Cholesterol Was Healthy in the End

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The idea that a high intake of saturated fat and a high cholesterol concentration in the blood lead to atherosclerosis and cardiovascular disease emanates from a variety of sources. When considered together, it is understandable that a whole world of doctors and medical scientists have embraced the diet-heart idea and the cholesterol hypothesis, in particular because two of the main supporters, Joseph Brown and Michael Goldstein, have been honored with the Nobel Prize.

According to Karl Popper, a scientific theory is genuinely scientific only if it is possible to create falsifiable predictions; no number of positive outcomes is able to prove a scientific theory, whereas contradictory and reproducible observations show that the theory is false. By this definition, the diet-heart idea and the cholesterol hypothesis indeed satisfy Popper's criteria, because there are a large number of observations that are falsifiable, and indeed have been falsified again and again, as will be shown in the following:

1   A high intake of saturated fat raises blood cholesterol.
2   Cholesterol is a main constituent of atherosclerotic plaques.
3   Premature atherosclerosis is seen in animals with hereditary, or dietary induced, hypercholesterolemia.
4   High cholesterol is a risk marker for coronary heart disease (CHD).
5   People with familial hypercholesterolemia (FH) run a greater risk of dying from CHD.
6   Cholesterol lowering prevents cardiovascular disease.

But it is also obvious that as soon as we start analyzing them, we find that all of them have been falsified again and again. Great problems also arise when we try to explain the pathogenic mechanisms, but let me start by reviewing the most striking falsifications.

The Effect of Saturated Fat on Blood Cholesterol

The idea that saturated fat raises blood cholesterol was originally based on a number of short-term laboratory studies. In a review from 1973, Reiser pointed at several types of methodological and interpretational errors [1]. Instead of natural saturated fat, many authors had used vegetable oils saturated by hydrogenation, and effects on cholesterol were attributed to increased or decreased intakes of saturated fat when it could be due to opposite changes of the intake of polyunsaturated fat.

In spite of these flaws, most authors maintain that saturated fat raises cholesterol, whereas monounsaturated and in particular polyunsaturated fat lowers it, and some saturated fatty acids are neutral [2–7]. These conclusions have been based mainly on mathematical formulas using data from a large number of trials. But as most trial directors have introduced similar types of bias, for instance by changing the intake of several fats at the same time without controlling for intake of *trans* fat, it is obviously difficult to rule out the effect of each type of fat.

No association has been found either in cross-sectional studies between total cholesterol (tC) or low-density lipoprotein cholesterol (LDL-C) and the intake of saturated fat, determined by questionnaires and interviews [9]. Also contradictory is that populations who live almost entirely on animal food have the lowest cholesterol ever measured in healthy people [10–12].

The strongest falsifications come from the controlled, randomized dietary trials. In a review of eight such trials, where the intake of saturated fat was reduced by 30–40%, the net reduction of tC was only 0–4% [13], and in more recent trials, where carbohydrates were substituted with saturated fat, not even intakes between 20 and 50% of calories influenced tC or LDL-C [14–23].

As cardiovascular disease is strongly associated with the concentration of small, dense LDL than with other lipid fractions, it is also contradictory that the intake of saturated fat is inversely associated with LDL size [24].

The Effect of Saturated Fat on Cardiovascular Disease

In a study considered as the strongest argument for the diet-heart idea, Keys selected 16 cohorts in seven countries and found a weak association between intake of saturated fat and the prevalence and 5-year incidence of coronary mortality. But within each country, there were great differences although intake of saturated fat was similar. Coronary mortality for instance was three times higher in Karelia than in West Finland and more than sixteen times higher on Corfu than on Crete [25].

Other epidemiological observations have been just as contradictory. More than twenty cohort studies found no difference between the intake of saturated fat in patients with CHD and healthy controls [9, 26]; and in seven of ten such studies stroke patients had eaten less [27–36].

