VARIANCE AND DISSENT
Dissent

Is atherosclerotic vascular disease related to a high-fat diet?

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1. Introduction

Does a diet high in saturated fats or cholesterol increase the risk of cardiovascular events? University researchers, august professional associations, governmental health administrations have all told us so for decades about the dangers of a high-fat diet. Food producers, processors, and to some extent restaurants, have responded to these appeals by modifying the fat content of food or offering more low-fat foods. Can these broad societal decisions be defended? In this issue of the Journal, Ravnskov [1] has argued quite forcefully that this cannot be defended, and that multiple observational studies and clinical trials have failed to prove a link between diet and the development of atherosclerosis and subsequent cardiovascular events. He goes on to argue that serum cholesterol is also not causally related to cardiovascular disease, and that the actions of statins in decreasing cardiovascular events are independent of effects on serum lipids. Can it really be that the emperor has no clothes? Furthermore, if it is difficult to demonstrate a relationship between diet and atherosclerosis, then why is it important to demonstrate this association? The reason is that there is reason to believe that this association is causal, and at least in part, fundamental, to our understanding of the process of atherosclerosis. Thus, with a view that considers the pathophysiology of atherosclerosis, the effect of secular trends in diet on cardiovascular events, response to pharmacologic therapy, and implications for future public policy, the role of dietary lipids becomes much more important.

How can an association between diet and atherosclerosis be adequately assessed, and how can an association be proven causal if it exits? We could define "cause" in an epidemiologic sense as an unbiased association in the absence of any confounding. This can only be shown in a perfect, or, in the real world, nearly perfect clinical trial. If there were no such trial data, then we could attempt to establish causation through such approaches as the Bradford Hill criteria [2] which are: (1) strength of association, (2) consistency of the evidence, (3) specificity, (4) temporality, (5) biologic gradient, (6) plausibility, (7) coherence, and (8) experimental evidence.

Not all of these criteria are perfectly met for diet or the cholesterol hypothesis, but almost all are. The epidemiologic data for diet are somewhat imperfect concerning the issue of strength of association and consistency. However, the relationship between serum lipids and atherosclerosis is far stronger for both strength of association and consistency of the evidence. Specificity is probably the weakest of the Hill criteria, and is generally considered invalid; that is, a cause does not have to have one effect, that is, cigarette smoking causes more than one disease. However, the diet hypothesis is certainly temporally consistent with atherosclerosis; eat a poor diet for decades and develop the disease. There is also evidence for a biologic gradient, at least for the relationship the serum cholesterol to outcome, which is the higher the cholesterol, the greater the chances of an event. The diet hypothesis is certainly plausible, and coherent, not interfering with other known information. However, lack of interfering information cannot prove the diet hypothesis, even though there is no interfering information to disprove it. There are both basic science and clinical trial experimental data to support the diet hypothesis. Thus, the diet hypothesis passes on temporality, plausibility, and coherence. As shall be shown, overall the evidence for the lipid hypothesis is overwhelmingly if not perfectly consistent. Let us begin with the basic science association, because this is intrinsic to understanding the diet hypothesis.

2. Basic science background

Dietary cholesterol (both dietary and enterohepatic) and triglycerides (as fatty acids and monoglycerides) pass through the intestinal enterocyte to enter the plasma as chlomicrons. Fatty acids are cleaved from the chylomicron by lipoprotein lipase, and then are taken up by peripheral tissues,

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with some residual and most of the absorbed cholesterol going to the liver. These chylomicron remnants are then taken up by a series of receptors in the liver, among which is the LDL receptor. The LDL receptor concentration on the hepatocyte is a major determinant of the plasma LDL concentration, and is regulated by the hepatic cholesterol concentration. Thus, the delivery of the cholesterol in chylomicron remnants reduces the clearance system for LDL, raising the blood concentration. LDL particles and perhaps chylomicron remnants can be taken up in peripheral tissues, more relevant to this discussion, into cells of the vasculature.

