comprehensive review may be appropriate in the future when more experimental and epidemiological data become available for review and evaluation. At that time, the probability of success in assembling a
scientific panel which could evaluate the topic objectively would be quite high. Selection of an expert panel would require not only careful attention to balancing the various scientific points of view, but also critical planning as to the most appropriate questions to be included in their scope of review and evaluation.

Finally, the study participants identified some important gaps in needed scientific knowledge and corresponding suggestions for future research.
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This report addresses the feasibility of conducting a comprehensive review and analysis of available data on the role of foods containing dietary fats and cholesterol in the etiology of coronary heart disease (CHD) and cancer in the same population. It covers the possible need for a comprehensive review, the availability and strength of scientific evidence necessary to conduct such a review, and the probability of success in undertaking the review. The report is based on the opinions of expert scientists who participated in the feasibility study and on a limited overview of published scientific literature.

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I. INTRODUCTION

The National Dairy Council (NDC) supports programs of nutritional research and education. Sources of scientific guidance for these programs include state-of-the-art analyses of research literature, dietary recommendations from governmental and private sources, and the advice of expert consultants. The NDC has a continuing interest in aspects of diet-health relationships including findings and interpretations of data from numerous investigations of diet and disease and the validity of dietary recommendations.

The NDC has noted disparate interpretations of data from studies on the roles of dietary fats and cholesterol in coronary heart disease (CHD) and certain cancers. While there are many studies of the role of dietary fats and cholesterol in either CHD or cancer, the Council has been unable to locate a meaningful number of reports of studies associating foods containing dietary fats and cholesterol with both CHD and cancer as the principal, simultaneous endpoints.

The NDC concluded that an independent, comprehensive evaluation of these issues would probably yield information and suggestions of value in their programs of research and education. Such an evaluation study would review, analyze, and report on the scientific evidence regarding the common or divergent role of foods containing dietary fat and cholesterol in both CHD and certain forms of cancer. This report by LSRO was undertaken to determine whether the type of expert, comprehensive review envisioned by NDC would be feasible and desirable at present.
II. OBJECTIVES AND SCOPE OF STUDY

The object of this study is to estimate the feasibility of conducting a review of the role of dietary fats and cholesterol in the etiology and prevention of both CHD and cancer. The LSRO feasibility evaluation considers:

1. the need for review of the evidence on the role of dietary fat and cholesterol in the etiology and prevention of CHD and cancer;

2. the strength of the existing evidence to address the questions raised by the NDC, especially the ability to quantify dietary fat and cholesterol intakes consistent with optimal human health, and the influence of the source versus the amount of calories on health maintenance; and,

3. the probability of success in assembling a scientific panel which can review and evaluate the topic questions objectively.

The NDC has concluded that a comprehensive and objective review of the role of dietary fats and cholesterol in the etiology and prevention of both CHD and cancer would be helpful in planning programs in nutrition research and nutrition education. The Council suggested further that such a comprehensive review and evaluation might be conducted by an ad hoc group of scientific and medical experts who would be asked to address the following questions.

- Is there sufficient scientific evidence to permit quantifying fat and cholesterol intakes and the degree of fat saturation that are compatible with health promotion and disease prevention?

- How strong is the scientific evidence on the role of dietary fat and cholesterol intake and the role of foods containing these substances in the etiology of CHD and cancer? What research observations need confirmation? What research still needs to be performed?

- Do the proportions of calories from protein, fat, and carbohydrate have a metabolic significance if total energy intake is at a level to maintain desirable body weight?

- On the basis of current scientific knowledge and recognizing that foods and diets are both complex mixtures of numerous substances, what
advice can be given to the general healthy population of the United States regarding consumption of foods containing fat and cholesterol?

Because the scope of these questions is quite broad and because an effort to address them responsibly would have far-reaching public health significance, the LSRO concluded that the feasibility of conducting such a comprehensive review and evaluation should be examined prior to undertaking the study.

This document is the report of the feasibility study. It addresses the three objectives listed on the previous page. The report is based on a preliminary literature review and the opinions and suggestions of the LSRO ad hoc Working Group on the Relationship of Dietary Fat and Cholesterol to Coronary Heart Disease and Cancer and other individuals who participated in this study (see Chapter VII).
III. BACKGROUND INFORMATION

The principal objective of this study is to examine the feasibility and desirability of conducting a comprehensive review of available data on relationships between dietary fats and cholesterol and development of CHD and cancer in 1987-1988. Thus, a detailed, in-depth literature review was not attempted as part of the current study. Instead, review of the literature was limited to selected reports and published reviews that are exemplary. The report is based on the interpretations of the information and the opinions of the members of the LSRO ad hoc Working Group and other consultants who participated in this feasibility study.

A. THE ROLE OF DIETARY FATS AND CHOLESTEROL IN CORONARY HEART DISEASE

In this report, the term coronary heart disease (CHD) includes such disorders as coronary artery disease, atherosclerotic heart disease, coronary insufficiency, myocardial ischemia, angina pectoris, fatal and nonfatal myocardial infarction, and sudden coronary death. With regard to the definition of the lipid hypothesis of CHD, leading investigators appear to differ in what concepts are included. Some restrict its definition to include only the relationships between serum cholesterol and CHD; others include the influence of dietary lipids as a component of the lipid hypothesis. In this report, both concepts of the lipid hypothesis are expressed.

Prevailing scientific opinion. Results from numerous investigations of the lipid hypothesis of CHD support the consensus that the incidence of CHD is directly proportional to serum cholesterol levels and that serum cholesterol levels vary directly with dietary levels of total fats, saturated fats, and cholesterol in population studies and in some individuals (American Heart Association, 1984; Carlson and Büttiger, 1972; Gofman et al., 1966; Inter-society Commission for Heart Disease Resources, 1984; Kannel et al., 1971, 1979; Keys et al., 1981; Levy, 1985; McNamara, 1982; Shekelle et al., 1981a; Stamler, 1984; Stamler and Stamler, 1984; Steinberg, 1985; World Health Organization, 1982; Zilversmit, 1982). The results of animal studies since the early 1900s support the lipid hypothesis of atherogenesis (Anitschkow, 1967; Mann and Andrus, 1956; McGill, 1979; Zilversmit, 1978).

Coronary heart disease is a multifactorial disease. Elevated serum cholesterol is one factor. The evidence relating blood cholesterol to CHD is derived from many different investigative approaches. Cholesterol and its esters have been identified as major components of atheromatous plaques in humans. Similar pathological changes have been induced in various animal
species, including the nonhuman primate, by feeding hypercholesterolemia-inducing diets rich in saturated fat and cholesterol. Recent clinical studies of lowering serum cholesterol suggested decreased progression of atherosclerotic lesions in man as well as animals, further supporting a causal role of diet-induced hypercholesterolemia in atherosclerosis. Inborn errors in lipid metabolism, characterized by severe hypercholesterolemia and early death from CHD, have been identified. In particular, study of the homozygous form of familial hypercholesterolemia has dramatically illustrated the consequences of high levels of low-density lipoproteins (LDL); even in the absence of other risk factors such as hypertension and cigarette smoking, affected individuals develop CHD and usually die in their first or second decades. Through studies of the genetic hyperlipidemias and of plasma lipids and lipoproteins, much has been learned about the normal pathways of lipid metabolism and the effects of various disruptions. Identification and characterization of the LDL receptor and its role in clearance of LDL cholesterol by the liver and studies of the effects of dietary saturated fat and cholesterol on receptor activity have clarified the mechanisms by which genetic abnormalities and dietary fats lead to pathological elevations in plasma cholesterol (Appelbaum-Bowden et al., 1984; Brown and Goldstein, 1984; Brown et al., 1981, 1984).

Many types of epidemiological studies, including case-control and prospective observational studies, international comparisons, and migrant studies have also related the level of cholesterol to the prevalence and incidence of atherosclerosis and CHD (Stamler, 1979). As reviewed by Bierman (1983), data from the Framingham study suggest a continuous, upward gradient of risk as serum cholesterol levels increase; for example, males and females between ages 30 and 49 years with serum cholesterol levels >260 mg/dl showed a relative incidence of myocardial infarction three to five times that of subjects whose serum cholesterol levels were <220 mg/dl. Kannel and Schatzkin (1983) noted that the lowest rates of CHD are associated with average values of serum cholesterol in study populations in the range of 140 to 180 mg/dl. Stamler et al. (1986) reported a strong, continuously graded, increased risk of death from CHD directly associated with rising levels of serum cholesterol in the range of 182 to 245 mg/dl in 356,222 middle-aged men who made up the cohort of the Multiple Risk Factor Intervention Trial.