A relevant objection against such studies is that dietary information is inaccurate. More reliable are analyses of fat tissue, because intake of saturated fat during the last weeks or months is reflected by the concentration of the short chain fatty acids 12:0–15:0 in fat cells [37–41]. Using this method, no difference was found between patients with CHD and healthy controls; in two studies, the content of the short-chain fatty acids was even significantly lower in the patients [42–46], and no association was found with degree of atherosclerosis, determined either by autopsy [47] or by coronary angiography [48]. These studies concerned only patients with first myocardial infarction or patients who were not on a diet, and a diet bias is therefore unlikely.

The most important argument for causality is improvement or disappearance of the disease after a decrease or discontinuation of the exposure to the suspected causal factor. Two meta-analyses of the clinical trials where the only intervention was a change of dietary fat found no effect, either on cardiovascular or total mortality [9, 49, 50].

Angiographic trials have given disparate results. In two studies, progress of the vascular changes was associated with the intake of saturated fat, but both of them were multifactorial, because in addition to lowering the intake of saturated fat, patients in the treatment group were also instructed to eat more fish, fruit and vegetables [51, 52]. In contrast, a highly significant inverse association was found between intake of saturated fat and progress of angiographic lesions in a 3-year follow-up study of 235 postmenopausal women with CHD [53]. No dietary advice was given in that study; instead, the participants' diets were recorded meticulously.

Two randomized, controlled dietary trials have succeeded in lowering both heart and total mortality by changing dietary fat. However, the effect was most likely due to an increased intake of omega–3 polyunsaturated fat, and it concerned sudden death only, not coronary death, and the effect was not due to cholesterol lowering, because no lowering was achieved [54, 55].

The Effect of High Cholesterol on Atherosclerosis

It is true that hypercholesterolemic rodents develop atherosclerosis, but it is also true that although these experimental models have been used for about 100 years, no one has ever been able to produce an occluding thrombus or a myocardial infarction by this method, and there is little evidence, if any at all, that high cholesterol causes atherosclerosis in man. If too much cholesterol should cause atherosclerosis, people with high cholesterol should be more atherosclerotic than people with low cholesterol, and the progress of atherosclerosis in a cholesterol-lowering trial should depend on the degree of cholesterol lowering, but this is not so.

Already in 1936, Landé and Sperry falsified the first prediction. In a study of a large number of healthy people who had died violently, they found that on average those with low cholesterol were just as atherosclerotic as those with high cholesterol [56], and their result has been confirmed by others [57–61]. Weak associations have

been present between blood cholesterol and degree of atherosclerosis in studies of selected patient groups. As these groups mainly included patients with cardiovascular diseases, individuals with FH must have been much more frequent than in unselected cohorts. In accordance, the associations disappeared after exclusion of people with extremely high cholesterol, or the association was inconsistent and present in small subgroups only [62–72] (table 1).

The second prediction is false as well. With a single exception, dose-response between degree of cholesterol lowering and the angiographic changes has not been found in any cholesterol-lowering trial [73]. In observational angiographic studies, no or even an inverse association was found between the spontaneous changes of cholesterol and the degree of progress [74–77].

The Effect of High Cholesterol on Cardiovascular Disease

If high cholesterol leads to CHD or ischemic stroke, people with these diseases should have higher cholesterol than others before the arrival of their disease, and the outcome of a trial should depend on the degree of cholesterol lowering. Also these predictions have been falsified in countless studies.

High cholesterol was found to be a risk factor for CHD for the first time in the Framingham project. However, at the 30-year follow-up, it appeared that high cholesterol was not a risk factor after age 47. Even more contradictory was that both coronary and total mortality was higher in those whose cholesterol had decreased during these years than in those whose cholesterol had increased. 'For each 1% mg/dl drop of cholesterol there was an 11 percent increase in coronary and total mortality' [78]. It is not too farfetched to assume that, being taken care of by the Framingham researchers, most of these people had been on cholesterol lowering treatment, which adds further strength to this falsification.

