THE CHOLESTEROL DELUSION

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A delusion is a false belief held with conviction despite incontrovertible evidence to the contrary. In the medical field no delusion has had wider acceptance and a longer run than the belief that cholesterol levels in the blood are a major factor in the causation of atherosclerosis and its two chief complications - heart attack and stroke.

Known as the Lipid Hypothesis or Cholesterol Theory, the seeds of this delusion were sown in the late 19th century by a German pathologist named Rudolph Virchow. He performed chemical analyses on arterial plaques taken from corpses and discovered that they contained large amounts of cholesterol. He theorized that cholesterol from the blood infiltrated the walls of the arteries and thus caused the plaques he found there. He called this process lipid insudation.

Further credence was given to this theory when researchers in the early 1900s fed rabbits and chickens a pure cholesterol diet and reported deposits on the arterial walls that they thought were atherosclerotic plaques.

At this point it was thought that all the cholesterol in the blood came from the diet. But in 1925 it was found that the human body produces 80-90% of its own cholesterol and that diet is relatively unimportant. This caused some to raise questions about the validity of the Cholesterol Theory.

Unfortunately it took many years for scientific technology to advance to the point where investigators could tell that the arterial lesions found in the cholesterol-fed chickens and rabbits were different from those in true atherosclerotic plaques. In fact they more closely resembled the arterial deposits seen in people afflicted with a rare type of genetic cholesterol storage disorder. Moreover, these lesions did not progress on to ulcerate or fissure and cause thrombotic complications such as heart attack and stroke.

before these facts became known and accepted, a huge boost to the Cholesterol Theory was given by Dr. Ancel Keyes in the early 1950s. He maintained that high fat diets would increase the blood cholesterol and lead to atherosclerosis and its complications.

In his Six Countries Study he correlated the percentage fat in the national diet of six countries with the incidence of death from coronary heart disease (CHD). His graph showed a near perfect correlation between the two. Critics later pointed out that the same data he correlated for six countries was, in fact, available for 22 countries at the time of his study. He picked the six that fit his theory and omitted the 16 that didn't. These included countries with a low percentage fat in their diet and a high incidence of death from CHD as well as those with a high fat diet and low incidence of CHD. It is truly incredible that his studies are still quoted by many people after they have been shown to be virtual textbook examples of how to lie with statistics.

The delusion was further reinforced by publication of results from the Framingham Study in the 1960s. Initiated in 1948 under the auspices of the NIH, this study sought to enroll as many healthy people as they could between the ages of 30 and 62 in the town of Framingham, Massachusetts.

These subjects filled out detailed questionnaires regarding their dietary patterns, levels of

exercise, numbers of cigarettes smoked daily, etc. They were then closely followed to see who died, had heart attacks, or other symptoms of CHD. The collected data were then analyzed to see if there were correlations between certain factors and the subsequent development of CHD.

After about 20 years the investigators felt they had enough data to say that there were significant correlations between high blood pressure, cigarette smoking, and elevated cholesterol levels with the later development of CHD. Thus the concept of "risk factors" for heart disease was established.

But in fact the correlations were quite weak and subsequent analysis has shown that none of the relationships for dietary fat or cholesterol are significantly related to the later development of heart disease.

By this time researchers and academics who were convinced that diet and elevated blood cholesterol were major causes of CHD were firmly in control of the National Heart, Lung, and Blood Institute (NHLBI - a branch of the NIH) and the American Heart Association - the two organizations responsible for the bulk of the funding for heart related research. They felt the time was then ripe for clinical trials to confirm the idea that lowering cholesterol would serve to reduce the incidence of CHD.

The Coronary Drug Project enrolled about 8000 men with a history of heart attack. They were divided into five groups of about 1000 each and a control group of about 3000. Each of the five treatment groups took a different drug and the control group a placebo.

Two of the five treatment groups took different doses of estrogen and the other three thyroid hormone, clofibrate, and niacin. Estrogen was given on the theory that it might be what afforded relative "protection" against heart attack to women while the other three all worked to lower cholesterol by different mechanisms.

Unfortunately, so many excess deaths occurred in the two estrogen groups and the thyroid group that the double-blinded coding had to be broken and the trial stopped prematurely. The clofibrate and niacin treatment groups showed no significant benefit when compared to the control group.

