An Examination of the Evidence Supporting the Association of Dietary Cholesterol and Saturated Fats with Serum Cholesterol and Development of Coronary Heart Disease

Marion G. Volk, MHSc (Complementary Medicine)

Abstract

The "lipid hypothesis" is the basis for much of the contemporary diet advice and drug therapy aimed at preventing coronary heart disease (CHD), and was developed from a sequential association of dietary lipids, cholesterol, and CHD nearly 100 years ago. The lipid hypothesis considers pathological changes that relate to the end stage of the complex chronic condition summarized as CHD, not to its genesis. Ongoing research provides only inconclusive evidence of the effects of modification of total, saturated, monounsaturated, or polyunsaturated fats on cardiovascular morbidity and mortality. 3-Hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors or "statins," the highest selling drugs in medical history, may provide evidence that the lipid hypothesis is based on erroneous assumptions, since some of the mechanisms of action of statins seem to be independent of cholesterol reduction.

This article assesses the methodology and assumptions underlying the early studies that gave rise to the current assumption of a causal relationship between dietary fat consumption and CHD. It argues that flaws in methodology have led to inaccurate and highly debatable conclusions. It assesses research supporting criticism of these early studies and considers other factors that may influence CHD. It offers alternative interpretations of the use of statins in controlling CHD. Finally, it provides an historical context suggesting different causes of CHD that have no relation to fat intake. *(Altern Med Rev* 2007;12(3):228-245)

Introduction

This article revisits the origins of the dietary fat-coronary heart disease (CHD) paradigm and discusses the methodological problems involved. Keys' linear association between dietary fat consumption and CHD found its empirical verification in the Framingham Heart Study and became the benchmark for prediction and treatment protocols of cardiovascular disease. The strong association between dietary fat consumption and CHD was repeated and quoted so often that it gained the status of fact. The increasing adoption of high-carbohydrate diets as a result of low-fat diet guidelines has been targeted by many authors as contributing to an increase in diabetes and obesity.[1-5]

The role of dietary fat and cholesterol in the etiology of CHD has been studied for a century, since Anitschkow first created fatty deposits in rabbit arteries by feeding them cholesterol and saturated fats.[6] The resulting plaques pointed more to protein than to cholesterol,[6] and the causative role of protein was raised in 1908 by Igantowsky and confirmed by Newburgh in the 1920s. Newburgh failed to identify which amino acid produced the plaques because methionine (1922) and homocysteine (1932) had not yet been discovered; so Anitschkow's 1913 cholesterol observation prevailed.

Marion G. Volk, MHSc (Complementary Medicine) – Charles Sturt University Bathurst NSW; consulting naturopath at Cambridge Health Centre.
Correspondence address: Cambridge Health Centre, 3/42 McCourt St West, Leederville Western Australia 6007
Email: marion@cambridgehealth.com.au

Keys' ecological studies of 1949 and 1957, which compared consumption rates of fats and CHD mortality in different countries, demonstrated a linear correlation in humans.[7] Yet despite a Consensus Conference decision in 1984 that declared a relationship between dietary fat, cholesterol, and CHD,[8] the debate on the contribution of fats to CHD continues.

Extensive reviews have demonstrated total serum cholesterol (TC-S) is not strongly regulated by diet.[9] Studies point to the importance of type of dietary fat rather than overall fat intake.[10,11] A systematic review of 27 trials of dietary cholesterol reduction reported decreases of nine percent in CHD mortality and 16 percent in CHD events, with no significant effect on total mortality. Despite such evidence, the strong association between dietary fat intake and mortality from heart disease has been taken as a proven fact since the 1950s.

This article examines the original studies that provided the basis of the lipid hypothesis, in order to point out methodological problems and inconsistencies. The methodological problems occur on various levels. First, the term CHD is used as an imprecise and collective term for a heterogeneous group of pathological states rather than as a specific disease term in epidemiology.[12] Second, the use of death certificates as means of identification for coronary heart disease mortality (CHD-M) causes difficulties because of the inaccuracies in certification.[13] Third, the evaluation of dietary data for a complex chronic disease state is incomplete and very heterogeneous across all cited studies.

The lipid hypothesis is the most widely accepted and studied hypothesis on the origin of coronary heart disease. Thomas Kuhn's concept of "paradigms" explains the development of a scientific theory as necessary for establishment of a theoretical framework.[14] Kuhn described theories or paradigms as "universally recognized scientific achievements that for a time provide model problems and solutions." Paradigms give meaning to facts. They provide scientists "not only with a map but also with some directions essential for map-making." In this sense, the lipid hypothesis of the development of CHD has become a guiding paradigm despite thousands of studies proving other influences. One reason for revisiting the original studies is because of their use as constant points of reference as verified epidemiological facts. This constant citation of the same studies, particularly if they contain flaws, can introduce bias in later studies.[15]

Keys' view on the relationship between serum cholesterol and CHD is based on a lecture presented at Mount Sinai Hospital in New York in 1953.[7] His Seven Countries Study[16] and the Framingham Heart Study[17] in the early 1960s validated the suggested correlation between saturated fat intake and blood cholesterol levels. Follow-up studies used the Keys scores as measurements. The Multiple Risk Factor Intervention Trial (MRFIT)[18] was conducted as a final verification. By the 1980s the lipid hypothesis was widely accepted by the nutritional community.[8] Most international recommendations for the prevention of heart disease, whether for primary prevention or for the treatment of patients who had developed the clinical manifestation of cardiovascular disease, made dietary restrictions of total and saturated fats and cholesterol a primary focus.

Today, clinicians are asked to calculate estimations of cardiovascular disease based on the Framingham risk equation. Dietary recommendations aim to reduce or eliminate the consumption of saturated fats and cholesterol – butter, whole milk, eggs, pork, and red meat, in particular. Margarine (containing trans-fatty acids, now known to contribute to heart disease) and vegetable oils are the only recommended fats.

This article summarizes studies that researched fat intake and cardiovascular mortality. It specifically analyzes the methodology of the three main studies that form the foundation for the lipid hypothesis, and the environment that made them so successful. Methodological errors and weaknesses of the respective studies are pointed out and the intrinsic logic of the development of a consensus on the relationship between fats, cholesterol, and CHD is discussed.

Methodology

The lipid hypothesis began with epidemiological evidence of a linear correlation between the consumption of saturated fat and cholesterol and death from CHD. To examine the beginnings of this hypothesis, all relevant studies discussing the correlation were sourced. The search was conducted using Medline and Cochrane Library databases.[19] Search terms were "diet and cholesterol" (n=27,322),"cholesterol and epidemiologic studies" (n=15,101),"cholesterol and heart disease" (n=23,988),"epidemiological studies and heart disease" (n=7), "saturated fat and heart disease" (n=11), and "heart disease and diet" (n=11,312). Using the Boolean

operator "and" reduced the initial search to articles combining two subjects. The following limits were applied: before 1994, humans only, English language articles, and adults only (ages 19 and over). The restriction to studies published before 1994 was applied for two reasons. First, in 1984 the cause-and-effect relationship between hypercholesterolemia and CHD risk was decided at a Consensus Conference by the U.S. National Institutes of Health[8] and all studies begun before this date would have been published by 1994. Second, after 1994 most trials included a statin control, not a feature of the original trials.

The search described above yielded 2,669 articles. From this group, the selection criteria were validity of research, importance of article, and applicability to the research question. Every attempt was made to avoid selection bias, and the limits were applied to help narrow the search.

Both cohort studies and cross-population studies were selected. Since this article analyzes evidence for the causality of dietary cholesterol and heart disease, end points could not be cholesterol levels or atherosclerosis, but cardiovascular death and death from all causes. Heart disease is a multi-factorial disease that develops over a long time-span, so articles reporting studies of less than five years' duration were not included. Selected were published primary prevention studies with the objective of observing changes in cholesterol and saturated fat intake on cardiovascular mortality and morbidity, with a duration of at least five years. Minimum parameters required were serum cholesterol level at baseline and CHD mortality. Clinical end points were defined as CHD-M and total mortality. A reduction in CHD-M would be expected following a reduction in dietary cholesterol. Total mortality is a robust marker of overall health. Only studies in free-living populations were included. Excluded were studies on children and young adults, intervention trials with cholesterol-lowering drugs or specific foods, animal studies, and secondary prevention trials.