However compelling the broad range of evidence cited above may be, the final link in the chain establishing the etiological significance of serum cholesterol is missing; that is, direct demonstration that lowering serum cholesterol reduces the rate of CHD is lacking. Many clinical trials of cholesterol lowering have been conducted. Diet and/or a variety of drugs have been employed, usually in individuals with clinical CHD (secondary prevention) but sometimes in healthy participants (primary prevention); for example, see the Lipid Research Clinics
Coronary Primary Prevention Trial (Lipid Research Clinics Program, 1984). However, no single study of dietary modification alone could be regarded as conclusive. Such factors as the failure to randomize, absence of a double-blind design, inadequate numbers, and statistical problems in analysis have been held as reasons for regarding these studies as inconclusive when examined on an individual basis. In addition to the above, marked genetic variations in the ability of dietary cholesterol to influence plasma cholesterol among individuals and populations have been reported (Bierman, 1983). Moreover, the reasons for substantial interindividual differences in response to diets designed to lower serum cholesterol are not clear.

Analysis of these studies taken in the aggregate has recently yielded additional information. In an analysis of primary and secondary prevention trials using diet, and in which randomization had been carried out, it was found that in general, the greater the serum cholesterol reduction, the greater the reduction in CHD risk; a 10% reduction in serum cholesterol conferred a 15 ± 6% reduction in risk. In a corresponding analysis of randomized studies of drug-induced cholesterol lowering, a 10% reduction in cholesterol was associated with a 21 ± 5% reduction in CHD risk (Mann and Marr, 1981). The investigations from which these estimates were derived included primary and secondary dietary prevention trials and multifactorial trials. Examples are the Los Angeles Veterans Administration Study (men 55-89 years old) (Dayton et al., 1969), the Finnish Mental Hospital Study (men and women, median age ranges 50.5-59 years and 47.5-50.5 years, respectively) (Miettinen et al., 1972; Turpeinen et al., 1979), and the Chicago Coronary Prevention Evaluation Program (high-risk men 40-59 years old) (Stamler, 1971). Dietary intervention resulted in lowering of serum cholesterol concentrations in many of the studies analyzed by Mann and Marr (1981); however, beneficial effects in terms of reducing the incidence of CHD were observed mainly in subjects with "high" entry levels of serum cholesterol.

Although a cause-and-effect relationship between ingestion of saturated fats and cholesterol and increased risk of CHD has not been demonstrated, the aggregate evidence from all sources has convinced public health authorities in several countries and some private professional organizations to recommend diets to help prevent CHD that are reduced in total fats, saturated fats, and cholesterol and moderately increased in polyunsaturated fatty acids (American Heart Association, 1984; Department of Health and Social Security, 1984; Inter-society Commission for Heart Disease Resources, 1984; Stamler, 1984; Steinberg, 1985; U.S. Department of Agriculture and U.S. Department of Health and Human Services, 1980; World Health Organization, 1982; Zilversmit, 1982). Such dietary measures along with improvement in control of other recognized risk factors such as hypertension, cigarette smoking, impaired glucose
tolerance, and obesity have been credited for the remarkable decreases in mortality from CHD in the United States since the early 1960s (Stamler, 1985).

However, a number of investigators (Ahrens, 1979, 1985; American Academy of Pediatrics, 1983; Harper, 1983; Mann, 1977; Mitchell, 1984; National Research Council, 1980; Oliver, 1985; Reaven, 1986; Reiser, 1978; Reiser et al., 1985) question the strength of the scientific data on which such dietary recommendations are based. The most frequently noted concern is the lack of scientific evidence in regard to the general U.S. population. For example, the preponderance of scientific data collected to date is derived from studies of adult males. Some of these investigators conclude that the paucity of corroborative evidence from long-term studies of children, adolescents, and women is a reason to not promulgate dietary recommendations for the population as a whole.

Other interpretations of the data. Interpretation of the available epidemiologic data on diet and heart disease is impeded by a number of inconsistencies. These include the apparent discrepancy between strong positive correlations of dietary intakes of lipids with serum cholesterol concentrations and risk of CHD in studies comparing population groups versus the weak or disappearing positive correlations in studies of homogeneous populations and individuals (McGill, 1979). Analyses of the differences between correlation coefficients computed from group means and those from individual values suggested that the different values obtained are not necessarily contradictions and that the true correlation coefficients probably lie between the values from the group means and the individual values (McGill et al., 1981). Additional approaches to interpretation and reconciliation of evidence from group and individual data are presented by Blackburn and Jacobs (1984) and Rose (1985).

Notwithstanding the well-established relationship between serum cholesterol levels and risk of CHD, most heart attacks apparently occur in persons whose serum cholesterol levels are in the "normal" range, i.e., <235 mg/dl (Kuller, 1983). The opinions of investigators who question the putative etiologic role of dietary lipids in the lipid hypothesis of CHD range from the view that there is no strong relationship between dietary lipids and CHD to the proposition that available scientific data are insufficient to justify recommendations that "all Americans" eat low-fat, high-carbohydrate diets. These investigators have raised the following points in support of their concerns.

- Proof is lacking that exogenous lipids have an etiologic role in CHD.
- The common or distinct biologic mechanisms leading to all types of CHD are essentially unknown.
Lowering intakes of dietary lipids by the generally recommended amounts has only a "trivial" effect on serum cholesterol concentrations.

Cholesterol is an endogenous material which, in a free-living society, is genetically determined and is minimally related to diet.

Some of the limited number of dietary intervention trials have reported suggestive, but not conclusive, evidence of a reduced frequency of CHD in the treated groups, but no reductions in total mortality. However, there is a paucity of well-designed and controlled, long-term dietary intervention trials aimed at demonstrating the effects of low-fat, low-cholesterol diets on development of CHD.

The metabolic effects of altering the composition of body lipids by changing the P/S ratio and types of fats in the diet are not well understood. Important questions needing more data include possible untoward effects on the kinetics of cholesterol transport, immunocompetence of lymphocytes, cell membrane permeability and receptor function, and coagulability of the blood.

The question whether practical, effective methods can be developed for bringing about major changes in traditional dietary habits of the general public has not been resolved.

Different people react differently to any given diet, and reliable means are not available for predicting individual responses to altered dietary regimens.

Each of these statements is true to some extent, but not to the degree that any one of them, or all of them taken together, provides convincing evidence that dietary lipids are not major causal factors in human CHD. Although serum cholesterol levels of 235 mg/dl may be in the average range for Americans, this should not be considered normal. A recent report based on over 350,000 men clearly shows a linear increase in heart attack risk above 180 mg/dl serum cholesterol (Stamler et al., 1986). Furthermore, studies of LDL receptor function suggest that LDL receptors function most efficiently below serum cholesterol concentrations of 170-180 mg/dl (Brown and Goldstein, 1984).

In summary, the combined evidence from epidemiologic, clinical, and animal studies suggests strongly a role for dietary sources of saturated fat and cholesterol and possibly the types of fats in the diet in atherogenesis and CHD. However, the relative importance of these environmental agents, along with those
of genetic influences and other recognized risk factors such as hypertension, diabetes, and cigarette smoking, are less well established. Because it is difficult to separate the influence of cholesterol from that of other dietary lipids, the significance of cholesterol, by itself, remains obscure. Attempts at dietary intervention by prescribing diets moderately low in total and saturated fats and with an increased P/S ratio have resulted in reductions of serum cholesterol approximating 10 to 15% and in suggestive evidence of a reduced frequency of CHD events. However, the question has not been resolved whether reduction of serum cholesterol concentration of this magnitude by diet alone, when applied to the general population, would reduce the risk of CHD. Much more drastic reductions in dietary fats and cholesterol may be required, such as in a vegetarian diet. The design of studies and problems of compliance with study protocols that would isolate dietary intervention from the confounding effects of other CHD risk factors constitute a major impediment to resolution of this issue. From a public health point of view, the most important question is what are the best methods of lowering plasma total or LDL cholesterol for a majority of the American public. The postulated relationships between diet and CHD remain controversial and opponents of a public health prescription of a low-fat diet for all Americans continue to identify experimental and epidemiological data that support their views.

