

**An examination of the evidence supporting the association of
dietary fats with the development of cardiovascular heart disease**

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Abstract

The 'lipid hypothesis' is the base of much contemporary diet advice 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, and not to its genesis. Ongoing research provides only inconclusive evidence of the effects of modification of total, saturated, mono-unsaturated or polyunsaturated fats on cardiovascular morbidity and mortality. The increasing adoption of high carbohydrate diets as a result of the low fat diet guidelines has been targeted by many authors as contributing to an increase in diabetes and obesity. [1,2,3,4,5] 3-Hydroxy-3-methyl-gutaryl coenzyme A (HMG-CoA) reductase inhibitors or statins have become the highest selling drugs ever in medical history and seem finally to provide evidence that the lipid hypothesis is based on erroneous assumptions, since they seem to act independently of cholesterol reduction..

It seems appropriate to revisit the origins of the cholesterol-CHD paradigm and discuss the methodological problems involved. Early in the last century fat and cholesterol fed to rabbits produced histological changes that resembled atherosclerosis in humans. Keys' linear association between dietary fat consumption and CHD found its empirical verification in the Framingham 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.

This thesis 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 debateable conclusions. It assesses alternative research to support criticisms 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 offers a wide historical context that suggests a different set of sources for CHD that has no relation to fat intake.

Introduction

The role of dietary fat and cholesterol in the aetiology of CHD has been studied for a century, since Anitschkow first created fatty deposits [6] in rabbits' arteries by feeding them cholesterol and saturated fats. The resulting plaques, however, 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 Aintschkow's [1913] cholesterol observation prevailed. Keys' ecologic 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 declaring that a relationship between dietary fat, cholesterol, and CHD was established [8], the debate on the contribution of fats to CHD continues.

Extensive reviews [9] have demonstrated that TC-S [Total blood cholesterol] is not strongly regulated by diet. Studies [10] point to the importance of types of fat rather than overall fat intake [11]. A systematic review of 27 trials of cholesterol reduction reported a reduction of 9% CHD mortality and 16% reduced 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 systematic review revisits the original studies that provided the base of the lipid hypothesis to point out methodological problems and inconsistencies. The methodological problems occur on various levels. Firstly, the term CHD is used as an imprecise and collective term for a heterogeneous group of pathological states [12] rather than as a specific disease term in epidemiology. Secondly, using death certificates as means of identification for CHD-M causes difficulties because of the inaccuracies in certification [13]. Thirdly, 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' [14] explains the development of a scientific theory as necessary development of a theoretical framework. Kuhn described

theories or paradigms as ‘universally recognised 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, may introduce bias in later studies [15].

Keys’ initial Six Country Study [7], his following Seven Countries Study [16], and the Framingham Study [17] in the early 1960s validated the suggested correlation between saturated fat intake and blood cholesterol levels. Follow-on studies used the Keys scores as measurements. The Multiple Risk Factor Intervention Trial [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 butter and lard, whole milk and eggs, bacon and steak. Margarine and vegetable oils are the only recommended fats.

This analysis summarizes studies that researched fat intake and cardiovascular mortality. It specifically investigates the methodology of the three main studies that formed 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 the Cochrane Library databases. Search terms were ‘Diet and Cholesterol’ [n=27322] ‘Cholesterol and epidemiologic studies’ [n=15101] Cholesterol and heart disease’ [n=23988], ‘Epidemiological studies and heart disease’ [n=7], ‘Saturated fat and heart disease’ [n=11], ‘Heart disease and diet’ [n=11312]. By using the Boolean operator ‘and’ the initial search was reduced to articles combining two subjects [19]. Then limits were applied: ‘Before 1994, humans only, English language articles and adults only [age groups from 19 – 80 and over]. The restriction to studies published before 1994 was applied for two reasons: in 1984 the cause-and effect relationship between hypercholesterolemia and CHD risk was decided at a Consensus Conference by the US National Institute of Health [8], and all studies begun before this date would have been published by 1994. After 1994, most trials included a statin control, not a feature of the original trials.