An attempt to apply the Oxford Centre for Evidence-based Medicine Levels of Evidence guide[20] to grade the studies proved impossible. Assessment of methodological quality depends on the quality of reporting (although incomplete reporting cannot be interpreted as lower methodological quality). Studies conducted prior to the establishment of these levels in 1992 cannot reflect current reporting practices and should not be graded by them. These were precisely the studies that were central to this analysis.

As the methodological quality ultimately determines the validity of the results, some other way of grading the studies was required. Validity and reliability of quality were established according to the type of study and its purpose. Studies that had a random selection of participants were ranked higher than those with convenience-sampled subjects. The decision was made to present cross-population studies and cohort studies separately and in chronological order.

Results

The studies that satisfied the selection criteria were analyzed and tabulated. A wide range of prospective studies has been conducted worldwide, but vast differences in methods make a geographical comparison of CHD incidences impossible. The still not fully published MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Project would have provided a methodological basis for a geographical comparison, but it was not a cohort study and did not collect individual data. As the name suggests, the World Health Organization's MONICA Project was designed to measure trends and determinants in cardiovascular disease mortality and CHD and cerebrovascular disease morbidity, and to assess the extent to which these trends are related to changes in known risk factors in 39 collaborative centers in 26 countries. One significant discovery of the MONICA data is the degree of misclassification and miscoding of ischemic heart disease mortality.[13]

Table 1 lists all selected cross-population studies in chronological order of commencement and indicates the end of data collection. Tables 2A and 2B list within-population studies. The Key to Abbreviations aids in understanding the data in the tables. The number of subjects is designated "n;" "subject selection" describes the selection mode and age-range of the sample; "diet evaluation" describes the mode of collection of information about dietary intake; "data collected" lists the different parameters evaluated; "clinical endpoints" are of great importance since soft surrogate endpoints like cholesterol levels or angiograms are inconclusive; and the "results" column gives each study's conclusions with regard to the validity of the lipid hypothesis.

Key to Abbreviations

ACM= all-cause mortality	D-CHOL= dietary cholesterol	RF= risk factor
AMP= anthropomorphic measures	DDH= death in hospital for CHD	RR= relative risk
BMI= body mass index	ECG= electrocardiogram	SA= significant association
BP= blood pressure	FA= fatty acids	SBP= systolic blood pressure
CA= cancer	HDL-C= high density lipoprotein cholesterol	SD= sudden death
CHD-M= coronary heart disease mortality	HT= hypertension	SFA= saturated fatty acids
CHF= congestive heart failure	ICD= international classification of disease	SI= special intervention group
CI= coronary insufficiency	LDL-C= low density lipoprotein cholesterol	SM= smoking
COD= cause of death	MI= myocardial infarction	TC-S= total serum cholesterol
CVC= cardiovascular causes	NHS= National Health Service	tFA= trans fatty acids
DBP= diastolic blood pressure	OGC= oral glucose challenge	TG= triglycerides
DC= death certificate	PUFAs= polyunsaturated fatty acids	UC= usual care group

The studies display strong heterogeneity. Several studies, including Whitehall, Israel, and Tecumseh, did not select subjects at random. The random selection of the Framingham subjects is highly disputable as it includes family members, and no data about refusals to participate or reasons for ending participation are reported. The multitude of reports about the MRFIT results, with different parameters and numbers of participants, makes unbiased interpretation impossible. The same is true of studies not reporting absolute figures, like Whitehall. The reporting of epidemiological papers in terms of relative risk (RR) of CHD without giving absolute risk or all-cause death makes results impossible to interpret. This goes together with using surrogate endpoints like lowering TC-S or electrocardiogram changes. All reported studies show a strong association between hypertension and smoking; Keys' studies and the Western Electric Study reveal a strong association between total fat intake and CHD-M. The Western Electric Study shows an especially strong association between egg consumption and CHD-M, whereas the Framingham study does not reveal any correlation between eggs and CHD-M.

The overall inadequacies in design, analysis, reporting, and quotation of the reviewed epidemiological publications is of great concern, an observation discussed in several recent papers about the standard of epidemiological studies.[37-39]

Keys' Studies

In a 1953 lecture, Keys summarized the complex of "degenerative heart disease" and included angina pectoris, coronary heart disease, myocardial infarction, chronic myocarditis, and myocardial degeneration.[7] He stated that these conditions, or at least some of them, in humans are related to "serum cholesterol and allied substances." Keys deduced a relationship between dietary and serum cholesterol levels and mortality rate in the adult population. Keys' published pilot study of six different countries contained a figure showing the relationship between the national death rate for men between ages 45-49 and 55-59 from "atherosclerotic and degenerative heart disease" and the proportion of fat calories available from the respective national diets.[7] The figure displayed a regular progression of fat consumption and increased heart disease from Japan through Italy, Sweden, England, Wales, Canada, and Australia to the United States. Keys stated, "It must be concluded that dietary fat somehow is associated with cardiac disease mortality at least in middle age." One year later the same graph was reproduced[40] with a stronger interpretation: "There appears to be a strong if not convincing correlation between the amount of fat in the diet and the death rate from degenerative heart disease." Keys himself strengthened the interpretation in 1955: "The analysis of international vital statistics shows a striking feature when the national food consumption statistics are studied in parallel.... No other variable in the mode of life besides the fat calories in the diet is known which shows anything like such a consistent relationship to the mortality ratio from coronary or degenerative heart disease."[41]

Table 1. Cross-Population Studies Concerning the Association between Dietary Fat Consumption and CHD[7,16,21,22]

Study Year	n=# subjects Subject Selection	Diet Evaluation	Data Collected	Clinical Endpoints	Results
Pilot Study (six countries); 1949[7]	Ecological Study	National food balance data	National statistics	CHD-M; mortality statistics	Strong correlation SFA:CHD-M
Seven Countries; 1958 - 1964[16]	n=12,763 males ages 45-49 and 55-59	7-day weighted record; composite analysis 16 food groups; 1986	Interview; TC-S; BP; ECG; AMP	CHD-M; mortality statistics	SA SFA:TC-S and SFA:CHD; SA between countries; no within-country SFA:CHD
Japan Honolulu San Francisco Ni-Hon-San Study; 1966 - 1984[21]	n=11,900 males (Japanese ancestry) living in Japan, Hawaii or California	24-hour diet recall	TC-S;BP; ECG; questionnaire	CHD-M; stroke and ACM; DC	HDL-C positively related to fish intake in men; TC-S and BP independent risk factors for CHD; CHD-M lowest in Japan
MONICA Project; 1980 - 1990[22]	n=10 million; (males & females); ages 25-64	n/a	National centers in 38 countries	CHD-M; MI; hospital data and DC	Strong HT:CHD; weak smoking:TC-S

Table 2A. Within-Population Studies Concerning the Association between Dietary Fat Consumption and CHD[23-31]

Study Year	n=# subjects Subject Selection	Diet Evaluation	Data Collected	Clinical Endpoints	Results
Framingham Heart Study 1948-1968[23]	n=2,336 males/ 2,873 females; random sample of 2/3 adults; ages 30-62	24-hr recall	TC-S; HDL-C*; LDL-C*; BP; AMP; SM	CHD-M; DC	males<50 TC-S assoc. w/ CHD; no assoc. for females or males >70; no CHD-M correlation with eggs; ↑TC-S= ↓stroke (intracranial hemorrhage)
Western Electric Study 1958-1982[24]	n=1,878 males; random sample; employed by Western Electric Chicago	Dietary intake of D-CHOL; all SFAs and PUFAs measured according to Keys score	TC-S; BP; BMI baseline 1958; repeated 1959	CHD-M; lung CA	Increased risk of lung CA with D-CHOL, especially eggs; correlation dietary SFAs and CHD-M
Tecumseh Study 1959-1987 [25, 26]	n=2,039[25] 2,181;[26] random, 88% of population	Food and portion recall for 24 hours	TC-S; HDL-C*; LDL-C*; OGC	CHD-M; DC; ICD codes 401-448	No correlation TC-S and TG with dietary intake of SFAs
Zutphen Study 1960-1980[27]	n=1,088; random sample; ages 40-59	Dietary history method; last 12 months	TC-S; BP; SM; AMP; Annual BP/TC-S	CHD-M; DC	107 ACM; 37 CHD-M; 44 CA; correlation D-CHOL and CHD-M after 10 y; insignificant after 20 y
Israel Ischaemic Heart Disease Study 1963-1983[28]	n=10,059; convenience sample; civil servants; ages 40-60	n/a	TC-S of 9,902 and HDL-C 6,562; 5-yr incidence MI, HT, and CHD-M	CHD-M; mortuary registry and ICD-9	HT without elevated TC-S worse prognosis than elevated TC-S with SBP<140; TC-S not major factor in ACM
Honolulu Heart Study 1965-19752[29, 30]	n=8,006;[29] 7,705[30]	WWII Selective Service Register living in Hawaii; ages 45-68	24-hr diet recall coded in 54 foods	SBP; TC-S (no HDL); physical activity	↑D-CHOL=CHD, ↓fat intake=↑ACM; inverse relation TC-S with stroke, lung disease, and CA; SBP higher risk for CHD than TC-S
Puerto Rico Heart Health Program 1965-1974[31]	n=9,824;census urban and rural; males age 45-64	24-hr diet recall	TC-S; BMI; BP/physical activity index**	CHD-M defined as MI, CI, and/or HT	Positive association fat intake and TC-S; no association dietary FA:CHD-M