It is clear that lipids [3], oxidation state [4], mechanical stress [5], thrombosis [6], and perhaps even infection [7] participate in the pathogenesis of atherosclerosis. The earliest event is thought to involve oxidative modification of lipoproteins in the subintimal space [8]. These modified lipoproteins elicit an immune-like response in the vessel wall, including stimulation of inflammatory cytokines. Chemoattractants and adhesion molecules recruit monocytes into the subintimal space, where they become lipid-laden foam cells and release large amounts of reactive oxygen species, which in turn, further oxidize lipoproteins. These heavily oxidized lipoproteins are avidly taken up by foam cells and are very biologically active.

Why do lipoproteins in the subintimal space evoke such an immune response? Of interest, antigenic proteins of several microbial agents are lipoproteins [9]. Thus, the inflammation observed in atherosclerosis represents a basic immune response that originally may have evolved to defend against invading micro-organisms. In addition, oxidation of lipoproteins is likely an attempt at an adaptive response. Unmodified lipoproteins are taken up via the LDL receptor of macrophages and other cells. This receptor is rather rapidly downregulated by the presence of excess amounts of LDL. In contrast, oxidized LDL is taken up by scavenger receptors, which are not subject to downregulation. Thus, lipoprotein oxidation permits macrophages to "clean up" large amounts of lipids from the subintimal space, but also causes an inflammatory reaction. The argument for the lipid hypothesis is that high levels of lipoproteins and, in particular, oxidatively modified lipoproteins in the subintimal space, promote this basic, and otherwise protective, immunologic response. Several risk factors, such as diabetes [10], cigarette smoking [11], and hormonal influences, especially angiotensin II [12,13], increase the oxidative state of the vessel wall, contributing to this cascade by amplifying the oxidation of lipoproteins.

Thus, a unifying theory of the development of atherosclerosis is that risk factors including family history, older age, male gender, diabetes, cigarette smoking, hypertension, lack of exercise, elevated serum lipids, obesity, and a diet rich in saturated fats may lead to oxidative stress on the vascular endothelium, inflammation, and the development of atherosclerosis. Although risk factor control can be successful in preventing the development of atherosclerosis, cardiovascular events remain common. Thus, there has been continuing interest in measures to decrease events through modification of serum lipids.

3. Pathologic and epidemiologic association of lipids and atherosclerosis

People and animals with diets high in saturated fat will have higher levels of total cholesterol and lower levels of HDL cholesterol [14–23]. The experimental evidence that cholesterol or saturated fat feeding of multiple animal species causes atherosclerosis is also overwhelming [24,25].

There is no longer any reasonable doubt that cardiovascular events are related to serum lipids. This has been confirmed in pathologic studies, especially in multiple publications from the Pathobiological Determinants of Atherosclerosis in Youth study [26], which has also shown a relationship between atheroscleosis and obesity [27]. This has also been confirmed in such major epidemiologic studies as Framingham [28], the Multiple Risk Factor Intervention study [29], and PROCAM [30]. In a recent publication from Framingham [31], Wilson followed 2,489 men and 2,856 women for 12 years, of whom 383 men and 227 women developed coronary disease. Coronary disease correlated with elevated blood pressure, total cholesterol, LDL cholesterol, and HDL cholesterol (all $P < .001$). The multivariate attributable risk percent associated with total cholesterol over 200 mg/dL was 27% in men and 34% in women. Two concerns are that there is increased risk with low cholesterol (the j-shaped curve) and inconsistent results in the elderly. Cholesterol levels will fall with comorbidity, and thus lack of relationship in the elderly and people with very low cholesterol levels is probably confounded [32]. In a major study in the elderly, the relationship between serum lipids and future events was confirmed [33].

4. Lipid-lowering trials and event rates

There is also no longer reasonable doubt that lowering serum lipids pharmacologically or even surgically [34] will reduce cardiovascular events. This has been shown most dramatically with the series of trials with statins [35–40], but has also been shown with bile acid sequestrants (LRC-CPPT) and niacin, which both lower LDL and raise HDL like fibric acid derivatives [41–44].