The remaining articles [n=2669] were viewed as summaries first, then as abstracts. The selection criteria were validity of research, importance of article, and applicability to the research question. Studies that fulfilled the selection criteria were obtained in full. 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 study analyses evidence for the causality of cholesterol and heart disease, end points could not be cholesterol levels or atherosclerosis, but cholesterol and fat intake and 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 the serum cholesterol [TC-S] level at baseline and the mortality from CHD. [CHD-M] Clinical end points were defined as mortality from CHD and total mortality. CHD-H reflects the benefit that might be expected following a reduction in 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 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 investigation.

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 seemed to fulfil the selection criteria were analysed and tabulated. A wide range of prospective studies has been carried out worldwide, but wide differences in methods make a geographical comparison of CHD incidences impossible. The still not fully-published MONICA project would have provided the methodological base for a geographical comparison, but it was not a cohort study and did not collect individual data. One significant result of the MONICA data was the discovery of the degree of misclassification and miscoding of ischaemic heart disease mortality [13].

Table 1 lists all selected studies in chronological order of commencement and indicates the end of data collection. 'N' accounts for the number of subjects. 'Subject selection' describes the selection mode and the age range of the sample. 'Diet evaluation' describes the mode of collection of information about dietary intake. 'Data collected' lists the different parameters that were evaluated. 'Clinical endpoints' are of great importance since soft surrogate endpoints like cholesterol levels or angiograms are inconclusive. The 'results' column gives each study's conclusions with regard to the validity of the lipid hypothesis.

Table 1: Studies concerning the association of dietary fat consumption and CHD

Cross Population Studies							
Study	Years	N	Subject selection	Diet Evaluation	Data Collected	Clinical Endpoints	Results
Six Countries [7]	1949 Pilot study SFA: CHD-M	Ecological study	NDR males 45-49 and 55-59	National food balance data	National Statistics	CHD-M Mortality Statistics	Strong correlation SFA:CHD-M
Seven Countries [16]	1958-1964 SFA: CHD-M	N= 12763 men	males 45-49 and 55-59	7-day weighed record, composite analysis, standardised to 16 food groups In 1986	Interview, TC-S, BP, ECG, APM	CHD-M Mortality Statistics	SA SFA:TC-S SFA:CHD SA SM:CHD SA between countries No within country SFA:CHD
Japan-Honolulu- San Francisco Study Ni-Hon-San Study 1977[21]	1966-1984 CHD-M risk	N=11900 men	Men of Japanese ancestry living in Japan, Hawaii and California Age 45-68	24hour diet recall	TC-S, BP, ECG Questionnaire	CHD-M stroke and ACM, DC	HDL-C positively related to fish intake in men not women ↓CHD-M and ↓TC-S CHD-M lowest in Japan
MONICA WHO 1994 [22]	1980-1990 CHD-M risk	N=10 million	CHD morbidity and mortality M/F aged 25-64		National centres in 38 countries	CHD-M MI, Hospital data and DC	Strong HT:CHD Weak smoking, TC-S

Within Population Studies

Study	Years	N	Subject selection	Diet	Data collected	End points	Results
Framingham 1963 [23]	1948-1968 CHD-M risk	N=2336 males 2873 females	Random sample of 2/3 adult population Age 30-62	24 hour recall	TC-S, HDL-C,* LDL-C* BP, APM, SM	CHD-MDC	M<50 ↑ TC-S-CHD, none for F or >70. No CHD-M correlation with eggs. ↑TC-S ↓Stroke
Western Electric Study [24] 1981	1958-1982 D-CHOL: CHD-M and Lung CA	N=1,878	Middle-aged M, random, employed in 1958 by the Western Electric Company in Chicago.	Dietary intake of D-CHOL, SFA and PUFA's measured according to Keys score.	TC-S, BP, BMI baseline 1958 and repeated 1 year later	CHD-M Lung CA	RR of lung cancer with D-CHOL, especially eggs. Correlation dietary SFAs and CHD-M
Tecumseh study [25] 1994 [26] 1976	1959-1987 Diet: TC and CHD death	N=2039 adults[Nicola] N=2181 [Carman]	88% Population Random sample	Food and portion recall for 24 hrs	TC-S, HDL-C,* LDL-C* OGC	CHD-M DC ICD codes 401-448	No correlation TC-S and TG and dietary intake ACM 455 151 IHD, 105 CHD, 199 non CHD
Zutphen Study [27] 1984	1960-1980 Diet: Other risk factors and CHD-M	N=1088 men	Random sample aged 40-59	Dietary history method Last 12 months	TC-S, BP, SM APM. Annual BP/TC-S	CHD-M DC	107 ACM 37 CHD-M, 44 CA correlation D-CHOL CHD-M after 10 years. Insignificant after 20 years [t=0.32, p>0.05]
Israel Ischaemic Heart Disease Study	1963-1983 TC-S: CHD-M	N=10059	Convenience sample Civil Servants aged 40-60	n/a	TC-S of 9902 and HDL-C of 6562 5 Yr incidence	CHD-M Mortuary Registry and ICD	HT without elevated TC-C worse prognosis than elevated TC-S in SBP

