The Cholesterol Myths

Exposing the Fallacy that Saturated Fat and Cholesterol Cause Heart Disease

by Uffe Ravnskov, MD, PhD

Foreword

by Michael Gurr, PhD

Whether diet plus plays a major role in heart disease is a question that interests us all. Author Ravnskov has a mission. To inform his readers that there is a side to this question other than the view usually presented to us.

Government and health authorities never tire of remaining those of us who live in industrialized countries that heart disease is a major cause of death. They go further and tell us that heart disease is eminently preventable. While conceding that genetic background interacts with numerous environmental factors to influence each individuals risk of succumbing to heart attack, they insist that diet is foremost among these factors as a cause of heart disease, and that modifying diet provides a straightforward means of preventing heart attacks. If only people would do what they are advised—reduce their intake of fats, especially those rich in saturated fatty acids—then the high toll of death and disability from this disease could be readily reduced. If only!

What is the scientific basis on which this advice is based? Although the many reports of "expert committees" acknowledge that diet may influence the underlying pathology of heart disease in several ways, current "dietary guidelines" are based mainly on what Dr. Ravnskov calls "the diet-heart idea." Greatly simplified (which it normally is!), this idea proposes that dietary fats rich in saturated fatty acids raise the concentration of cholesterol in the blood. This in turn is involved in the initiation if arteriosclerosis, which through its restriction of blood flow to the myocardium and its tendency to generate thrombi, leads to myocardial infarction.

Dr. Ravnskov's contention is that the diet-heart idea is built on sand. He leads us through the history of the concept in an interesting and readable way. His writing clearly demonstrates the enormous depth and range of his reading on this subject. Step by step he examines the evidence for the diet-heart idea, and step by step he shows us how that evidence may be flawed and contradicted by other research that is rarely acknowledged and quoted.

Medical science has generally been highly regarded by the public, who have rarely questioned its findings because it is perceived as helping to improve mankind's lot. It will come as a surprise to many readers to learn how many studies of diet and heart disease were poorly designed and conducted, how many did not produce the results that have been claimed for them and have been quoted irrelevantly or misleading, and how many published studies exist whose results seriously question or contradict the diet-heart idea but are never acknowledged or quoted. Some of these tactics are not only misleading but also sometimes amount to scientific fraud.

Dr. Ravnskov is well qualified to write such a book. He is a general practitioner who regularly needs to advice patients who have heart disease or who are worried that they might have it. The book begins with an insight into problems of one such patient, an otherwise healthy woman who began to worry after a company health screen revealed that she had high cholesterol and who was told by the company medical officer that she might have a heart attack in five years if she didn't do anything. Dr. Ravnskov and many like him are concerned that public health messages

based on poor science may not only be ineffective but also may cause unnecessary worry to people who were previously free of health cares.

As well as conducting his medical practice, Dr. Ravnskov is also a scientist who has published a number of papers, including some penetrating analyses of the diet-heart literature. He is one of a growing number of scientists who have found what they have read disconcerting.

Why do we hear so little about this alternative view? Few scientists seem willing to stand up and question what has been accepted dogma? Dr. Ravnskov lists a few at the end of his book and outlines their views and credentials. Most are, like the author, individuals with inquiring minds who are not directly involved in heart disease research. Some, however, have been eminent researchers into heart disease; their firm stand against conventional has often alienated them from the establishment community. By contrast, many who support the consensus view have made their reputations in this view, have been supported by research grants often amounting to millions of dollars and have a vested interest in continuing to support and sustain the diet-heart idea.

Another dimension is this story that Dr. Ravnskov discusses is the approach to lowering cholesterol by drugs, which has almost always been more effective than diet. The cholesterol story, therefore, has the backing of the multimillion-dollars drug industry. While this backing is not reprehensible to itself, the distinction between the ability of drug and dietary treatment to lower blood cholesterol has often become so blurred that lay people are frequently confused into believing that dietary modification could achieve exactly the same effect as drug treatment when it clearly cannot. Alternatively, many may be persuaded that they need drugs when clearly they do not.

Quite apart from showing us the flimsiness of the scientific evidence upon which dietary advice to prevent or reduce heart disease is based, Dr. Ravnskov also addresses an even more serious problem. Could attempts to reduce cardiovascular mortality by lowering blood cholesterol actually do harm? Several authors have reflected that it might and have cited the evidence. To this end, Ravnskov discusses the worrying observation that even when cardiovascular deaths have been reduced in some intervention trials, subjects died of other causes—sometimes cancer, sometimes suicide or other forms of violence—resulting in no overall change in death rate. Many "expert" committees reviewing this evidence have tended either to ignore this phenomenon or have argued that it can safely be disregarded, but the admonition "do no harm" comes back to haunt us.

Many with establishment views will regard Dr. Ravnskov as a crank. That would be a grave mistake. He has done his homework, he is not a lone voice in the wilderness, and he deserves to be taken seriously. Above all, this book will make us all think more deeply about the true role of diet in heart disease and about the quality of the information that we receive.

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Author's Foreword

When the cholesterol campaign was introduced in Sweden in 1989 I became much surprised. Having followed the scientific literature about cholesterol and cardiovascular disease superficially I could not recall any study showing a high cholesterol to be dangerous to the heart or the vessels, or any type of dietary fat to be more beneficial or harmful than another one. I became curious and started to read more systematically.

Anyone who reads the literature in this field with an open mind soon discovers that the emperor has no clothes, and so did I. But I also learned that the critical analyses or comments, that I sent to various medical journals, were most often met with little interest from the editors and mocking answers from the reviewers. Besides, the inaccuracies, the misinterpretations, the exaggerations and the misleading quotations in this research area were so numerous that to question them all demanded a book.

The first edition was published in Sweden 1991and in Finland 1992. The books made little impact. In Sweden the science journalists usually lost their interest in the subject when they, after having read the book, consulted the researchers or health authorities that I had criticised. In Finland the book was put on fire in a television show on channel 2 after having been belittled by some of the Finnish proponents to the cholesterol campaign.

The uncritical introduction of the cholesterol campaign in Sweden was most probably due to its promotion by large American health and research institutions such as the National Heart, Lung and Blood Institute and the American Heart Association and their influential members. Evidently, the Swedish health authorities must have thought that such prestigious authorities could not be wrong. But Sweden and Finland are small countries. I thought that, maybe I could reach more critical and independent journalists and researchers by publishing the book in English. Several years of searching among editors and literature agents was unsuccessful, however; the book was considered of no commercial interest.

With the advent of internet I saw a way to inform the public and in 1997 I published selected sections of the book on the web. According to the search engine Direct Hit my website soon became one of the top ten most popular sites about cholesterol and from email letters I learned that many laymen and researchers were just as skeptical to the cholesterol campaign and the diet-heart idea as I, or at least they became skeptical after having read my website. One of the responders was the author and publisher of Nourishing Traditions, Sally Fallon. As an academic nutritionist she had reached to similar conclusions as I and asked if she might publish my book.

All researchers are standing on the shoulders of their predecessors and so do I. Hopefully, I have paid credit to most of them in the book. But there are other important individuals that have contributed to this book in some way or another. First of all I would like to thank Bodil Jönsson and Olof Holmqvist for their many ingenious comments to the first draft. I am also greatly indebted to Linda Newman for her tremendous and unselfish work changing my first, broken translation of the Swedish edition to good English. At a later stage, when I had destroyed some of Linda's good work by updating and revising the text, Sally Fallon repaired the damage. I would also like to mention here Lars Werkö who has given me invaluable support and encouragement through the years.

The following individuals have been important in various ways, either by giving me valuable, critical comments to the various drafts or simply by showing me their qualified appreciation of my work. The list includes, in alphabetic order, Poul Astrup, Jonas Bergström, Christer Enkvist, Michael Gurr, George Mann, James McCormick, Peter Nilsson-Ehle, Robert E. Olson, Eskil Richardson, Ray Rosenman, Kari Salminen, the late Petr Skrabanek, Lars Söderhjelm, and Nicolai Worm.

Last, but certainly not least, this book would never have been written without the patience and encouragement of my wife Bodil.

Introduction: The Diet-Heart Idea: A Die-Hard Hypothesis

The great tragedy of Science—the slaying of a beautiful hypothesis by an ugly fact.

Thomas Huxley (1825-1895)

Did you know…

- Cholesterol is not a deadly poison, but a substance vital to the cells of all mammals?
- Your body produces three to four times more cholesterol than you eat?
- This production increases when you eat only small amounts of cholesterol and decreases when you eat large amounts?
- The "prudent" diet, low in saturated fat and cholesterol, cannot lower your cholesterol more than a small percentage?
- The only effective way to lower cholesterol is with drugs?
- The cholesterol-lowering drugs are dangerous to your health and may shorten your life?
- The cholesterol-lowering drugs, called statins, do lower heart-disease mortality a little, but this is because of effects other than cholesterol lowering? Unfortunately, they also stimulate cancer.
- You may become aggressive or suicidal if you lower your cholesterol too much?
- Polyunsaturated fatty acids, those which are claimed to prevent heart attacks, stimulate infections and cancer in rats?
- If you eat too much polyunsaturated oil you will age faster than normal? You will see this on the outside as wrinkled skin. You can't see the effects of premature aging on the inside of your body, but you will certainly feel them.
- People whose blood cholesterol is low become just as atherosclerotic as people whose cholesterol is high?
- More than thirty studies of more than 150,000 individuals have shown that people who have had a heart attack haven't eaten more saturated fat or less polyunsaturated oil than other people?
- Old people with high cholesterol live longer than old people with low cholesterol?
- High cholesterol protects against infections?
- Many of these facts have been presented in scientific journals and books for decades but proponents of the diet-heart hypothesis never tell them to the public?
- The diet-heart idea and the cholesterol campaign create immense prosperity for researchers, doctors, drug producers and the food industry?

A sorry story

Karla didn't know it.

Karla and I live in the southern part of Sweden, a prosperous country where nobody needs to starve. If anything, overweight is a problem for many people.

In Sweden people grow old; the people of Sweden enjoy one of the longest life spans in the world. Therefore, heart disease is a common cause of death simply because heart disease is a disease of old age. But man is never satisfied, and great efforts are made to prolong life. One of these efforts is to determine which people have high cholesterol because scientists say that lowering cholesterol may prevent heart disease and give you a longer life. When you have read this book you will know that nothing could be more wrong. But first let me tell a little more about Karla.

Karla has been my patient for several years. On her occasional visits, she had always been cheerful and optimistic.

Now she is tired and depressed, not at all the way she used to be.

Karla is sixty-two. She works as a cleaner in the offices of a large factory. Two years ago the doctor at the company called all employees in for a medical checkup.

“Your cholesterol is too high,” he told her. “There is a great risk that you will have a heart attack within five years if you don’t do anything about it.”

“I felt fit as a fiddle, but he scared me to death,” Karla told me. She doesn’t feel fit any longer.

Karla was sent to the medical clinic at the nearest hospital where the doctor told her to go on a diet. Karla loves to eat and to prepare good food. According to her husband, Karla’s homemade sausages and cheese-cake are famous in their village.

But now they eat mostly vegetable oil and high-fiber foods. When they buy a steak for a special occasion, they cut off all the fat.

“And that’s the tasty part,” Karla sighed. “If only the diet had lowered my cholesterol, but it didn’t.”

“Diet is not enough,” the doctor said. “You also need pills.”

Karla hated the diet, but it was nothing compared to the drug.

“You have to stand a little discomfort,” the doctor told her.

The diet made it easy to slim down, and what was left of her appetite disappeared completely when she started the nauseating medication.

Add to this the demise of her positive attitude. She had looked forward to retirement with her husband, but now all seemed bleak. She felt she had nothing to look forward to.

Her cholesterol went down but not enough, the doctor said, and the dietician looked at her with great skepticism when Karla told her what she ate.

“It’s impossible. You must have eaten more fat than that,” the dietician scolded.

In fact, Karla had eaten some cheesecake the day before, but it hadn’t been a pleasure; she felt terribly guilty afterwards.

Do you think that Karla is unique? Let me tell you about the result of a health project in Luleå, Sweden, headed by Birger Grahn, one of the general practitioners in the district. The aim of the study was to lower the incidence of coronary heart disease. Participants were sent a computerized letter containing a description of their "health profile." Afterwards Birgitta Olsson, a social scientist, questioned one hundred of the recipients.

Twenty-six of these healthy individuals said the letter frightened them. "It was like a shock," or "as if the world collapsed," some of them answered. One stated that she was "almost paralyzed."

Those with high cholesterol were the most frightened. "The risk that you will have a coronary in five years is estimated to be considerably higher than the average risk for inhabitants of Luleå of the same age and sex as you," the letter said.

When Birgitta Olsson asked again half a year later, after all the health-promoting activities had started, a further thirteen suffered from anxiety.[1]

You may think that anxiety about cholesterol is something peculiar to the Swedes, but that is not the case. According to a recent Gallup poll in the United States, 56 percent of all Americans worry about fat and cholesterol, 45 percent think that the food they like is not good for them, and 36 percent have guilt feelings when they eat the food they like.

Apart from the fact that worrying about your health may provoke heart trouble, all this stress and anxiety are unnecessary. Karla and millions of others around the world with high blood cholesterol do not know that the cholesterol campaign is medical quackery of the first order. In fact, the eminent American physician and scientist George Mann called the diet-heart idea "the greatest scientific deception of this century, perhaps of any century."

Unfortunately, Karla and millions of others do not know that high blood cholesterol is nothing to worry about.

This book has been written to give you and your doctor some facts about cholesterol and coronary heart disease. They are facts that even your doctor may not know because these facts have been misunderstood; or because many scientists, health authorities and representatives of the drug companies have suppressed them altogether.

To begin, let me tell you a little about how scientists work.