The effectiveness of statins has been shown in major subgroups including, women, the elderly, and diabetic patients [45,46]. The effectiveness of statins in the elderly greatly limits concerns of lack of relationship in epidemiologic studies. The fall in event rates matches the fall in serum lipids, as shown in Figure 1 [47]. Although statins may have other effects, they certainly lower LDL cholesterol. The strength and consistency of this finding suggest, although it cannot prove, that this is more than epiphenomenona. The recent Heart Protection study [40] has been particularly instructive because it showed that event rates could be lowered even

in the subgroup with LDL cholesterols below 100 mg/dL. The angiographic trials have not shown much regression, but coupled with modification of serum lipids, have shown decreased events [48,49]. This has suggested that lipid modification may result in plaque stabilization.

The effectiveness of lipid lowering with other interventions reveals that it is not only the nonlipid-lowering effect of statins that confer benefit. In POSCH [34], 838 patients men (90.7%) and women, mean age 51 years, who had survived a first myocardial infarction were randomized to partial ileal bypass or control, with mean follow-up of 9.7 years. The surgery group had a total plasma cholesterol level 23.3% lower (P < .0001), a LDL cholesterol 37.7% lower (P < .0001), and an HDL cholesterol level 4.3% higher (P = .02). Overall mortality and mortality due to coronary heart disease tended to be reduced, but not significantly so (deaths overall 62 vs. 49, P = .164; deaths due to coronary disease, 44 vs. 32, P = .113). The combined end point of death due to coronary heart disease and confirmed nonfatal myocardial infarction was 35% lower in the surgery group (125 vs. 82 events; P < .001). During follow-up, 137 control-group and 52 surgery-group patients underwent coronary-artery bypass grafting (P < .0001).

In the Helsinki Heart study [42], 4,081 men at risk of heart disease with non-HDL cholesterol over 200 mg/dL were randomized to gemfibrozil or placebo and followed for 5 years. Gemfibrozil caused a marked increase in HDL cholesterol and persistent reductions of total, LDL, and non-HDL cholesterol and triglycerides. There were minimal changes in serum lipid levels in the placebo group. At 5 years the cardiac event rate was 2.73% in the gemfibrozil group and 4.14% in the placebo group (P < .02). The decline in incidence in the gemfibrozil group became evident in the second year and continued throughout the study. There was no difference between groups in the total death rate, nor did the treatment influence the cancer rates.

In the VA-HIT trial [44], 2,531 men with coronary heart disease, an HDL cholesterol level of <40 mg/dL, and an LDL cholesterol level of <140 mg/dL, were random to gemfibrozil or placebo. The primary study outcome was nonfatal myocardial infarction or death from coronary causes. At 1 year, HDL cholesterol was 6% higher, triglycerides 31% lower, and the total cholesterol level 4% lower in the gemfibrozil group. LDL cholesterol levels did not differ significantly between the groups. At 5 years a primary event occurred in 21.7% of placebo vs. 17.3% gemfibrozil assigned patients (P = .006). There were no significant differences in the rates of coronary revascularization, hospitalization for unstable angina, death from any cause, and cancer. VA-HIT is important, as it demonstrates that the effect of lipids on heart disease incidence is more complex than a simple relationship to LDL cholesterol.