Study [28] 1990			aged 40-60		of MI AP. 7yr and 15ys CHD- M.	-9	<140 ACM predicted by age, diabetes, AP, SBP and S TC-S not major factor ACM
Honolulu Heart Study [29,30] 1984	1965-1975 Diet : CHD-M	N=8006 [McGee] 7705 [Yano]	WW2 Selective Service Register M of Japanese ancestry living in Hawaii age 45-68	24 h diet recall [coded in 54 foods]	SBP, TC-S, [no HDL] Physical activity	Total CHD, MI, CHD-M, AP or Cif	↑D-CHOL =CHD; ↓Fat intake = ↑ACM Inverse relation TC-S with stroke, lung disease and CA SBP higher risk to CHD than TC- S
Puerto Rico Heart Health program [31] 1980	1965 - 1974 CHD-M risk	N= 9824	House to house census: urban and rural Puerto Rican M age 45-64	24 hour diet recall	TC-S, BP/Physical activity index(1) BMI	CHD-M defined as MI, Cif, AP,	Positive association fat intake and TC-S. No association dietary FA:CHD- M
Whitehall Study [32] 1983	1967 – 1977 CHD-M risk	N= 18403 males aged 40- 64	civil servants by invitation 40-64	n/a	BP/BMI/ TC-S after overnight fast capillary blood samples, glucose test 50g load/TC	CHD-M Records tagged by Central Registry of NHS DC	CHD-M 721 ↑RF for stroke or CHD=BP Social gradient in CHD-M

Co-op Lipoprotein Phenotyping Study [33] 1989	1970-1986 TC-S and CHD-M Autopsy study	N= 2122 men	1545 probability sample. 577 included because of ↑TC-S in first HHS. Autopsies on 83,	n/a	TC-S HDL-C, LDL-C	CHD-M Autopsy study on 83	CHD-M 23 [30%] CA 34 [41%] 24 [19% others] HDL-C significantly inverse associated with atherosclerosis of cerebral arteries
MRFIT 1970 [18, 53-59]	1975-1982 TC-S: CHD-M	N=128 66	Enrolled for ↑risk due to ↑ TC-S, ↑DBP SM Ages 35-67	SI group med forHT SI – Diet plan UC- no diet	TC-S HDL-C,LDL-C, L-C, BP Diet recall	COD assigned Mortality Review Committee CHD-M: 1)MI, 2) SD 3)CHF 4)DDH	260 ACM in UC: 124 CHD-M 145 CVC ACB ST:265 115 CHD-M 138 CVD. ACM 2.1% higher for the SI HDL-C inverse CHD-M risk

Nurses Health Study [34, 10] 1993	1976-1990 Relation dietary intake of specific types of fat, and risk CHD	N=872 45 F, aged 34-59	Bi-annual mail survey. All who replied to first mail-out	Diet survey 61 food items incl portion size.		major CHD [defined as nonfatal MI or CHD-M	939 cases of nonfatal MI or CHD-M. Total fat no CHD risk. SA with intake of tFAs SA smoking and CHD [rr of 5.48, 95%CI 4.67 to 6.42]
New Haven, Conn, cohort of the Established Population for the Epidemiologic	1984-1989 TC-S and ACM and CHD-M	N=997	Subjects who consented to blood test. M/F >70	n/a	TC-S, BP, HDL-C, LDL-C	CHD-M DC	↑TC-S, ↓HDL-C Not associated with ACM, CHD-M

Study of the Elderly (EPESE)[35]							
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(1) 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 Study.