The scientific method

To bring a little order into a chaotic and hostile world, we try to find the laws that govern the "mess" that we observe. Medical researchers want to discover the threats against human life and health, and to know what causes disease and premature death, in order to cure or prevent these problems. To this end, we have developed a laborious but highly successful technique called the scientific method.

When we use the scientific method, the first step is to record all the facts about a disease. Who are the victims—men or women, young or old? How do they live and what do they do for a living? What do they eat and drink? What is the chemical makeup of their blood? How clean or

dirty is the air they breathe? Scientists meticulously weigh, measure and analyze anything that may be of importance.

Every new piece of the puzzle leads us to speculate about the causes of the disease and to formulate a hypothesis—a theory that we must prove. To see if our hypothesis is correct, we test it in all possible ways. Is some factor present in all cases of the disease? Can the disease be produced by this factor, and can we prevent or cure the disease if we eliminate the factor?

If it doesn't pass all the tests, then our hypothesis is wrong and must be rejected. Then we construct a new hypothesis that we hope will conform better to reality. We test and observe again. If necessary—and it often is necessary—we reformulate our hypothesis and repeat our tests a third and fourth and fifth time until, at last, we have a little nugget of pure truth in our hands. True scientists put the solution to a medical problem first and not the preservation of their own hypothesis, no matter how clever the hypothesis may seem or how proud of themselves they may be for creating it.

Scientists know that it is very rare for their first inspired thought to solve a scientific problem. Therefore, in our search for solutions, we scientists are as much interested in test results that destroy our hypothesis as we are in results that confirm it. And we do not blame anybody for a bad idea, providing that it is abandoned as soon as its flaws become obvious.

Defining our terms

This book is about the idea—the false idea—that a high level of cholesterol in the blood is the main cause of atherosclerosis and coronary heart disease. But what is atherosclerosis? And what is coronary heart disease?

When we grow old our arteries become stiff. The smooth muscle cells and the elastic fibers that surround our blood vessels when we are young are gradually replaced by more or less fibrous and rigid tissue. At the same time, or later on, cholesterol, various fats and even calcium become embedded in the blood vessel wall.

Arteries probably become stiff as a protective measure, to prevent the pressure of the blood inside them from causing them to widen too much. Thus, the remodeling of the arteries does not occur evenly. It is most pronounced where the strain to the artery wall is highest, for instance, where the blood vessels branch. Such localized thickening is called an atheroma or plaque. Atherosclerosis increases with age, as does the blood pressure, and atherosclerosis is most pronounced in individuals with high blood pressure.

The fact that arteries that are prevented from widening, such as those that pass through the bony channels in the skull and the few branches that pass through the heart muscle (most branches lie on the surface of the heart), never become sclerotic also suggests that stiffening of the arteries may be a protective measure. Furthermore, veins never become sclerotic, probably because the blood pressure in veins is very low. If a surgeon replaces a clogged artery with a section of vein, however, this vein, now exposed to the high arterial blood pressure, soon becomes sclerotic.

For unknown reasons, in some people the embedding of cholesterol in the arterial wall becomes irregular and protrudes into the interior of the artery. Sometimes these localized protrusions, called raised lesions, even change into a material similar to limestone. The embedding of

cholesterol and lime may also progress until the vessel becomes so narrow that the heart gets too little blood and thus too little oxygen. These constrictions were considered to be the cause of heart attacks, either directly, or by starting the formation of a clot.

When the blood flow to the heart becomes insufficient, symptoms of discomfort radiating from the chest may result, especially if the heart's need for oxygen is increased during exercise. These symptoms are called angina; they disappear if you stop exercising. But if the blood flow is totally arrested, or if it is reduced too much for too a long time, the part of the heart that is supplied by the obstructed branch of the artery will die. This is called a heart attack, or a coronary, or, more precisely, a myocardial infarction. Angina and myocardial infarction taken together is what we call coronary heart disease, often shortened to CHD.

Atherosclerosis is said to be the cause of coronary heart disease, but the matter is not that simple. Anything that obstructs the coronary arteries may produce coronary heart disease. Studies of the hearts of people who have died from a heart attack have revealed that in about a fifth of the patients there is no evidence of coronary atherosclerosis. The arrested blood flow in such cases may have been due to a spasm of the artery, or to a clot that dissolved before death, but we don't know for sure.

To further complicate the story, a coronary artery may be totally obstructed without any symptoms and without any damage to the heart. The explanation is that the fine branches of the three coronary arteries communicate with each other. If blockage of an artery develops slowly enough, the communicating branches gradually widen, allowing the neighbor to carry more of the blood supply.

Thus, a myocardial infarction may occur even though the coronary arteries are totally normal, and coronary heart disease may be absent even though the coronary arteries may be completely blocked. Obviously, atherosclerosis and coronary heart disease are separate conditions, but many researchers have confused our thinking by considering them as one.

The Diet-Heart idea

In the search for the causes of atherosclerosis and heart disease, researchers since the early 1950s have focused on a single hypothesis or idea. This is the diet-heart idea, sometimes called the lipid hypothesis. As I will explain in this book, the diet-heart idea is a hypothesis that has not passed the basic scientific tests, a hypothesis that is filled with obvious absurdities.

The diet-heart idea is not scientifically sound, but it survives. In fact, the diet-heart idea is hopelessly incorrect, but it seems to have eternal life. It lives on because the researchers who created it and defend it—I will call them the proponents—have not followed the principles dictated by the scientific method.

Those principles demand open-mindedness and objectivity, but the proponents of the diet-heart hypothesis routinely belittle, deny or explain away any scientific observations that contradict their idea. They take the weakest association that supports their idea and call it strong evidence, and they refuse to consider any conflicting observation. In the process, logic becomes as remote as a town in Siberia. Proponents of the diet-heart idea often ask, "What is wrong?" but when they ask this, they mean what is wrong with the conflicting evidence and not with their pet hypothesis. Masses of valid scientific evidence should have destroyed the diet-heart idea by now.

Yet, like the ancient Greek Hydra, a mythological monster that grew new heads whenever its old ones were chopped off, the cholesterol Hydra continues its life as if nothing had happened.

But before we look at evidence that should destroy the diet-heart idea, let's first consider what that idea is.

According to diet-heart proponents, coronary heart disease is the third and final step of a three-step process. In the first step, or so the proponents claim, the amount and the type of fat in our diet determines the level of cholesterol in our blood. They say that if we eat an atherogenic diet, our blood cholesterol will be high. And by an atherogenic diet they mean a diet containing too much cholesterol and saturated fat (found mainly in animal products, such as meat, milk, eggs but also in palm oil and coconut oil) and too little polyunsaturated fat (found mainly in marine animals and commercial vegetable oils). According to the proponents, step two occurs because high blood cholesterol is the main cause of atherosclerosis. And in step three, or so the proponents claim, atherosclerosis causes coronary heart disease by blocking the blood vessels of the heart. The idea sounds simple, and most of us are familiar with it after reading about low-fat recipes and low-fat diets for years in popular magazines and newspapers.

At first glance, the diet-heart hypothesis does indeed appear simple, logical and well founded. It is also an attractive idea, because it almost promises that death from coronary heart disease can be prevented. If animal fat and high blood cholesterol are the villains, then cholesterol-lowering diets and cholesterol-lowering medicines appear to be wise choices. It's easy to understand why doctors, politicians, pharmaceutical companies and the manufacturers of vegetable oils and low-fat frozen dinners have embraced the diet-heart idea.

But very few people know that it is built on nothing more than circumstantial evidence. Nobody has ever seen the villains in action. There are many diseases that we have explained from circumstantial evidence but only when all the evidence has pointed in the same direction. As for the diet-heart hypothesis, the evidence is contradictory and confusing. In fact, huge numbers of published medical studies reveal results that are totally at odds with this idea.

For many years, millions of people have endured a tasteless, tedious diet or have suffered serious side effects from cholesterol-lowering drugs because of the diet-heart idea. And billions of dollars have been spent in vain because previous research, reviewed in the chapters to come, had already demonstrated the diet-heart hypothesis to be completely worthless.

Medical experts and health authorities will criticize this book and its author because their prestige is at stake. They will probably describe the author as unscientific or incompetent, and they will say that prestigious committees all over the world have decided that the diet-heart idea has been proved beyond all reasonable doubt.

This book is written for people who can think for themselves. And if you find that something I have written seems too incredible, please consult the references. Then go to a university library and read the original papers yourself. By doing this systematically, as I have done, you will not only see that I am correct, but you will also learn more about cholesterol and the heart than most researchers have. Judging from their papers, many of those researchers seem to have read only reviews, and reviews written by the proponents are notoriously unreliable. In the chapters to follow, I shall give you many examples of misquotations from such reviews.

One of my objections to the diet-heart idea is that its proponents are selective about their data. They lean on studies that support their idea—or that they claim, not always truthfully, support it—and ignore those that contradict them.

One of the proponents once accused me of pointing only to studies that do not support the diet-heart idea and, thus, of using a technique similar to the one the proponents use.

He was right.

What he failed to remember is that, if a scientific hypothesis is sound, it must agree with all observations. A hypothesis is not like a sports event, where the team with the greatest number of points wins the game. Even one observation that does not support a hypothesis is enough to disprove it. The proponents of a scientific idea have the burden of proof on their shoulders. The opponent does not have to present an alternative idea; his task is only to find the weakness in the hypothesis. If there is only one proof against it, one proof that cannot be denied and that is based on reliable scientific observations, the hypothesis must be rejected. And the diet-heart idea is filled with features that have repeatedly been proven false.

The history of science is one in which many attractive ideas have been discarded when found to conflict with observed fact. For instance, the earth was considered to be a flat planet around which the sun and the other planets revolved. Anyone could ascertain this by looking at the horizontal skyline. And, with his own eyes, anyone could see how the sun, like the moon, circled around the earth.

Our ancestors did not know better because they had only the naked eye and lacked the technology needed to discover the truth. But the proponents of the diet-heart idea ought to know. Instead, their cocksure writings demonstrate that for them the idea has become a fact, the cholesterol earth is flat.

Or is it only a game? Those of you who read this book will realize that scientists who support the diet-heart idea and who are honest must be ignorant, either because they have failed to understand what they have read or else, by blindly following the authorities, they have failed to check the accuracy of the studies written by those authorities. But some scientists must surely have realized that the diet-heart idea is impossible and yet, for various reasons, have chosen to keep the idea alive.

In both politics and religion, ideas can be more powerful than any army. In medicine, ideas can also have powerful consequences.

Let us now explore a medical hypothesis, the diet-heart idea, which, although it seriously conflicts with the laws of logic, has dominated scientific thinking for many years—with many unfortunate consequences.

Myth 1: High-Fat Foods Cause Heart Disease

Some circumstantial evidence is very strong, as when you find a trout in the milk.

Henry David Thoreau (1817-1862)

A challenge

In 1953 Ancel Keys, director of the Laboratory of Physiological Hygiene at the University of Minnesota published a paper, which, looking back seems to have been an early kick-off for the cholesterol campaign.[2]

The horizon for the US Public Health Service is too limited, he wrote; any major disease should be prevented, not only those of infectious or occupational origin.

It doesn't matter that the necessary measures are not yet known. The mere hope that the incidence of a disease may be altered is sufficient reason to invest money and manpower.

What Dr. Keys had in mind was coronary heart disease. This disease is a threat, he continued. While all other diseases are decreasing in the United States, there has been a steady upward trend in the death rate from coronary heart disease. On this particular point the Americans are inferior to other countries; in the US, for instance, four to five times more die from a heart attack than in Italy.

Dr. Keys's reservations regarding the preventive measures were mere rhetoric; he already knew what to do. He considered a defeatist attitude about coronary heart disease despicable. According to Dr. Keys it was "abundantly clear" that heart attacks could be prevented. And he knew the preventive measures. What was possible for the Italians should be possible for Americans also, he added, "These figures are a challenge."

Remember that Dr. Keys was directing these words to Americans, a proud people for whom the word aggressive is a word of honor, in health care as in other matters. In the US more diagnostic tests are made than in any other country; surgery is preferred over drugs, and when drugs are chosen high doses and strong preparations are used.[2] Ancel Keys's words did not go unheeded either.

According to Dr. Keys, fat food was the culprit. His proof was a diagram, which showed that the intake of fat food and the death rates from coronary heart disease followed each other closely in six countries (fig. 1A). The points of the diagram lay as on a string, so that the curve he had drawn looked more like the result of a physical experiment than a biologic relationship. If you prolong the curve at the left it intersects the origin (= the intersection of the axes), thus suggesting that if you avoid fat food completely you will never have a coronary. Wrote a commentator in *The Lancet* the following year, "The curve shows an almost convincing relationship between the fat content of the food and the risk of dying from coronary heart disease."

But why did Dr. Keys use the figures from six countries only? At that time information was available from 22 countries and if all of them were included the association was in fact rather

weak. For instance, the death rate from coronary heart disease in some countries was 3-4 times higher than in countries where the consumption of fat was the same (fig. 1B).

