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Cholesterol does not cause coronary heart disease in contrast to stress

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Abstract
The belief that coronary atherosclerosis is due to high cholesterol from increased saturated fat intake originated from experiments in herbivorous animals. It was reinforced by reports allegedly demonstrating this sequence of events in various populations but ignoring contradictory data. The idea has been perpetuated by powerful forces using similar tactics to preserve the profit and the reputations of those who promote this doctrine. Opponents find it difficult to publish their scientifically supported opinions. The advent of statins has further fuelled this fallacious lipid hypothesis, despite compelling evidence that their effect is not due to cholesterol lowering and that serious side effects have been suppressed and alleged benefits have been hyped. The adverse effects of the cholesterol campaign on health, quality of life, the economy and medical research are inestimable. It is imperative that public health officials, physicians and patients are apprised of proof that it is misguided, malicious and malignant.

Key words: *Cholesterol, LDL, stress*

> "*All truth passes through three stages. First, it is ridiculed, Second, it is violently opposed, and Third, it is accepted as self-evident.*"
>
> *Arthur Schopenhauer*

The presence of cholesterol in human atheroma was first described in 1856 by Virchow. He termed the formation of atheroma *endarteritis deformans* to explain that it resulted from an inflammatory process that injured the intimal lining of arteries, noting,

> "*We cannot help regarding the process as one which has arisen out of irritation of the parts stimulating them to new, formative actions; so far therefore it comes under our ideas of inflammation, or at least of those processes which are extremely nearly allied to inflammation.*" (1)

Osler similarly attributed atherosclerosis as being due to,

> "*the normal wear and tear of life, the acute infections, the intoxications [including smoking, diabetes mellitus, obesity], and those combinations of circumstances which keep the blood tension high*" (2)

Osler's list of CHD (coronary heart disease) risk factors that are still recognized today did not include fatty foods or cholesterol and little attention was paid to cholesterol until Ignatowski fed rabbits large amounts of meat, eggs and milk. He reported in 1909 that this produced macroscopic lesions reminiscent of those seen in human atherosclerosis (3). The following year, Windaus showed that such intimal atheromatous deposits contained 6 times as much free cholesterol and 20 times as much esterified cholesterol compared to a normal arterial wall (4). Anitschkow subsequently demonstrated that the same vascular lesions Ignatowski described could be produced without protein by feeding cholesterol purified from egg yolks to rabbits for 2 or more months and that the earliest lipid laden lesions appeared in the aortic arch and then proceeded caudally (5). However, these deposits did not have the microscopic inflammatory stigmata characteristic of obstructive atherosclerotic plaque in

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humans. In addition, rabbits don't eat meat or eggs, and attempts to reproduce atheromatous lesions in experimental animals that did failed completely. Moreover, cholesterol is a large, inert molecule and it was hard to understand how it could infiltrate the intimal lining of a coronary artery to incite an inflammatory response. As Virchow had originally emphasized, atherosclerotic plaque in humans is a response to inflammation – not the deposition of cholesterol as commonly claimed.

Ancel Keys' seven countries study and the low fat, low cholesterol campaign

Few physicians or researchers in the USA knew anything about Anitschkow or his hypothesis that increased cholesterol intake elevated blood cholesterol, which caused atherosclerosis. Nor was there much interest in this. Coronary heart disease was not a major problem, since prior to the 1920s; heart disease caused less than 10% of all USA deaths. However, by the 1950s this had escalated to over 30%. Ancel Keys, who chaired the first conference of the Food and Agriculture Organization of the UN in Rome in 1951 was curious about this rise in middle-aged men and asked the audience whether this might be due to dietary changes. A University of Naples professor told him that there was no such heart attack problem in his or nearby cities. Keys visited Naples, where he confirmed that there were almost no coronary heart disease patients under the age of 60. The only exception was a small class of wealthy people who dined on meat every day, in contrast to the general population, who only had meat once a week or less and primarily ate pasta, fruits and vegetables. He also found average cholesterol levels to be low, save for the upper class, and concluded that there was an association between a high fat diet, serum cholesterol and coronary heart disease as Anitschkow proposed.