• Lipoproteins were included later in the study; the view of fat transports involving triglycerides was developed in the 1960s [Olson 36].

Key to abbreviations

ACM=All-cause mortality

ALC=Alcohol

APM=Anthropomorphic measures

BMI=Body mass index

BP=Blood pressure

CA=Cancer

CHD-M Coronary heart disease mortality

CHF=congestive heart failure

Cif= coronary insufficiency

COD-Cause of death

CVC=Cardiovascular causes [incl CHD]

DBP=Diastolic blood pressure

D-CHOL dietary cholesterol

DDH=Death during hospital stay for CHD

DC=death certificate

FA=Fatty acids

HT=Hypertension

HDL-C =High density lipoprotein cholesterol

MFA=Monounsaturated fatty acids

NHS=National Health Service

NDR-National death rates

OGC=Oral glucose challenge

PUFA=Polyunsaturated fatty acids

RF=Risk Factor

RR=Relative risk

SA=Significant association

SD-Sudden death

SFA=saturated fatty acids

SI=Special intervention group

SM=Smoking

Strong=↑

SPB=Systolic blood pressure

TC-S=Total serum cholesterol

TG=Triglycerides

tFA=trans fatty acids

UC= usual care group

ICD-international classification of disease

Weak= ↓

IHD= ischaemic heart disease

LDL-C =Low density lipoprotein cholesterol

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 end-points like lowering TC-S or ECGs. All reported studies show a strong association between hypertension and smoking; Keys' studies and the Western Electric Study reveal a strong association between fatty acid intake and CHD-M. The Western Electric Study shows an especially strong association between egg consumption and CHD-M; Framingham does not reveal any correlation between eggs and CHD-M at all.

The overall inadequacies in design, analysis, reporting, and quotation of the reviewed epidemiological publications is of great concern, an observation that has been discussed in several recent papers about the standard of epidemiological studies [37,38,39].

Keys Studies

In a 1953 lecture Keys [7] summarized the complex of 'degenerative heart disease' and included angina pectoris, coronary heart disease, myocardial infarction, chronic myocarditis, and myocardial degeneration. These conditions, or at least some of them, in humans are related to 'serum cholesterol and allied substances'. He deduced a relationship between diet and the concentration of cholesterol and allied substances in the serum, and the mortality rate of the adult population. Keys' [7] published pilot study of six different countries contained a figure which showed the relationship between the national death rate for men between the ages 45-49 and 55-59 from 'atherosclerotic and degenerative heart disease' and the proportion of fat calories available from the respective national diets. The figure displayed a regular progression from Japan through Italy, Sweden, England, Wales, Canada, and Australia to the United States. Keys stated that '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 increased the interpretation in 1955 [41]: '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'.

Unfortunately Keys did not include any information concerning the basis on which the six countries were selected, when data for 22 countries were available [42]. The available data for males aged 55-59 for all 22 countries [42] greatly reduce the strength of the association. But even the wider-spread variables did suggest some association between cholesterol, saturated fat and CHD. The index of fat as a percentage of total calories that was 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 that '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 variety, and were derived from different definitions, reporting patterns and diagnostic habits and standards of the medical profession in the respective countries. Keys was well aware of the limitations of his data [7]: 'There is no guaranty that the main points of this discussion are actually about arteriosclerosis or the particular variety labelled atherosclerosis.' In 1957 Yersuhalmy and Hilleboe [42] created a figure by plotting the death rates from heart disease for 22 countries against the per cent of fat and animal protein available for consumption; they demonstrated an equally strong association with both. Keys' lipid hypothesis was strongly disputed, since his data were subject to considerable limitations. In particular, the presumed association was not specific, and Yersuhalmy and Hilleboe concluded that 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 organised a study of coronary heart disease in seven countries [16, 43]. Sixteen local populations in the Netherlands, Yugoslavia, Finland, Japan, Greece, Italy, and USA were selected. Investigators studied two or three groups of people in each country, recording diet, weight, measured blood pressure, exercise, and smoking habits. Men between 40 and 59 were followed, initially for 5 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 $\text{mg}\cdot\text{dl}^{-1}$ [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 coronary heart disease were found among the cohorts. The ecological relationship of mean serum cholesterol at entry to late coronary heart disease death rate during the 10-25 year follow up was reported as weak, 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 heart attacks and diet within the countries.