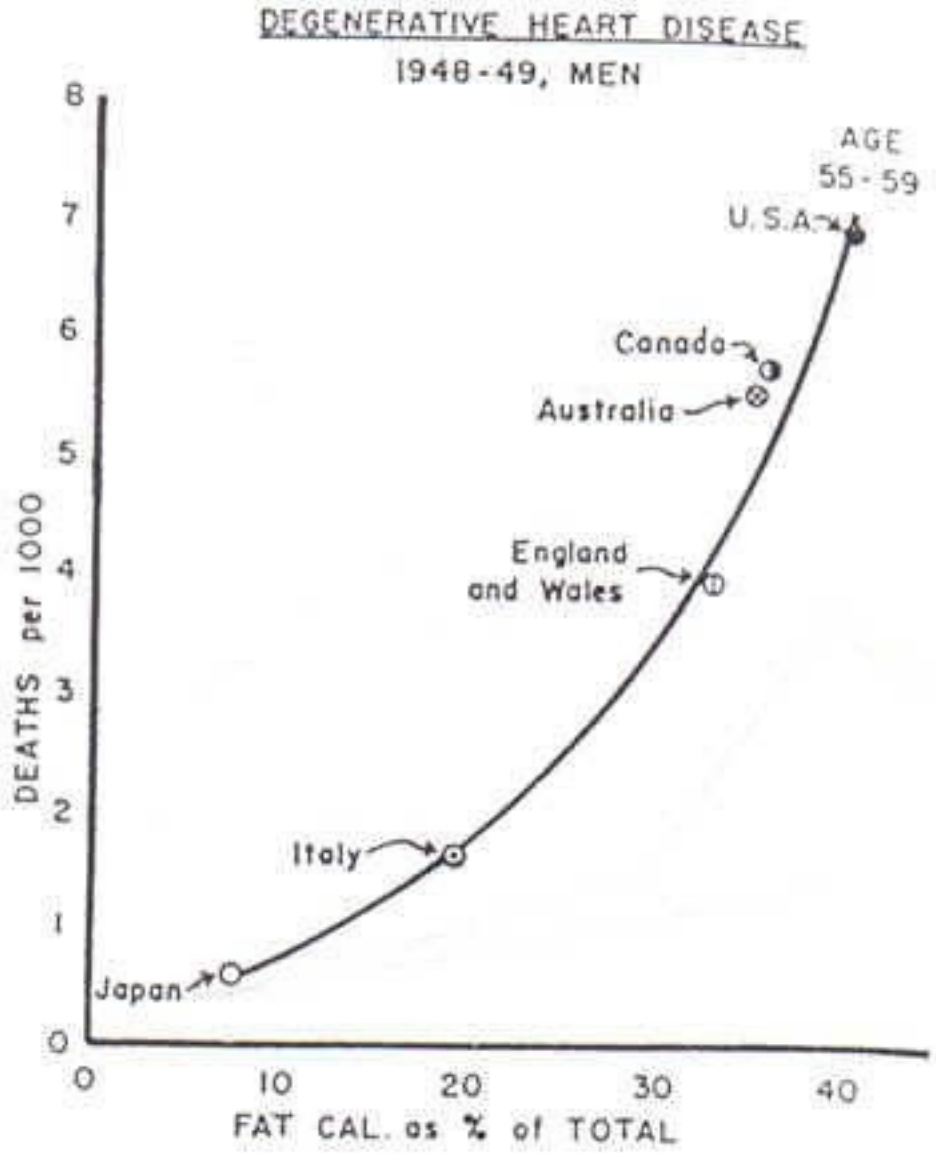

Fig. 1A. Correlation between the consumption of animal fat in percent of the total calorie consumption, and mortality from coronary heart disease in six countries. Data from Keys.[2]

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Fig. 1B. Same as fig. 1A, but including all countries where data were available when Dr. Keys published his paper Data from Yerushalmy and Hilleboe.[3]

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Are consumption data accurate?

Let us have another look at the figures 1A and !B because we need to understand the data there. Similar figures are presented again and again by upholders of the diet-heart idea. What do the figures really mean?

Firstly, “Calories from fat” does not mean the amount of fat eaten in each country, only the amount available for consumption. By that is meant the sum of what is produced in the country and what is imported minus food used for purposes other than human nutrition. From this figure, which is the one used in figures 1A and 1B, should be subtracted the amount of fat that is never delivered to the consumers because it is lost, stolen, eaten by rats or mice, or disturbed because of bad storage. Further, some of it is eaten by dogs, cats and other pet animals; and some is thrown away in the kitchen or left on the plate. In the US where eating fat is considered almost as a sin much fat certainly disappears that way. In poor countries, however, where famine is a greater threat than overweight or heart disease, it is not so. Here, the diet includes even brain and bone marrow, both of which are crammed with animal fat and cholesterol.

Thus, the figures for fat consumption in various countries are most unreliable, to put it mildly. But the figures for heart mortality, those on the vertical axis are even more erroneous.

Are death certificates true?

When statisticians write their reports about numbers and causes of death in a population they consult the death certificates. Do you think that what is written on this piece of paper is the truth and nothing but the truth?

Certainly not. Again and again great differences have been found between the diagnosis set by the doctor while the patient was alive and the findings at the post-mortem. Even doctors with access to modern diagnostic equipment name the wrong diagnosis on the death certificate in one out of three cases.[4] For instance, most doctors consider sudden, unexpected death to be caused by a heart attack due to coronary heart disease. Dr. George Lundberg from University of California and Professor Gerhard Voigt from University of Lund, Sweden showed this to be wrong. In 51 of one hundred such cases, the cause of death was due to something else.[5]

The situation is no better when patients actually have died of heart attacks. Drs. Edwin Zarling, Harold Sexton and Pervis Milnor from Memphis, Tennessee, found that among one hundred patients who died from a heart attack according to the postmortem only fifty-three had a correct diagnosis before they died.[6]

Consider that these studies were not performed in small local hospitals but at university hospitals with access to the finest diagnostic tools of modern medical science in the hands of experienced academic doctors.

Maybe you think that it is unimportant what the doctor diagnoses as cause of death because mistakes will be corrected by the coroner. But postmortems are performed only in a minority of cases; in the US in one out of five, in other countries much less often.

So, if the diagnostic accuracy is that bad in a modern, Western hospital, how do you think it is in poor countries where the cause of death is rarely written by doctors, much less by a coroner?

But even frequent postmortems are no guarantee of a correct diagnosis. This was amply demonstrated by the British professors D. D. Reid and Geoffrey Rose.[7] They collected summaries from the hospital records of ten patients who had died from various heart, kidney and lung diseases. Except for the diagnoses, the summaries contained all information relevant to the cause of their death including results of the physical and laboratory examinations, statements from the X ray department and the post-mortem descriptions. Then, a number of experienced, academically trained doctors from university hospitals in Norway, England and the US were told: *"Read the records and write the death certificates!"*

Any scientist who considers statistics based on death certificates as a source of truth should look carefully at the fact that coronary heart disease was used as a diagnosis by the American doctors 33 percent more often than by the English doctors, and 50 percent more often than by the Norwegian doctors.

Someone who is not a physician may find it odd that doctors from countries with similar medical traditions and education systems act so differently when they put a diagnosis on the death certificate. The explanation is that there may be serious changes in many organs in a dying person, but on the death certificate and in the statistical tables there is room for only one diagnosis. Thus, in complicated cases American doctors, by unknown reason, are inclined to blame the death on changes of the vessels to the heart, whereas English and Norwegian doctors may instead hold lung or brain diseases responsible. Interestingly, the official death statistics from these three countries show the same tendency.[8]

If death is labeled so differently in the US, England and Norway, where the medical education is similar, how is it labeled in countries such as Japan, Ceylon (Sri Lanka) or Mexico where the culture and medical traditions are fundamentally dissimilar?

Clearly, official death statistics are based on diagnoses which in at least half of the cases are plain wrong, and if they are not wrong, they do not tell the whole truth.

Television—a risk factor?

But let us assume that heart attacks are more common in countries where people eat much animal fat. What does it mean?

From Table 1 you can see that other factors than eating animal fat are associated with heart disease.

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Factor	Correlation Coefficient
Number of cigarettes sold per inhabitant	0.64
Number of cars sold per 100 inhabitants	0.58
Total consumption of protein*	0.72
Consumption of animal protein*	0.73
Total consumption of fat*	0.56
Consumption of animal fat*	0.65
Consumption of cholesterol	0.69
Consumption of sugar*	0.68
*amount available for consumption	

Table 1. Correlation coefficients between various consumption factors and mortality in coronary heart disease for men age 55-64 in 22 countries.

The correlation coefficient in the right-hand column of the table tells how well various factors follow the number of deaths from heart attacks in the countries that were studied. The largest coefficient is 1, the weakest is zero. The table thus tells us that in countries where heart attacks are common (meaning where the diagnosis coronary heart disease is commonly used) people eat more protein, fat, cholesterol and sugar. They also smoke more cigarettes and buy more cars than in countries where heart attacks are less common.

What the statistics actually tell you is that the risk of having the diagnosis coronary heart disease written on one's death certificate is greater for people in prosperous countries than for people in poor countries. Therefore, anything that follows with or from prosperity is automatically associated with mortality from coronary heart disease. Calories from animal fat, for instance, are more expensive than calories from other nutrients; people in prosperous countries therefore eat more animal fat than people in poor countries. And since the cause of death more often is called coronary heart disease in prosperous countries than in poor ones, intake of animal fat becomes statistically associated with the number of deaths from coronary heart disease.

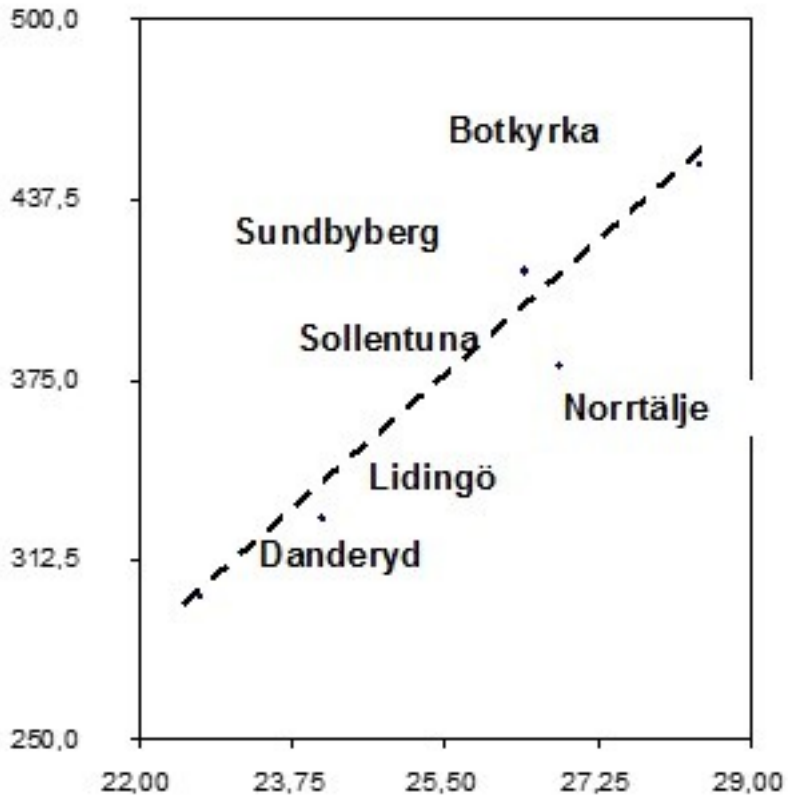
Thus, population studies may point to factors that are associated with a certain diagnosis on the death certificates but they cannot tell us the cause of the disease; only experiments can. Factors

which are statistically associated with a disease are called risk factors. A risk factor may be the cause of the disease, but most often it is not. Several hundred risk factors are known for coronary heart disease, for instance smoking, overweight, high blood pressure, lack of exercise, psychological stress, baldness, snoring, and eating too much or too little of a steadily increasing number of various food items, but the cause of the disease is still unknown. What the table demonstrates are just a few examples of risk factors for coronary heart disease.

Because a risk factor and the cause of a disease may stem from a common factor, for instance a country's prosperity, it is self-evident that the elimination of the risk factor does not automatically prevent the disease; the main cause is still there.

Let us assume that the real cause of coronary heart disease is car exhaust. (This is most likely totally wrong but that doesn't matter; I have made this assumption only to demonstrate how factors that vary together may create false associations.) More people are exposed to car exhaust in prosperous countries because cars are more common in prosperous countries, and as we assumed that coronary heart disease was due to car exhaust, heart attacks should also be more common. Logically, death rates from coronary disease in various countries become associated with the number of cars sold. But people in prosperous countries buy many other things more often, for instance television sets, and thus the coronary death rates also become associated with the number of television sets sold. You may therefore call "possession of a television set" a risk factor although it was not the television set but the car exhaust which caused coronary heart disease. Clearly, it is a bad idea to throw the television set out the window to save the heart.

To carry our example one step further, see figure 1C, which shows the correlation between the tax rate and death from heart disease in the municipal tax districts of the county of Stockholm, Sweden. The graph implies that if the municipal tax rate is lowered to 9.95 percent, no one will



die from a heart attack—a challenge to all politicians!

Figure 1C. Correlation between tax rate and heart mortality in the municipal tax districts of the county of Stockholm.

Vertical axis: Heart mortality per 100,000; Horizontal axis: Municipal tax rate 1976; percentage

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Another example. People with yellow fingers die more often than others from a heart attack. "Yellow fingers" is therefore a risk factor for coronary heart disease. But it doesn't help to scrub away the yellow color, because the discoloration is due to cigarette smoking. The cause of coronary heart disease is not the yellow color, but either the smoke from the tobacco or the paper, or the mental stress that starts the habit of smoking, or a factor associated with the habit of smoking or the feeling generated by nicotine.

Risk factors do not necessarily produce disease. But most diet-heart supporters rarely distinguish between risk factor and cause. They consider every new risk factor as something that should be reduced or eliminated.

Seven random countries

To prove his idea Dr. Keys organized a study of coronary heart disease in seven countries. To this end he selected sixteen local populations in the Netherlands, Yugoslavia, Finland, Japan, Greece, Italy and the US. Men between the age of 40 and 59 were studied. In cooperation with local doctors, scientists and health authorities anything which might conceivably cause coronary heart disease was investigated. The men were followed for about five years, and all heart symptoms and all deaths were recorded.[9]

In each country two or three groups of people were studied. Among other things the investigators looked at the diet, they measured the blood pressure and weighed all participants, and asked how much they smoked and exercised.

The conclusion from this gigantic project was that what best could predict the number of heart attacks in a country was how much animal fat people ate in that country. In countries where people ate much animal fat, heart attacks were common; in countries where people ate little such fat, heart attacks were rare.