Keys subsequently embarked on his famous Seven Countries Study in healthy middle-aged men that showed a remarkable straight-line relationship between saturated fat consumption, serum cholesterol and deaths from coronary disease. In East Finland, where serum cholesterol averaged over 260, the number of fatal heart attacks per 1000 men over a 10-year period was about 70. In contrast, Japan had less than 5 such deaths, which Keys attributed to the fact that the average cholesterol was about 160. The contribution of saturated fats to the total daily caloric intake in Finnish men was over 20%, almost ten times higher than the 2.5% for Japanese men. Keys concluded that risk of fatal heart attacks was proportional to the blood cholesterol level, which, in turn, was proportional to saturated fat intake (6). This was widely heralded as definitive proof of these causal links, and one leading authority triumphantly proclaimed, "No other variable in the mode of life beside the fat calories in the diet is known which shows such a constant relationship to the mortality rate from coronary or degenerative heart disease".

This produced an avalanche of research in cholesterol-induced atherosclerosis in the mid-1950s that turned the relatively obscure Anitschkow into an international celebrity. In a 1958 *Annals of Internal Medicine* editorial, William Dock, chairman of the department of pathology at Stanford University Medical School, compared his research to Harvey's explanation of how blood circulated through the body and Koch's discovery of the tubercle bacillus (7). Keys, nicknamed "Mr. Cholesterol", was featured on the January 13, 1961 cover of *Time* and his achievements and the tremendous publicity given to his conclusions stimulated numerous attempts to reduce coronary disease by dietary interventions. The Anti-Coronary Club Project, launched in 1957, compared two groups of New York businessmen 49 to 59 years old. One group followed a "Prudent Diet" with corn oil and margarine instead of butter, cold cereal rather than eggs, and chicken and fish instead of beef. A control group ate eggs for breakfast and meat three times per day. The results published a decade later revealed that cholesterol levels of those on the Prudent Diet averaged 30 points lower than the control group eating eggs and meat but there were eight deaths from heart disease in the Prudent Dieters compared to none in the control group (8).

In a further attempt to prove his point, Keys fed middle-aged men a very high cholesterol diet but found that their blood cholesterols were no different than a control group who consumed less than half as much. Twenty years later, he was forced to admit, "There's no connection whatsoever between cholesterol in food and cholesterol in blood. And we've known that all along. Cholesterol in the diet doesn't matter at all unless you happen to be a chicken or a rabbit." None of this was surprising to skeptics, who pointed out that although he had data from 22 countries, Keys had "cherry picked" only 7 in order to prove his theory. Had all the countries been included, the results would have been quite different. Indeed, figures from five others would have led to the conclusion that the more saturated fat and cholesterol consumed, the lower the incidence of deaths due to coronary disease. The statistician, Russell H. Smith, who later reviewed over 2000 references on the link between dietary cholesterol and health, wrote,

"*The word 'landmark' has often been used to describe Ancel Keys' Seven Countries study, commonly cited as proof that the American diet is atherogenic . . . the dietary assessment methodology was highly inconsistent across cohorts and thoroughly suspect. In addition, careful examination of the death rates and associations between diet and death rates reveal a massive set of inconsistencies and contradictions. It is almost inconceivable that the Seven Countries study was performed with such scientific abandon. It is also dumbfounding how the NHLBI/AHA alliance ignored such sloppiness in their many 'rave reviews' of the study . . . In summary, the diet-CHD relationship reported for the Seven Countries study cannot be taken seriously by the objective and critical scientist.*" (9).