Keys declared that coronary heart disease 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 could be found by him or by other researchers. While North Karelia [East Finland] took rank position 1 in the first decade of observation, West Finland took rank 4 with a difference of over 100 CHD deaths per 1000. 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 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% higher in Belgrade, 35% higher in Velika Krsna, and 45% higher in Zrenjanin than in 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 ageing population. The validity of the results is restricted to the particular population and the specific historic period during which they were studied. The results cannot be generalised or taken as base for other studies.

After the pilot study, Keys carried out 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 acids. This formula has been reported to have been used in the Western Electric study. Epstein, for instance, points out that 'The quintessence of all geographical epidemiology is that dietary fat and cholesterol intake, the main determinants of population levels of serum cholesterol and low-density lipoprotein, play a fundamental role in explaining cross-cultural differences in the frequency of CHD. Serum lipids, in accordance with Key's 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 Study

The Framingham heart study was conducted at the University of Boston in conjunction with the United States National Heart Institute (now the national Heart, Lung and Blood Institute, or NHLBI) The original study cohort consisted of a random sample of 2/3 of all adults, 30 to 62

years of age, residing in Framingham, Massachusetts in 1948. Of the original 5209 participants, approximately 1095 were known to be alive in February 1998.

The objective of the Framingham Heart Study was to identify the 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, sex, 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 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 ranks, and time frames. In a 1987 study from [17] the authors refer to a cohort of '1959 men and 2415 women aged between 31 and 65 who were free from cardiovascular disease and cancer'. In another report [23] the group is said to consist of 2283 men and 2844 women between the ages of 30 and 62. In a 1998 Special Report [47] the numbers of participants (now called patients) of the original study are given as 2489 men and 2856 women, aged 30 to 74 at baseline, with 12 years of follow-up. The oldest study obtainable [49] mentions that originally 6510 inhabitants of the city of Framingham, Massachusetts between the ages of 30 and 59 and of either sex were invited to take part. Because only 70 per cent 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 analysing factors contributing to CHD, those subjects with arterial hypertension were included and the study later developed the term 'risk factors'. The subjects did not receive treatment within the study, but 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 aggregation of genetic physical or psychological characteristics, as well as of lifestyle and dietary habits. In particular, familial hypercholesterolemia should have been of concern. As well as these issues, the wide age distribution of those finally taking part caused the calculating

risks for age groups to span several decades, a problem in particular when it comes to disorders with various manifestations and with marked age dependence, like CHD. 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 generalisations to the wider population may not be appropriate.

Despite this, a statement to healthcare professionals from the American Heart Association [50] postulated that the Framingham Study contributed importantly to a wider understanding of the causes of coronary heart disease [CHD], stroke, and other cardiovascular diseases.

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. Agostino et al remark that 'The Framingham functions were developed to assess the relative importance of CHD risk factor to quantify the absolute level of CHD risk for individual patients' [48]. Yet, as Grundy et al point out, developed guidelines have found entry in programs on 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' [50].

The Framingham results did not demonstrate a gradient and linear correlation between cholesterol blood 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 1959 men and 2415 women aged between 31 and 65 years who were free of cardiovascular disease (CVD) and cancer: Anderson note that

Under age 50 years, cholesterol levels are directly related with 30-year overall and CVD mortality; overall death increases 5% and CVD death 9% 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% overall and 14% CVD death rate increase per 1 mg/dL per year drop in cholesterol levels) [17].

Despite the limitations noted above about 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 [51] due to marked regional differences in the incidence of CHD in Europe. 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 the Italian population [52] as well. 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 aged 35-75 without pre-existing vascular disease determined which of the screened men had a CHD risk of 3.0% per year or higher by the Framingham function and so should be targeted for statin treatment [53]. The report stated that '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 Study is of particular importance because from it a CHD predictor model was developed, and this 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 Multiple Risk Factor Intervention Trial [MRFIT] and the Tecumseh study [18, 47].