5. Dietary fat, artherosclerosis, and event rates

Ravnskov's major point is that the epidemiologic studies have not shown much effect of diet on atherosclerosis or event rates. Although this is the major thrust of Ravnskov's argument, the effect of diet on events should be viewed as less important evidence for the lipid hypothesis. This is because this type of study is extremely difficult to conduct. It is difficult to accurately assess diet and difficult to assess differences in diet within a cohort. Diet may also change over time. Response to diet is also quite variable. Lipids in the diet may be confounded by other dietary components, and diet may be confounded by other lifestyle characteristics. In particular, if calories from lipids in the diet are replaced by a greater number of calories from carbohydrates, then the result could be catastrophic. Ravnskov has previously reviewed the epidemiologic studies, ecologic, cross-sectional and cohort, finding little relationship [50]. Despite all the difficulties alluded to above, a dissent to this review was offered by Golomb [51], finding evidence for association within Ravnskov's own review, and also pointing out the difficulties of epidemiologic studies of diet.
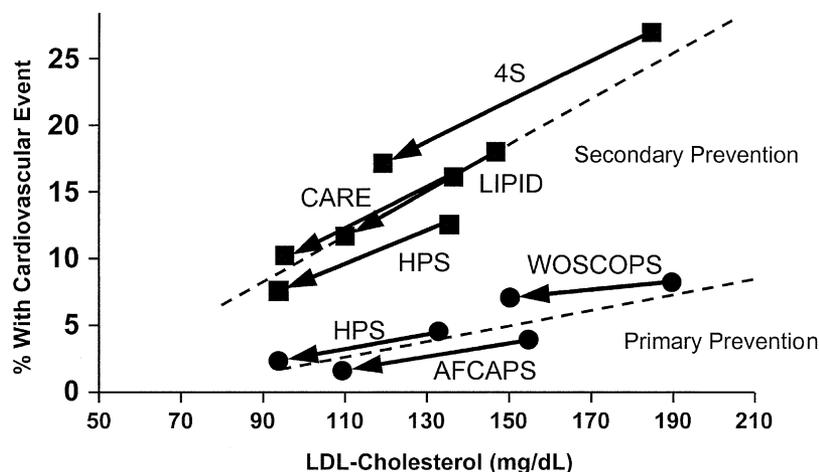

Fig. 1. The relationship between LDL-C and event reduction in the randomized clinical trials of statins, both in primary and secondary prevention.

The decline in coronary heart disease death and stroke death in the United States since the mid-1960s is totally consistent with the reduction of dietary cholesterol, which fell from approximately 500 mg/day to 300 mg/day, and saturated fats from 18% to 11% of calories, respectively, over a 30-year period. Total fats did not decline, but the major change in the American diet was replacement of fat from animal sources (saturated fats) to vegetable sources with their high content of unsaturated fats. Multiple experiments have shown that plasma LDL cholesterol is raised by saturates fats and reduced by unsaturated fats. Dietary cholesterol is more potent is raising LDL in the presence of saturated fats than unsaturated fats.

Although some studies have not shown a relationship of dietary lipids to events, others have. A review conducted jointly by the American Heart Association and the National Heart, Lung, and Blood Institute found a relationship between dietary cholesterol, fats, and subsequent event rates, and provides a detailed if slightly dated set of references in support of this hypothesis [52]. Dietary cholesterol has correlated with cardiovascular events in the Western Electric Study [53]. The Western Electric Study is particularly instructive because dietary habits were systematically evaluated as opposed to other studies with single 24-hr recall. At 25 years follow-up, the relative risk of death from all cardiovascular diseases from the first to fifth quintiles of cholesterol intake (a difference of 184 mg cholesterol/1,000 kcal intake) was 1.46 (95% confidence interval 1.10–1.94) after adjustment for age, intake of other dietary lipids, and other coronary risk factors (including serum cholesterol).

In the Atherosclerosis Risk of Communities Study (54) diet was assessed in 13,148 people by food frequency questionnaire. Carotid wall thickness was measured by ultrasound. After adjustment for age and energy intake, animal fat, saturated fat, monounsaturated fat, and cholesterol were positively related to wall thickness, while vegetable fat and polyunsaturated fat were inversely related to wall thickness. These associations persisted after further adjustment for smoking, hypertension race, and gender.

Fifteen-year follow-up is available from the Seven Countries Study [55]. Of the 11,579 men aged 40–59 years and "healthy" at entry, 2,288 died. Age, blood pressure, serum cholesterol, and smoking explained 46% of variance in death rate from all causes, 80% from coronary artery disease, 35% from cancer, and 45% from stroke. The death rate was positively related to saturated fatty acids, negatively to monounsaturated fatty acids, and unrelated to polyunsaturated fatty acids, proteins, carbohydrates, and alcohol. The death rate was negatively related to the ratio of monounsaturated to saturated fatty acids [55].