Since then, numerous studies have shown that for most populations high cholesterol is not a risk factor. They included Canadian men [79], diabetics [80–93], patients with renal failure [94, 95], patients who already had CHD [96–101], and almost all studies have found that it is not a risk factor for women [102] or for old people either [103]. Indeed, old people with high cholesterol live longer than old people with low cholesterol [104–120]. The two last-mentioned falsifications are particularly strong, because at least in Sweden more than 90% of all cardiovascular deaths occur after age 65.

The Effect of High Cholesterol in Familial Hypercholesterolemia

If high cholesterol is the cause of atherosclerosis and early CHD in FH, those with the highest values should of course be at greater risk than those whose cholesterol is only a little higher than normal. This is not so, however.

Table 1. Studies of the association between the concentration of cholesterol in the blood and degree of atherosclerosis at autopsy

Study	Type of investigated individuals	Association between blood cholesterol and degree of atherosclerosis
Landé and Sperry [56]	healthy people who have died from accidents	none
Paterson et al. [57]	unselected group of war veterans	none
Mathur et al. [58]	healthy people who have died from accidents	none
Marek et al. [59]	healthy people who have died from accidents	none if those with very high cholesterol were excluded
Schwartz et al. [60]	unselected hospital patients	none for women, weak for men
Méndez and Tejada [61]	healthy people who have died from accidents	none
Rhoads et al. [62]	a selection of hospital patients	very weak
Feinleib et al. [63]	a selection of dead people	men: very weak women: none
Sadoshima et al. [64]	a selection of dead people	cerebral arteries: none aorta: none in old people
Oalman et al. [65]	a selection of dead people	Black people: none White people: none if those with very high cholesterol were excluded
Sorlie et al. [66]	a selection of dead people	coronary arteries: weak aorta: very weak
Solberg et al. [67, 68]	a selection of dead people	weak
Okumiya et al. [69]	a selection of dead people	weak
Reed et al. [70]	a selection of dead people	large arteries: weak small arteries: none
Reed et al. [71]	a selection of dead people	coronary arteries: weak (tC) cerebral arteries: none (tC) none anywhere for LDL-C

At least eight studies have shown that neither the incidence nor the prevalence of cardiovascular disease is associated with the lipid levels [121–128]; in one of these studies, mean cholesterol was even lower in those who died from CHD [125]. A striking fact is also that in people with FH and severe atherosclerotic changes in their coronary arteries, no changes were seen in the cerebral arteries [129, 130].

That the vascular changes in FH are independent of blood cholesterol was noted even by Brown and Goldstein. In a 1983 paper, they wrote the following: 'Among patients with FH (both heterozygous and homozygous), there is considerable variation in the rate of progression of atherosclerosis, despite uniformly elevated LDL levels' [132].

The number of those who die at a young age from CHD is not very large either. In the Simon Bromee study, the authors followed almost 3,000 individuals with FH for many years and found that their mean life span was similar as for normal British citizens of the same age and sex; more died from heart disease, but fewer died from cancer and other diseases [133].

A possible cause of cardiovascular disease in FH may be inborn errors of the coagulation system. In cohort studies of people with FH, plasma fibrinogen and factor VIII were significantly higher in those with CHD than in those without [134], whereas tC and LDL-C did not differ significantly. Recently, Kastelein's group found that polymorphism in the prothrombin gene is strongly associated with cardiovascular risk in people with this disorder [128]. The reason why statin treatment is of benefit in FH may therefore be their antithrombotic effects, not their effect on cholesterol.

The Effect of Cholesterol Lowering

If high cholesterol causes cardiovascular disease, the most important prediction is that its lowering alone should reduce that risk. Most studies used as support before the statins were introduced were multifactorial. But a meta-analysis of all controlled and randomized cholesterol lowering trials performed before the advent of the statins found no effect on coronary mortality, and total mortality was increased [135].