*Lipoproteins were included later in the study; the concept of fat transport involving triglycerides was developed in the 1960s by Olson.[36]

**Physical activity was calculated as a weighted sum of the number of hours spent in five levels of activity. Weights used for calculation are from the Framingham Heart Study.

See Key to Abbreviations

Table2B. Within-Population Studies Concerning the Association between Dietary Fat Consumption and CHD (cont.)[10,18,32-35,53-59]

Study Year	n=# subjects Subject Selection	Diet Evaluation	Data Collected	Clinical Endpoints	Results
Co-op Lipoprotein Phenotyping Study 1970-1986[33]	n=2,122 men; 1,545 probability sample; 577 included because of ↑TC-S in first NHS; 83 autopsies	n/a	TC-S; HDL-C; LDL-C	CHD-M; autopsy study on 83	CHD-M 23 (30%); CA 34 (41%); 24 others (19%); HDL-C significant inverse association with atherosclerosis of cerebral arteries
Whitehall Study 1967-1977[32]	n=18,403 civil servants by invitation; ages 40-64	n/a	BP/BMI/TC-S; capillary blood samples; glucose 50g load/TC-S	CHD-M; records tagged by Central Registry of NHS, DC	CHD-M 721; HT= RR of stroke or CHD; social gradient in CHD-M
MRFIT 1975-1982[18,53-59]	n=12,866 enrolled for ↑risk due to ↑TC-S, ↑DBP, SM; ages 35-67	SI group med for HT; SI diet plan; UC=no diet	TC-S; HDL-C; LDL-C; BP; diet recall	COD assigned mortality review committee; CHD-M; MI; SD; CHF; DDH	ACM 2.1% higher for SI group; HDL-C inverse association with CHD-M risk
Nurses Health Study 1976-1990[10,34]	n=872 female nurses ages 34-59 who replied to mailed request	Diet survey 61 items, incl portion size	Bi-annual survey	Major CHD defined as nonfatal MI or CHD-M	939 nonfatal MI or CHD-M; total fat=no CHD risk; SA of tFAs and CHD; SA smoking and CHD
EPESE Study 1984-1989[35]	n=997 subjects who consented to blood test; males/females; >age 70	n/a	TC-S; BP; HDL-C; LDL-C	CHD-M; DC	↑TC-S, ↑HDL-C not associated with ACM, CHD-M

Unfortunately, Keys did not include any information concerning the basis on which the six countries were selected, although data for 22 countries were available.[42] The available data for males ages 55-59 for all 22 countries greatly reduce the strength of the association.[42] But even the wider-spread variables suggested some association between cholesterol, saturated fat, and CHD. The index of fat as a percentage of total calories used in Keys' original study[7] was based on the amount of fat available for consumption (national production of fat plus import, minus food not for human consumption), not actual food consumption. Yerushalmy and Hilleboe note, "Since estimates of national average levels of food consumption are thus obtained through food balance sheets as residual quantities, it means that their validity depends on the reliability of the national statistics on production, marketing and utilization."[42]

The other variable in Keys' figure of association was mortality data, derived from population estimates and death certificates. These data also showed great regional and national variation, and were derived from different definitions, reporting patterns, diagnostic habits, and standards of the medical profession in the respective countries. Keys was well aware of the limitations of his data: "There is no guaranty that the main points of this discussion are actually about arteriosclerosis or the particular variety labeled atherosclerosis."[7] In 1957, Yerushalmy and Hilleboe created a figure by plotting the death rates from heart disease for 22 countries against the percent of fat and animal protein available for consumption; they demonstrated an equally strong association with both.[42] Keys' lipid hypothesis was strongly disputed, since his data were subject to considerable limitations. In particular, the presumed association was not specific, and Yerushalmy and Hilleboe concluded, "The suggested association between national death rates from heart disease and percentage of fat in the diet available for consumption cannot at the present time be accepted as valid."[42]

To validate his dietary fat hypothesis, Keys conducted a study of coronary heart disease in seven countries.[16,43] Sixteen local populations in The Netherlands, Yugoslavia, Finland, Japan, Greece, Italy, and the United States were selected. Investigators studied two or three groups of people in each country, recording diet, weight, blood pressure, exercise, and smoking habits. Men ages 40-59 were followed, initially for five years, and all heart symptoms and deaths were recorded. The observation period was then extended to 25 years. Risk factor measurements were taken at entry and at subsequent examinations in years 5 and 10. The analysis focused on serum cholesterol, measured on a casual blood sample and expressed in mg/dL^{-1}.[44] Mortality data were collected over the 25-year period. Final causes of death were determined by a single reviewer, based on death certificates, medical histories collected from physicians or relatives, and hospital and medical records.[44] Death rates were adjusted by age distribution of the whole population. Analyses were based on computation of regression equations and correlation coefficients.

Large differences in the 25-year death rates from CHD were found among the cohorts. The ecological relationship of mean serum cholesterol at entry to late coronary heart disease death rate during the 10- to 25-year follow-up was reported as proven, with an R-square of 0.39 and a p value of 0.0095 for the mean of years 0, 5, and 10.[44] There was no correlation between myocardial infarction and diet within the countries.

Keys declared CHD was five times more common in Finland than in Japan due to differences in diet,[16] but no interpretation of the discrepancy of death rates within the countries was found by him or other researchers. While North Karelia (East Finland) ranked position 1 in the first decade of observation, West Finland ranked 4 with a difference of over 100 CHD deaths per 1,000 deaths. Similar drastic differences were evident in the CHD death rates in Zrenjanin/Serbia and Dalmatia (both formerly Yugoslavia). There was an increase in mortality rates during the 25-year observation period.[44] This result was not entirely unexpected since the cohorts were between ages 40 and 59 at the time of initial assessment, but cholesterol changes did not match the rate of survival after 25 years. In the Serbian cohort alone, the average cholesterol level in survivors after 25 years was 15-percent higher in Belgrade, 35-percent higher in Velika Krsna, and 45-percent higher in Zrenjanin than entry levels. Changes of cholesterol level in cohorts had minimal impact on long-term survival.

These results neither support nor invalidate the lipid hypothesis; they present a long-term follow up of an aging population. The validity of the results is restricted to the particular population and the specific historical period during which they were studied. The results cannot be generalized or taken as a basis for other studies.

After the pilot study, Keys conducted a series of metabolic ward experiments[45] resulting in a formula named after him.[46] The formula indicates that the serum cholesterol-raising effect of saturated fatty acids is twice as potent as the lowering effect of polyunsaturated fatty acids. This formula reportedly was used in the Western Electric Study. Epstein, for instance, points out, "The quintessence of all geographical epidemiology is that dietary fat and cholesterol intake, the main determinants of population levels of serum total cholesterol and low-density lipoprotein, play a fundamental role in explaining cross-cultural differences in the frequency of CHD. Serum lipids, in accordance with Keys' original views, set the stage for geographical variations, while the actual levels of mortality are determined by the interplay with additional factors."[45]

The Framingham Heart Study

The Framingham Heart Study was conducted at Boston University in conjunction with the U.S. National Heart Institute (now the National Heart, Lung and Blood Institute, or NHLBI). The original study cohort consisted of a random sample of two-thirds of all adults, ages 30-62, residing in Framingham, Massachusetts, in 1948. Of the original 5,209 participants, approximately 1,095 were known to be alive in February 1998.