But within the countries the number of heart attacks did not follow the diet. Here I shall tell about the two Finnish populations; the one from East Karelia and that from Turku; in another chapter I shall tell about the people on two Greek Islands.

At the start, forty-two of 817 men from East Karelia had coronary heart disease, in the district of Turku only fifteen of 860. And during the next five years sixteen men died from a heart attack in Karelen, but only four in the district of Turku. Taking all factors in consideration heart attacks wee seen five times more often in Karelen than in the district of Turku.

If you think that the natives lived especially carelessly in Karelen you are wrong. The living conditions in the two areas were practically identical. These people lived isolated as farmers or lumberjacks, their body weight and height were identical, they smoked equally much, and they ate the same amount of polyunsaturated fat. The blood pressure was a few percent higher in Karelen, and here they also ate a few percent more animal fat than around Turku.

Dr. Keys declared that coronary heart disease was five times more common in Finland than in Japan because of the food, but he did not explain why coronary heart disease was five times more common in eastern than in western Finland although the difference between the common risk factors was only marginal. He mentioned it as a minor, abnormal finding which he (erroneously) stated would be explained by further studies.

This way of arguing is common among the proponents to the diet-heart idea. Observations that support this idea are trumpeted forth as positive proofs while unsupportive findings, if they are mentioned at all, are considered as “rare exceptions” or “something which cannot yet be explained.”

Up and down in statistics

To see if fat food causes heart attacks it should be of interest to study how the eating habits in a country have changed during a period of time and to ask if the number of heart attacks has changed in the same direction. If animal fat is an important cause of coronary heart disease the number of heart attacks should increase during periods of increasing intake of such fat; and it should decrease when less animal fat is eaten.

But even if these figures follow each other up and down, we have not proved that eating animal fat is the cause of the increasing mortality. Again an unknown factor could create parallel changes in fat intake and heart mortality. Let me give an example.

During World War II people in Finland, Norway, Sweden and Great Britain died less often from heart attacks than before the war. Said Haquin Malmroos, a professor of medicine in Lund, Sweden: *"this is because people ate less animal fat."*

But other things of importance for heart disease occurred during the war. For instance, people's body weight and blood pressure went down considerably, fewer people smoked, and the lack of gasoline for cars and other machinery should also have favored a healthier way of life. A common denominator of the war was lack of goods—lack of fat food for instance, but also lack of other nutrients and of gasoline and cigarettes. Nobody knows which of these factors, if any, caused the decrease in heart disease. The explanation that people ate less animal fat is unlikely because it has never been possible to lower the death rate from coronary heart disease with a low-fat diet in experiments of the same length as World War II. Furthermore, the mortality curves turned upwards again long before the increase of the consumption of animal fat took place.

Thus, although a risk factor changes parallel to the death rate it is not necessarily the cause. But if the risk factor is the cause, its rise and fall must be reflected in the death rate from the disease. If heart attacks are caused by eating too much animal fat, heart attacks should of course become more frequent if people started to eat more of such fat. Likewise, if people changed their diet and ate less animal fat, fewer heart attacks should occur. This is not so.

From World War I up to the 1980s, the number of deaths from heart attacks increased substantially in most countries while the intake of animal fat decreased or was unchanged. For instance, the death rate from cardiovascular diseases of middle aged Yugoslavians increased three to four times between 1955 and 1965, while the intake of fat decreased by 25 percent.[10]

In England the intake of animal fat has been relatively stable since at least 1910 while the number of heart attacks increased ten times between 1930 and 1970.

In the US coronary mortality increased about ten times between 1930 and 1960, leveled off during the 1960s and has since decreased slowly. During the decline of heart mortality the consumption of animal fat declined also, but during the thirty years of sharply rising coronary mortality the consumption of animal fat decreased.

In Framingham the number of fatal heart attacks went down during the decline of animal fat consumption, but the number of non-fatal heart attacks increased with the same number. The authors of the Framingham report explained this discrepancy by saying that it takes much longer

time to lower the number of non-fatal heart attacks than to lower the number of fatal cases.[11] (A much better explanation is, that to-day more people survive a coronary because of improved treatment).

In Japan the number of fatal heart attacks between 1950 and 1970 increased as did the intake of animal fat appearing to confirm the diet-heart idea. But the increase in coronary mortality was seen only above the age of 70 and especially above 80. In the latter age group, the increase in coronary mortality more than counterbalanced the decrease in the other age groups. In other words, younger Japanese people died less often of coronary disease, although they ate more animal fat. During the same period mortality from most diseases decreased in Japan. Thus, the increasing death rate from coronary disease among old people in Japan could not be caused by an increased intake of animal fat; if it were, the number of coronary deaths should have increased in all age groups. The explanation is that the general health in Japan has improved steadily since the war, as has the people's mean length of life. Many more have become old, and since coronary heart disease is a disease of old age, the death rate due to heart disease has of course increased. [12]

This torpedo against the diet-heart idea was presented as the first paper at an international conference in 1981. Yet the paper created no intellectual explosions. The author of the paper, Dr. Kimura concluded: *"… if this food supply and nutrient intake pattern continues the same evolution in Japan, incidence of ischemic heart disease will increase in the future."*

And the conference continued with paper after paper acknowledging the diet-heart idea. But in spite of a continuing increase in the intake of animal fat in Japan also after 1970, and a steady increase of the mean serum cholesterol level the number of fatal heart attacks decreased in all age groups, contrary to Dr. Kimuras prophecy.

While the death rate from coronary disease increased in most countries after World War II it decreased in Switzerland. If this decrease had been followed by a decline in the intake of animal fat, Switzerland would have been a model for health care in other countries. But Switzerland is never mentioned because parallel with the declining heart mortality, the Swiss intake of animal fat increased by twenty percent.[13]

The shepherds of Kenya

The many exceptions to Ancel Keys's hypothesis indicate that something in the Western life style other than fat food is the cause of coronary heart disease. To be absolutely sure it is necessary to study people who eat just as much animal fat as we do but who are not exposed to the menaces of Western civilization. If the diet were the most important factor people in such countries would have equally high cholesterol and die just as often from heart attacks as we do.

In the early 1960s, Professor George Mann and his team from the Vanderbilt University in Nashville, went to Kenya in Africa with a mobile laboratory to study the Masai people.[14] The diet-heart idea had just started its triumphal progress. Professor Mann had heard that the Masai people did not eat anything but milk, blood and meat. Wouldn't it be a good idea to test the diet-heart idea on the Kenyan plateau? Shortly before and with the same purpose Dr. Gerald Shaper from the Makerere University of Uganda had traveled a little further north to another tribe, the Samburus.[15]

The Samburus and the Masai people are slender people who have survived as shepherds for thousands of years. Their life is free from the mental stress and competition of Western civilization, but you cannot call it comfortable. Every day they walk or run many miles with their cattle, searching for food and water.

Their own diet is extreme. According to their view, vegetables and fibers are food for cows; they themselves eat milk, meat and blood only, or at least the younger men do. A male Samburu may drink almost a gallon of milk each day. He has never heart about the cholesterol campaign, and therefore he drinks the creamy milk as it is, which means that his intake of animal fat is far above that of most Western people. Also, his intake of cholesterol is high, especially during periods when he adds 2-4 pounds of meat to his daily diet.

Masai people drink "only" half a gallon of milk each day. However, they eat more meat than the Samburus. Their parties are sheer orgies of meat; on such occasions 4-10 pounds of meat per person is not unusual, according to Professor Mann.

If the diet-heart idea was correct, coronary heart disease should be epidemic in Kenya. But Mann found that no Masai dies from a coronary. Rather, the Masai people would die of laughter if they heard about the cholesterol campaign.

But this was not the only surprise. The cholesterol of the Masai tribesmen was not sky-high as Mann had expected; it was very low. In fact, their cholesterol was among the lowest ever measured in healthy people, about fifty percent of the value of most Americans.

Another cholesterol safari

Now to Dr. Bruce Taylor from Chicago. He was the first to induce a coronary in an ape by cholesterol feeding (see Chapter 6). The papers about the Samburu and the Masai people were published shortly after Dr. Taylor's successful experiment. Certainly he must have asked himself why the cholesterol of his laboratory animals skyrocketed on their fat diet, but not the cholesterol of the Masai and the Samburu people. To answer this question he was on his way to Kenya with his own expedition a few years later.

Like other mammals, we produce cholesterol ourselves, day and night. When we eat lots of cholesterol or animal fat, our own production of cholesterol decreases automatically. If we eat only a little, our production increases. This mechanism keeps the cholesterol level in the blood fairly constant and explains why it is so difficult to lower cholesterol with diet. After his investigations Dr. Taylor reached an unusual conclusion about this balancing mechanism in the Masai people.

According to Dr. Taylor the African tribes do not contradict the diet-heart idea because their ability to reduce their own cholesterol production is superior to other people. Because the Masai people have been isolated from other tribes for many thousands of years, they have developed this ability so well that it has been built into their genes, Taylor said. Taylor and his colleagues considered their results so important that they published them with minor variations in four different scientific journals.[16]

In science there are often alternative explanations to a new observation, and most scientists therefore discuss which model or hypothesis the new piece of evidence fits into the best. But

Taylor did not. He could have considered the possibility that it is not the Masai people who are superior to others in reducing their cholesterol production but instead, we who are inferior, perhaps because of environmental factors, perhaps because we are less active than the Masai people, or perhaps because of something we haven't yet imagined. But he did not.

It would have been possible to get an answer to these questions if he had continued his expedition to the city of Nairobi and studied Masai people there to see if some factor associated with the more comfortable life style of a big city might have increased their cholesterol. This method is often used by the defenders of the diet-heart idea to demonstrate that low cholesterol goes up when people from poor, undeveloped countries with a low fat intake move to a more prosperous and technologically developed country where the fat intake is high.[17]

But in this case, the study concerned human beings who already ate more fat than ever recorded. After migration to Nairobi their diet most probably became more diversified, and if the diet-heart idea was true their blood cholesterol should have become even lower.

What had happened with the cholesterol of the urbanized Masai people? Why did Taylor and his colleagues not proceed to Nairobi to get an answer to this simple question?

Taylor's explanation that the low cholesterol of the Masai people is genetic is not a valid one. Acquired properties are not transferred to people's descendants. This idea was abandoned as scientifically wrong many years ago. An inborn metabolic trait—in this case the ability to reduce the body's own production of cholesterol when presented to large amounts of cholesterol in the diet — is either present in the genes, or it arises by mutation. If the property is important for survival, the number of individuals with this property increases over time, and eventually these people may outnumber those without it. But this will happen only if the inborn trait improves survival before sexual maturity. Individuals with a trait that protects them against a disease, which strikes after sexual maturity, such as coronary heart disease, do not outnumber individuals without this trait, because the latter transfer their defective genes to their children before they develop the disease.

And, contrary to Taylor's statements, the Masai people are not an isolated tribe. They are warlike people who have taken cattle and women from the neighboring tribes for thousands of years. In this way they have achieved a steady genetic renewal in their cattle and in themselves.

But what finally proved that Taylor was wrong was a study of Masai people living in the big city of Nairobi performed by Dr. José Day at St. Mary's Hospital in London. Again, if the low cholesterol of the Masai was inherited it should have been even lower in Nairobi, because here their diet should most likely include less animal fat than the diet of the Masai tribesmen. But the mean cholesterol level in twenty-six males in Nairobi was twenty-five percent higher than that of their cattle-breeding colleagues in the countryside.[18]

Taylor's genetic explanation has been popular among upholders of the diet-heart idea, such as Dr. Keys. He wrote: *"… the fact is that the peculiarities of those primitive nomads have no relevance to diet-cholesterol-coronary heart disease relationships in other populations."*[19]

Taylor studied not only blood cholesterol but also atherosclerosis in the Masai. It was important to show that their low cholesterol level protected the Masai people from atherosclerosis. Ten

aortas from deceased Masais were sent to New York where the pathologists said that atherosclerosis was almost absent.

But Professor Mann studied a much greater number of hearts and aortas from Masai people of all ages and found that the coronary vessels of Masai people were just as atherosclerotic as those from US citizens, perhaps even more. But severe sclerotic changes, so-called plaques or raised lesions, were rare; the sclerotic changes were situated inside the vessel walls whereas the inner surface of the vessels was smooth. And in the fifty hearts he studied there was no evidence of myocardial infarctions in any.

Professor Mann thought that the Masai were protected from coronary heart disease by the size of their coronary arteries. These were much wider than those of most Western people, probably because the hearts of the Masai have worked hard while the men were running after the cattle. Many of the Masai people Mann examined were splendidly fit, as good as, or better than, superior sportsmen. It is no coincidence that the world's best runners tend to come from Kenya.

Thus, it is possible to gorge on cholesterol and animal fat and still keep the blood cholesterol very low. The diet-heart idea should be smashed after such evidence, and the message about the Masai and Samburu people should challenge any defender of the diet-heart idea. But the idea is still flourishing, and nobody seem challenged. In fact, the Masai and the Samburu people are not mentioned at all in the official reviews of the diet-heart idea.

It is worth mentioning another interesting observation from Kenya. In that country there are many Indian emigrants. Although they all come from India their diet are not similar. Non-Muslim Indians from Gujarat live on a lactovegetarian diet while Muslim Indians from Punjab eat eggs and meat and drink twice the amount of milk as their compatriots from Gujarat, and they never use vegetable oil. The non-Muslim Indians thus live as if they had been listening to the cholesterol campaign to avoid coronary heart disease, while the Muslims act as if they're doing what they can to get it. But the mortality rate from coronary heart disease is equal in both populations.[20]

However, this aberration from the diet-heart idea seems petty compared with the next one. Curiously, Dr. S. L. Malhotra from Bombay, India is never cited in the many reviews advocating for the prudent diet. He studied coronary heart disease among more than one million male employees of the Indian railways. During a five-year period he recorded 679 deaths from that disease. Most cases, 135 per 100.000 employees, were noted in Madras in southern India; fewest cases, 20 per 100.000 employees, were noted in Punjab in northern India.[21]

Thus, death from coronary heart disease was seen about seven times more frequently in Madras, and those who died were on average twelve years younger than in Punjab. But in Punjab, people ate 10-20 times more fat, and they smoked eight times more cigarettes. And while the small amount of fat that people ate in the weak-hearted province of Madras was mainly of vegetable origin, the fat they gorged on in the strong-hearted Punjab was mainly of animal origin.