B. THE ROLE OF DIETARY FATS AND CHOLESTEROL IN CANCER

In this report cancer is considered generically and also by target organs such as breast, lung, colon, endometrium, and prostate gland. Again, because of the nature of this feasibility study, a comprehensive literature review was not attempted, and background emphasis is limited to some of the findings and conclusions of selected investigators, expert groups, and recently published reviews.

Recognition of a possible link between diet, nutrition, and cancer stimulated considerable epidemiologic, clinical, and laboratory animal research as well as numbers of conferences during the past 15 years (Byers and Graham, 1984; Carroll and Khor, 1975; Cohen, 1986; Doll and Peto, 1981; Feinleib, 1983; Graham, 1983; Graham and Mettlin, 1979; Greenwald and Cullen, 1985; Kritchovsky and Klurfeld, 1981; Mendeloff, 1983; Miller, 1986; National Research Council, 1982; Sidney and Farquhar, 1983; Sugimura, 1986; Thompson, 1984; Weisburger, 1985; Willett and MacMahon, 1984a,b; Wynder, 1984).

Based upon an analysis of available literature, the Committee on Diet, Nutrition, and Cancer of the National Academy of Sciences (National Research Council, 1982) found that cancer risk increases for certain sites with higher dietary intakes of fats and protein and lower intakes of beta-carotene, vitamin C, and dietary fiber. The Committee's dietary recommendations for
the American public included advice to lower intake of fats to 30% of calories and to increase consumption of fruits, vegetables, and whole-grain products as a means of supplying additional amounts of beta-carotene, vitamin C, and dietary fiber.

1. Epidemiologic data

The hypothesis that dietary fat is a powerful risk factor for cancer at certain sites is supported by a large body of animal research and the results of several human epidemiologic studies (most notably international correlation studies and migration studies). In support of the theory, Reddy et al. (1980) and Wynder (1984) documented this view in terms of data from epidemiologic (including metabolic epidemiology) and laboratory animal studies as well as recent concepts of the possible biologic mechanisms. Positive associations between cancer prevalence or mortality and consumption of fats and/or cholesterol (as well as meats) have been observed in various types of epidemiologic investigations. For example, Phillips (1975) reported a direct association between colon cancer and the consumption of high-fat foods by Seventh-Day Adventists. Frequent consumption of foods high in saturated fat and low in dietary fiber was positively associated with colon cancer in blacks in California (Dales et al., 1979), and high-fat diets were associated with increased frequency of colorectal cancer in a Canadian case-control study (Jain et al., 1980). In international epidemiologic studies, strong positive correlations were reported between estimated per capita fat intake or availability and cancers of the colon (Liu et al., 1979), breast, prostate, and intestine (Carroll and Khor, 1975), and colon, rectum, breast, prostate, uterus, ovary, and testis (Armstrong and Doll, 1975). However, the weakness of retrospective dietary estimates as well as inconsistencies in apparent associations between dietary fats and cholesterol and cancer morbidity and mortality detract from the credibility of available data.

Some studies have shown negative or only weakly positive associations between levels of intake of dietary fats and cholesterol and cancer. For example, see: Bingham et al., 1979; Graham et al., 1982; Miller et al., 1978; Modan et al., 1975; Stemmermann et al., 1984. In general, results of studies of associations between dietary intakes of fats and cancer of the colon in individuals have been inconsistent (Willett and MacMahon, 1984b). This inconsistency is also apparent from studies of dietary fats and meats and breast cancer. Furthermore, two of the most recent reports do not support a positive association between dietary intake of fat and the incidence of breast cancer within the range of fat consumption of women in the United States (Jones et al., 1987; Willett et al., 1987).

In summary, the epidemiologic evidence of an association between increased prevalence of or mortality from certain cancers and prolonged consumption of foods rich in saturated fats tends
to be positive, but continues to be confounded by numerous other genetic and environmental factors associated with the population groups studied.

2. **Other issues**

a. **Animal protein and cancer**

In some studies, consumption of meat has been positively associated with increased risk of colon and rectal cancer (Armstrong and Doll, 1975; Berg and Howell, 1974; Haenszel et al., 1973; Howell, 1975; Leveille, 1975; Manousos et al., 1983; Phillips, 1975) and breast cancer (Lubin et al., 1981). Results of other studies do not support these findings (Bjelke, 1978; Graham et al., 1978; Haenszel et al., 1980). Meats are important sources of fats and cholesterol, however, the role of meat consumption and animal proteins, per se, in the etiology of cancer is among the unresolved issues in the nutritional aspects of cancer.

b. **Energy intake and expenditure**

Excess caloric intake in relation to levels of physical activity generally leads to overweight which, in turn, has been positively associated with increased risk of several site-specific types of cancer in some, but not all, human studies (Garfinkel, 1985; Hill et al., 1979; Kritchevsky and Klurfeld, 1981; Lew and Garfinkel, 1979; Miller, 1986; Willett and MacMahon, 1984b). In its large-scale, prospective analysis of body weight indices and cancer mortality, the American Cancer Society found that overweight men had higher mortality ratios for colorectal and prostatic cancer than average-weight men, and overweight women had higher mortality ratios for cancer of the breast, endometrium, ovary, cervix, and gallbladder than average-weight women (Garfinkel, 1985). The mortality ratio for breast cancer was 1.53 in women who were overweight by 40% or more. Mortality ratios for endometrial cancer ranged from 1.36 to 5.42 in subjects 10 to 19% overweight and in those 40% or more overweight, respectively.

The positive association between "excess" caloric intake and breast cancer appears to predominate in postmenopausal women (Miller, 1986; Willett and MacMahon, 1984b). In a long-term cohort study of Seventh-Day Adventists, overweight was positively associated with risk of fatal rectal cancer in males and females and with colon cancer in males (Phillips and Snowden, 1985). In another study of 8006 Japanese men aged 45 to 68 years, body mass index (BMI) was positively associated with increased risk of colon cancer in men aged 65 years or older as was weight gain since age 25. Low BMI and weight loss since age 25 were associated with increased risk of stomach cancer, and weight loss alone
with increased lung cancer (Nomura et al., 1985). Results of some human studies have not shown a definite, positive association between levels of energy intake and cancer risk (Miller, 1986).

Reddy (1986) reviewed the available information on the caloric influence on carcinogenesis and concluded that, because of methodologic problems, the epidemiologic evidence for a separate caloric effect is only indirect and that case-control studies suggest fat is more important than total energy intake. However, in animal models, both dietary fat and total calories are determinants of enhanced carcinogenicity.

In rodents, some studies have demonstrated a positive association between "excess" caloric intake and frequency of mammary tumors (Kritchevsky et al., 1984; Willett and MacMahon, 1984b). The protective effect against spontaneous and artificially-induced tumors as well as an increase in life expectancy in rodents fed diets moderately restricted in calories is also well-defined (Pariza, 1986; Tannenbaum, 1955; Willett and MacMahon, 1984b). In a rat model of 7,12-dimethylbenz[a]-anthracene (DMBA)-induced mammary tumors, more tumors were observed in animals fed a low-fat, high-calorie diet than in those fed a low-calorie, high-fat diet, and caloric restriction plus increased dietary fat resulted in inhibition of tumor formation (Kritchevsky et al., 1984).

The question whether excess caloric intake is a significant risk factor for human cancer is not settled. The relationships among caloric intake, energy expenditures, and risk of cancer are extremely complex, involving multiple interacting variables. Some investigators believe that total, non-fat caloric intake does not relate significantly to risk of cancer (Sidney and Farquhar, 1983). Nevertheless, the hypothesis that overnutrition enhances the risk of human cancer appears to deserve increased research emphasis (International Life Sciences Institute/Nutrition Foundation, 1987; National Research Council, 1982; Pariza, 1986).

c. Serum cholesterol level and cancer

McMichael et al. (1984) reviewed four major human experimental studies in which blood cholesterol concentrations were deliberately lowered in attempts to reduce risk of CHD. One study reported definitely increased cancer mortality in the treated group; in the second, excess cancer mortality in treated subjects occurred when mean serum cholesterol concentrations were 225 mg/dl but not higher, and the other two studies showed no significant changes in cancer mortality. In the one study which showed an increased cancer risk (Pearce and Dayton, 1971), McMichael et al. (1984) emphasized that since the non-adhering subgroups within the two randomized groups who differed
least in their subsequent diets showed the greatest difference in their cancer risk, interpretation of the data must, to say the least, be difficult. Reports of 11 prospective observational studies on risk factors in cardiovascular disease indicated an inverse relationship between entry level serum cholesterol and cancer mortality, as did the results of two case-control studies (McMichael et al., 1984). Their overall conclusion regarding the studies in which blood cholesterol concentrations were deliberately lowered in attempts to reduce CHD risk was that in all the experiments, whether cholesterol-lowering was achieved by either drugs or diet, the intervention did not appear to alter the risk of cancer, either general cancer incidence or incidence of specific types.