The flaws of framingham and failures of MRFIT

The Framingham project was initiated in 1950 by the National Institutes of Health (NIH) in Framingham, a small manufacturing town in Massachusetts near Boston, and is still ongoing. It has had more of an impact on CHD research than any other epidemiological study by allegedly providing the first "solid evidence" that people with a high cholesterol were more likely to have a heart attack and that smoking and hypertension also increased risk. William Kannel, Director of the Framingham Study during the 1960's, told the press that the Framingham results essentially proved that cholesterol was a powerful predictor of CHD. However, this was not supported by data showing that half of heart attacks occurred in people with normal or low cholesterol.

A dietary analysis study in the 1950's found that Framingham participants had widely varying cholesterol levels and concluded that "something explains this inter individual variation but it is not diet." It was never published. A direct association was later reported between falling cholesterol levels over the first 14 years of the study and increased mortality rates over the following 18 years. A 30-year follow-up study in 1987 stated, "The most important overall finding is the emergence of the total cholesterol as a risk factor of CHD in the elderly". No data were presented to support this erroneous claim. Indeed, for men above the age of 47, those with low cholesterol had mortality rates greater than those with high cholesterol. In addition, those whose cholesterol had decreased spontaneously over 30 years were at greater risk of dying from heart disease than those whose cholesterol had increased. "For each 1% mg. drop in cholesterol there was an 11% increase in coronary and total mortality." (10).

Although the study found that a drop in cholesterol was associated with increased coronary deaths, it was cited as supporting the cholesterol-CHD link in *The Cholesterol Facts*, a joint American Heart Association-NIH publication stating that "The results of the Framingham study indicate that a 1% reduction in cholesterol corresponds to a 2% reduction in CHD risk." (11). The real truth about diet and cholesterol came out in a 1992 *Archives Of Internal Medicine* article stating that, "in Framingham, Mass, the more saturated fat one ate, the more cholesterol one ate, the more calories one ate, the lower the person's serum cholesterol". The author was William Castelli, Director of the Framingham study at the time (12).

The MRFIT (Multiple Risk Factor Intervention Trial) was the largest and most serious attempt to prove the links between diet, cholesterol and heart disease based on the Framingham risk factors. Between 1973 and 1976, researchers carefully screened over 350 000 men at high risk of heart disease based on elevated cholesterol, hypertension and smoking cigarettes. From this group, 12 866 healthy men aged 35 to 57 with no history or evidence of heart disease, were randomly assigned to either an intervention group that received treatment or a control group that received usual care. In the treatment group, cholesterol consumption was cut by 42%, saturated fat consumption by 28% and total calories by 21%. Hypertension was reduced by medication and smoking was also curtailed. After ten years, those adhering to this dietary fat restriction had slightly lower coronary heart disease death rates. However, this benefit was far outweighed by significantly increased total death rates, especially from hemorrhagic stroke, cancer, suicide, accidents and violence. In addition, the intervention group, in whom the additional risk factors of hypertension and smoking were also reduced, had mortality rates that were not significantly different from the usual care controls (13). The highest death rates were seen in hypertensives treated with diuretics. Little was said about these negative findings and the findings emphasized the relationship between cholesterol and mortality shown in Figure 1.

The Coronary Primary Prevention Trial, NIH consensus conference and MONICA

What the cholesterol crusaders desperately needed was something to show that lowering cholesterol reduced heart attacks. In 1984, their prayers were seemingly answered with the publication of the Lipid Research Clinics' Coronary Primary Prevention Trial, in which 35–59 year old men with very elevated cholesterols were placed on a low

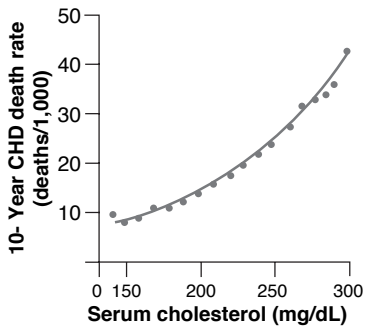

Figure 1. Curve showing the relationship between cholesterol and relative risk of death due to coronary heart disease in over 360 000 men originally screened for participation in MRFIT. This is designed to imply a causal relationship and no data is given for absolute risk. (See subsequent discussion of this frequently used artifice.)