That cholesterol lowering by the HMG coenzyme A inhibitors is able to lower the risk of cardiovascular disease in high-risk patients is seen as evidence of the cholesterol hypothesis. However, and as mentioned above, no trial has found any association between the degree of cholesterol lowering and the clinical or angiographic outcome; those whose cholesterol was lowered a little only had the same small benefit as those whose cholesterol was lowered by more than 50%. Lack of exposure response means that the statins must have other effects that are more beneficial than cholesterol lowering, as suggested already after the publication of one of the first clinical statin trials [136], and several such effects have indeed been documented.

But even if the lowering of cholesterol by these drugs were unimportant, there should have been exposure response between cholesterol and outcome, because both the pleiotropic effects and cholesterol lowering are caused by the same drug. A more complete blockage of the mevalonate pathway should result in stronger pleiotropic effects and a more pronounced lowering of cholesterol, and vice versa. As this was not the case, the findings imply that high cholesterol is protective and that its lowering therefore counteracts exposure response. There is indeed much support to that interpretation.

Table 2. Studies of the lipoprotein immune system

Study	Microbial product	Source of lipoproteins	Methods used to demonstrate inactivation and/or binding of the microbial products by the lipoproteins
Humphrey [139]	Streptolysin S	man	inhibition of streptolysin S
Stollerman et al. [140]	Streptolysin S	man	inhibition of streptolysin S
Skarnes [141]	LPS *(S. enteritides)*	rodents	immunodiffusion
Shortridge et al. [142]	Togaviruses	man	inhibition of hemagglutination
Whitelaw et al. [143]	*S. aureus* δ-hemolysin	man	inhibition of δ-hemolysin
Freudenberg et al. [144]	*S. abortus equi*; *S. minnesota*	rat rat	crossed immunoelectrophoresis
Ulevitch et al. [145]	LPS *(S. minnesota)*	rabbit	binding of LPS to apoA1
Bhakdi et al. [146]	*S. aureus* α-toxin	man	hemolytic titration; EM
Seganti et al. [147]	Rhabdovirus	man	inhibition of hemagglutination
van Lenten et al. [148]	LPS *(Escherichia coli)*	man, rabbit	inhibition of scavenger receptor
Huemer et al. [149]	herpes simplex	man	EM
Flegel et al. [150]	LPS *(E. coli)*	man	inhibition of endotoxin activation
Cavaillon et al. [151]	LPS *(E. coli)*	rabbit	inhibition of cytokine response
Northoff et al. [152]	LPS (?)	man	inhibition of cytokine response
Superti et al. [153]	SA rotavirus	man	inhibition of viral hemagglutination and replication; EM
Weinstock et al. [154]	LPS *(S. typhi)*	man	inhibition of endotoxin production
Flegel et al. [155]	LPS *(S. typhi)*	man	inhibition of endotoxin production
Feingold et al. [156]	LPS *(E. coli)*	man	endotoxin sensitivity
Netea et al. [157]	LPS *(E. coli)*	mouse	LD50 after experimental infection

See text for more details.

The Lipoprotein Immune System

It is little known that the lipoproteins partake in the immune system. For many years, a normal serum factor, named antistreptolysin S because it was able to neutralize the hemolytic effects of streptolysin S, was considered to be an antibody. In 1937, Todd et al. [137] found that it did not behave as a normal antibody because its titer fell below normal values in patients with rheumatic fever at the peak of the clinical symptoms,

and a few years later, Stollerman and Bernheimer noted that, in contrast to the anti-streptococcal antibodies, the antistreptolysin S titer did not rise above its normal level during convalescence [138]. Humphrey discovered that antistreptolysin S was located within the lipid fraction of the blood [139], and Stollerman et al. [140] identified it as a phospholipoprotein complex. Since then, at least a dozen research groups have established that antistreptolysin S is identical with the lipoproteins and constitutes a nonspecific host defense system able to bind and inactivate not only streptolysin S but also other endotoxins and several virus species as well (table 2) [139–157]. In rodents, the main bulk of cholesterol is transported by high-density lipoprotein (HDL), and in these species HDL has the main protective effect [144, 145], whereas most human studies have found that all lipoproteins participate in the nonspecific defense system.