The objective of the Framingham Heart Study was to identify common factors that contribute to CHD by following its development over a long period in a large group of participants who had not yet developed overt symptoms of CHD or suffered a heart attack or stroke.[17] The original study included questions about age, gender, family history, occupation, educational level, national origin, serum lipid levels, and physical activity, and related these to CHD. Due to the large number of non-responders, many of those questions were omitted from the evaluation. No information on refusals or dropouts was given. More clinical questions were added in later years.[23]

The analysis of the Framingham Heart Study provides logistical problems for an outsider since it is difficult to ascertain the total number of people involved in the study. Different publications, all referring to "the original Framingham study," contain different numbers of subjects, age ranges, and time frames. In a 1987 study,[17] the authors refer to a cohort of 1,959 men and 2,415 women, ages 31-65, who were free from cardiovascular disease and cancer. In another report,[23] the group is said to consist of 2,283 men and 2,844 women, ages 30-62. In a 1998 special report,[47] the numbers of participants (now called patients) of the original study are given as 2,489 men and 2,856 women, ages 30-74 at baseline, with 12 years of follow-up. The oldest study obtainable mentions that originally 6,510 inhabitants of the city of Framingham, Massachusetts, between the ages of 30 and 59 and of either gender were invited to take part.[48] Because only 70 percent responded to the invitation, 734 volunteer subjects were included. Of those selected, 53 men and 29 women were excluded because of pre-existing cardiovascular disease.

Since the study aimed at analyzing factors contributing to CHD, those subjects with arterial hypertension were included and the study later developed the term "risk factors." Although participants did not receive treatment as part of the study, their personal physicians were notified.[23] The principal aim of the study was male mortality and morbidity; yet when the population sample was originally drawn, the decision was made to invite families to take part, not individuals.[23] This inclusion reduced the number of independent subjects, because of the possibility of aggregations of genetic physical or psychological characteristics, as well as of lifestyle and dietary habits. In particular, familial hypercholesterolemia should have been of concern. In addition to these issues, the wide age distribution of those finally taking part caused risk calculation for age groups to span several decades, a problem in particular when it comes to disorders like CHD with various manifestations and marked age dependence. The mode of selection of subjects for the Framingham study leads to the conclusion that the study results are applicable to the particular white, suburban, middle-class population that participated, but that broad generalizations to the wider population may not be appropriate.

Despite this, a statement to healthcare professionals from the American Heart Association postulated that the Framingham Heart Study contributed importantly to a wider understanding of the causes of coronary heart disease, stroke, and other cardiovascular diseases.[49]

Framingham research helped define the quantitative and additive nature of these causes, thereafter called "cardiovascular risk factors." Besides defining the complex problem of cardiovascular diseases, the Framingham study had, according to this statement, developed mathematical functions for predicting risk of clinical coronary heart disease events. D'Agostino et al remark: "The Framingham functions were developed to assess the relative importance of CHD risk factors to quantify the absolute level of CHD risk for individual patients."[50] Yet, as Grundy et al point out, guidelines developed from Framingham have found entry in programs on a national level: "The National Cholesterol Education Program (NCEP) has made extensive use of Framingham data in developing its strategy for preventing CHD by controlling high cholesterol levels. The NCEP guidelines adjust the intensity of cholesterol lowering therapy with absolute risk as determined by summation of risk factors."[49]

The Framingham results did not demonstrate a gradient and linear correlation between serum cholesterol levels and risk of CHD, as later interpretations suggest. In a "30-year follow-up from the Framingham study,"[17] from 1951 to 1955 serum cholesterol levels were measured in 1,959 men and 2,415 women ages 31-65 years who were free of cardiovascular disease (CVD) and cancer. Anderson noted that:

"Under age 50 years, cholesterol levels are directly related with 30-year overall and CVD mortality; overall death increases five percent and CVD death nine percent for each 10 mg/dL. After age 50 years there is no increased overall mortality with either high or low serum cholesterol levels. There is a direct association between falling cholesterol levels over the first 14 years and mortality over the following 18 years (11-percent overall and 14-percent CVD death rate increase per 1 mg/dL per year drop in cholesterol levels). Under age 50 years these data suggest that having a very low cholesterol level improves longevity. After age 50 years the association of mortality with cholesterol values is confounded by people whose cholesterol levels are falling – perhaps due to diseases predisposing to death."[17]

Perhaps the increased mortality has a direct relationship with decreased cholesterol levels in individuals over age 50. There is current, ongoing research on the correlation between reduction of cholesterol and increasing cancer rates.

Despite the limitations noted regarding the validity of the Framingham study as a benchmark, several studies have applied the measures of estimates of CHD risk by the Framingham function to other populations. A recommendation by the European Society of Cardiology to use the Coronary Risk Chart based on data from the Framingham Heart Study has been questioned due to marked regional differences in the incidence of CHD in Europe.[51] The conclusion was that the Framingham risk score would "lead to a significant overestimation of coronary risk" in a Danish population; it showed a marked overestimate for an Italian population as well.[52] Researchers concluded that the relative odds for Framingham, at the average values for risk factors, was about twice that of other studies.[52] Measures of the relative risk of CHD for 206 consecutive hypertensive men ages 35-75 without pre-existing vascular disease determined which of the screened men had a CHD risk of 3.0 percent per year or higher by the Framingham function and so should be targeted for statin treatment.[53] The report stated, "Framingham risk function predicts relative risk of CHD with reasonable accuracy. However, lipid lowering drug therapy is best targeted at absolute CHD risk…. Ordinary doctors cannot estimate absolute CHD risk accurately and simple but accurate aids to risk assessment are needed. Several of these have been developed, all of them based on the Framingham risk function."[53]

The Framingham Heart Study is of particular importance because a CHD predictor model was developed from it, which has been used as baseline for epidemiological studies as well as for treatment protocols ever since. The Framingham study was also used to estimate CHD risk in men participating in the MRFIT and Tecumseh studies.[18,47]

Steinberg,[8] in reference to the failure of the Framingham Heart Study to demonstrate a significant correlation between CHD and serum cholesterol, wrote: "However, failing to find a good correlation between dietary composition and risk does not necessarily disprove the underlying hypothesis!" Despite the difficulties of drawing clear conclusions from the Framingham studies, researchers continue to use them. This is questionable scientific method and may in part explain why there is still such debate about the connection between both dietary and serum lipids and CHD.

Multiple Risk Factor Intervention Trial

In July 1970, the NHLBI convened a task force on arteriosclerosis. With the aim to develop a broad long-range plan for the study, control, and possible prevention of arteriosclerosis, the task force proposed that multiple risk factor intervention trials be undertaken to ascertain whether modification of elevated serum cholesterol levels, hypertension, and cigarette smoking in individuals at increased risk of death from heart attacks would result in reduction of coronary death rates. The study was restricted to men because of statistically higher risk of premature heart attack compared with women, a result of the Framingham Heart Study. More than 30 original research papers on the screenings were published by the MRFIT group and associated researchers in the following years. The MRFIT design called for the recruitment of 12,000 men ages 35-57 at increased risk of death from CHD with no clinical evidence of CHD at time of recruitment.[18] People were designated as having increased risk if levels of three risk factors – cigarette smoking, serum cholesterol, and blood pressure – were sufficiently high at a first screening visit to place them in the upper 15 percent of a risk-score distribution. The numbers of participants varied between reports. Depending on which reference is applied, 361,662[18] or 361,629[54] men were recruited for a first screening visit to determine CHD risk eligibility; several exclusion criteria were applied. The first screenings took place between November 1973 and November 1975. Within one month, 25,545 (25,529) men were invited to the second screening; 22,080 (22,970) men attended. The final number of 12,866 subjects selected after a third screening is the same in all reports.

The aim of the three-stage screening was to obtain the required 12,000 men willing to participate in a study. The exclusion questions in the first screening for previous heart disease asked if the respondent had had a heart attack that required a hospital stay for two weeks or was receiving prescription medication for diabetes. No controls were undertaken to verify whether respondents were being truthful. More than 330,000 men were excluded during the first stage. The second screening was performed within a month and included an electrocardiogram; 4,588 men (20.7%) were excluded on medical grounds – either previous CHD or diabetes – based on data from the Framingham Heart Study.