cholesterol and saturated fat diet. Subjects were divided into two groups, one of which took cholestyramine, a cholesterol-lowering drug and the other a placebo. The study allegedly showed that cholestyramine might reduce major coronary events in half of all men with high cholesterols. As a result, the 1984 NIH Consensus Conference on Lowering Blood Cholesterol to Prevent Heart Disease declared that lowering blood cholesterol should be a public health goal for everyone. Its major conclusion, published in the *Journal of the American Medical Association* and widely referred to, was, "It has been established beyond a reasonable doubt that lowering definitely elevated blood cholesterol levels (specifically, blood levels of low density [LDL] cholesterol) will reduce the risk of heart attacks caused by coronary heart disease." (14). In addition, the NIH also established the National Cholesterol Education Program to teach physicians and patients how to diagnose and deal with high cholesterol. All doctors received a kit describing the advantages of cholesterol-lowering drugs, the benefits of a low fat diet, the need to replace butter with margarine and to periodically measure cholesterol in everyone.

All of this was trumpeted in a massive media blitz about the potential to eradicate coronary disease and widely heralded as definitive proof of the lipid hypothesis. The lead article in one cardiology journal was "*The Lipid Hypothesis Is Proven"* (15) and the cover of *Postgraduate Medicine* proclaimed, "*Coronary Disease Prevention: Proof of the anticholesterol pudding.*"

George Mann, Professor of Biochemistry at Vanderbilt and an early Framingham researcher, was appalled at all the hoopla and recommendations and had this to say about the CPPT panel, "They have held repeated press conferences bragging about this cataclysmic break-through which the study directors claim shows that lowering cholesterol lowers the frequency of coronary disease. They have manipulated the data or reached the wrong conclusions. . . . The managers at NIH have used Madison Avenue hype to sell this failed trial in the way the media people sell an underarm deodorant." (16). What he was referring to was that treatment with cholestyramine, a bile acid binding resin, seemed to reduce major coronary events by 19% as shown in Figure 2. But many men stopped taking it almost after the first day and very few were able to take the full 24 g daily. Although there were fewer heart attack deaths, there was no decrease in total mortality, especially from accidents, homicide, suicide and cancer. In addition, only 35–59 year old men with extremely high cholesterols were included. There was no indication that lowering cholesterol in women and men in other age groups without high cholesterols would provide any benefits, or prove to be safe.

As seen in Figure 2, the emphasis was now on LDL rather than cholesterol, and the projection that almost half of all men with high cholesterol would benefit was based on the same flawed conclusions of other studies cited, namely, that for every 1% fall there would be a 2% reduction in coronary disease. You can't prove a statistic by using another statistic, but as Harry Truman noted, "If you can't convince them, confuse them". Benefits refer to lowering "risk" of heart disease, rather than lowering heart disease, and this refers to relative risk rather than absolute risk. Statin manufacturers also use this approach. A study might show that over five years, patients on a statin had 34% fewer heart attacks than controls on a placebo, a 34% relative risk reduction. This implies that taking the drug will reduce your chance of getting a heart attack by more than a third.

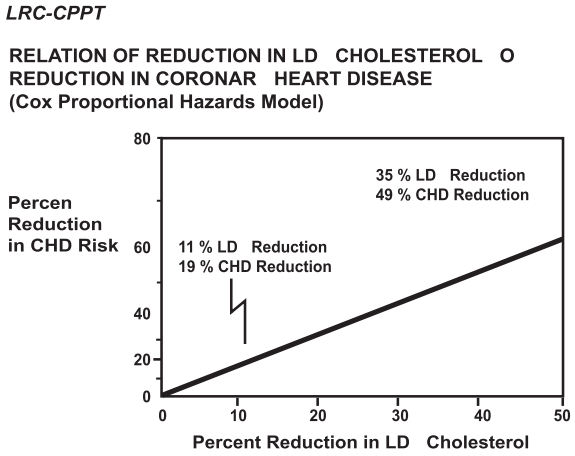

Figure 2. Relationship between decreased LDL cholesterol and reduction of CHD in The Cholestyramine Coronary Primary Prevention Trial. The implication here is that for every 1% fall there would be a 2% reduction in risk of coronary disease, but does not state that this only refers to relative risk.