The immunoprotective role of the lipoproteins has been shown by their inhibition of the biological effects of various microorganisms and endotoxins, such as hemagglutination, hemolysis, the cytokine response of human monocytes, and virus replication (table 2).

That lipoproteins also form complexes with microbial products was shown first by Skarnes [141]. By using immunodiffusion with anti-endotoxin and serum from various rodents that had been injected with *Salmonella enteridis* endotoxin, he demonstrated lipoprotein-positive staining and esterase activity on the precipitation lines. Using crossed immunoelectrophoresis, Freudenberg and Galanos [144] found that the HDL peak of rat plasma changed position after injection with various lipopoly-saccharides (LPS), and Ulevitch et al. [145] found evidence of complex formation between LPS from S*almonella minnesota* and apoprotein A1, the major protein of rabbit HDL.

Bhakdi et al. [146] have documented that human lipoproteins complex with microbial components as well. By electron microscopy (EM), they found that the inactivation of *Staphylococcus aureus* α-toxin by purified human LDL led to oligomerization of 3S native toxin molecules into ring structures of 11S hexamers that adhered to the LDL molecules.

Lipoproteins also form complexes with viruses. Thus, using various techniques Huemer et al. [149] found that all lipoprotein subclasses were able to bind purified herpes simplex virus, as demonstrated by EM, enzyme-linked immunoabsorbance assay technique, and column chromatography. Superti et al. [153] confirmed that all human subclasses of lipoproteins were able to inhibit the infectivity and hemagglutination by SA-11 rotavirus, and complex formation was visualized by EM.

The lipoprotein immune system may be particularly important in early childhood as, in contrast to antibody-producing cells, this system works immediately and with high efficiency. For instance, human LDL inactivated up to 90% of *S. aureus* α-toxin [146], and it inactivated an even larger fraction of bacterial LPS [150]. In agreement with these findings, hypocholesterolemic rats injected with LPS had a markedly increased mortality compared with normal rats, which could be ameliorated by injecting purified human LDL [156]. On the other hand, hypercholesterolemic mice

challenged with LPS or live bacteria had an 8-fold increased LD50, compared with normal mice [157]. That high levels of lipoproteins protect against infectious diseases is also evident from clinical and epidemiological studies.

The Benefits of High Cholesterol

If the lipoproteins have an immunoprotective role, high cholesterol should be an advantage, not a risk factor, and there is indeed many observations in support. Thus, a meta-analysis of 19 cohort studies including almost 70,000 deaths found an inverse association between tC and mortality from respiratory and gastrointestinal diseases, most of which are of an infectious origin [102]. It has been argued that low cholesterol was secondary, but this explanation was disproved by Iribarren et al. [158, 159]. They followed more than 20,000 healthy individuals for 15 years and found a strong inverse association between tC and the risk of being admitted to hospital because of an infectious disease. The association included all types of infection, and it was statistically significant for most of them. As regards respiratory diseases, the association was significant for pneumonia and influenza, but not for asthma. As all of the participants were healthy at the start, it is obvious that their low cholesterol could not be secondary to a disease they had not yet manifested.

There is evidence that subclinical infections participate in chronic heart failure. In accordance, patients with heart failure and low cholesterol run a greater risk of premature death than patients with high cholesterol [160]. Low cholesterol is also a risk factor for HIV and AIDS [161, 162], hepatitis B [163], and for death due to an infectious disease in patients with chemotherapy-induced neutropenia [164].

The protective role of high cholesterol is also evident from observations in people with inborn errors of cholesterol metabolism. For instance, the frequent and severe infections in children with extremely low cholesterol that are found in the Smith-Lemli-Opitz syndrome are alleviated by the addition of cholesterol to their diet [165].