After the third screening the men were randomly placed into two groups of approximately equal size. Men in the first group, "usual care" (UC), were referred to their personal physicians or other community medical facilities for treatment of risk factors as appropriate. The other group received a "special intervention" (SI) program aimed at cessation of cigarette smoking and reduction of elevated serum cholesterol and blood pressure levels. Upon assignment to the SI group, each smoker was counseled individually by a study physician and invited to a series of weekly group discussions addressing all three risk factors. Each group included approximately 10 men and met for 10 sessions.

SI group subjects were seen an average of every four months by a group of behavioral scientists, including nutritionists, nurses, physicians, and general health counselors. Blood pressure was monitored and weight reduction was advised for overweight men before drug prescription. Drugs to reduce hypertension were prescribed according to a stepped-care protocol, beginning with the use of either hydrochlorothiazide or chlorthalidone (thiazide diuretics). Reserpine, hydralazine, guanethidine (antiadrenergic), or certain alternate drugs were sequentially added if goal blood pressure was not achieved. The protocol also included a provision for mild sodium restriction. Initially, saturated fat intake of less than 10 percent of calories and dietary cholesterol intake of less than 300 mg/day was recommended; but in 1976 the nutrition pattern was changed to specify that saturated fat be less than 8 percent of calories and dietary cholesterol less than 250 mg/day.

Only one source mentioned the exclusion of more than 1,000 men because of excessive alcohol consumption.[55] Further reasons for exclusion included a refusal to consider smoking cessation and excessive weight. Analysis of mortality of participants of the first screening was first mentioned in 1983.[56] The retrospective analysis of mortality and risk factors[57] was based on death certificates, obtained to determine survival status as of February 28, 1982 (six years after the last day of randomization), when telephone or mail contact was attempted with each subject not known to be deceased.

The MRFIT group described the way mortality data were obtained.[18] Cause of death was assigned by a Mortality Review Committee. Some papers report six percent of death certificates were missing;[57] others do not mention missing certificates but include detailed causes of death.[58,59]

Serum cholesterol distribution was one main feature of the study design, but was very difficult to obtain in a way that allowed a comparison by the reader. Cholesterol values were variously given in deciles,[57] quintiles,[58] or mmol/L.[28] One report stated that the risk of dying from a heart attack with a cholesterol level above 265 mg/dL was 413-percent greater than with a cholesterol level below 170 mg/dL.[57] Four-hundred-ninety-four men (1.3%) in the highest cholesterol range died of heart attacks; 98.7 percent were still alive after six years. Of the lowest cholesterol group only 0.3 percent died; therefore, the difference between the number of deaths in the highest and lowest levels of cholesterol after six years in a group of high-risk men was one percent. Using the relative risk (1.3 is 413% of 0.3) the figure was statistically correct.

The use of relative risk measurements is common practice in peer-reviewed papers. It provides no insight into the background event rate or the susceptibility of the population to the outcome of interest. An absolute difference is a subtraction, a relative difference is a ratio – only useful if a starting point is given.

The overall result of the MRFIT intervention trial was unexpected. As of February 28, 1982, after a follow-up period of seven years, there were 260 deaths among UC men, of which 124 were ascribed to CHD and 145 to cardiovascular causes (including CHD). Of 265 SI deaths, 115 were classified as CHD and 138 as CVD (including CHD). The death rate for all causes was 2.1-percent higher for the SI men. The corresponding life table (log rank) Z values for the endpoints were +0.6, +0.4, and -0.2. None of these is statistically significant. Based on design risk factor calculations and Framingham risk functions, 442 deaths (including 187 from CHD) were expected by the end of six years of follow-up among the 6,438 UC men; only 219 (including 104 from CHD) occurred. By the end of follow-up for all participating men, the total of 260 UC deaths (including 124 from CHD) was still below the number expected for the six-year follow-up period. The number of deaths from non-cardiovascular causes was also similar in the two groups (116 SI versus 109 UC). There were 81 cancer deaths in the SI group and 69 in the UC group, including lung cancer (34 SI versus 28 UC), colorectal cancer (8 SI versus 6 UC), other gastrointestinal neoplasms (20 SI versus 11 UC), and other neoplasia (19 SI versus 24 UC). Despite the negative outcome of the study, the summary gave a positive result: "In conclusion, we have shown that it is possible to apply an intensive long-term intervention program against three coronary risk factors with considerable success in terms of risk factor changes."[18]

Selection Problems

Epidemiological study designs that address the relationship between nutritional intake and disease face the problem of precise measurement of long-term dietary exposure. There are also issues concerning the degree such studies are able to identify and account for confounding factors. Particularly important is the amount of modification caused by genetic factors, such as the inclusion of family groups (Framingham) or whole communities (Tecumseh). Large numbers of subjects with familial hypercholesterolemia may be interpreted as the result of exposure to a factor that is a risk for the total population, when it actually affects only an unidentified subgroup. This becomes obvious when the participation rate of the cited studies is addressed. No study gave information about dropouts; and several gave no details of exclusion criteria. The fraction of participants who dropped out might have been less interested in health; if so, their absence may indicate a selection bias in the remaining sample. People responding to invitations to participate in cohort studies may have different health and dietary practices than the general population.

That there is an association between CHD and high serum cholesterol does not necessarily imply causation. Trials involving reduction of TC-S (MRFIT) showed no reduction in total mortality. Framingham showed no association between elevated TC-S and CHD in women or men above age 50. Neither the Tecumseh Study, nor the Puerto Rico Heart Study, nor the Israel Study showed any relationship between CHD-M and dietary cholesterol levels. There is a correlation between saturated fatty acids, dietary cholesterol, and TC-S in studies that compare populations from different parts of the globe, but not in studies concerned with a single cultural community or individuals.

Determining Cause of Death

Keys based proof of association on death certification. Death certificates were crucial in all other studies except the autopsy group of the Lipoprotein Phenotyping Study.[33] MRFIT demonstrates severe inconsistencies regarding death certification and missing data. Data obtained from death certificates or medical records are haphazard, biased, and often grossly inaccurate, as a study resulting from the MONICA Project indicates.[13] Errors may be clerical, such as miscoding, but even establishing a cause of death is difficult owing to the presence of concurrent co-morbid illnesses, low autopsy rate, and inadequate understanding of complex disease processes.

A recent report from the Framingham Heart Study compared causes of death among 2,683 decedents as identified by death certificates and by a physician panel.[60] Of 942 certificates that listed the cause of death as CHD, only 645 (67%) were confirmed by the physician panel. The deviation was even greater for stroke, where the corresponding positive predictive value of the death certificate was only 59 percent. Inaccurate reporting of death from CHD was strongly related to increasing age: among patients ages 65-74, 75-84, and ≥85, differential rates of reported versus confirmed CHD deaths were 18-, 31-, and 109 percent, respectively. Lozano claims a mistaken certification of cardiovascular death is assumed to be constant across countries. Findings show that, "Mortality rates in some countries such as Japan, Greece or France need to be corrected by 30 percent."[13] Claims about mistaken certification were supported by the more than 25-percent increase in recorded ischemic heart disease mortality rates in Japan between 1994 and 1995, with the change from ICD-9 to ICD-10.[61] For example, there are a number of cardiovascular codes that can be used for ischemic heart disease according to the International Classification of Disease (ICD-9 codes 410-414 or ICD-10 120-125) and atherosclerosis generalized is coded 440.9 (ICD-9) and 170 (ICD-10). Lozano reports a huge variation in coding practices among countries.[13] Adjusting the mortality rates in Greece, France, and Japan would greatly reduce the conclusion about the causative role of dietary fat and cholesterol in Keys' studies and lend to reinterpretation of the French Paradox.

Problems of Dietary Assessment

Nutritional epidemiology uses measures of association that estimate relative risk and are not biological constants. The assessment of the importance of a single risk factor for a chronic disease of multifactorial etiology is complicated by the inter-correlation of dietary components with individual genetic nutritional demands, absorption, and exposure to environmental factors that also influence disease risk. For instance, high-fat diets, which may be high in sugar, are often low in fiber, antioxidants, carotenes, flavonoids, ascorbic acid, and folate. The lack of those components correlates with other accepted risk factors for CHD, such as low antioxidant and high homocysteine levels. Dietary structures cluster with economic, religious, socio-cultural, and demographic variables. High day-to-day variations in consumption make accurate estimates of nutritional intake very difficult, as do the complex structures of processed food products.[62,63] In addition, most of the knowledge about fatty acids is fragmented and biased by assumptions that guided the experimental structure of investigation into fatty acids. This is especially true in the case of saturated fatty acids, which have mainly been studied for the potential to influence lipoprotein metabolism and cholesterol transport within the blood.