In a study of 20 economically advance countries, Liu et al. [56] found that diets high in saturated fat correlate with the incidence of coronary disease. Gillman et al. [57] found that a diet with high fruits and vegetables reduced the risk of stroke among middle-aged men over 20 years of follow-up using the Framingham Study data. An association between dietary lipids and coronary events was noted in younger but not older men from the Framingham study [58]. This study was limited by lipid consumption being assessed by a single 24-hr recall.

Key et al. [59] studied the relationship of dietary habits with mortality in a cohort of vegetarians and other health conscious people (4,336 men and 6,435 women). At 16.8 years follow-up there were 1,343 deaths before age 80. Overall, the cohort had a mortality about half that of the general population. Within the cohort, daily consumption of fresh fruit was associated with significantly reduced mortality from ischemic heart disease [rate ratio adjusted for smoking 0.76 (95% confidence interval 0.60 to 0.97)], cerebrovascular disease [0.68 (0.47 to 0.98)], and for all causes combined [0.79 (0.70 to 0.90)].

Ravnskov's noted several papers appearing since his review [50], noting a relationship between the ratio of polyunsaturated fatty acids to saturated fatty acids (PUFA/SFA) to be predictive of events in one [60] not in another [61]. In the Nurses' Health Study 80,082 women age 34 to 59 without known coronary disease, stroke, cancer, hyper-cholesterolemia, or diabetes were followed for 14 years [60]. Information on diet was obtained at baseline and updated during follow-up using validated questionnaires. A 5% increase in energy intake from saturated fat was associated with a relative risk of 1.17 (95% CI 0.97 to 1.41; P = .10). However, the relative risk for a 2% increment in energy intake from *trans* unsaturated fat was 1.93 (95% CI, 1.43 to 2.61; P < .001), a 5% increment from monounsaturated fat 0.81 (95% CI 0.65 to 1.00; P = .05), and a 5% increment from polyunsaturated fat 0.62 (95% CI 0.46 to 0.85; P = .003). Total fat intake was not found to be significantly related to risk. The negative study that Ravnskov quotes is more nuanced, showing, as in the Nurses' Health Study, an increase in risk with *trans* unsaturated fats [61]. This gets to the difficulty of studying diet, as pointed out by Golomb [51]. The issue of diet and cardiovascular disease is a complex one, making an accurate assessment difficult; inadequate assessment of dietary *cis* vs. *trans* unsaturated fat could result in failure to appropriately assess risk.

Not all polyunsaturated fats may be beneficial [62]. In particular, diets rich in omega-6 fatty acids have not been shown to be associated with lower rates. In contrast, there has been interest for a number of years in assessing whether diets rich in omega-3 fatty acids could reduce cardiovascular events [63]. Fish and other marine life are rich in omega-3 fatty acids, so named because of the first of several double bonds that occur three carbon atoms away from the terminal end of the carbon chain. Diets rich in omega-3 fatty acids lower triglycerides levels [64], while having little effect on LDL cholesterol [65], and do not result in deterioration of glucose tolerance [66]. Diets rich in omega-3 fatty acids may also increase endothelial nitric oxide production [67]. Small studies have shown a beneficial effect of omega-3 fatty acids on blood pressure and endothelial function [68,69]. Furthermore, omega-3 fatty acids also have a beneficial effect on the coagulation profile [70], and have been shown to

have a modest effect in preventing the progression of coronary disease [71].