In some studies (Bjelke, 1974; Kagan et al., 1981; Rose et al., 1974; Williams et al., 1981), but not all (Committee of Principal Investigators, 1978; Dyer et al., 1981; Kozarevic et al., 1981; Westlund and Nicolaysen, 1972; Yaari et al., 1981), lower blood cholesterol levels were related to increased mortality from colon cancer, predominantly in men. In general, when subjects who died of cancer within 2 years following entry into a study were eliminated from statistical follow-up, the apparent inverse relationship tended to disappear. This has suggested a putative "preclinical cancer effect" as a possible cause of the low cholesterol levels.

In about half the published studies, data do not indicate an inverse relationship between serum cholesterol concentration and risk of cancer (McMichael et al., 1984; Sidney and Farquhar, 1983); however, the evidence in half the published reports of a significant inverse relationship was considered impressive, but not conclusive, by Sidney and Farquhar (1983). In conclusion, the available data do not clearly establish a causal relationship between low serum cholesterol levels and increased risk of cancer, particularly colon cancer, but the subject deserves additional investigation (Feinleib, 1983; National Research Council, 1982).

d. Influence of the composition of dietary fats

The available information relating the effects of the type of dietary fat to the frequency of human cancer is sparse. Because cholesterol intake is closely associated with the ingestion of other nutrients, particularly fat, it is extremely difficult to tease out and define the exclusive effect of dietary cholesterol. With regard to international mortality rates from human breast cancer, a positive correlation with estimated dietary intakes of both saturated and unsaturated fats has been documented (Reddy et al., 1980). In a trial of dietary intervention against cardiovascular disease, diets high in polyunsaturated fats and low in saturated fats and cholesterol were fed to 424 men in a Los Angeles Veterans Administration hospital.
Total cancer mortality in the group fed polyunsaturated fats significantly exceeded that in the controls (Pearce and Dayton, 1971).

Ederer et al. (1971) compared these findings with those from four other dietary intervention trials to lower serum cholesterol conducted in Oslo, London, Helsinki, and Fairbault, Minnesota. The diets had increased proportions of polyunsaturated fats, decreased saturated fats, and low levels of cholesterol. The combined data from the four studies indicated a risk of 0.75 for development of cancer in the experimental groups relative to controls. When combined with the Los Angeles data, the estimated relative risk for cancer incidence was 1.15. The authors concluded that none of the relative risks was statistically significant and that cholesterol-lowering diets do not influence cancer risk.

Some studies have indicated that rats fed saturated fats have fewer chemically-induced tumors than those fed unsaturated fats (Broitman et al., 1977; Carroll and Khor, 1971; Reddy, 1979). Total yield of breast tumors in the DMBA rat model was low when the animals consumed fats low in linoleate (n-6), such as coconut oil or tallow, compared with yields in rats fed dietary fats rich in linoleate, such as corn oil or sunflower seed oil (Carroll and Khor, 1971, 1975). Results of other studies with the same rat tumor model suggested a threshold proportion of 2% linoleate in the dietary fat was necessary for optimal enhancement of tumor growth (Hopkins and Carroll, 1979).

In studies with the dimethylhydrazine (DMH) rat tumor model, the type of dietary fat used apparently did not influence tumor incidence when fed at the 20% level; at 15%, polyunsaturated fatty acids appeared to enhance tumorigenesis. However, there was no conclusive evidence that polyunsaturated fats enhance DMH-induced tumorigenesis in rats more than saturated fats (Reddy et al., 1980). In their review of nutrition and cancer, Reddy et al. (1980) concluded that total fat was more important than type of fat in enhancing production of breast tumors in the DMBA rat model and that a quantitative threshold exists for essential fatty acids in order to produce full expression of the high-fat effect.

Studies by Ip et al. (1985) have extended the observations on the influence of linoleate. Prostaglandin synthase inhibitors, such as indomethacin, reduce the enhancement of transplantable tumors by linoleate (Hillyard and Abraham, 1979; Kollmorgen et al., 1983). Finally, dietary n-3 fatty acids (for example, linolenate) diminish tumor production in some animal models (Karmali et al., 1984).

Thus, available data on the influence of the composition of dietary fats do not permit reliable differentiation of the carcinogenic effects of saturated versus unsaturated fats in
the human diet. Prevailing expert opinion suggests that total fat, more than the composition of fat, is perhaps a more important risk factor in human cancer and in animals except that, in some rat models, polyunsaturated fats fed at or above a threshold level enhance tumorogenesis when compared with saturated fats.

In summary, a number of issues remain to be resolved. There are important questions on relationships between diet and possible risk of cancer including the effects of consuming animal proteins, the influence of imbalances between energy intake and expenditure, the effect of the types of fats consumed and their degree of unsaturation, and the significance of low serum cholesterol levels that have been reported for some subjects in dietary intervention studies.
IV. OBSERVATIONS OF THE AD HOC WORKING GROUP

During the meeting, the participants were requested to address the issues set forth in the feasibility study objectives (see Chapter II), present related information and opinion based upon their research and other professional experience, identify gaps in knowledge and needed research, and recommend key references.

The term atherosclerosis was suggested as being more appropriate than CHD in discussing the issues involved. However, since the major focus of this study is on atherosclerosis of the coronary arteries, CHD is the term of choice. It is not intended that CHD as used in this report should be construed as synonymous with heart attack, coronary thrombosis, or myocardial infarction, although it includes manifestations of these events. Although CHD is the most important clinical manifestation of its sequelae, atherosclerosis also contributes substantially to stroke (where hypertension is the major risk factor) and to peripheral vascular disease (where smoking is dominant). Reference to mortality statistics from CHD is clearly identified as such.

The possibility that intake of foods containing lipids, as opposed to dietary intakes of fat and cholesterol, may have atherogenic and/or carcinogenic effects was discussed briefly. The usefulness of available data on effects of individual foods was considered limited; few specific references were found in the literature review and participants were not immediately aware of ongoing long-term studies addressing the question. Numerous studies of the effects of individual foods on risk factors associated with cardiovascular disease, such as the effects of egg consumption on serum cholesterol, are available. In some epidemiological studies, the association of particular foods (such as meats and dairy products), as well as food components, with the occurrence of cardiovascular disease and cancer has been reported. However, few efforts to analyze these sets of data have been reported. As with studies of individual food components, investigations of the long-term effects of particular foods are time-consuming, expensive, and hard to manage. Their results are also difficult to interpret. For example, the influence of a particular food on disease promotion or prevention may be modified by the type of diet in which it is consumed or other lifestyle factors. The possible atherogenic or carcinogenic effects of any one food cannot be established by a single data set. Ideally, data from several studies should be pooled to provide sufficient power to establish a quantifiable effect that could be attributable to the food. The effects of specific foods (as opposed to food components) are important issues that merit attention despite the difficulties in conducting and interpreting such research (see p.A-3, A-6, and A-7).
A. DIETARY FATS, CHOLESTEROL, AND CORONARY HEART DISEASE

The participants considered the evidence of a firm positive correlation between risk of CHD and dietary levels of total fats to be overwhelming, of saturated fats to be strong, and of cholesterol also strong but less well established than for total and saturated fats. Nevertheless, they identified a number of unresolved issues in the lipid hypothesis that require investigation (see Appendix). A majority of the participants considered it unnecessary to undertake a comprehensive review of all available data on the role of dietary fats and cholesterol in coronary heart disease at this time. They suggested that such a review would probably add little to existing reviews or to those about to be published (e.g., The Surgeon General's Report on Nutrition and Health and the review of diet and health now in progress by a committee of the National Research Council). On the other hand, some members of the Working Group suggested that expert reviews of more limited scope would be desirable (see Appendix).

B. DIETARY FATS, CHOLESTEROL, AND CANCER

Most participants considered the scientific evidence relating dietary levels of fats and cholesterol to cancer incidence to be unclear despite epidemiologic data from population studies showing positive correlations with several types of cancer. They noted that when studies are focused on individuals, these positive associations often disappear. The study participants agreed that a causal relationship linking dietary fats and cholesterol to cancer has not been documented.