Have coronary patients eaten more fat?

A way of searching for the cause of a disease is by using the so-called case-control study. In a case-control study scientists question randomly selected control persons of the same age and sex and from the same geographic area as the patients with the disease under investigation. In which

way do the patients differ from the controls? What do they do for a living? How much do they smoke and drink? What do they eat? Are they fatter or slimmer than the controls? How is their blood composed? Are they exposed more than the controls to environmental pollutants? Only your imagination and your money put a limit to your questions.

In North Dakota in the USA, Dr. William Zukel and his team performed a case-control study. They studied all the men who had had heart symptoms during one year; for each case they chose two healthy men of the same age as the controls. Dr. Zukel was especially interested in the diet of the participants during the month before the first symptoms or before the interview. If the interviewee had died, his wife or nearest relatives were questioned.[22]

Altogether 228 men had had symptoms of coronary disease. A detailed description of the diet was gained from 162 of them. The conclusion of the study was that control individuals were more often manual workers, and patients were more often smokers. But the diet did not differ between patients and control individuals; they ate the same amount of saturated and polyunsaturated fat, and their caloric consumption did not differ either.

In Ireland another group of researchers under the guidance of Dr. Aileen Finegan performed a similar investigation. For a whole year they studied the diet of one hundred men who had suffered from a heart attack. Their diet was compared with that of fifty healthy men of the same age.[23]

Dr. Finegan and her team could not find any dietary differences; the patients had eaten practically the same amount and kind of fats as the control individuals.

A similar study was performed in collaboration between researchers from Harvard and the University of Dublin in Ireland under the guidance of Dr. Lawrence Kushi. Irish men and their brothers who had been living in Boston for at least ten years were selected. These two groups were compared with each other and with a third group of adult sons of Irish emigrants in Boston, a total of one thousand men. Now to the questions. How many would die from a coronary during the next twenty years? And did their way of living differ from that of the others?[24]

The researchers did not get a simple answer. Relatively speaking, more Boston brothers had died from a heart attack than either of the other two groups, but the difference was so small that it could well have been due to chance. It could also have been because the Boston brothers smoked more often and because their blood pressure was higher. The notion that their diet played an important role is unlikely because, contrary to the diet-heart idea, the men in Boston had eaten less animal fat and less cholesterol than the Irish brothers, and more polyunsaturated fat than the emigrants' sons. And there was no difference between the blood cholesterol values of the three groups. Yet, in spite of these negative findings this study is often cited as a strong support of the diet-heart idea.

Another "proof" of the diet-heart idea is a study performed in cooperation between the National Heart, Lung and Blood Institute and the University Hospital in Puerto Rico, conducted by Dr. Tavia Gordon. In Framingham, Puerto Rico and Honolulu more than sixteen thousand healthy, middle-aged men were questioned about their dietary habits. Six years later the dietary habits of those who had had a heart attack were compared with the habits of those who had not.[25]

In Puerto Rico and Honolulu heart attack victims had eaten less starch than the others; in Framingham they had eaten smaller amounts of other carbohydrates. Eating starch or other carbohydrates should therefore protect against coronary heart disease according to the authors of the report.

But the percentage of calories from starch did not differ between the healthy individuals and the patients except in Framingham, where those who had suffered a heart attack had eaten more starch than the others.

In Puerto Rico and in Honolulu those who had had a heart attack had eaten more polyunsaturated fat than those who had not had an attack. Although this observation is contrary to what was expected and thus most discouraging for those who advise people to eat more of such fat it was not mentioned in the summary of the paper.

A similar study was performed by researchers from Framingham and Honolulu, led by Dr. Daniel McGee of the Framingham Heart Study. They asked 8000 Japanese migrants in Hawaii about their diet over a 24-hour period, and ten years later they compared the diet of those who had suffered a heart attack during the ten years with the diet of those who had not.[26]

Those who had suffered a heart attack had eaten just as much animal fat and protein but less carbohydrates as the others. The authors therefore recommended either eating more carbohydrates or less animal fat; either way should have the same preventive effect. In the summary of the report from the study, the authors did not mention that the difference between the diets in the two groups was not greater than what could have been produced by chance.

Today (1998) a total of 27 similar studies have been published including 34 groups (cohorts) of patients and control individuals.[27] Totally, the incredible number of more than 150,000 individuals have been investigated. In three of these 34 cohorts patients with coronary disease had eaten more saturated or animal fat than the control individuals, in one cohort they had eaten less, in the rest no difference was seen. In three cohorts the patients had eaten more vegetable or polyunsaturated fat than the control individuals, in only one they had eaten less.

In the studies mentioned above, the researchers try to press the figures down into the cholesterol shoe, but neither heels nor toes fit in. According to some authorities, we should eat less saturated fat; according to others we should eat more polyunsaturated fat. Still others recommend carbohydrates, if not starch, or fibers, or vegetables, depending on the haphazard results of the most recent investigation.

More critical diet-heart supporters object that information about the diet is unreliable; people simply cannot remember exactly what they have eaten. This objection is correct, of course. The point is, however, that these unsupportive results are used as support, even in the most prestigious reviews. Listen for instance to the words from the review *"Diet and Health,"* published by the *National Research Council*: *"Percentage of calories from SFAs [saturated fatty acids] was positively associated with risk of CHD in the rural sample of the Puerto Rican and the Ireland-Boston studies."*[28]

If you go to the library and look into the tables of these papers you will see that the differences found were not statistically significant, which means that the results were simply due to chance.

And why did the authors of Diet and Health only cite these two studies? Why didn't they mention that, if anything, coronary patients have eaten more polyunsaturated fatty acids?

Or listen to the joint statement by the American Heart Association and the National Heart, Lung, and Blood Institute: *"… showing the link between diet and CHD particular impressive results [were produced in] the Western-Electric, the Honolulu Heart, the Zutphen, and the Ireland-Boston studies."*[29]

Looking into the tables from these reports it appears that only in the Honolulu Heart study the patients had eaten significantly more saturated fat, but in that study they had eaten significantly more polyunsaturated fat also, opposite to what we should expect.

In conclusion, there is a weak association between the coronary mortality in various countries and the amount of fat available for them to eat, but no difference between the amount of fat eaten by coronary patients and by healthy individuals. This is no paradox, but typical of factors that follow each other roughly because they have a common cause. The mean income in various countries, for instance, parallels the number of heart attacks; coronary heart disease is common in rich countries and low in poor countries. But in rich countries poor people die more often from heart attacks than rich people.

Again, calories from animal food are more expensive than calories from vegetable food. The common denominator for countries where people eat lots of animal food is prosperity. In prosperous countries fat food is abundant, but so also are stress-provoking factors. Also more people smoke, fewer people perform manual labor, industrial pollution of the environment is most often worse, and the ability to diagnose coronary heart disease is better. People in prosperous countries also live longer; instead of dying from infectious diseases or malnutrition when they are young they die from diseases related to old age such as coronary heart disease. Any of these factors, or their combination, or something else that I have not thought about, may explain why people die more often from a heart attack in prosperous countries.

Prosperity, fat food, and coronary heart disease thus follow each other. Statistical correlations may therefore arise when different countries are compared, especially if countries that do not follow the usual pattern are excluded. But inside the countries there is no correlation because it is not prosperity or the fat food itself that cause coronary disease.

Triglycerides

Most of the fatty acids in the diet and in the blood are bound to a type of alcohol called glycerol. Usually each glycerol molecule is attached to three fatty acids, and this molecule complex is called a triglyceride. Often shortened to TG. As with cholesterol, high TG levels in the blood have been found to be associated with a higher risk of coronary heart disease. Does that mean that we should lover the level of TG in our blood?

To answer this question satisfactorily demands careful reading and a long explanation. However, if you understand the fallacy of the cholesterol hypothesis, then it will be easy for you to understand that you do not need to bother about your TG either because even the most zealous proponents of pharmaceutical intervention admit that the evidence for high TG causing atherosclerosis and cardiovascular disease, is weak, much weaker than for high cholesterol. Thus, if it is weak or nonexistent for cholesterol, why bother about TG?

The TG level in the blood depends on many factors. Normally TGs go up after a meal. The more fats and carbohydrates you eat—and the more alcohol you drink—the higher your TG level becomes. Almost 12 hours must pass before the level returns to "normal." An analysis of TG is therefore meaningless if the patient hasn't been fasting the previous 12 hours.

Furthermore, overweight people have higher levels of TG than thin people, smokers have more than non-smokers, diabetics have more than non-diabetics, people who lead a sedentary lifestyle have more than physically active people, and people under stress have more than people who are on ease. For instance, you could ask whether overweight, smoking, inactive and stressed diabetics with high TG are more at risk than overweight, smoking, inactive and stressed diabetics with normal TG.

In addition, analysis of TG is highly inaccurate and the normal fasting levels are highly variable. If a blood analysis finds 200 mg per deciliter, the true TG level may be anything between 100 and 300. To get a more reliable measure of your normal TG, it is therefore necessary to calculate the average of three measurements made at three different occasion, each time preceded by a 12-hour fast.

So, when researchers say that high TGs predict an increased risk for heart disease, the question is, whether this is caused by sedentary lifestyle, or smoking, or overweight, or mental stress, or diabetes, or a risk factor we don't know about yet; or whether it is caused by a high TG. And even if a 10-20 percent higher fasting value of TG is associated with an increased risk, it seems senseless to try to lower TG when TG rises after each meal to levels that can be several hundred present higher than the fasting state. All of us who eat three times a day and drink a glass of wine or whisky now and then simply have "too high" TG most of the time.

Myth 2: High Cholesterol Causes Heart Disease

In our need to understand, to explain, and to treat, the temptation to impute causality to association is pervasive and hard to resist. It is the most important reason for error in medicine.

Petr Skrabanek and James McCormick

Authors of *Follies and Fallacies in Medicine*

Large and small percentages

Framingham is a small town near Boston, Massachusetts. Since the early-1950s a large number of Framingham citizens have taken part in a study surveying all factors that may play a role in the development of atherosclerosis and heart disease. Among other things their cholesterol was measured frequently.[30]

After five years the researchers made an observation, which should become one of the cornerstones in the cholesterol issue. When they classified the citizens into three groups with low, medium and high cholesterol values they saw that in the latter group more had died from heart attacks than in the two other groups. A high cholesterol level predicted a greater risk of a heart attack, they said; high cholesterol is a risk factor for coronary heart disease.

The predictive value of blood cholesterol levels was confirmed in the greatest medical experiment in history, the Multiple Risk Factor Intervention Trial, also called MR.FIT. In that trial researchers measured the blood cholesterol of more than 300.000 American middle-aged men.

Six years later the director of MR.FIT, professor Jeremiah Stamler and his coworkers from Chicago asked how many of these men had died and from what.[31] The participants were then divided into ten groups of equal size, so-called deciles, according to their cholesterol values. The first decile thus consisted of the tenth of the men with the lowest cholesterol, the tenth decile of the tenth with the highest cholesterol.[32]

The researchers analysis showed that in the tenth decile four times more men had died of a heart attack than in the first decile. Professor Stamler's team put it in another way: *"the risk of dying from a heart attack with cholesterol above 265 mg/dl (6.8 mmol/l) was 413 percent greater than with cholesterol below 170."*

With statistics you can change black to white, or vice versa; as any politician will tell you. Four hundred and thirteen percent! A frightening figure.

But let us look at the real figures and not only at the percentages. How many men had, in fact, died from a heart attack?

The total number was 2258, or 0.6 percent of the more than 300,000 men investigated. We could also describe these results by saying that 99.4 percent did *not* die from a heart attack.

Among those with the highest cholesterol value (the tenth decile) 494, or 1.3 percent, died from a heart attack. Said in another way, 98.7 percent of those with the very highest cholesterol values were alive after six years.

Among those with the lowest values, the first decile, ninety-five men, or 0.3 percent, died from a heart attack, while the rest, 99.7 percent survived. Thus, the difference in numbers of death between the first and the tenth decile was only one percentage point (99.7% — 98.7%).

One percentage point doesn't have the same alarming effect as Dr. Stamler's 413 percent, but both figures are correct because 1.3 is 413 percent of 0.3.

The excess of deaths was most pronounced in the tenth decile. It should be remembered that almost all individuals with the rare, inherited abnormality called familial hypercholesterolemia must have been included in the tenth decile. These people have considerably higher cholesterol values than normal individuals and some of them have severe atherosclerosis and cardiovascular disease in early life. A little less than one percent of humanity have familial hyper-cholesterolemia or some other kind of genetic problem that interfere with cholesterol metabolism. This means that about ten percent of the tenth decile (10 x 1 percent) were abnormal in this respect. Thus, in a complicated way, the statistics demonstrated what we already knew— that patients with an inborn error of cholesterol metabolism have a greater risk of dying from heart disease.

There are more ways that risk factor statistics can be used to magnify trivial differences. Let us go back to the Framingham study.

Great or small differences?

To illustrate the association between blood cholesterol and the risk of dying from a heart attack the researchers from Framingham constructed an interesting graph, shown in **figure 2A**.[33] Two bell-shaped curves are seen. The horizontal axis, or x-axis, represents levels of blood cholesterol whole the vertical or y-axis concerns the number of individuals.