The benefit of fish oil consumption, which is rich in omega-3 fatty acids, has been generally, although not uniformly, positive. In some studies omega-3 fatty acids prolonged life by decreasing the incidence of sudden death [72,73]. In the physician's health study, Albert et al. [74,75] found that a diet with frequent consumption of fish was associated with a lower incidence of sudden death, although not total mortality. Other reports from the physician's health study did not find a relationship between fish oil consumption and subsequent myocardial infarction [76,77]. The study by Daviguls [78] was more positive. The Chicago Western Electric Study database was used to examine the relation between baseline fish consumption and the 30-year risk of death from coronary heart disease. There were 1,822 men, age 40 to 55 years, free of cardiovascular disease at baseline. Fish consumption, as determined from a detailed dietary history, was stratified (0, 1 to 17, 18 to 34, $\geqslant$35 g per day). During follow-up, there were 430 deaths from coronary heart disease; 293 were due to myocardial infarctions (196 sudden, 94 nonsudden, 3 unclassifiable). For men who consumed 35 g or more of fish daily compared with those who consumed none, the relative risks of death from coronary heart disease and from sudden or nonsudden myocardial infarction were 0.62 (95% confidence interval, 0.40 to 0.94) and 0.56 (95% confidence interval, 0.33 to 0.93), respectively.

6. Trials of dietary intervention

Over 30 years ago the Arteriosclerosis Task Force of the National Heart Institute decided not to conduct a trial of dietary intervention, due to many anticipated problems including the impossibility of blinding and maintaining a constant diet [79]. Nonetheless, clinical trial data have also supported dietary intervention. Although metabolic ward studies can be used to assess the short-term effects of directly varying dietary lipid composition on serum lipid levels, a trial that will be conducted for several years will require a more realistic intervention that cannot be as thoroughly controlled, i.e, diets have to be chosen that people can consistently stay on. In the Diet and Reinfarction Trial [80], 2,033 men recovering from a myocardial infarction were allocated to receive or not to receive advice on each of three dietary factors: a reduction in dietary fat and an increase in the ratio of polyunsaturated to saturated fat, an increase in dietary fatty fish, and an increase in cereal fiber. The advice on fat was not associated with any difference in mortality, perhaps because it produced only a small reduction (3–4%) in serum cholesterol. However, patients advised to eat fatty fish had a 29% reduction in 2-year all-cause mortality compared with those not so advised, independently of 10 potential confounders. Advice on fiber had not significant effect. The 2-year incidence of reinfarction plus death from ischemic heart disease was not significantly affected by any dietary regimen.

In a study from India, Singh et al. [81] randomized patients with acute coronary syndromes to a diet rich in fruits, vegetables, grains, and reduced fat ($n = 204$) vs. reduced fat alone ($n = 202$). Serum lipids and weight fell significantly in the experimental group (cholesterol fell by 0.74 mmol/L vs. 0.32 mmol/:, 95% CI of the difference 0.14 to 0.70, and weight by 7.1 vs. 3.0 kg). The incidence of cardiac events and mortality was lower in the experimental group (50 vs. 82 had events, P < .001 and 21 vs. 38 died, P < .01).

The Lyon Diet Heart Study has been one of the most important studies in this area [82,83]. A total of 423 patients recovering from acute myocardial infarction were randomized to a Mediterranean-type diet (which is rich in the omega-3 linolenic acid) vs. standard care. Assessment of nutritional intake in a subset reveal consumption of fewer calories and a smaller fraction of calories from lipids. There was also a shift from omega-6 to omega-3 fatty acids in the experimental compared to the control group. The primary end point was a composite of death plus myocardial infarction. During just under 4-years follow-up there were 14 events in the Mediterranean diet group vs. 44 in the standard diet group (P = .0001). For a composite of death, myocardial infarction, unstable angina, stroke, heart failure, and pulmonary or peripheral embolism there were 27 events in the Mediterranean diet group vs. 90 in the standard therapy group (P = .0002). In the three trials just reviewed the intervention was just advice on diet.

The other trial of particular importance concerning fish oil was the GISSI prevention study [84]. The investigators studied the effects of these substances as supplements in patients who had myocardial infarction. Between 1993 and 1995, 11,324 patients surviving a recent myocardial infarction were randomly assigned supplements of omega-3 fatty acids, vitamin E, both, or none for 3.5 years. The primary end point was death, nonfatal myocardial infarction, and stroke, with analyses according to a factorial design (two-way) and by treatment group (four-way). Treatment with omega-3 fatty acids, but not vitamin E, significantly lowered the risk of the primary end point [relative-risk decrease 10% (95% CI 1–18) by two-way analysis, 15% (2–26) by four-way analysis]. Benefit was attributable to a decrease in the risk of death [14% (3–24) two-way, 20% (6–33) four-way] and cardiovascular death [17% (3–29) two-way, 30% (13–44) four-way].