Even in FH, a high cholesterol seems to protect against infections. Thus, before the year 1900, when infectious diseases were the commonest cause of death, the life span of people with a 50% risk of having FH was longer than for other people [166].

Cholesterol and Cancer

Many cohort studies have found that low cholesterol is a risk factor for cancer. The usual explanation is that cancer causes low cholesterol because cholesterol is consumed by the cancer cells. However, in the Framingham project low cholesterol was a risk factor for cancer even after 18 years of follow-up [167], and as mentioned, cancer mortality in people with FH is lower than in the general population. Many

observations are also in better accord with the opposite interpretation that low cholesterol predisposes to cancer.

First, in a review of cholesterol-lowering experiments in laboratory animals, the authors concluded that most studies produced cancer [168]. As this effect was seen also after nonstatin drugs, and as no chromosomal aberrations were noted in the animals, there is reason to suspect that the culprit was not the drugs, but rather their effect, the lower concentration of cholesterol; an interpretation that is supported by epidemiological observations and human experiments.

In 4S, the Scandinavian Simvastatin Survival Study [169], and in HPS, the Heart Protection Study [170], the two first simvastatin trials, nonmelanoma skin cancer was observed more often in the treatment groups. The difference was statistically significant when the results from both studies were combined (in the simvastatin groups, 256 of the 12,490 participants, and in the control groups, 208 of the 12,490 participants; $p = 0.028$). For unknown reasons, the number of nonmelanoma skin cancers has not been reported in any of the trial reports that followed.

The clinical appearance of a cancer depends on its location. Lung cancer, for instance, is not diagnosed until after decades of smoking, whereas superficial nonmelanoma cancers may be observed much earlier. An increased number of patients with skin cancer in a trial is therefore alarming because this is the first cancer type that we should expect to find under conditions of general carcinogenicity.

In CARE, the Cholesterol and Recurrent Events Trial [171], 12 of the 286 women in the pravastatin group but only 1 of the 290 in the placebo group had breast cancer at follow-up ($p = 0.002$). Again, breast cancer is a superficial malignancy that is easier to observe and should therefore occur much earlier than for instance a cancer located in the pancreas. Furthermore, several of these breast cancers were recurrences, and recurrences may appear earlier than primary cancers. However, it is not possible to test the hypothesis that cholesterol lowering by statin treatment may provoke recurrences because after the publication of the CARE report, previous cancer has become an exclusion criterion in all trials.

Dormant cancer is a common finding in elderly people, and a carcinogenic effect should therefore appear earlier in that patient group. Indeed, in the PROSPER trial [172], which included elderly people only, 245 of the 2,891 participants in the pravastatin group but only 199 of the 2,913 in the placebo group had new cancer. The difference was already obvious after 1 year, and it increased steadily during the trial period to become statistically significant ($p = 0.02$) after 4 years. The authors claimed that a meta-analysis of all pravastatin trials did not confirm a carcinogenic effect. This is not reassuring because the mean age in these trials was about 25 years lower than in the PROSPER trial.

In a cohort study of 47,294 Japanese patients treated with low-dose simvastatin and followed for 6 years, the authors found that the number of cancer deaths was significantly higher in patients whose tC at follow-up was less than 160 mg/dl than in those whose cholesterol was 200–219 mg/dl (relative risk = 3.16; 95% CI = 1.72 to 5.81; $p = 0.001$) [173].

Another argument in support of carcinogenicity is a report by Iwata et al. [174], who found that recent or previous statin treatment was seen twice as often in patients with lymphoid cancer compared with patients admitted to the hospital for noncancer diseases. Again, lymphoid cancer belongs to the types of malignancies that are easy to diagnose at an early stage.