The curves in figure 2A are called Gaussian or "bell" curves. When plotted in a diagram like figure 2A, all measurements in biology usually produce a Gaussian curve with a distinctive parabolic or bell shape that rises slowly from the baseline on each side and then rapidly increases in slope at the center. The total area under the curve gives the number of individuals investigated. If, for example, you graph the heights of a random number of people, short individuals will be situated in the area beneath the curve's left slope, and tall individuals will be situated in the area beneath its right slope. When a bell curve is symmetrical, the mean value of the group lies at the top of the curve.

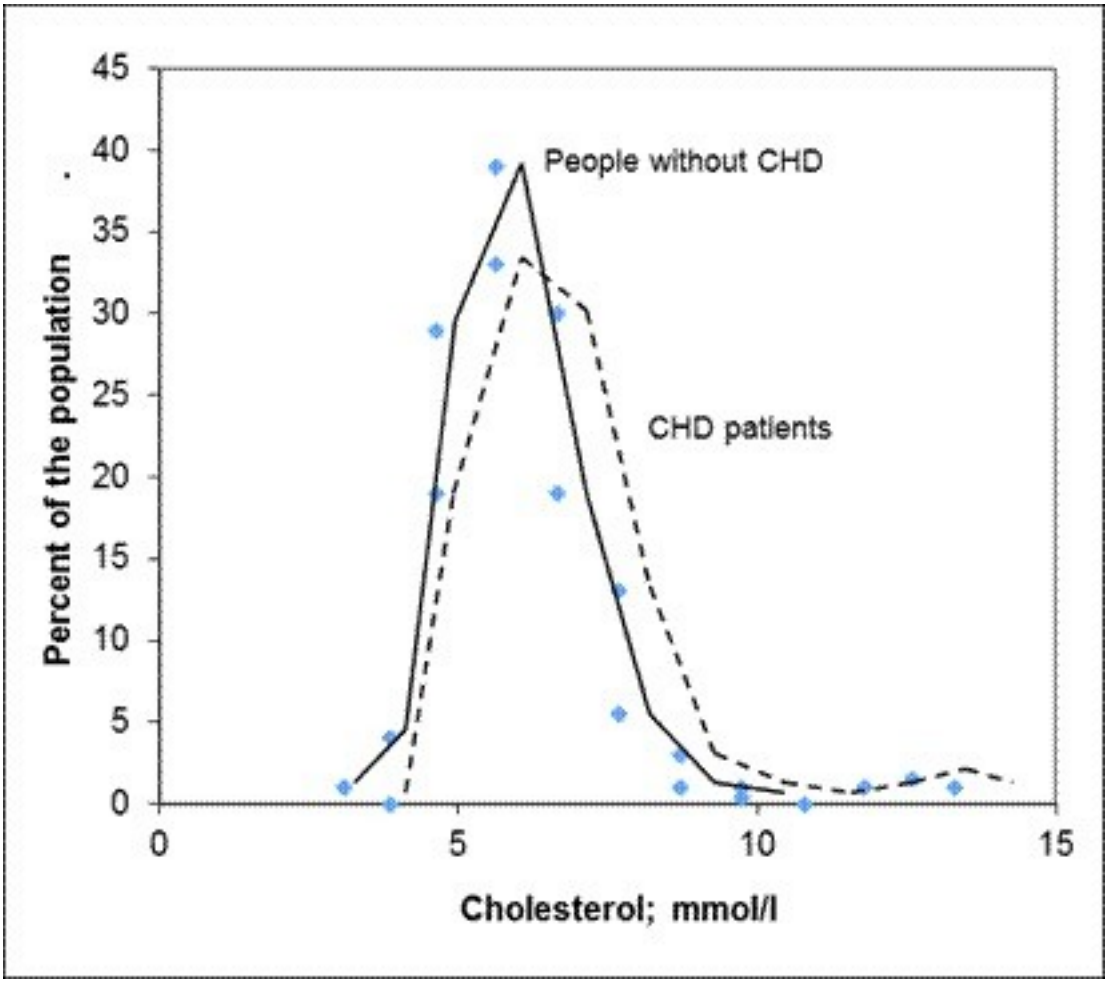

Figure 2A. The distribution of the participants in the Framingham project according to their initial blood cholesterol. The solid line represents 1378 individuals without coronary disease at follow-up; the broken line represents 193 individuals who had coronary disease at follow-up. Data from Kannel and others. [34]

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Let's take a careful look at figure 2A. The broken line represents the cholesterol level of all middle-aged men in the Framingham study, who sixteen years after the start of the project had suffered a heart attack. The unbroken line represents the cholesterol levels of the men who had not. The first group consisted of 193 individuals, the other of 1378, but the curves are of an equal size because the vertical y-axis gives percent instead of the number of individuals.

The curve representing the patients is slightly asymmetrical with a little hump far to the right. Otherwise, the two curves appear identical except that the curve of the coronary patients is placed a little to the right; their cholesterol values are approximately 5-10 percent higher than the values of those who remained free of cardiovascular disease.

Most people probably think that those who have a heart attack almost always have large amounts of cholesterol in their blood. The curves demonstrate however that the difference is marginal. In fact, the graph shows that almost half of those who had a heart attack had low cholesterol.

According to the diet-heart idea this small difference in blood cholesterol is one of the most important causes of atherosclerosis and coronary heart disease. But as we shall see, the difference may be due to several other factors.

No risk after forty-seven

Thirty years after the first cholesterol measurement in Framingham the researchers again asked themselves what had happened.[34] This time, a few more of those with high cholesterol had died. I use the words *few* for a reason. On average one percent of all men with high cholesterol died each year during these 30 years. During the first ten years about a quarter of one percent died each year. As time passed the percentage that died each year naturally grew larger ad larger. Among those with the lowest cholesterol values only half as many died; and as in almost all earlier investigations women with low cholesterol died equally often as did women with high cholesterol.

But these figures concerned *all* causes of death. Nothing was said about *heart* mortality! (Why did the researchers from Framingham forget to tell about heart mortality, the main issue of the whole project?)

Now to the most interesting point. For men above forty-seven no difference was seen. Those who had low cholesterol at the age of forty-eight died just as often as those with high cholesterol.

Thus, the Framingham study showed that if you reach age forty-seven, it doesn't matter whether your cholesterol is high or low! I have never met any believer in the diet-heart idea who has even raised an eyebrow when confronted with this astonishing fact.

Blood cholesterol is usually at its highest level at about the age of fifty. It is after this age that heart attacks usually appear, increasing in frequency year by year. After age fifty atherosclerosis also accelerates, but the first signs of atherosclerosis in the artery appear much earlier, between the ages of 20 and 30.

Atherosclerotic lesions are a kind of inflammation involving the smooth muscle cells, the elastic fibers and the white blood cells. In the early stages cholesterol may not be present at all. Much later, usually after age 50, cholesterol and various lipids may be deposited in the lesions, eventually resulting in the dangerous raised lesions.

With these facts in mind how do you explain that high cholesterol is dangerous at the age of 30, but not after 47? If high cholesterol produces atherosclerosis because its level in the blood is a little higher than usual, why is high cholesterol a risk factor at the age of thirty, where cholesterol is rarely found in he arteries, but not after 47, the period of life where most of arterial cholesterol is produced?

Furthermore, few die from a heart attack before the age of 48, and most of them who do die are diabetics or have a rare, genetic problem. More than 95 percent of all heart attacks occur in

people older than 48. If cholesterol has importance only for the very few who have a heart attack before 48, why should the rest of us worry about high-fat food and blood cholesterol?

The Framingham findings are not a rare exception. High cholesterol has no importance in old Australians either, according to a study by Dr. L. A. Simons and his coworkers at St. Vincent's hospital in Sydney.[35] Similar findings were uncovered in a study by Dr. Peter Zimetbaum and his coworkers at the Albert Einstein College of Medicine in the Bronx, NY.[36] They found that neither total nor LDL cholesterol predicted the risk of having a heart attack or any other cardiovascular disease in very old men. Curiously, the authors concluded that, "The findings of this study suggest that an unfavorable lipoprotein profile increases the risk for cardiovascular morbidity and mortality."

Unfortunately this happens all too frequently. Researchers get a result that is contrary to the cholesterol hypotheses, and yet they write conclusions indicating hat their findings are in support. These misleading conclusions are most often written up in the summary of the papers, the only part of the paper that most doctors and researchers are likely to read. To find the contradictory results, you have to read the whole paper and meticulously study the tables.

In the elderly high cholesterol even seems to be protective. This was the surprising finding of Dr. Harlan Krumholz at the Section of Cardiovascular Medicine at Yale University and his coworkers. They followed 997 elderly men and women living in the Bronx, NY for four years. During a four year period about twice as many of the individuals with low cholesterol had a heart attack or died from one, compared to those with the highest cholesterol levels.[37]

Let me return to the study of the Framingham group. Perhaps you think that the cholesterol campaign was cancelled after the results of he Framingham study came in. Not at all. The reason low cholesterol levels were associated with greater mortality, said the investigators, was that people with low cholesterol levels were dying of other diseases. But their results contradicted that explanation. Wrote the authors: "Those whose cholesterol had *decreased* by itself during these 30 years ran a *greater* risk of dying than those whose cholesterol had *increased*. To cite the report: *For each 1 mg/dl drop of cholesterol there was an 11% increase in coronary and total mortality."*

Thus, not only total mortality but also coronary mortality had increased.

Now, stop for a moment! For many years we have been told how important it is to lower our cholesterol to prevent coronary heart disease. But the Framingham study demonstrated that if the cholesterol decreases by itself, the risk of dying *increases*.

Few people know about this alarming finding and the study is rarely discussed in the medical reviews of cholesterol and heart disease. Even worse, when the study is noted, it is cited as *supporting* the diet-heart idea! Consider the joint statement by the American Heart Association and the National Heart, Lung, and Blood Institute in their review entitled *The Cholesterol Facts: "The results of the Framingham study indicate that a 1% reduction...of cholesterol [corresponds to a] 2% reduction in CHD risk."*[38]

Please go back to the citation from the Framingham report. Yes, you are right. According to the original report mortality *increased*, and by 11% for each 1mg/dl reduction in blood cholesterol. But the review stated that mortality *decreased*.

Your next thought might be that the distinguished authors of the review referred to another of the numerous reports from Framingham, but they did not. And as we shall see, this was not their only "mistake." For example, in 1987, the same authors published a new report concerning the 30 years of follow-up in Framingham.[39] Without presenting anything other than complicated ratios and statistical calculations, and without referring to their previous report, they stated: "*The most important overall finding is the emergence of the total cholesterol concentration as a risk factor for CHD in the elderly.*"

Isn't it strange that the cholesterol liner continues its voyage without any reactions from the passengers or crew? The few who have observed that the ship is leaning are calmed by the captain's assurances that it has only struck an iceberg.[40]

Rule with many exceptions

Most supporters of the diet-heart idea think that the increased risk of coronary heart disease is present at all cholesterol levels. This concept is of course pleasant to the drug producers, for it implies that almost everyone should be treated, including those with a normal cholesterol.

This is not true, however. In most studies, the increased risk is present only above a certain level.[41] As a matter of fact, the relationship between the cholesterol level of the blood and the risk of coronary heart disease seems to be rather unsystematic. Women, for instance, should stop worrying immediately, because high cholesterol is not a risk factor for the female sex.[42] Few words have been aimed at this peculiar fact in the vast literature on cholesterol. When it is mentioned at all, it is said that the female sex hormones protect against heart attacks.

In fact, it seems more dangerous for women to have low cholesterol than high. Together with his team Dr. Bernard Forette, a French researcher from Paris, France, found that old women with a very high cholesterol lived the longest. The death rate was more than five times higher for women with very low cholesterol. The French doctors warned, of course, against lowering the cholesterol in elderly women,[43] but they could as well have warned against cholesterol lowering in any women, or, to be more precise, at all.

It is also notable that whereas high cholesterol has a slight association with increased risk for men in the US, it has no association for men in Canada. This conclusion was reached by Dr. Gilles Dagenais and his team in Quebec after having followed almost 5000 healthy middle-aged men for 12 years.[44] They explained away their surprising finding away by assuming that more than twelve years were needed to see the harmful effect of high cholesterol; obviously they were ignorant of the result from the 30-year follow-up study results.

Neither is blood cholesterol important for those who already had a heart attack. For instance, Dr. Henry Shanoff and his team at the University Hospital of Toronto studied 120 men ten years after their recovery from a heart attack and found that those with low cholesterol had suffered a second one just as often as those with high cholesterol.[45] Many others have confirmed their findings.[46]

In Sweden, Professors Lars-Erik Böttiger and Lars A. Carlson at the Karolinska Hospital found that the risk of coronary heart disease was higher for men with the highest cholesterol, but the risk was considerably lower than in Framingham.[47] They also found that if all kinds of

vascular disease caused by atherosclerosis were considered the risk was not increased at all. Those with low cholesterol died as often from vascular disease as those with high.[48]

And there are more exceptions, for instance the Maori people, who originally are Polynesians, but have migrated to New Zealand for several hundred years ago. Unlike the native Polynesians, Maoris often die from a heart attack, but they do it whether their cholesterol is low or high.[49]

In Russia, a *low* cholesterol is associated with an increased risk of coronary heart disease. This was the surprising finding of Dr. Dmitri Shestov from the Russian Academy of Medical Sciences in St. Petersburg. Dr. Shestov and his colleagues, one of them was Professor Herman Tyroler from the Department of Epidemiology at the University of North Carolina, had also analyzed HDL and LDL cholesterol, the “good” and the “bad” cholesterol. They found that a low LDL cholesterol was also associated with an increased risk and this was not due to low levels of HDL-cholesterol. In fact, those with low LDL values had the highest HDL values.[50]

Thus, a high cholesterol is dangerous for Americans but not for Canadians, Stockholmers, or Maoris, and a low cholesterol is dangerous for Russians. A high cholesterol is dangerous for men, but not for women; it is dangerous for healthy men, but not for coronary patients; and it is dangerous for men of thirty, but not for those of forty-eight and may even be beneficial for older people. Such discrepancies indicate that the association between high cholesterol and coronary heart disease is not due to simple cause and effect. The most likely interpretation is that a high cholesterol is not dangerous by itself but a marker for something else.