An inverse relationship between serum cholesterol levels and risk of cancer in males has been documented in many investigations; however, numerous other studies have not shown such a relationship. In the opinion of the study participants, in an otherwise healthy individual, a low serum cholesterol level has not been shown to be a precursor of cancer. In a small number of cases, a low serum cholesterol may serve as a possible genetic marker of increased cancer risk.

Most participants considered it infeasible at present to undertake a comprehensive review of the relationships between dietary fats and cholesterol and risk of human cancer. This judgment takes into account the inadequacies of existing data bases in such areas as quantitative dietary intake data, the paucity of controlled dietary intervention studies, and lack of consistency of apparent diet-cancer associations in populations versus individuals. However, some members favor an expert review, noting, for example, that a truly comprehensive analysis of the role of dietary fats in the promotion of human carcinogenesis has not been published. All participants agreed that reviews of more limited scope would be useful.
C. ROLE OF OTHER DIETARY, ENVIRONMENTAL, AND INTRINSIC VARIABLES

Study participants emphasized the probable importance of interactions of multiple factors in the pathogenesis of CHD and cancer such as energy balance, physical activity, lifestyle, heredity, and other dietary factors in addition to fats and cholesterol. Inconsistencies in the literature on relationships between diet and cancer may result from multiple interactions among dietary components combined with an overlay of genetic and other environmental influences. For example, some dietary factors appear to be protective, others damaging; thus, knowledge of their combined, net effects in the total diet on health or disease is essential. The concept of interacting influences includes not only dietary factors, but also all other putative risk factors for CHD and cancer. Although it may not be feasible to design studies to examine the interactive effects of such aggregates of factors, the study participants regard this as a legitimate and potentially crucial research goal.

Human cohort studies with repeated assessment of dietary intakes and dietary intervention studies could probably produce some of these data, but their design is difficult. Further studies on certain vitamins such as A, C, and E, certain minerals such as calcium and selenium, and other regulatory substances such as protease inhibitors are needed. However, elucidation of their interactive effects on susceptibility to CHD and cancer will require consideration of factors such as dietary levels, bioavailability from foods, digestion, metabolism, and excretion. The multivariate nature of the associations that may be present is further complicated by a need to consider energy or total caloric intakes, caloric balance, dietary fat intakes, and changes in body weight or lean body mass.
V. CONCLUSIONS ON STUDY FEASIBILITY

A. NEED FOR A COMPREHENSIVE REVIEW

The study participants agreed that there is a need for a better understanding of the relationships of dietary fats and cholesterol to the etiology of atherosclerosis and cancer. However, they expressed concern as to whether currently available data on the combined endpoints, CHD and cancer, in relation to estimated dietary intakes of foods containing fats and cholesterol in common study populations are sufficient for a meaningful comprehensive review. Although some participants considered it probable that the amounts of available data on dietary fats and cholesterol are sufficient for such a review, none supported this idea as practical because of its diffuse nature, global scope, and the paucity of quantitative data on actual intake of specific foods or dietary components.

On the other hand, most participants favored the conduct of reviews of more limited scope as an approach to improved understanding of available data and for identification of needed research. Some examples of these are identified in the Appendix.

B. STRENGTH OF AVAILABLE SCIENTIFIC EVIDENCE

The frame of reference for this question is human health in terms of preventing or reducing susceptibility to CHD and cancer in an apparently healthy American population. Available data do not permit precise estimates of the amounts of fat and cholesterol in the diet that are consistent with optimal human health in terms of prevention of both CHD and cancer. Estimates of dietary intakes in most published studies related to CHD or cancer are generally inadequate for quantitative use. However, some study participants consider general recommendations for reducing intakes of foods containing fats and cholesterol to be prudent and without additional risk to the U.S. population. Increasing attention to the problem of obtaining accurate dietary intake estimates is evident from recent publications of some leading investigators of dietary relationships with CHD and cancer.

**Coronary heart disease.** Available data on the relationships between dietary fats and cholesterol and CHD are sufficient to support recommendations for reducing serum cholesterol by decreasing dietary intakes of fat and cholesterol. However, behavioral and social scientific data are insufficient to formulate methods of applying available nutritional knowledge successfully to large populations. Moreover, although a scientific consensus exists which supports public health recommendations for adult Americans to reduce total dietary fat intake to 30% of caloric intake, not all nutritional intervention studies support
the consensus, and these dietary recommendations have generated considerable controversy (Frank et al., 1978; Frantz et al., 1975; Lapidus et al., 1986; Mann, 1977; Mitchell, 1984; Nichols et al., 1976; Reaven, 1986).

Cancer. Numerous studies of population groups, international correlations, and animal experiments have shown positive correlations between dietary levels of total and saturated fats and cancer at several sites such as breast, lung, colon, and prostate. Available data suggest that increased dietary cholesterol may be associated with a small-to-moderate increase in risk of cancer of the colon. However, these positive associations with dietary fats and cholesterol tend to disappear when investigations are focused on individuals as in case-control, cross-sectional, and cohort studies or when other confounding, independently significant risk factors are controlled. A principal flaw in the available data is the uncertainty of the estimates of dietary intakes of fats and cholesterol in the study populations (see for example, Byers and Graham, 1984; Willett and Stampfer, 1986). Some long-term prospective cohort studies now in progress or planned are expected to have more precise dietary intake estimates that should permit derivation of more reliable correlations between dietary fats or cholesterol and cancer. Examples are the Harvard Nurses Health Study (Willett et al., 1987) and the Harvard Health Professional Follow-up Study. Another investigation that should yield valuable data when completed is a dietary intervention study being sponsored by the National Cancer Institute altering patterns of food consumption to restrict intake of dietary fats and its effects on the incidence of breast cancer.

A majority of the members of the ad hoc Working Group regard the scientific evidence relating dietary fats and cholesterol to carcinogenesis as inconsistent, unclear, and incomplete. None of the participants considers the available evidence sufficient to show a causal relationship between dietary fats and cholesterol and human cancer. The inconsistencies in the literature on diet and cancer may result from multiple interactions among dietary components coupled with other environmental and genetic factors. The inverse relationship between serum cholesterol concentrations and risk of cancer observed in some studies does not appear to be causal; in an otherwise healthy individual, low serum cholesterol concentration has not been shown to be a precursor of cancer. Some members of the Working Group suggested that dietary recommendations for lowering blood cholesterol and preventing CHD would probably be beneficial in cancer prevention as well, or at least would not cause cancer. However, a majority of the participants agreed the available epidemiologic data do not provide justification for public health recommendations for reducing consumption of dietary fats and cholesterol as a means of preventing or reducing the risk of cancer.
The question whether prospective epidemiologic investigations can generate valid data on relationships of dietary fats and cholesterol to cancer was debated during the meeting. One point of view held that the results of such studies do not justify their support; for example, some participants were of the opinion that it is extremely unlikely that observational epidemiological studies can resolve issues of the relationship between dietary fat and cancer. Nutrition is essentially an experimental science and depends primarily on natural human experiments such as trends over time, geographic variations, unique populations (i.e., Seventh-Day Adventists or migrant studies), animal experimental studies, and human experimentation (both metabolic laboratory studies and human experimental randomized clinical trials).

After 20 years of case-control and prospective observational epidemiological studies, there is still no consensus on the relationship between dietary fat and cancer. It is not primarily a question of the quality of the data, but rather a weakness of the method. Philosophically, the relationship between fat intake and disease is an example of a common source exposure and effect similar to consumption of any dietary constituent and the subsequent occurrence of disease. The qualitative relationship can be described; however, it is extremely difficult within consumers to quantify in terms of dose-response, the amount of fat or other dietary constituent consumed and the subsequent severity of disease.

Some study participants held that only sound human experimental and natural experimental studies and laboratory animal research will resolve these issues. Controlled human metabolic studies and dietary intervention trials, although expensive, may be the most useful. However, a majority of participants considered that carefully designed prospective epidemiologic studies of diet and health are an essential component of ongoing and future research programs.

Combined endpoints: CHD and cancer. No reports were identified in which both CHD and cancer were evaluated simultaneously, with equal weight, in the same study population during investigations aimed at determining possible etiologic roles of dietary fats and cholesterol. However, cancer mortality, but usually not morbidity, has been included in long-term prospective studies examining the relationship between serum cholesterol levels and CHD. Dietary intake data in the reports of these studies are generally sparse and not suitable for estimating quantitative relationships of either foods per se or dietary fats and cholesterol with the incidence of cancer. As examples, the Working Group identified the studies summarized in Table 1 (see p.26-27).