Studies can include only a fraction of the 30,000 foods now available,[64] and statistically analyzing the interrelationships among all food components represents a near-impossible task. The degree of industrial and domestic processing of foodstuff and potential loss of nutrients is impossible to assess by means of nutritional epidemiology. Most studies base their data on 24-hour recall, coded in food groups. The Seven Countries Study coded 16 food groups;[16] the largest groupings are found in the Honolulu Heart Study (54 food groups)[29,30] and the Nurses Health Study (61 food groups and portion sizes).[10,34] This heterogeneity of food grouping and the nearly 30-year time span covered by the studies render interpretative comparison among studies purely speculative.

In addition to problems of procedure, researchers must contend with participant behavior. Bias can be introduced by dietary modification undertaken by participants independently during a study. Intervention trials to study the effects of moderate changes (MRFIT, for example) were compromised by unexpected attitude changes within the control group.[18]

The subjective nature of nutritional epidemiology, the wide variations in methodologies among studies, the interconnection of uncontrolled variables, and the actions of the participants make findings not replicable and scientifically suspect. One thing that is clear from the cited studies is that none of them show a valid association between serum cholesterol and saturated fat and heart disease, other than for men younger than age 47. Anderson et al, commenting on the Framingham study, note, "After age 50 years there is no increased overall mortality with either high or low serum cholesterol levels."[17] Since Keys stated in 1953 that, "A major characteristic of the sclerotic artery is the presence of abnormal amounts of cholesterol," and "This cholesterol is derived from the blood,"[7] only the level above which cholesterol becomes dangerous is debated; the role of cholesterol itself is never questioned.

The unproven conclusion that serum cholesterol causes atherosclerosis was adopted without qualification by later studies. Dietary cholesterol and saturated fats are *assumed* to represent the lipids that accumulate in the arteries, and a decrease of those dietary components is often recommended, even when research demonstrates that arterial plaque is primarily composed of unsaturated fats. Felton et al comment, "These findings imply a direct influence of dietary polyunsaturated fatty acids and not of saturated fats on aortic plaque formation and suggest that current trends favoring increased intake of polyunsaturated fatty acids should be reconsidered."[65]

Discussion

Keys' studies assert there is a positive ecological correlation between national dietary cholesterol and fat intake and CHD mortality. The MONICA Project claims to discover a strong link between smoking and hypertension and CHD. The Western Electric Study alleges an increased death rate from CHD due to egg (a main source of dietary cholesterol) consumption, while the Framingham Heart Study explicitly reports no connection between eggs and CHD. Vast differences in collecting data and large time spans make it impossible to draw valid dietary comparisons among these studies.

Comparisons become more fraught with apparently contradictory evidence. For example, the Honolulu Heart Study shows an increase of death from all causes among subjects with lowered cholesterol levels,[29] findings also borne out by the Framingham Heart Study, which in a 30-year follow-up found a direct association between falling cholesterol levels over the first 14 years and higher mortality levels over the ensuing 18 years.[17] These studies oppose the findings of Keys – if the lipid hypothesis were valid in its present form, a lower cholesterol level should predict a better survival rate. The Tecumseh, Israel, and Puerto Rico studies discover no correlation between dietary fat and serum cholesterol and CHD-M. The Whitehall study measures a social gradient and discovers stress as a parameter. The Honolulu Heart Study shows that Japanese-Americans on average have higher TC-S levels and eat more saturated fats than Japanese living in Japan, but the determining factor for heart disease is the degree of acculturation to Western culture.[66] All studies find a strong association between smoking and CHD, and hypertension and CHD. These cited studies, in particular Keys' Seven Countries Study and the Framingham Heart Study, while holding historic relevance, are used as the basis for implementation of the lipid hypothesis in everyday practice. Health policy in the Western world is still narrowly based on the lipid hypothesis, expressed in the food pyramid guides. Medical software uses cardiovascular risk scores based on the Framingham risk equation, while the Keys score is used as a parameter of fat consumption.

Almost all risk scores based on the Framingham risk equation fail to provide an accurate assessment of an individual's cardiovascular risk. Gross under- and overestimations have been reported in recent studies.[47,52,67] The Framingham guidelines, which include age as a parameter, would identify 75 percent of the Australian and American adult population as being at risk, and 90 percent of individuals over age 50 requiring external monitoring. Many individuals, by these standards, would also require medication to modify those risk factors, which have been calculated by medical software for 10 years to within a single digit and presented by general practitioners to patients as validated.

Recommendations on dietary advice based on the prevailing diet-heart disease paradigm have arguably failed to reduce CHD risk and may have possibly "inadvertently exacerbated dyslipidemia, insulin resistance, and weight gain, particularly among individuals who are older, female, sedentary, or obese."[5] This may be particularly important if fat is not replaced by fruit, vegetables,

and whole grain products, but by highly processed and refined carbohydrates with a high glycemic index.[1-5,68]

The lipid hypothesis of atherosclerosis is based on several unvalidated premises, including fallacious national mortality statistics, biased age and subject selection, and methodological inaccuracies. The inclusion of subjects who suffer from familial hypercholesterolemia and present with severe vascular changes at an early age, along with healthy subjects, will necessarily produce skewed statistics and a correlation between high serum cholesterol and atherosclerosis. All of the cited studies include subjects with familial hypercholesterolemia, among other biochemical metabolic problems, without identifying the subjects in published results. Non-specific CHD was inappropriately used as a surrogate for atherosclerosis, and causality was assumed and implied by classifying statistical correlates of CHD as atherogenesis risk factors. Statistical data pertaining to CHD but with no scientific applicability to atherosclerosis, as well as publication and citation bias,[15,69] have caused the results to be repeated until they became valid.

Disease classification consisting of non-ambiguous definitions based on etiological or pathogenic mechanisms are preferable to definitions based on pathological lesions or anatomical sites.[12] The term CHD is an aggregated diagnostic term for a heterogenous collection of pathological states and diseases producing myocardial ischemia. Initially, the Framingham researchers considered CHD as epidemiologically not definable,[23] but still held it legitimate to define CHD in terms of clinical syndromes (angina pectoris, myocardial infarction, sudden death). Ischemic heart disease exists without atherosclerosis,[12,70] and atherosclerotic severity cannot conclusively be measured during life.[23] Klevay lists 21 contributing factors to ischemic heart disease,[71] and lipid metabolism is only one of them.

There are many reasons why the dietary fat-cholesterol-heart disease hypothesis should be revised. One relatively new aspect is the fact that statins might be acting differently than by reducing cholesterol. Researchers report anti-inflammatory and immunomodulatory effects of HMG-CoA reductase inhibitors with reduced cardiovascular mortality in patients treated with statins. Extensive research conducted in the last decade suggests the clinical benefits of these drugs could be related to an improvement in endothelial function, a reduction in blood thrombogenicity, anti-inflammatory properties, and immunomodulatory actions.[72,73] From such research, statins appear to decrease T-cell activation and the recruitment of monocytes and T cells into the arterial wall and enhance the stability of atherosclerotic lesions. Many of these effects are related to the inhibition of isoprenoid synthesis, which serves as a lipid attachment for a variety of proteins implicated in intracellular signalling.[72] The anti-inflammatory and immunomodulatory effects of statins impact the components of ischemic heart disease listed by Klevay[71] and affect atherosclerotic lesion formation, insulin resistance, platelet activation, and alterations in the coagulation cascade leading to a prothrombotic state. Dyslipidemia acts synergistically with hypertension in increasing cardiovascular risk. Because of pleiotropic effects, statins affect the whole pathophysiology of atherogenesis, from deposition to plaque rupture and thrombogenesis.[73]

Other researchers postulate that statins act as vitamin D analogues. Grimes claims the unexpected and unexplained clinical benefits produced by statins have also been shown to be properties of vitamin D.[74] The active form of vitamin D3 (1,25-dihydroxyvitamin D3) is a steroid hormone that, aside from bone mineral homeostasis, regulates the growth and differentiation of many cell types and has pronounced immunoregulatory and anti-inflammatory properties. "It seems likely that statins activate vitamin D receptors."[74]

By reducing CHD through biochemical changes irrespective of cholesterol levels, the action of statin drugs leads back to the initial research objective of Keys, Framingham, and other studies – identifying the causative agent of CHD. The focus by conventional medicine on the assumed causality of cholesterol and saturated fats in the etiology of CHD may have overlooked important aspects of dietary modification over the last century. Field studies of 20th century hunter-gathers (HG) showed them to be generally free of the signs and symptoms of CHD. Consequently, the characterization of HG diets may have important implications in designing therapeutic diets that reduce the risk for CHD in Westernized societies. Significant dietary and lifestyle changes occurred parallel to the onset of CHD early last century, and need to be considered as part of the discussion concerning the causes of CHD.