However, over five years, 2.7% of patients on this statin had a heart attack compared to 4.1% taking a placebo, meaning only a 1.4% absolute risk reduction. The same study shows that if this statin is taken by 71 people every day for five years, it will prevent one person from having a heart attack – but it is not known if that person will be you. Absolute risk reduction and number of patients needed to treat data are rarely given, which is why statin ads always refer to reducing risk (without specifying relative risk). In some countries, this must be followed by a disclaimer stating that this drug has not been shown to prevent heart attacks.

The World Health Organization project MONICA (Monitoring of Trends and Determinants in Cardiovascular Disease), a huge cardiovascular epidemiologic study, assessed 21 countries over 10 years. Results published in 2000 also failed to find any correlation or connection between heart attacks and fat consumption or cholesterol. All the countries in the top eight of saturated fat consumption had lower cardiac mortality rates than all of the eight countries that consumed the least fat. France consumed three times as much saturated fat compared to Azerbaijan but had one-eighth the rate of heart disease deaths. The heart disease death rate in Finland was four times greater than in Switzerland, even though the amount of fat consumed in the two countries was the same. There was also no correlation between the Framingham risk factors of cholesterol, smoking and hypertension and cardiac deaths (17).

Association never proves causation, risk "factors" versus risk "markers", and stress

There are numerous alleged heart attack risk factors, including: a deep earlobe crease, arcus senilis, premature gray hair or vertex baldness, carotid and peripheral vascular disease, living in Glasgow or Eastern Finland, a high saturated fat diet, diabetes, having a pot belly, elevated hemoglobin, excess vitamin D, deficiency of copper, magnesium, or selenium, etc. However, these are merely markers that show some statistical association with heart attacks and in many instances, they simply reflect a common genetic predisposition. Eliminating or correcting them does not reduce heart disease deaths. The same holds true for the standard Framingham risk factors of cholesterol, hypertension and smoking, as demonstrated in the MRFIT study.

There is no single cause of CHD. Coronary atherosclerosis is a multifactorial disorder that is most likely due to sub clinical inflammation that many factors can contribute to, such as chronic infection, homocysteine, increased clotting tendencies and other irritants. It is not generally appreciated that stress is a common denominator for many of these, since stress can:

- Increase homocysteine, C reactive protein and fibrinogen, all of which promote inflammation or coagulation
- Cause coronary vasoconstriction, spasm and increased platelet adhesiveness and aggregation that favors the formation of clots
- Cause increased visceral fat deposits that contribute to insulin resistance, diabetes, elevated triglycerides and other manifestations of metabolic syndrome
- Produce myocardial necrosis in the absence of coronary occlusion by increased secretion of catecholamines at nerve endings in the ventricle

Depression, anxiety, anger, hostility, major life change events, and especially job stress have all been linked to increased coronary events and deaths in scientific studies. Type A behavior is as significant a "risk factor" for heart attacks as elevated cholesterol, hypertension and smoking (18). For what it's worth, stress elevates cholesterol far more than dietary fat intake and also contributes to smoking and hypertension. In contrast to cholesterol, some studies have shown that reducing coronary prone Type A behavior, depression, hostility and anger can help lower cardiac morbidity and mortality. Nevertheless, the cholesterol juggernaut rolls on. A recent review of the ten greatest advances in cardiology in the last century listed Framingham in second place with "Lipid Hypotheses" and Atherosclerosis in third (19).

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