A few investigators have examined the relationship of serum cholesterol to mortality from CHD (or cardiovascular disease) and cancer (Beaglehole et al., 1980; Kark et al.,
1980; Peterson et al., 1981) or CHD, cancer, and other endpoints (Westlund and Nicolaysen, 1972). Of 3751 men whose records were analyzed by Westlund and Nicolaysen (1972), 1111 were overweight; however, only those who were overweight by >25% showed an excess mortality from all causes. Other investigations have included dietary intake estimates (McGee et al., 1985; Shekelle et al., 1981a,b) and dietary intervention to reduce serum cholesterol (Miettinen et al., 1972; Pearce and Dayton, 1971; Research Group of the Rome Project of Coronary Heart Disease Prevention, 1986). Summary information from these studies is presented in Table 2 (see p.28-29).

Unpublished data on cancer mortality probably exist in the files of investigators who were involved in prospective studies of diet and CHD; however, whether such data would be worth seeking and analyzing in terms of possible progress in understanding etiologic relationships among fats, cholesterol, CHD, and cancer in the same population study groups appears questionable for at least two reasons. First, the associated cancer statistics were probably limited to crude mortality data; second, the dietary estimates were probably not adequate for quantification and characterization of dietary intakes of foods or fats and cholesterol.

A majority of the study participants were of the opinion that the effort and expense that would be required to retrieve and evaluate such unpublished data would not be justified by the probable results. However, some study participants regarded such data as potentially useful.

C. PROBABILITY OF SUCCESS

The National Dairy Council sought the advice of the Life Sciences Research Office on the feasibility and desirability of conducting a major, comprehensive, expert review of relationships between dietary fats and cholesterol and risk of CHD and cancer in the same population. The study participants concluded that there are few published studies in which the investigators attempted to relate dietary intakes of fat and cholesterol to morbidity and mortality from CHD and cancer in the same population study groups. Although there are many reports relating serum cholesterol to CHD or to cancer, most do not include quantitative data on dietary intakes of fats and cholesterol. Furthermore, the serum cholesterol concentrations in these studies were nearly always single determinations made at entry into the study. Recently, Blank et al. (1986) reported considerable variation in blood cholesterol determinations that are related to differences in analytical methodologies routinely used in clinical screening and studies.
As indicated on the previous page, it is possible that more definitive data on dietary intakes of fats and cholesterol, coupled with estimates of morbidity and mortality from CHD and cancer from past investigations, may exist in unpublished form. However, the dietary intake data collected in these studies may be inadequate for accurate qualitative and quantitative estimates. Therefore, the LSRO study participants concluded that available published and unpublished data are insufficient for quantification of dietary intakes of fats and cholesterol and statistical association of such estimates with morbidity and mortality from CHD and cancer in the same study populations.

Despite this negative conclusion, the study participants agreed that such a study would be appropriate in the future when more experimental and epidemiological data are available for review and evaluation. At that time, the study participants considered the probability of success in assembling a scientific panel which could review and evaluate the topic questions objectively to be quite high. Selection of such a panel would need to take into account the broad range of scientific opinion and varied interpretations of data that can be expected to exist at that time. Such an expert panel would require not only careful attention to balancing the various scientific points of view, but also critical planning as to the most appropriate questions to be included in their scope of review and evaluation.

The LSRO study participants also concluded that reviews and analyses of more limited aspects of these subjects are feasible and would be useful in planning future research. These suggestions are discussed in the Appendix.
Table 1. Examples of prospective studies of relationships between serum cholesterol and coronary heart disease or other endpoints.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of Study</th>
<th>Subjects</th>
<th>Duration</th>
<th>Data</th>
<th>Mortality</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyer et al., 1981</td>
<td>3 Chicago cohorts Gas Co. Western Elec. Chicago Heart</td>
<td>1233 men 1899 men 6890 men 5750 women</td>
<td>18 y 17 y 5 y 5 y</td>
<td>Baseline serum cholesterol Baseline serum cholesterol Baseline serum cholesterol Baseline serum cholesterol</td>
<td>CHD 143; CA 99 CHD 163; CA 78 CHD 157; CA 116 CHD 22; CA 55</td>
<td>Death rates are also given; results do not support inverse relationship between cholesterol and CA</td>
</tr>
<tr>
<td>Garcia-Palmieri et al., 1981</td>
<td>Cohort (Puerto Rico)</td>
<td>9824 men</td>
<td>8 y</td>
<td>Baseline serum cholesterol</td>
<td>CHD 43; CA 51</td>
<td>CA mortality inversely related to serum cholesterol</td>
</tr>
<tr>
<td>Kagan et al., 1981</td>
<td>Cohort (Honolulu)</td>
<td>7961 men</td>
<td>9 y</td>
<td>Baseline serum cholesterol</td>
<td>Total 598 CHD 150; CA 185</td>
<td>Showed inverse relation, CA/cholesterol (mainly colon CA)</td>
</tr>
<tr>
<td>Kozarevic et al., 1981</td>
<td>Cohort (Yugoslavia)</td>
<td>11,121 men</td>
<td>7 y</td>
<td>Baseline serum cholesterol</td>
<td>Total 758 CHD 100; CA 224</td>
<td>CHD deaths positively related to cholesterol; no significant CA-cholesterol association</td>
</tr>
<tr>
<td>Rose and Shipley, 1980</td>
<td>Cohort (Whitehall)</td>
<td>17,718 men</td>
<td>7.5 y</td>
<td>Baseline serum cholesterol</td>
<td>Plasma chol. &lt;150: CHD 48; CA 67 Plasma chol. &gt;260: CHD 77; CA 27</td>
<td>Mortality for other cholesterol levels is also given</td>
</tr>
<tr>
<td>Kark et al., 1980*</td>
<td>CVD cohort used to relate serum cholesterol and cancer (Georgia)</td>
<td>3102 white and black men and women</td>
<td>12-14 y</td>
<td>Baseline serum cholesterol</td>
<td>Noncancer CVD 282 NonCVD cancer 89</td>
<td>All types of incident cancers including skin cancers</td>
</tr>
</tbody>
</table>

Abbreviations: CA = Cancer; CHD = coronary heart disease; Chol. = cholesterol; CVD = cardiovascular diseases including CHD.

* Reported two or more major endpoints.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of Study</th>
<th>Subjects</th>
<th>Duration</th>
<th>Data</th>
<th>Mortality</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persson and Johansson, 1984</td>
<td>Cohort, to relate serum cholesterol and CHD (Malmö, Sweden)</td>
<td>464 men</td>
<td>22 y</td>
<td>Baseline and one followup serum cholesterol</td>
<td>CHD 41; CA 26</td>
<td>Concluded high serum cholesterol levels increase risk of CHD and CA</td>
</tr>
<tr>
<td>Peterson et al., 1981*</td>
<td>Population study: serum cholesterol and noncoronary mortality (Malmö, Sweden)</td>
<td>10,000 men</td>
<td>5 y</td>
<td>Baseline serum cholesterol</td>
<td>Total, all causes 86</td>
<td>CA mortality peaked at low cholesterol values</td>
</tr>
<tr>
<td>Lipid Research Clinics Program,</td>
<td>Prospective cholesterol-lowering study of CHD and other clinical endpoints</td>
<td>3806 men</td>
<td>7.4 y</td>
<td>Serial plasma cholesterol;</td>
<td>CHD 44 (placebo group)</td>
<td>13.9% reduction of plasma cholesterol in high-compliance,</td>
</tr>
<tr>
<td>1984</td>
<td>with primary hypercholesterolemia</td>
<td></td>
<td></td>
<td>moderate cholesterol-lowering</td>
<td>CHD 32 (treated group)</td>
<td>cholestyramine group</td>
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<td></td>
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<td></td>
<td></td>
<td>diet</td>
<td>CA 15 (placebo group)</td>
<td></td>
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<td></td>
<td></td>
<td>CA 16 (treated group)</td>
<td></td>
</tr>
<tr>
<td>Beaglehole et al., 1980*</td>
<td>Cohort (New Zealand); mortality analysis</td>
<td>630 Maori men and women</td>
<td>11 y</td>
<td>Baseline serum cholesterol</td>
<td>CVD 56; CA 30</td>
<td>Overall and cancer mortality inversely related to serum cholesterol</td>
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</tr>
<tr>
<td>Westlund and Nicolaysen, 1972*</td>
<td>Cohort (Norway); mortality/morbidity analyses</td>
<td>3751 men</td>
<td>10 y</td>
<td>Baseline serum cholesterol</td>
<td>morbidity: CHD 283; CA 89 mortality: CHD 86; CA not given</td>
<td>Serum cholesterol predicted CHD mortality, no distinct association between serum cholesterol and CA (however, prevalent and incident cases of cancer were analyzed together)</td>
</tr>
</tbody>
</table>

Abbreviations:  CA = Cancer;  CHD = coronary heart disease;  CVD = cardiovascular diseases including CHD.