The next major undertaking was the Multiple Risk Factor Intervention Trial (MR. FIT). Over 360,000 healthy middle-aged men were screened and about 12,000 with the highest risk factor profile were selected. Most were heavy smokers, hypertensive, and had elevated cholesterol levels.

The treatment group was given intensive dietary education and advice designed to reduce fat and cholesterol consumption and increase the intake of polyunsaturated fats. Their blood pressures were aggressively treated and they were subjected to a number of interventions to reduce or eliminate cigarette smoking. The control group merely remained on their normal diet and continued their same level of smoking and blood pressure control.

The study was successful in the sense that the treatment group achieved and maintained significant reductions in fat and cholesterol in the diet, cut way down or eliminated smoking, and reduced their blood pressure readings considerably. But after 10 years of followup, there was no significant difference between the two groups in either CHD mortality or total mortality.

Running almost concurrently with the MR. FIT study was a clinical trial that would come to be seen as the one that provided the definitive proof of the Cholesterol Theory. The Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) screened about half a million healthy middle-aged men and selected about 3800 with the highest cholesterol levels.

Half were given cholestyramine, a bile sequestrant resin that lowers cholesterol, and half a placebo. After 10 years the number dying from coronary heart disease (CHD) plus those suffering a non-fatal myocardial infarction (NFMI) were totaled for both groups. The total incidence in the cholestyramine group was 7.0% and the control group 8.6%.

This small difference of 1.6% was reported as a 19% reduction in death and heart attack by using relative risk reduction (the difference of 1.6% is roughly 19% of 8.6) in place of the less misleading absolute risk reduction (1.6%).

Furthermore, this tiny difference was given the designation of "statistically significant" by changing the criteria originally given for determination of significance after the data was in. This statistical manipulation was subjected to a withering critique by a Professor of Statistics in an article published in The Journal of the American Medical Association (JAMA).

The final "evidence" for the efficacy of cholesterol reduction came with the development of the statin drugs in the late 1980s. These drugs reduce cholesterol levels considerably more than those used previously.

A number of clinical trials were carried out with a few different statin drugs. They generally showed small reductions in CHD deaths and in NFMI in those who had a prior history of CHD. But these were never more than a few percentage points in absolute risk reduction. They have shown no benefit at all for those without a history of prior CHD.

But what was most interesting was that those that did benefit showed a total disconnection between the improved outcome and both the initial cholesterol level and the degree of cholesterol lowering attained. Those whose cholesterol level went down a relatively small amount benefited to the same degree as those whose cholesterol declined a lot.

This disconnection is known as "lack of normal exposure-response" and generally means that the factor under consideration is not the true cause of the disorder. It turns out that statins have some anti-thrombotic and anti-inflammatory properties similar to aspirin that may account for the small differences noted. In fact meta-analysis of trials of aspirin and other anti-platelet drugs show about the same degree of "protection" as the statins.

I find most convincing the paradigm described by Dr. William Stehbens who says we must differentiate between two different phases of atherosclerosis. First there is the slow progressive development of atherosclerosis that is an inevitable part of aging and is ubiquitous although varying in the degree of severity among different individuals. This phase plays out over several decades.

The second phase consists of the complications of atherosclerosis - most often heart attack or stroke. These complications are sudden and abrupt events brought about by a disruption in the endothelial lining of arteries.

While the underlying atherosclerosis certainly helps set the stage for the endothelial disruption, it does not provide a satisfactorily complete explanation as many myocardial

infarctions are known to occur in areas where the underlying plaque was quite small.

In other words, we may be talking about two related but otherwise distinct phenomena - the slow evolution of atherosclerosis over a considerable period of time and the sudden development of a vascular complication due to endothelial disruption. Each may have its own distinct causation.

While inflammation may be involved in either one or both I would not recommend statins as therapy. The supposed benefit provided by statins in reduction of non-fatal heart attacks by a few percentage points is no greater than that achieved with other anti-platelet and/or anti-inflammatory drugs. Therefore I would never subject a patient to the potentially severe side effects of statins in order to achieve a questionable benefit that can be provided by drugs of much lower risk.

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David Getoff's note:
It appears that the anti-inflammatory benefits of Cod Liver or Fish oils (coupled with Unique E™ to protect these oils) would give far more risk reduction without any potential side effects. I recommend a tablespoon of Carlson's cod liver oil per day. Adding adequate vitamin C with each meal also has sufficient research in reducing the oxidized cholesterol formation, I usually recommend 1000mg with each meal for my patients