Indeed, in this wider context, CHD does not seem to be the result of increased intake of dietary saturated fat at all. Saturated fats and cholesterol have been primary components of the human diet for thousands of years. CHD is a relatively recent phenomenon that only attracted attention at the beginning of the last century. The appearance of agriculture and domestication of animals some 10,000 years ago and the Industrial Revolution of the 18th and 19th centuries introduced new dietary pressures without providing the necessary time for human adaptation. The discordance between the hunter-gatherer genome and industrially modified, modern dietary intake may require more adaptation than genetic heritage can provide. The "inevitable discordance" that Eaton and Eaton point out[75] may be the root cause of CHD and other chronic diseases of civilization. Changes in food staples and food processing procedures between the Neolithic and Industrial era have fundamentally altered several crucial nutritional characteristics of our ancestral diet and may have contributed far more to the increase of CHD than the consumption of saturated fats, which have been a natural diet component for thousands of years.

Return to the macronutrient composition of high-fat, HG diets would be detrimental, since changes have taken place in meat composition. The hunter-gatherers acquired significant amounts (45-65%) of energy from animal-based food. Consumption of wild ruminant meat represented the primary lipid source for pre-agricultural humans.[76,77] Game meat and organs contained a high proportion of cardio-protective omega-3 fats. A similar tissue lipid composition was found in pasture-fed cattle, the food source of present day hunter-gatherer populations. On the other hand, meat from intensely farmed, grain-fed cattle, does not have a high concentration of omega-3 fatty acids.[75] An increasingly sedentary lifestyle further accelerates the effects of a nutritionally imbalanced diet and may, as much as any other factor, contribute to increases in CHD.

Conclusion

The hypothesis of coronary heart disease as the result of excessive intake of saturated fats may no longer be sustainable. Recent research indicates that dietary consumption of cholesterol is not reflected in serum levels, and that very low serum cholesterol levels seem to contribute to all-cause mortality. The powerful cholesterol-lowering statin drugs exert anti-inflammatory and immunomodulatory effects irrespective of LDL levels, and affect biological pathways other than lipid metabolism. Nutritional deficiencies need to be included in the spectrum of causes of chronic disease. The overall impression of the cited studies is that they vary widely in regard to methodological quality, content, and style. This carries the serious risk that some epidemiological publications may reach misleading conclusions. The many problems associated with research into fats and CHD make it logical to conclude that the lipid hypothesis of atherosclerosis is based on several false premises, including linear causation, fallacious national mortality statistics, biased age and subject selection, and methodological inaccuracies.

References

1. Halton TL, Willett WC, Liu S, et al. Potato and french fry consumption and risk of type 2 diabetes in women. *Am J Clin Nutr* 2006;83:284-290.
2. Daly ME, Paisey R, Paisey R, et al. Short-term effects of severe dietary carbohydrate-restriction advice in type 2 diabetes – a randomized controlled trial. *Diabet Med* 2006;23:15-20.
3. Musick T, Cymet TC. Carbohydrate and calories: it is not what we used to think. *Compr Ther* 2006:32:47-50.
4. Pins JJ, Keenan JM. Dietary and nutraceutical options for managing the hypertriglyceridemic patient. *Prog Cardiovasc Nurs* 2006;21:89-93.
5. Mozaffarian D. Effects of dietary fats versus carbohydrates on coronary heart disease: a review of the evidence. *Curr Atheroscler Rep* 2005;7:435-445.
6. McCully KS. Atherosclerosis, serum cholesterol and the homocysteine theory: a study of 194 consecutive autopsies. *Am J Med Sci* 1990;299:217-221.
7. Keys A. Atherosclerosis: a problem in newer public health. *J Mt Sinai Hosp N Y* 1953;20:118-139.
8. Steinberg D. The cholesterol controversy is over. Why did it take so long? *Circulation* 1989;80:1070-1078.
9. Rosenman RH. The independent roles of diet and serum lipids in the 20th-century rise and decline of coronary heart disease mortality. *Integr Physiol Behav Sci* 1993;28:84-98.
10. Hu FB, Stampfer MJ, Manson JE, et al. Dietary fat intake and the risk of coronary heart disease in women. *N Engl J Med* 1997;337:1491-1499.
11. Hooper L, Summerbell CD, Higgins JP, et al. Reduced or modified dietary fat for preventing cardiovascular disease. *Cochrane Database Syst Rev* 2001;(3):CD002137.
12. Stehbens WE. The hypothetical epidemic of coronary heart disease and atherosclerosis. *Med Hypotheses* 1995;45:449-454.

13. Lozano R, Murray CJL, Lopez AD, Satoh T. Miscoding and misclassification of ischaemic heart disease mortality. Global Programme of Evidence for Health Policy Working Paper No12. WHO 2001. http://www.who.int/healthinfo/paper12.pdf. [Accessed April 21, 2006]
14. Kuhn TS. *The Structure of Scientific Revolutions*. Chicago, IL: The University of Chicago Press; 1970.
15. Ravnskov U. Quotation bias in reviews of the diet-heart idea. *J Clin Epidemiol* 1995;48:713-719.
16. Keys A. Coronary heart disease in seven countries. 1970. *Nutrition* 1997;13:250-252.
17. Anderson KM, Castelli WP, Levy D. Cholesterol and mortality. 30 years of follow-up from the Framingham study. *JAMA* 1987;257:2176-2180.
18. No authors listed. Multiple Risk Factor Intervention Trial. Risk factor changes and mortality results. Multiple Risk Factor Intervention Trial Research Group. *JAMA* 1982;248:1465-1477.
19. http://www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/HOME?CRETRY=1&SRETRY=0 [Accessed July 27, 2007]
20. http://www.cebm.net/levels_of_evidence.asp [Accessed March 15, 2006]
21. Robertson TL, Kato H, Rhoads GG, et al. Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California. Incidence of myocardial infarction and death from coronary heart disease. *Am J Cardiol* 1977;39:239-243.
22. Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, et al. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. *Circulation* 1994;90:583-612.
23. Dawber TR, Kannel WB. Coronary heart disease as an epidemiology entity. *Am J Public Health Nations Health* 1963;53:433-437.
24. Shekelle RB, Shryock AM, Paul O, et al. Diet, serum cholesterol, and death from coronary heart disease. The Western Electric Study. *N Engl J Med* 1981;304:65-70.
25. Carman WJ, Barrett-Connor E, Sowers M, Khaw KT. Higher risk of cardiovascular mortality among lean hypertensive individuals in Tecumseh, Michigan. *Circulation* 1994;89:703-711.
26. Nichols AB, Ravenscroft C, Lamphiear DE, Ostrander LD Jr. Daily nutritional intake and serum lipid levels. The Tecumseh Study. *Am J Clin Nutr* 1976;29:1384-1392.
27. Kromhout D, de Lezenne Coulander C. Diet, prevalence and 10-year mortality from coronary heart disease in 871 middle-aged men. The Zutphen Study. *Am J Epidemiol* 1984;119:733-741.
28. Goldbourt U, Yaari S. Cholesterol and coronary heart disease mortality. A 23-year follow-up study of 9902 men in Israel. *Arteriosclerosis* 1990;10:512-519.
29. Yano K, Reed DM, McGee DL. Ten-year incidence of coronary heart disease in the Honolulu Heart Program. Relationship to biologic and lifestyle characteristics. *Am J Epidemiol* 1984;119:653-666.
30. McGee DL, Reed DM, Yano K, et al. Ten-year incidence of coronary heart disease in the Honolulu Heart Program. Relationship to nutrient intake. *Am J Epidemiol* 1984;119:667-676.
31. Garcia-Palmieri MR, Feliberti M, Costas R Jr, et al. An epidemiological study on coronary heart disease in Puerto Rico: The Puerto Rico Heart Health Program. *Bol Asoc Med P R* 1969;61:174-179.
32. Fuller JH, Shipley MJ, Rose G, et al. Mortality from coronary heart disease and stroke in relation to degree of glycaemia: the Whitehall study. *Br Med J (Clin Res Ed)* 1983;287:867-870.
33. Castelli WP, Doyle JT, Gordon T, et al. HDL cholesterol and other lipids in coronary heart disease. The cooperative lipoprotein phenotyping study. *Circulation* 1977;55:767-772.
34. Willett WC, Stampfer MJ, Manson JE, et al. Intake of trans fatty acids and risk of coronary heart disease among women. *Lancet* 1993;341:581-585.
35. Cornoni-Huntley J, Ostfeld AM, Taylor JO, et al. Established populations for epidemiologic studies of the elderly: study design and methodology. *Aging (Milano)* 1993;5:27-37.
36. Olson RE. Discovery of the lipoproteins, their role in fat transport and their significance as risk factors. *J Nutr* 1998;128:439S-443S.
37. Pocock SJ, Collier TJ, Dandreo KJ, et al. Issues in the reporting of epidemiological studies: a survey of recent practice. *BMJ* 2004;329:883.
38. Chan AW, Altman DG. Identifying outcome reporting bias in randomised trials on PubMed: review of publications and survey of authors. *BMJ* 2005;330:753.
39. Gotzsche PC. Believability of relative risks and odds ratios in abstracts: cross sectional study. *BMJ* 2006;333:231-234.
40. Leitner ZA. Diet and coronary disease. *Med World* 1954;81:249-254.
41. Keys A, Anderson JT. Symposium on Atherosclerosis. National Research Council Publication 338: 1955.
42. Yerushalmy J, Hilleboe HE. Fat in the diet and mortality from heart disease; a methodologic note. *N Y State J Med* 1957;57:2343-2354.
43. Keys A, Menotti A, Aravanis C, et al. The Seven Countries Study: 2,289 deaths in 15 years. *Prev Med* 1984;13:141-154.
44. Menotti A, Blackburn H, Kromhout D, et al. Changes in population cholesterol levels and coronary heart disease deaths in seven countries. *Eur Heart J* 1997;18:566-571.
45. Epstein FH. Cardiovascular disease epidemiology: a journey from the past into the future. *Circulation* 1996;93:1755-1764.