Ornish et al. [85] randomized 28 patients to an intervention consisting of low-fat vegetarian diet, stopping smoking, stress management training, and moderate exercise) and 20 to a usual-care control group. One hundred ninety-five coronary artery lesions were analyzed by quantitative coronary angiography. The average percentage diameter stenosis regressed from 40.0 $\pm$ 16.9% to 37.8 $\pm$ 16.5% in the experimental group yet progressed from 42.7 $\pm$ 15.5% to 46.1 $\pm$ 18.5% in the control group.

7. Summary and conclusions

Although intensive dietary interventions such as that proposed by Ornish may dramatically decrease events, less in-

tense dietary interventions may not be beneficial. Thus, the problem with the epidemiologic studies may relate to lack of sufficient variation in diet within a population, confounding, misclassification or a diet that is insufficient to change serum lipids. In fact, it is surprising that a single assessment of diet at baseline would ever reliably predict the development of atherosclerosis years later, as the assessment may be faulty or there may be a change in diet over time [86].

As shown by Brown and Goldstein [87,88], serum lipids are regulated by the LDL receptor. Plasma LDL may be many times higher than necessary to saturate and downregulate the LDL receptor [87,88]. This is also suggested by the effect of statins in preventing events in patients with "optimal" LDL cholesterol [40]. In this setting modest changes in diet will have little effect on serum lipids, and thus none on atherosclerosis. Intensive dietary modification may alter this relationship. This paradigm provides a more complete view of how atherosclerosis develops. Multiple risk factors interact to damage the endothelium. Elevated lipids are central to the development of atherosclerosis. The elevated levels of lipids are related to our contemporary life-style. This can be changed with intensive diet modification in many people, but it is difficult for most people to accomplish. Elevated lipids are related to diet and cause atherosclerosis but will often require pharmacologic measures for control.

This editorial review has been largely concerned with fat in the diet, but what we substitute for fat and how much of it we eat are also of great importance, given the increase in obesity, diabetes, and the recognition of the importance of the metabolic syndrome in the development of vascular disease [89–91]. Indeed, to the extent that diet has changed from higher in fat and lower in calories to higher is carbohydrates and higher in calories, the result has been more obesity, diabetes, and risk of cardiovascular disease [92]. A cautionary note is needed here as well, as it is difficult to disentangle the effects of increased carbohydrates, increased calories, and decreased exercise on obesity.

Establishing a relationship, especially a causal relationship, between diet and cardiovascular disease is difficult. How then do we prove anything? Science rarely advances by deduction from first principles to proof. Rather, science uses inductive reasoning of association. David Hume [93] first pointed out the impossibility of proof of causation by association in the 17th century. Karl Popper [94] addressed this issue, pointing out that science advances by a process of elimination he called "conjecture and refutation." Another point of view, first advanced by Bayes [95], postulates that the probability of a hypothesis being true, given the evidence, depends on the prior knowledge. This type of reasoning even undoes deduction as first principles cannot be known with certainty. Although we must accept that absolute proof is not possible, we should be able to consider that a hypothesis is quite likely. Disproving a proposition is also more difficult than Ravnskov claims. Ravnskov states that "even if many studies were supportive, one single study that

falsifies it and which is based on verifiable observations should suffice for its rejection." This is only true if the "study that falsifies it" followed unquestionable deductive logic, a situation that occurs quite rarely, if ever. What we are left with is the weight of the evidence and being satisfied with fulfilling criteria such as those offered by Bradford Hill. Although Ravnskov challenges us to rethink and better defend the lipid hypothesis, from whatever philosophical approach one takes, in the end the overwhelming weight of the evidence from many types of studies supporting the central role of lipids in general and dietary lipids in particular in the development of atherosclerosis remains thoroughly convincing.

Acknowledgments

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