* Reported two or more major endpoints.
Table 2. Examples of studies of relationships between dietary intakes, coronary heart disease (CHD), and cancer (CA).

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of Study</th>
<th>Subjects</th>
<th>Duration</th>
<th>Data</th>
<th>Mortality</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>McGee et al., 1985</td>
<td>Prospective cohort</td>
<td>8006 men</td>
<td>10 y</td>
<td>24-h Recall; food composition</td>
<td>Total 542 CHD 99; CA 104</td>
<td>Intakes of total fat/calories inversely related to total mortality; percent fat varied inversely with total and cancer mortality; directly with CHD mortality</td>
</tr>
<tr>
<td>Pearce and Dayton, 1971</td>
<td>Intervention trial to lower cholesterol; Veterans Administration (Los Angeles)</td>
<td>846 men</td>
<td>8 y</td>
<td>Control group ate normal diet; treated group a high P:S diet</td>
<td>CVD treated 48 controls 70 CA treated 31 controls 17</td>
<td>Data showed Inverse relationship between serum cholesterol and cancer frequency</td>
</tr>
<tr>
<td>Miettinen et al., 1972</td>
<td>Intervention trial, to lower cholesterol; two mental hospitals (Finland)</td>
<td>Hospital N men 1003-1022 women 1773-2169 Hospital K men 880-1273 women 1963-1429</td>
<td>12 y</td>
<td>Control group ate normal diet; treated group a high P:S diet</td>
<td>CHD treated 107 controls 205 CA treated 74 controls 62</td>
<td>Diet crossover at 6 years; marked decrease in CHD deaths in treated men; less pronounced women in hospital K. No consistent effect on CA mortality</td>
</tr>
</tbody>
</table>

Abbreviations: CHD = coronary heart disease; CVD = cardiovascular diseases; P:S = polyunsaturated/saturated fatty acids ratio; PUFA = polyunsaturated fatty acids; PUF = polyunsaturated fats
<table>
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<tr>
<th>Reference</th>
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<th>Duration</th>
<th>Data</th>
<th>Mortality</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research Group of the Rome Project of Coronary Heart Disease Prevention, 1986</td>
<td>Primary CHD prevention trial (Rome)</td>
<td>6027 men (3131 treated; 2896 controls)</td>
<td>8 y</td>
<td>Test diet low in total and saturated fats and cholesterol; PUF increased</td>
<td>CHD treated 58 controls 70 rate, treated 19* rate, controls 249*</td>
<td>Treatment group had special advice and clinical surveillance to counter all principal CHD risk factors</td>
</tr>
<tr>
<td>Shekelle et al., 1981a,b</td>
<td>Prospective diet-health epidemiologic survey (Chicago)</td>
<td>1900-1954 men</td>
<td>19 y</td>
<td>Dietary intake estimates for cholesterol, saturated fatty acids, and PUFAs; two serum cholesterol levels and mean baseline diet score</td>
<td>CHD positive association at 19 y risk of CHD death with serum cholesterol level and mean baseline diet score; CA 208</td>
<td>19 y risk of CHD death presented as percentile associations with baseline level of dietary variables</td>
</tr>
</tbody>
</table>

Abbreviations: CHD = coronary heart disease; CVD = cardiovascular diseases; P:S = polyunsaturated/saturated fatty acids ratio; PUF = polyunsaturated fats

* Cumulative rate per 1000.
VI. LITERATURE CITED


VII. STUDY PARTICIPANTS

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APPENDIX

SUGGESTIONS FOR ADDITIONAL RESEARCH

While the study participants were asked to focus on the three objectives of the feasibility study (see page 3), their deliberations included discussion of the four topics suggested for inclusion in the comprehensive review. They identified a number of gaps in extant knowledge and offered a number of suggestions for future research. Although by no means complete, the issues raised and research topics suggested are indicative of the scientific information and opinions that would be included in a comprehensive review. Further, they do provide information that may be useful to the National Dairy Council. For these reasons, these suggestions for additional research have been prepared as an appendix to the feasibility study report.

A. DIETARY FATS, CHOLESTEROL, AND CORONARY HEART DISEASE

The study participants indicated that there are sufficient data on the relationships between dietary fats and cholesterol and CHD to support the lipid hypothesis of atherogenesis, but that certain aspects of the concept need further investigation (for examples, see Eder, 1984)*. An exhaustive, scholarly review and analysis of all available data on the role of dietary fats in atherogenesis and CHD has not been published recently. The feasibility and desirability of such an enormous undertaking are questionable; however, all participants agreed that expert reviews of selected topics in this broad area of interest would be helpful. Some suggested reviews are listed in the following material.

The study participants acknowledged that many reports and conferences have identified research needs and opportunities. These include the NIH Conference on the decline in coronary artery disease mortality (Havlik and Feinleib, 1979), the report of a symposium on diet and health sponsored by the American Society of Clinical Nutrition (Ahrens and Connor, 1979), the report of the NIH Consensus Development Conference, "Lowering Blood Cholesterol to Prevent Heart Disease" (Steinberg, 1984), and the observations of Glueck (1979) and McGill (1979) in their authoritative reviews. The following research suggestions represent opinions of the study participants on investigations and reviews that, if implemented or expanded, would aid in addressing some of the problems identified in this report.

* See Literature Cited, Section VI, for citations.
Gaps in knowledge. The study participants emphasized several areas in which the influences of dietary fats and cholesterol on cholesterol metabolism and atherogenesis are not well understood. Examples are the differential cholesterolemic and atherogenic effects of various types of animal and plant lipids found in foods, the effects of each of the common dietary fats on specific lipoprotein classes and subclasses, and the role of each of these subclasses in atherogenesis. It is widely suspected that some lipoproteins, particularly some of the lower density lipoproteins (including the postprandial lipoproteins) are much more "atherogenic" than others (such as high-density lipoproteins).

The reasons for substantial interindividual variation in responses to diets designed to lower serum cholesterol are not clear. Additional data are needed to explain weak individual correlations and strong population correlations in the dietary lipid, serum cholesterol, CHD chain of risk factors underlying the lipid hypothesis. This variability is usually attributed to genetic differences in lipoprotein metabolism and responses to diet. Confirmation of this widely recognized concept is needed. An area of basic significance which is not well understood involves the effects on atherogenesis of the biochemical and biophysical interactions of all dietary ingredients acting in concert or serially including the macro- and micronutrients as well as nonnutritional substances in the diet. Although this is exceptionally complex, investigative approaches are needed which could foster meaningful research.

Effective methods are needed for implementing any major recommended changes in the "national diet" such as modifications that might lead to the reduction of serum total cholesterol; also needed are techniques to modify components of the food supply in terms of consumer needs as well as acceptance. Finally, there is a paucity of epidemiologic data on the incidence of CHD in adult women as related to intakes of dietary fats and cholesterol. Prospective studies are needed.

Research Suggestions:

- A review and analysis should be commissioned on the effects of different kinds of dietary fats such as monounsaturated, n-3, and n-6 fatty acids on serum cholesterol concentrations, atherogenesis, and blood pressure. Postprandial effects and genetic control of response should be included. This effort should identify additional research opportunities.

- Investigation of the basic mechanisms of atherogenesis requires expanded efforts to refine concepts and permit more precise methods of intervention including dietary approaches. Examples are the effects of dietary lipids on specific serum lipoprotein classes and subclasses and
their role in atherogenesis, as well as the influence of dietary lipids on nonlipid factors that are associated with complications of atherosclerosis, such as platelet function.

Without modification in the type and quantity of the available food supply, prospects for substantial reduction of the serum cholesterol level in the U.S. population are marginal. Most studies suggest no more than 5 to 10% reduction in serum cholesterol as a result of dietary modifications involving moderate decreases in saturated fats and increases in polyunsaturated fats. There is a major need to develop new methods of providing usual foods that are much lower in saturated fat and cholesterol, and/or total fat, yet are palatable, less costly, and have reasonable shelf life. A review of the availability of lower fat and cholesterol foods and their uses, costs, and palatability would probably be worthwhile. Workshops should be sponsored to define research approaches to improving methodology for implementing recommended changes in the nation's diet and for planning appropriate corresponding changes in processed foods by industry. The food industry needs an accurate perspective of what the public wants as well as what it needs.