Many scientists who are critical of the diet-heart idea still have the impression that an increased level of cholesterol in the blood may be dangerous just because of its association with coronary mortality. Few know that the association is unsystematic and even rather weak. And even if the association had been both systematic and strong, this would not prove that it is the high cholesterol level itself that causes atherosclerosis or heart disease. There are at least five other plausible explanations for the higher cholesterol of patients with coronary heart disease.

Guilt by association

Familial hypercholesterolemia is one of them. Individuals suffering from this disease run a greater risk of dying early from a heart attack and they also have a raised cholesterol level. It is a widespread dogma that the increased cholesterol level, by promoting atherosclerosis, is the direct cause of their troubles. But as I shall discuss later it is questionable if the vascular changes seen in familial hyper-cholesterolemia is the same as atherosclerosis.

Smoking generates a slight increase of the blood cholesterol[51] but may induce heart disease by several other mechanisms, for instance by producing many free radicals. Smoking may induce a heart attack *and* an elevated cholesterol level.

Being overweight increases blood cholesterol a little, and weight reduction lowers it a little. Excess weight means an excess burden to the heart. Excess weight may induce a coronary *and* an elevated cholesterol level.[52]

High blood pressure is also associated with changes of blood cholesterol. Hypertension, untreated or treated, is seen in about a third of all individuals with a cholesterol level above 260 mg/dl but only in 15-20 percent of those with a cholesterol less than 220 mg/dl.[53] High blood

pressure, or rather the underlying cause, such as stress, may provoke a heart attack *and* raise blood cholesterol.

But the sharpest rise in cholesterol is seen as a result of emotional stress. An academic exam, blood sampling or surgery, conflicts at work or at home, loss of a spouse or a close friend, and various types of performance demands, have been found to increase the cholesterol level by ten to fifty percent.[54] Psychological stress may provoke a heart attack (for instance by spasm of the coronary vessels) *and* an elevated cholesterol level. A likely explanation is that during stress more cholesterol is produced by the liver because cholesterol is used in the manufacture of various stress hormones.

That a high cholesterol is a risk factor for heart disease may have other explanations, but none of them are ever discussed in the papers written by the proponents of the diet-heart idea.

"Look at Finland and Japan"

Perhaps you will ask why it is so scary that death from a heart attack is more common in Western societies, since dying from a heart attack may not be too bad. After all, most of us prefer to die quickly, without spending many years in a nursing home, crippled or senile. And remember that coronary heart disease is a disease of old age. In fact, on average, those who die from a heart attack have lived just as long as other people. Nevertheless, since the association between average blood cholesterol and death rates from coronary disease in various countries has been used as an argument for the diet-heart idea, let us look at some of the facts.

In the Seven Countries study Keys pointed to the association between blood cholesterol and heart mortality. The correlation is obvious, Professor Keys wrote and he illustrated his words with a graph.

It is not apparent from Keys's paper how the graph is constructed, but it is possible to draw a graph oneself by using the numbers from his tables. I have drawn such a graph choosing the *hard data*, meaning the number who died from coronary heart disease in the various districts, and compared them with the blood cholesterol values (**figure 2B**). If the diet-heart idea is correct heart attacks should, of course, be rare in the districts where cholesterol was low and common where it was high. But as seen from my chart, they were very far from that. Oddly, this important chart is not included in Keys's paper, although his paper is loaded with more or less relevant graphs.[55]

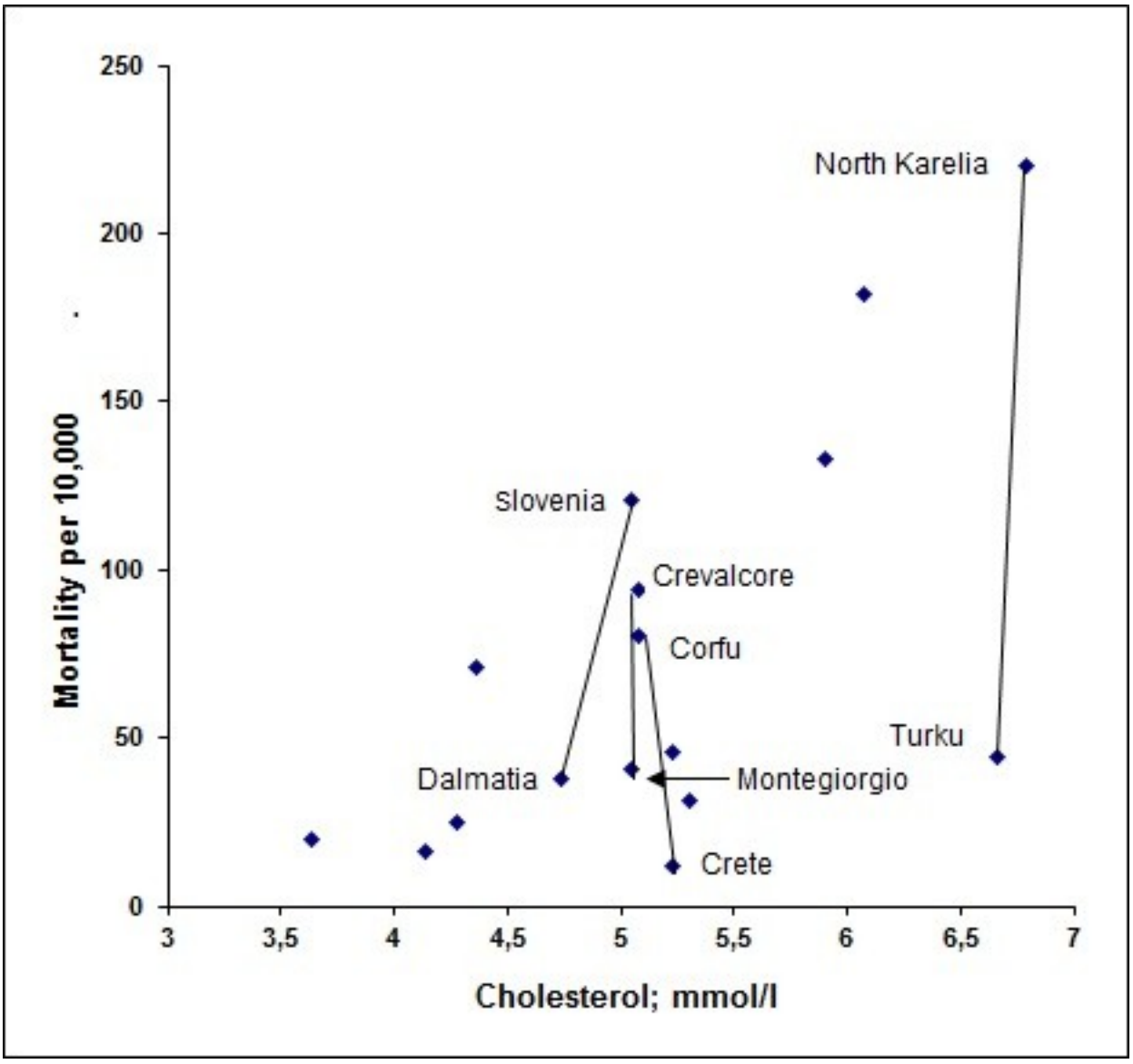

Figure 2B. Five year mortality of coronary heart disease and mean blood cholesterol in 15 populations in the Seven-Countries study. The populations that have been connected with lines are from the same country; see text. The figure is constructed from table data in the report of the Seven-Countries study. Note the great differences in coronary mortality at similar blood cholesterol levels.

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There is a notable scattering of the points in the figure. Note for instance that in the districts where fatal heart attacks were uncommon (less than 100 per 100.000) the cholesterol levels vary between the lowest and the second highest value. It is difficult from this figure to see that the number of heart deaths and the level of blood cholesterol are related. Possibly they are statistically related, but we should be skeptical about correlations that depend on just one or two observations. For instance, cover the point labeled Karelen with your hand and the slight impression of an association disappears completely.

Any suggestion of an association also disappears if you look at each country individually (symbols representing various populations in the same country are connected with a line). In Crevalcore, Italy, the number of deaths from heart disease was 2.5 times greater than in Montegiorgio, Italy, although the average blood cholesterol was identical. In Slavonia three times more died from heart disease than in Dalmatia, although the mean cholesterol in Slavonia was only insignificantly higher. In Finland people living in Karelia died five times more often from a heart attack than people living in the area of Turku although blood cholesterol differed only little. And finally, on the Greek island Corfu people died five times more often from a heart attack than on nearby Crete, although their cholesterol was lower.

If you go to the tables of Ancel Keys's paper again and do a little calculating you will discover another surprising finding: no correlation was found between the diet and the major electrocardiographic findings at entry. Considering that all electrocardiograms were analyzed in the American study center this finding should carry more weight than the correlation with the clinical diagnosis or the diagnosis on the death certificate, settled as they were on location by various physicians with varying competence and diagnostic habits.

But in his conclusion Ancel Keys wrote that the only factor which could explain the great differences between the number of heart attacks in the sixteen areas was the cholesterol level of the blood. And again and again the Seven Countries study is mentioned as a proof of the diet-heart idea: *Look at Finland and Japan*.

Instead, look at the figure once again. It is almost heart-breaking. Eager to prove his hypothesis, Keys unintentionally covered up one of the most interesting tracks. I suspect that many of you already have asked the question that Keys had the opportunity to answer twenty years ago. It is doubtful that the question can be answered so many years later. But, to ask it anyway, what is the factor that protects the inhabitants of Dalmatia, Montegiorgiu, Turku and Crete from coronary heart disease and that is absent in Slavonia, Crevalcore, Karelia and on Corfu?

Or, to turn the question around: why does death from coronary heart disease occur 3-5 times more often in the latter areas? We can blame none of the well-known risk factors because Keys found that they were evenly present in each pair of areas. If Ancel Keys and his coworkers had concentrated all their efforts in these eight places, if they had observed, investigated, questioned and turned every stone upside down they might perhaps have found something helpful to mankind.

This is the most tragic aspect of the cholesterol folly. Interesting side tracks are left unexplored, observations which do not fit with the idea are put aside, and any opportunity for a new discovery is allowed to slip by.

The Japanese Paradox

In Japan cholesterol levels are very low, and few people die from heart disease. This has been known for a long time and was confirmed by the Seven Countries study. Professor Keys also found that Japanese emigrants to the mainland USA had high blood cholesterol and died almost as often from heart attacks as Americans did, while the figures for Japanese emigrants to Hawaii lay somewhere in between.

Professor Keys was convinced that the difference was caused by the food, which in Japan was lean, while on Hawaii, and especially in the continental US, it was rich in animal fat.[56]

As usual Keys had no other explanation. And what he did not mention was that while coronary mortality increased after the Japanese had migrated to the US, stroke mortality decreased just as much and total mortality decreased much more.[57]

There is an alternative explanation to the increased coronary mortality after migration from Japan to the US.

As I mentioned earlier, calories from animal fat are usually expensive, and such food is therefore mostly consumed in rich countries, such as the Western, industrialized nations.

Calories from carbohydrates and vegetable oils are cheaper and such food therefore predominates in poor countries with a low degree of industrialization and a low standard of living. When Ancel Keys gathered his data in the early 1960s Japan belonged to this category. It was still a poor nation, successfully recovering from war, not the rich nation triumphant in industry that we know today.

Immigrants from a poor country are exposed in their new, richer country to many other things besides high-fat food. A multitude of factors in the Western environment or lifestyle may adversely effect the heart and the blood vessels, such as less physical activity, more stress, and more environmental and industrial pollutants.

In his doctoral thesis about coronary heart disease in Japanese immigrants, British physician Dr. Michael Marmot presents some interesting insights into the relationship between blood cholesterol levels and social factors, eating habits and lifestyle.[58] Dr. Marmot demonstrated that it was not the food that raised the cholesterol of the Japanese immigrants, nor high cholesterol values that increased their risk of coronary heart disease. He found that if they maintained their cultural traditions, they were protected against heart attacks, even though their cholesterol increased as much as in Japanese immigrants who adopted a Western lifestyle and who died from heart attacks almost as often as did native-born Americans. The most striking of Dr. Marmot’s findings was that *emigrants who maintained the Japanese traditions but preferred high-fat American food ran a smaller risk of heart disease than those who became accustomed to the American way of life but ate the lean, Japanese food.*

Thus, according to Dr. Marmot's study, there is something in the Japanese way of living that protects against coronary heart disease, and it is not the food.

Dr. Marmot himself points to the traditional Japanese culture, which is still a major factor shaping life in present-day Japan. In particular, the Japanese place great emphasis on group cohesion, group achievement, and social stability. Members of the stable Japanese society enjoy support from other members of their society and thus are protected from the emotional and social stress that Marmot believes to be an important cause of heart attacks. The Japanese traditions of togetherness contrast dramatically with the typical American emphasis on social and geographic mobility, individualism, and striving ambition.

Ignoring embarrassing data

We do not know whether Dr. Marmot's explanation is correct or not. However, if his *findings* are correct, the diet-heart idea must be wrong. But Dr. Marmot's results, as well as the many other embarrassing contradictory findings, have been ignored in the official reviews.

In 1979 for instance, the American Health Foundation organized an international conference with the aim of finding "the optimal cholesterol level." In a later step, the level was to be lowered in the countries where the conference participants thought it was too high. The written report from this conference[59] presented a meticulous account of Dr. Marmot's results including detailed information about the Japanese food, cholesterol levels and risk of heart disease. But Marmot's message (and the epidemiological data on which it was founded), was ignored.