Several authors have claimed that statin treatment prevents cancer. However, a bias is introduced by the method used in these studies because in all of them patients on statin treatment were compared with untreated individuals. The first group is a selection of people who initially had high cholesterol, which has been lowered for a few years only; the second is dominated by people who might have had low cholesterol for most of their life and are therefore at an increased risk of cancer.

The Pathogenic Mechanism

Today, most researchers agree that atherosclerosis starts as an inflammation in the arterial wall. What is also common knowledge is that the starting point of the occluding thrombosis is the vulnerable plaque. Therefore, any credible hypothesis must be able to explain how and why the inflammation starts and how a vulnerable plaque is created.

According to the current view, the first step is endothelial dysfunction or damage caused by hypercholesterolemia or other toxic factors in the circulation allowing the migration of LDL-C and monocytes into the arterial wall. Here, LDL is said to be modified by oxidation leading to an accumulation of T cells and the production of LDL autoantibodies. Modified LDL is taken up by macrophages that are converted to lipid-laden foam cells, considered as the early lesion of atherosclerosis. The inflammatory processes, probably aggravated by antigens from microbes such as chlamydia, herpes simplex and cytomegalovirus, are followed by smooth muscle cell proliferation and the synthesis of extracellular matrix. The macrophages may become overloaded and die resulting in the creation of a vulnerable plaque that by bursting initiates the formation of an occluding thrombus [175]. There are a number of contradictions to this hypothesis, however.

There is no association between the concentration of LDL-C in the blood and the degree of endothelial dysfunction [176]; the atherosclerotic plaques seen in extreme hyperhomocysteinemia due to inborn errors of methionine metabolism do not contain any lipids in spite of pronounced endothelial damage [177].

A more likely mechanism is that aggregated complexes formed by lipoproteins and microorganisms or their toxins may occlude vasa vasorum of the major arteries because of the high extracapillary pressure, resulting in local ischemia, liberation of microorganisms that are attached to the complexes and the formation of a microabscess, the vulnerable plaque. Rupture of the latter may result not only in local clot

formation around the rupture, but also in an emptying of the microbial content of the vulnerable plaque into the circulation [178].

Extensive aggregation may occur in severe infections, and it may be furthered by hyperhomocysteinemia, because homocysteine thiolactone, the reactive cyclic anhydride of homocysteine, reacts with free amino groups of protein to form peptide-bound homocysteine [179]. In accordance, in vitro experiments have shown that thiolated LDL becomes aggregated and subject to spontaneous precipitation in vitro [180]. Thiolated and oxidized LDL may also stimulate the formation of anti-LDL autoantibodies [181], furthering complex formation and aggregation.

As macrophages take up aggregated LDL by phagocytosis after modification by vortexing or by digestion with phospholipase C [182], they may do it with LDL molecules modified by complex formation, oxidation or thiolation as well and in this way be converted to foam cells. In support of that, in vitro experiments have shown that LPS from *Chlamydia pneumoniae* [181] and also from several periodontal pathogens [182] is able to convert macrophages to foam cells in the presence of human LDL.

The suggested mechanism explains how cholesterol enters the arterial wall, the many associations between cardiovascular and infectious diseases and the similarities between their clinical and laboratory symptoms and signs, why many bacterial and viral remnants are present in atherosclerotic lesions [183, 184], why neutrophils are found in the vulnerable plaques but not in the stable, fibrous plaques [185], why the temperature of vulnerable plaques is higher than that of its surroundings [186], why leucocytes are found preferably around vasa vasorum [187], and why bacteremia and sepsis are often seen in myocardial infarction complicated with cardiogenic shock [188].

Our hypothesis is open for falsification as well. Viable microorganisms and endotoxins in the arterial wall should be located within developing vulnerable plaques. Arteries of germ-free animals should have fewer foam cells and fatty streaks than their conventionally reared littermates.

A blood culture should be taken in all patients with unstable angina or myocardial infarction, and we anticipate that if it is positive, the course of the disease should be improved with an appropriate antibiotic.

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