Steinberg [8], in reference to the failed significance in Framingham to demonstrate a correlation between CHD and cholesterol, wrote: 'However, failing to find a good correlation between dietary composition and risk does not necessary disprove the underlying hypothesis!' Despite the difficulties of drawing clear conclusions from the Framingham studies, researchers continue to use them. This is certainly not good scientific method and may in part explain why there is still such debate about lipids and CHD.

Multiple Risk Factor Intervention Trial [MRFIT]

In July 1970, the National Heart and Lung Institute (NHLI) convened a task force on arteriosclerosis. The aim was to develop a broad long-range plan for the study, control, and possible prevention of arteriosclerosis, and 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 persons at increased risk of death from heart attacks would result in reduction of coronary death rates. The study was restricted to men because of their much higher risk of premature heart attack compared with women, a result of the Framingham 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 aged 35 to 57 years who were at increased risk of death from CHD but had no clinical evidence of CHD at time of recruitment [18]. People were designated as at 'increased risk' if levels of all 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% of a risk score distribution. The numbers of participants varied considerably between reports. 361662 [18] men or 361629 [54] were recruited for a first screening visit to determine CHD risk eligibility and apply several exclusion criteria. The first screenings took place between November 1973 and November 1975. 25545 [25529] were invited to the second screening within 1 month, of whom 22080 [22970] attended. The final number of 12866 subjects selected after a third screening is the same in all reports.

The aim of the three-stage screening was to obtain the required 12000 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 2 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 first stage. The second screening was performed within a month and included an electrocardiogram; 4588 men [20.7%] were excluded on medical grounds, either previous coronary heart disease 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 counselled individually by a study physician and invited to a series of weekly group discussions addressing all three risk factors. Each group included about ten men and met for about ten sessions.

SI group subjects were seen, on average, every four months by a group of behavioural scientists including nutritionists, nurses, physicians, and general health counsellors. 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 to less than 10% of calories and dietary cholesterol intake to less than 300 mg/day was recommended; but in 1976 the nutrition pattern was changed to specify that saturated fat be less than 8% of calories and dietary cholesterol less than 250 mg/day.

Only one source [55] mentioned the exclusion of more than 1000 men because of excessive alcohol consumption. Further reasons for exclusion included a refusal to consider stopping smoking and excessive weight. The analysis of the mortality of the 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 Feb 28, 1982 (six years after the last day of randomization), when telephone or mail contact was attempted with each man not known to be deceased.

The MRFIT group [18] describes the way mortality data were obtained. Cause of death was assigned by a Mortality Review Committee. Some papers [57] report 6% of death certificates were missing; others [57,58,59] do not mention missing certificates but include detailed causes of death.

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 10mg/p [28]. One report [57] stated that the risk of dying from a heart attack with a cholesterol level above 265mg/dl was 413% greater than with

a cholesterol level below 170mg/dl. 494 men [1.3 %] in the highest cholesterol range died of heart attacks; 98.7% were still alive after 6 years. Of the lowest cholesterol group only 0.3% died. The difference between the number of deaths in the highest and lowest levels of cholesterol after 6 years in a group of high-risk men was 1%. 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 Feb 28, 1982, after a follow-up period of seven years, there were 260 deaths among UC (usual care) 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% higher for the SI (special intervention) 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 well 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 v 109 UC). There were 81 cancer deaths in the SI group and 69 in the UC, including lung cancer (34 SI v 28 UC), colorectal cancer (8 SI v 6 UC), other gastrointestinal neoplasms (20 SI v 11 UC), and other neoplasia (19 SI v 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

All epidemiological study designs that address the relation between nutritional intake and disease face the problem of precise measurement of long-term dietary exposure. There are also issues concerning to what 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 familiar hypercholesteronaemia 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.