The efficacy of different intervention methods to lower blood cholesterol levels should be evaluated. This should include an assessment of the cholesterolemic effects of different foods and/or food groups fed over extended periods of time to different age groups of subjects.

There is a need for the biomedical community to provide more information and interpretation of scientific studies to the general public. Specific areas include a better explanation of the limits of extrapolating data from animal studies to human risks, the problems and limitations of analytical technologies used to unravel relationships between nutrients and disease, and the difficulties in studying the contributions of foods and nutrients to health and disease. Reviews of these important topics, particularly as they bear on the influence of diets, foods, and the nutrients contained in individual foods, could be commissioned as generally available public information. Such reviews should be written with the view of providing individuals with information that would equip them with a better understanding of the role of foods in providing nutrients and the role of nutrients in maintaining health and preventing disease. Another area needing improved public information is the translation of nutritional recommendations into practical advice on food intake.
For example, to recommend a diet high in fiber and low in fat is a generic recommendation. To develop a series of menus or lists of foods to provide such diets for an extended period of time is a topic of practical public information because most people do not know how to alter their diets to reduce their fat intake from 40-50% to 30-20% or increase their complex carbohydrate intake from 40 to 50%.

- Although not a unanimous opinion, some study participants suggested that an expert review and analysis of all available data on the role of dietary fats in atherogenesis should be commissioned. Such a monograph would be a major undertaking and would require considerable time for a recognized expert or scientific panel to condense and incorporate the wide range of pertinent data and their interpretations.

- Development of a dietary cholesterol tolerance test and "markers" for responsiveness should be given a high priority.

B. DIETARY FATS, CHOLESTEROL, AND CANCER

Gaps in knowledge. In the area of dietary fats, cholesterol, and cancer, the study participants identified a number of topics in need of additional attention. The significance of dietary fats and cholesterol in the initiation and promotion of human cancer is only partially understood. For example, the differential effects of various kinds of dietary fats and their mixtures in the diet on modification of cellular events leading to cancer are not clear. Examples of lipids of interest include various types of saturated, monounsaturated, and polyunsaturated fats and fish oils. The relative significance of total energy intake versus dietary fats in cancer etiology is not well understood. This includes the effects of energy restriction in human subjects.

There is a need for a better understanding of the influence of energy regulation -- intake, storage, and expenditure -- on susceptibility to cancer, and the relationships of individual nutrients, individual foods, and food groups to energy balance (for example see Willett and Stampfer, 1986).

Little is known about the effects on human carcinogenesis of the chemical and physical interactions of the varieties of food ingredients and other substances in typical American diets. This includes the macronutrients and micronutrients such as vitamins A, C, and E, selenium and calcium, non-nutritive components such as fiber and phytate, and other putative protective or toxic substances in addition to known carcinogens. An example is the effect on risk of cancer
resulting from interactions of various sources of cholesterol and dietary fats. Methodology for approaching the analysis of such an array of variables is needed.

With regard to cholesterol-cancer relationships, the effects of increased dietary cholesterol on risk of cancer, especially colon cancer, are not clearly established. Low serum cholesterol levels have been associated with increased risk of cancer in several reports. Although most investigators contend that the inverse relationship is more apparent than real, some consider that the subject is still open to further investigation.

There is a lack of epidemiologic information relating dietary fats and cholesterol to cancer morbidity and mortality in people aged 70 years and older. For example, the effect of aging on cellular responses to dietary fats and cholesterol is a little-studied aspect. Cancer research is somewhat impeded by the absence of an intermediate biochemical marker clearly linked with cancer risk.

Another area of interest for which there are few data involves the effect on risk of cancer of diets typical of major human age groups such as childhood, adolescence, young and middle-age adulthood, and old age. Finally there is a lack of a current, exhaustive, scholarly review and analysis of all available data on the role of various types of dietary lipids in human cancer.

Research Suggestions:

- Some study participants favored a major shift in emphasis from observational epidemiologic investigations to direct, controlled experiments with human subjects such as dietary intervention studies. Others defended the merits of prospective epidemiologic investigations, noting that methods to estimate dietary intakes in prospective cohort studies have reached a point where accurate and dependable data can be obtained.

- The relative carcinogenic potential of different kinds and mixtures of dietary fats should be explored further in animal studies. Monounsaturated, polyunsaturated, n-3, n-6, and saturated fats should be included. When methodology permits accurate qualitative and quantitative estimates of these types of fats in human diets, such measurements should be included as part of prospective cohort and/or case-control studies of diet and cancer.
Studies should be planned to evaluate the impact of different levels of both energy intake and fats (as well as other nutrients) on wellness (maintenance of good health) as well as susceptibility to various diseases, including cancer, CHD, other degenerative disorders, and infectious diseases. The scope, direction, and dimensions of such studies should be formulated by means of expert literature reviews and planning workshops.

Investigations are needed to define the roles of levels of energy intake in conjunction with, and as distinguished from, intakes of dietary fats on the risk of developing cancer. The effects of "excess" energy intake as well as energy restriction should be included.

The study participants recognize that there continues to be a lack of documentation that the dietary recommendations of the Committee on Diet, Nutrition, and Cancer (National Research Council, 1982) will prevent or reduce the incidence of human cancer. They noted further that the only feasible way to obtain such evidence would be a program of carefully controlled testing in human volunteers. They considered this an indispensable step in proving the underlying hypotheses and establishing the validity of the dietary recommendations. However, they also recognized that such studies have extreme ethical and moral constraints which have confounded the biomedical community for many years. Resolution of the need for such data in the face of ethical constraints is a formidable hurdle that has not yet been resolved.

Additional data are needed on the influence of energy regulation on susceptibility to cancer. Energy balance, including intake, storage, and expenditure, is considered a key factor affecting cancer risk. Related issues concern the effects of individual nutrients, commonly consumed food groups, and specific foods such as dairy products, meat, and high-fiber foods.

The influence of chemical and physical interactions of all dietary constituents on risk of cancer needs elaboration. One of the priority considerations should be the nature and effects of interactions of dietary fats and cholesterol. Determining the feasibility of, and approaches to, the investigation of such a complex aggregate of variables will require extraordinary scientific endeavor.

Investigations of diet-cancer relationships should be extended to include subjects 70 years of age and older. This should include basic laboratory investigations of the effects of aging on cellular responses to dietary fats and cholesterol.
Methodology is needed for assessing the impact of any one food on risk of cancer while taking into account additional dietary and other known risk factors. The study participants recognize that such studies would need to involve large numbers of individuals, would have to be prospective, and that information derived from such studies would have to undergo complex multivariate analyses if meaningful associations were to be established.

Additional research is needed to quantify the influence of dietary cholesterol on risk of developing cancer, in particular human colonic cancer. Furthermore, adequate, representative estimates of serum cholesterol concentrations should be a part of most studies of human cancer etiology until the serum cholesterol-cancer question is settled. Data acquisition should be designed to permit estimates of intra- and interindividual variance in serum cholesterol concentrations.

Methodologic issues that need further research and development include: (1) identifying an intermediate biochemical marker linked with cancer risk; (2) improved means for accurate estimation of current and past dietary intakes for use in epidemiologic investigations and population surveys (both improved assessment instruments and physiological/biochemical markers of dietary intake); (3) means for assessing the impact of any one food on risk of cancer; (4) improved statistical analytic methodology to examine dietary patterns or interactions between foods and/or nutrients rather than the effects of single foods or nutrients; and, (5) additional and/or improved analytical and statistical methods for interpreting the unique data sets generated by diet-related studies of diseases.

A thorough, expert review and analysis of all available data on the relationships of dietary fats to cancer risk should be considered. It would probably help to clarify some issues and would aid in identifying additional research and in modifying existing hypotheses or formulating new ones. Such a comprehensive review should be conducted by recognized expert investigators who are well established and broadly experienced. Such a major undertaking would require realistic funding and ample time, such as 1 to 2 years. Benchmarks for such a review and analysis could be Chapter 5 of the report of the Committee on Diet, Nutrition, and Cancer (National Research Council, 1982) and Chapter 6 of their 1983 report (National Research Council, 1983), as well as several other recent, expert reviews concerning diet and cancer.