46. Keys A, Anderson JT, Grande F. Serum cholesterol response to changes in the diet, IV: particular fatty acids in the diet. *Metabolism* 1965;14:776-787.
47. Wilson PW, D'Agostino RB, Levy D, et al. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998;97:1837-1847.
48. Dawber TR, Meadors GF, Moore FE. Epidemiological approaches to heart disease: the Framingham study. *Am J Public Health Nations Health* 1951;41:279-281.
49. Grundy SM, Balady GJ, Criqui MH, et al. Primary prevention of coronary heart disease: guidance from Framingham: a statement for healthcare professionals from the AHA Task Force on Risk Reduction. American Heart Association. *Circulation* 1998;97:1876-1887.
50. D'Agostino RB Sr, Grundy S, Sullivan LM, et al. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. *JAMA* 2001;286:180-187.
51. Thomsen TF, McGee D, Davidsen M, Jorgensen T. A cross-validation of risk scores for coronary heart disease mortality based on data from the Glostrup Population Studies and Framingham Heart Study. *Int J Epidemiol* 2002;31:817-822.
52. Haq IU, Ramsay LE, Yeo WW, et al. Is the Framingham risk function valid for northern European populations? A comparison of methods for estimating absolute coronary risk in high risk men. *Heart* 1999;81:40-46.
53. Brindle PM, McConnachie A, Upton MN, et al. The accuracy of the Framingham risk-score in different socioeconomic groups: a prospective study. *Br J Gen Pract* 2005;55:838-845.
54. Kuller L, Neaton J, Caggiula A, Falvo-Gerard L. Primary prevention of heart attacks: the multiple risk factor intervention trial. *Am J Epidemiol* 1980;112:185-199.
55. Neaton JD, Grimm RH Jr, Cutler JA. Recruitment of participants for the Multiple Risk Factor Intervention Trial (MRFIT). *Control Clin Trials* 1987;8:41S-53S.
56. Wentworth DN, Neaton JD, Rasmussen WL. An evaluation of the Social Security Administration master beneficiary record file and the National Death Index in the ascertainment of vital status. *Am J Public Health* 1983;73:1270-1274.
57. Stamler J, Wentworth D, Neaton JD. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA* 1986;256:2823-2828.
58. MacMahon SW, Cutler JA, Neaton JD, et al. Relationship of blood pressure to coronary and stroke morbidity and mortality in clinical trials and epidemiological studies. *J Hypertens Suppl* 1986;4:S14-S17.
59. Neaton JD, Wentworth D. Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease. Overall findings and differences by age for 316,099 white men. Multiple Risk Factor Intervention Trial Research Group. *Arch Intern Med* 1992;152:56-64.
60. Lauer MS, Blackstone EH, Young JB, Topol EJ. Cause of death in clinical research: time for a reassessment? *J Am Coll Cardiol* 1999;34:618-620.
61. ICD = International Classification of Diseases published by the World Health Organization (WHO).
62. Tarasuk VS, Brooker AS. Interpreting epidemiologic studies of diet-disease relationships. *J Nutr* 1997;127:1847-1852.
63. Freudenheim JL. Study design and hypothesis testing: issues in the evaluation of evidence from research in nutritional epidemiology. *Am J Clin Nutr* 1999;69:1315S-1321S.
64. Stanton RA. Nutrition problems in an obesogenic environment. *Med J Aust* 2006;184:76-79.
65. Felton CV, Crook D, Davies MJ, Oliver MF. Dietary polyunsaturated fatty acids and composition of human aortic plaques. *Lancet* 1994;344:1195-1196.
66. Marmot MG, Syme SL, Kagan A, et al. Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California: prevalence of coronary and hypertensive heart disease and associated risk factors. *Am J Epidemiol* 1975;102:514-525.
67. Wannamethee SG, Shaper AG, Lennon L, Morris RW. Metabolic syndrome vs Framingham Risk Score for prediction of coronary heart disease, stroke, and type 2 diabetes mellitus. *Arch Intern Med* 2005;165:2644-2650.
68. Willett WC. Dietary fat and obesity: an unconvincing relation. *Am J Clin Nutr* 1998;68:1149-1150.
69. Ravnskov U. Cholesterol lowering trials in coronary heart disease: frequency of citation and outcome. *BMJ* 1992;305:15-19.
70. Stehbens WE. Coronary heart disease, hypercholesterolemia, and atherosclerosis. II. Misrepresented data. *Exp Mol Pathol* 2001;70:120-139.
71. Klevay LM. Ischemic heart disease as deficiency disease. *Cell Mol Biol (Noisy-le-grand)* 2004;50:877-884.
72. Blanco-Colio LM, Tunon J, Martin-Ventura JL, Egido J. Anti-inflammatory and immunomodulatory effects of statins. *Kidney Int* 2003;63:12-23.
73. Varughese GI, Patel JV, Lip GY, Varma C. Novel concepts of statin therapy for cardiovascular risk reduction in hypertension. *Curr Pharm Des* 2006;12:1593-1609.
74. Grimes DS. Are statins analogues of vitamin D? *Lancet* 2006;368:83-86.
75. Eaton SB, Eaton SB. Paleolithic vs. modern diets – selected pathophysiological implications. *Eur J Nutr* 2000;39:67-70.
76. Cordain L, Miller JB, Eaton SB, Mann N. Macronutrient estimations in hunter-gatherer diets. *Am J Clin Nutr* 2000;72:1589-1592.
77. Cordain L, Eaton SB, Miller JB, et al. The paradoxical nature of hunter-gatherer diets: meat-based, yet non-atherogenic. *Eur J Clin Nutr* 2002;56:S42-S52.