There is no doubt that there is an association between CHD and high serum cholesterol, but association does not necessarily imply causation. Trials of dietary 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 50. Neither the Tecumseh Study, nor the Puerto Rico Heart Study, nor the Israel Study showed any relation between CHD-M and cholesterol levels. There is a correlation between SFA and dietary cholesterol 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. For instance, the Seven Countries Study reported a correlation between dietary cholesterol and CHD-M. After 5 years the study recorded 477 cancer deaths, with a significant excess of lung cancer deaths among those in the 20% bottom cholesterol distribution [43]. Trend analysis indicated an increasing risk of lung cancer death at levels below 170mg/dL. In contrast, on an individual level, the highest cancer rates occurred in Northern Europe, where the population's cholesterol level was also highest [43].

Determining of cause of death

Keys based his proof of association on death certification. Death certificates were crucial in all other studies except the autopsy group of the Lipoprotein Phenotyping Study. MRFIT demonstrates severe inconsistencies regarding death certification and missing data. Data obtained from death certificates or from 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, a low autopsy rate, and inadequate understanding of complex disease processes. A recent report from the Framingham Heart Study [61] compared causes of death among 2,683 decedents as identified by death certificates and by a physician panel. Of 942 certificates which gave 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%. Inaccurate reporting of death from CHD was strongly related to increasing age: among patients aged 65 to 74, 75 to 84, and ≥ 85 , differential rates of reported versus confirmed coronary heart disease deaths were 18%, 31%, and 109% respectively. Lozano claims that a miscertification 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%’ [13]. Claims about miscertification were supported by the more than 25% increase in recorded ischaemic heart disease mortality rates in Japan between 1994 and 1995, with the change from ICD-9 to ICD-10 [62]. 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.

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 aetiology 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 relatively low in fibre, lack the antioxidants carotene and ascorbic acid, and are low in folate. The lack of those components correlates with other accepted risk factors for CHD such as antioxidant and homocysteine levels. Dietary structures cluster with economic, religious, socio-cultural and demographic variables. High day-to-day variations in consumption structures make accurate estimates of nutritional intake very difficult, as do the complex food structures of processed food products [63,64]. In addition, most of the knowledge about fatty acids is fragmented and biased by assumptions that guided the experimental structure of investigations into fatty acids. This is especially true in the case of saturated fatty acids, which have mainly been studied for their potential to influence lipoprotein metabolism and cholesterol transport within the blood.

Studies can include only a fraction of the 30,000 foods now available [65], and statistically analysing the interrelationship between 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; the largest groupings are found in the Honolulu Heart Study (54 food groups) and the Nurses Health Study (61 food groups and portion sizes). This heterogeneity of food grouping and the nearly 30-year time span covered by the studies render any interpretative comparison between studies purely speculative.

In addition to these problems of procedure, researchers must contend with participant behaviour. Bias can be introduced by diet modification undertaken by participants by themselves during a study. Intervention trials to study the effects of moderate changes [MRFIT] were compromised by unexpected attitude changes among the control group [18].

The subjective nature of nutritional epidemiology, the wide variations in methodologies between studies, the interconnection of uncontrolled variables, and the actions of the

participants, make findings irreplicable and scientifically suspect. One thing that is clear from the cited studies is that none of them show a valid association between cholesterol and saturated fat and heart disease other than for men younger than 47. Anderson et al, commenting on the Framingham study, note that ‘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 that ‘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 favouring increased intake of polyunsaturated fatty acids should be reconsidered’ [66].

Discussion

Keys' studies assert there is a positive ecological correlation between national fat and dietary cholesterol 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 consumption; Framingham explicitly reports no connection. The vast differences in collecting data and the great time span makes it impossible to make valid dietary comparisons between these studies.

Comparisons become more fraught with apparently contradictory evidence: the Honolulu study shows an increase of death from all causes among subjects with lowered cholesterol levels, findings also borne out by the Framingham Study which in a 30-year follow-up [17] found a direct association between falling cholesterol levels over the first 14 years and higher mortality levels over the following 18 years. 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. Tecumseh, Israel, and Puerto Rico studies discover no correlation between dietary fat and cholesterol and CHD death. 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 that the determining factor for heart disease is the degree of acculturation to Western culture [67]. All studies do find a strong association between smoking and CHD, and hypertension and CHD. These cited studies, in particular Keys' Seven Countries Study and the Framingham Study, not only hold historic relevance but also are used as the base of implementation of the lipid hypothesis in everyday practice. Health policy in the western world is still 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 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 over-estimations have been reported in recent studies [47,52,52,68]. The Framingham guidelines, which include age as a parameter, would identify three-quarters of the Australian adult population as being at risk, and 90% of over-50s as requiring external monitoring. Many, 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 not only failed to reduce CHD risk but have possibly ‘inadvertently exacerbated dyslipidaemia, insulin resistance, and weight gain, particularly among individuals who are older, female, sedentary, or obese’ [5]. This may be particularly so if the fat was not replaced by fruit, vegetables and whole grain products but by highly processed and refined carbohydrates with a high glycaemic index. [1,2,3,4,5]

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 cholesterol and atherosclerosis. All of the cited studies include subjects with familial hypercholesterolemia among other biochemical metabolic problems without mentioning or marking the subjects in published results. Non-specific coronary heart disease (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, publication, and citation bias [70,71] have repeated the results until they became valid.

Disease classification consisting of non-ambiguous definitions based on aetiological 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 heterogeneous collection of pathological states and diseases producing myocardial ischaemia. 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] as indicators. Ischaemic heart disease exists without atherosclerosis [12, 73], and atherosclerotic severity cannot be measured during life [23]. Kleavy [74] lists 21 contributing factors to the Ischaemic Heart disease phenomenology, and lipid metabolism is only one of them.

There are many reasons why the dietary-heart-cholesterol hypothesis should be revised, and one relatively new aspect is the way statins might be acting differently than by reducing cholesterol. Grimes postulates that rather than being cholesterol-lowering drugs *per se*, statins act as vitamin D analogues. He claims that the unexpected and unexplained clinical benefits produced by statins have also been shown to be properties of vitamin D: 'It seems likely that statins activate vitamin D receptors' [75]. Other authors report anti-inflammatory and immunomodulatory effects of HMG CoA reductase inhibitors which demonstrate a reduced cardiovascular mortality in patients treated with statins. Extensive research carried out mainly in the last decade suggests that the clinical benefits of these drugs could be related to an improvement in endothelial dysfunction, a reduction in blood thrombogenicity, anti-inflammatory properties, and, recently, immunomodulatory actions [76, 77]. From such research, it would seem that statins 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 [76]. All these anti-inflammatory and immunomodulatory effects of statins affect some of the components of ischaemic heart disease listed by Klevay [74] and their participation in the different steps of atherosclerotic lesion formation, insulin resistance, platelet activation and alterations in the coagulation cascade leading to a prothrombotic state. Dyslipidaemia acts synergistically with hypertension in increasing cardiovascular risk. Statins affect the whole pathophysiology of atherogenesis from deposition to plaque rupture and thrombogenesis because of its pleiotropic effects [77].

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 concentration on the assumed causality of cholesterol and saturated fats in the aetiology of CHD may have overlooked important aspects of diet modification over the last century. Field studies of twentieth 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 Westernised 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 human diet for thousands of years. CHD is a relatively recent phenomenon that only attracted attention in 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 eighteenth and nineteenth centuries introduced new dietary pressures without providing the necessary time for human adaptation. The discordance between our hunter-gatherer genome and our industrially modified, modern dietary intake may require more adaptation than our genetic heritage can provide. The 'inevitable discordance' that Eaton and Eaton point out [78] may be the root cause of CHD and other chronic diseases of civilisation. 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. An increasingly sedentary lifestyle further accelerates the effects of a nutritionally imbalanced diet. This, as much as any other causation, may affect recent rates of CHD.

Summary

The hypothesis of coronary heart disease as result of excessive intake of the wrong type of fat is no longer 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 causes of mortality. The powerful cholesterol-lowering statin drugs work irrespective of LDL levels, and on biological pathways other than lipid levels. Nutritional deficiencies need to be included in the spectrum of causes of chronic disease. The overall impression of the cited studies is of a great variety of methodological quality, content, and style. This carries the serious risk that some epidemiological publications may reach misleading conclusions. Indeed, this is the case; and the many methodological 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.

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