Let's look at a few more examples of the researchers sweeping contradictory findings under the rug. A large review written in 1984 by Dr. William Kannel, head of the Framingham project, and his colleagues, stated that *there is a strong association between population means of total cholesterol and CHD incidence*, and here Dr. Kannel refers to Ancel Keys's Seven Countries study.[60] (*Total cholesterol* simply means cholesterol. The term *total cholesterol* is used in texts where subfractions such as LDL- and HDL-cholesterol are also mentioned.)

The largest review, *Diet and Health*, published in 1989, comes from the prestigious *National Research Council* and concluded as follows:

"*Epidemiological findings among populations and for individuals within populations consistently indicate a strong, continuous, and positive relationship between TC [Total Cholesterol] levels and the prevalence and incidence of, as well as mortality from, atherosclerotic CHD.*"[61]

Many supporters of the diet-heart idea seem to have stopped thinking critically. Perhaps, as members of a worldwide alliance that includes many distinguished researchers, they have become overconfident, too willing to assume that an idea must surely be valid if great numbers of people endorse it.

But if they were familiar with the way science has progressed through the centuries, they would know that the truth cannot be ruled out by the majority or decreed by consensus.

Another myth: "good" and "bad" cholesterol

Cholesterol is a peculiar molecule. It is often called a lipid or a fat, but the chemical term for a molecule such as cholesterol is alcohol, although it doesn't behave like alcohol. Its numerous carbon and hydrogen atoms are put together in an intricate three-dimensional network, impossible to dissolve in water. All living creatures use this indissolubility cleverly, incorporating cholesterol into their cell walls to make cells waterproof. This means that cells of living creatures are able to regulate their internal environment undisturbed by chemical changes in the surrounding milieu. The fact that cells are waterproof is especially critical for normal functioning of nerves and nerve cells. Thus, the highest concentration of cholesterol in the body is found in the brain and other parts of the nervous system.

Because cholesterol is insoluble, it circulates in the blood inside spherical particles composed of fats (lipids) and proteins, the so-called lipoproteins. Lipoproteins are easily dissolved in water because their outside is composed mainly of water-soluble proteins. The inside of the lipoproteins is composed of lipids, and here we have room for water-insoluble molecules like cholesterol. Like submarines, lipoproteins carry cholesterol from one place in the body to another.

These submarines, or lipoproteins, are categorized according to their density. The best known are HDL (High Density Lipoprotein), and LDL (Low Density Lipoprotein).

The main task of HDL is to carry cholesterol from the peripheral tissues, including the artery walls, to the liver. Here it is excreted with the bile, or used for other purposes, for instance as a starting point for the manufacture of important hormones.

The LDL submarines mainly transport cholesterol in the opposite direction. They carry it from the liver, where most of our body's cholesterol is produced, to the peripheral tissues, including the artery walls. When cells need cholesterol, they call for the LDL submarines, which then deliver cholesterol into the interior of the cells.

Between 60 and 80 percent of the cholesterol in the blood is transported by LDL and is called "bad" cholesterol. Only 15-20 percent is transported by HDL and is called *"good"* cholesterol. A small part of the circulating cholesterol is transported by other lipoproteins.

You may ask why a natural substance in our blood with important biologic functions, is called "bad" when it is transported from the liver to the peripheral tissues by LDL, but *"good"* when it is transported in the other direction by HDL. The reason is that a number of follow-up studies have shown that a lower-than-normal level of HDL-cholesterol and a higher-than-normal level of LDL-cholesterol are associated with a greater risk of having a heart attack, and conversely, that a higher-than-normal level of HDL-cholesterol and a lower-than-normal LDL-cholesterol are associated with a smaller risk. Or, said in another way, a low HDL/LDL ratio is a risk factor for coronary heart disease.

By now you know that a risk factor is not necessarily the same as the cause, and that something may provoke a heart attack and at the same time lower the HDL/LDL ratio. Let us have a look at some factors known to influence this ratio.

The cholesterol ratio caper

As mentioned above, people who reduce their body weight also reduce their cholesterol. A review of 70 studies showed that, on average, weight reduction lowers cholesterol by about 10 percent, depending on the amount of weight loss. Interestingly, it is only cholesterol transported by LDL that goes down; the small part transported by HDL goes up. In other words, weight reduction increases the ratio between HDL and LDL-cholesterol.

An increase of the HDL/LDL ratio is called *favorable* by the diet-heart supporters; cholesterol is changed from "bad" to *"good."* But is it the ratio or the weight reduction that is favorable? When we become fat, other harmful things occur to us. One is that our cells may become less sensitive to insulin, so that some of us even develop diabetes. And people with diabetes are much more likely to have a heart attack than people without diabetes, because atherosclerosis and other

vascular damage may occur early in diabetics, even in those without lipid abnormalities. In other words, overweight may increase the risk of a heart attack by mechanisms other than an unfavorable lipid pattern, while at the same time overweight lowers the HDL/LDL ratio.

You may also recall that smoking increases cholesterol a little. Again, it is LDL-cholesterol that increases, while HDL-cholesterol goes down, resulting in an *unfavorable* HDL/LDL ratio. What is certainly unfavorable is chronic exposure to the fumes from H paper and tobacco leaves. It should be obvious that instead of considering a low HDL/LDL ratio as bad, we should consider the possibility that smoking in and of itself is bad. Smoking may provoke a heart attack and, at the same time, lower the HDL/LDL ratio.

Exercise decreases the so-called bad LDL-cholesterol and increases the so-called good HDL-cholesterol.[62] In well-trained individuals the good HDL is increased considerably. In a comparison between distance runners and sedentary individuals, Dr. Paul D. Thompson and his team from Providence, Rhode Island, found that the athletes on average had a 41 percent higher HDL-cholesterol level.[63] Most population studies have shown that physical exercise is associated with a lower risk of heart attacks and a sedentary life with a higher risk. A well-trained heart is better guarded against obstruction of the coronary vessels than a heart always working at low speed simply because the vascular channels in the well-trained heart are broader; remember the wide coronary arteries of the Masai people who ran all day long after their cattle in Kenya. A sedentary life may predispose people to a heart attack and, at the same time, lower the HDL/LDL ratio.

Univariate and multivariate

Thus, the risk of having a heart attack is greater than normal for people with high LDL-cholesterol, but so is the risk for fat, sedentary and smoking individuals. And since such individuals usually have elevated levels of LDL cholesterol, it is, of course impossible to know whether the increased risk is due to the previously mentioned risk factors (or to risk factors we do not yet know) or to the high LDL-cholesterol. A calculation of the risk of high LDL-cholesterol that does not consider other risk factors is called a univariate analysis and is, of course, meaningless.

To prove that high LDL-cholesterol is an independent risk factor, we should ask if fat, sedentary, smoking individuals with a high LDL-cholesterol level are at greater risk for coronary disease than fat, sedentary, smoking individuals with low or normal LDL-cholesterol.

Using complicated statistical formulas, it is possible to do such comparisons in a population of individuals with varying degrees of the risk factors and varying levels of LDL-cholesterol, a so-called multivariate analysis. If a multivariate analysis of the prognostic influence of LDL-cholesterol also takes body weight into consideration, it is said to be *adjusted for body weight.*

A major problem with such calculations is that we know a great number of risk factors, but not all of them. Another problem is that the data generated by these and other complicated statistical methods are almost impossible for most readers, including most doctors, to comprehend. For many years researchers in this area have not presented primary data, simple means, or simple correlations. Instead, their papers have been salted with meaningless ratios, relative risks, p-values, not to mention obscure concepts such as *the standardized logistic regression coefficient,*

or the pooled hazard rate ratio. Instead of being an aid to science, statistics are used to impress the reader and cover the fact that the scientific findings are trivial and without practical importance. Nevertheless, let us have a look at some of the studies.

The "good" one

Publications almost beyond counting have studied the prognostic value of the *"good"* HDL cholesterol. The reason is, of course, that it is hard to find any prognostic value. If HDL-cholesterol had a heart-protecting effect of real importance, it would not be necessary to use the taxpayers' money to demonstrate the effect again and again in expensive studies. To be brief I shall tell you only about a few of the largest studies.

In 1986 Dr. Stuart Pocock and his team from London and Birmingham, England published a report concerning more than 7000 middle-aged men in 24 British towns.[64] The men had been followed for about four years after a detailed analysis of their blood. During this period 193 of the men had suffered a heart attack. As in most previous studies, these men had on average a lower HDL-cholesterol at the beginning than the men who did not have a heart attack. The mean difference between the cases and the other men was about 6 percent. This difference was small of course, but thanks to the large number of individuals studied it was statistically significant.

But this was a univariate analysis and as mentioned, the difference could therefore be explained in many ways. A multivariate analysis adjusted for age, body weight, cigarette smoking and non-HDL-cholesterol reduced the difference to an insignificant 2 percent. This means that those who had suffered a heart attack had a lower HDL-cholesterol mainly because they were older, fatter and smoked more than those who had not had a heart attack.

The British scientists compared their findings with those of six other studies. In five of them the differences were just as small. Only one study found a considerable difference, but it included 39 individuals only and thus was highly susceptible to bias. Dr. Pocock and his colleagues concluded that a low HDL-cholesterol level is not a major risk factor for coronary heart disease.

Their results were challenged in 1989 by nine American scientists headed by Dr. David Gordon at the National Heart, Lung and Blood Institute. They had analyzed the predicative value of HDL-cholesterol in four large American studies, including more than 15,000 men and women. [65] They thought that the British scientists had used an incorrect way to adjust their figures. Using another formula, the American researchers wrote, showed HDL-cholesterol to be a much better predictor.

But in one of the four studies the number of fatal heart attacks was identical in the first and second HDL tertile (individuals were classified into three groups, or tertiles, according to their HDL-cholesterol). In one of the studies the number of fatal cases was identical in the second and the third tertile, and in one study more deaths were seen in the third tertile (those who had the largest amount of the "good" cholesterol) than in the second tertile. And these figures were the unadjusted ones.

After adjustment the differences were even smaller. In three of the four studies, the differences lost statistical significance. And remember that the figures were not adjusted for physical activity, not to mention the risk factors we do not know yet.

Dr. Pocock and his colleagues returned with a new analysis later the same year, now using the same way of analyzing as had Dr. Gordon and his colleagues. At that time the participants in the study had been followed for 7.5 years and a total of 443 heart attacks had occurred.[66]

This time a difference was noted between the HDL-cholesterol of the heart patients and the others. The difference was small but statistically significant, even after adjustment. However, *the largest difference was noted for total cholesterol.* The authors therefore concluded that a determination of HDL-cholesterol may be of marginal additional value in screening and in intervention programs for risk of coronary heart disease. They could also have added that they did not adjust for all risk factors so that the difference could as well be due to the heart patients being, for instance, more stressed or less active physically than the others.

And even if the difference had remained after adjustment of all the known risk factors the crucial question is if HDL-cholesterol has any importance whatsoever. From what you have read till now and especially from the chapters to come, you will realize that there is little or no evidence, that blood cholesterol plays a role in coronary heart disease. If total cholesterol, a better predictor than HDL-cholesterol, is unimportant, how could HDL-cholesterol be important?

I am tempted to discuss the many other studies which did not find HDL-cholesterol a good predictor. But to avoid boring you, I shall mention only the 24-year follow-up of the Finnish group in the Seven Countries study, because this is one of the longest follow-up studies of HDL-cholesterol.[67] A total of 518 healthy men from three areas in Finland were followed. **Table 2A** gives the number of fatal heart attacks and the starting average HDL-cholesterol in each area.

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Country	**Initial HDL-cholesterol (mg/dl)**	**Mortality from Coronary heart disease Per 1000 men 24 years later**
Helsinki	44.8	81
West Finland	43.2	105
North Karelia	47.6	183

Table 2A. Mean HDL-cholesterol in three Finnish areas and coronary mortality 24 years later.

If HDL cholesterol were good for the heart, the smallest number of men should have died from heart attacks in North Karelia, where HDL-cholesterol was the highest. Instead, the number was twice as large as in Helsinki.

In their paper, Keys and his co-authors mentioned two equally large and long-lasting studies that also found lower HDL-cholesterol in the healthy survivors than in those who had died from coronary disease. But in the summary of the paper they wrote: *"These 24-year findings are not necessarily in conflict with reports in the literature on an inverse relationship between coronary heart disease incidence and HDL cholesterol."*

It is fortunate that low HDL-cholesterol itself does not increase the risk of a heart attack, because the prudent diet has a surprising effect on the HDL-cholesterol level. A French study by Dr. Frédéric Fumeron and his colleagues in Paris and Lille investigated the effect of two different diets on 36 healthy individuals. One diet contained 70 grams of butter, the other 70 grams of sunflower margarine; otherwise the diets were similar. Each individual ate both diets for three weeks; half of them started with the butter diet, half with the "prudent" margarine diet.[68]

As in many previous studies, analysis of the blood lipid levels before and after each period showed that the "prudent" diet lowered blood cholesterol. But it also lowered the "good" HDL-cholesterol, especially two of its subfractions called HDL-2 and LpA-I. Other studies have shown that these subfractions are especially "good." The authors also reviewed seven other studies with similar results.

The "bad" one

LDL has the strongest and most consistent relationship to individual and population risk of CHD, and LDL-cholesterol is centrally and causally important in the pathogenetic chain leading to atherosclerosis and CHD. These words you will find in the large review *Diet and Health*.

A scientific review is, like this book, an analysis of what has been done and what has been written about a certain subject. Reviews usually do not present observations or experiments performed by the authors themselves. Reviews help researchers by sparing them the tedious work of seeking the primary observations themselves in the library or in the electronic data bases. Furthermore, in their papers researchers can refer to a few reviews instead of to a large number of original works. But, of course, the researcher must be sure that the reviews are complete and correct and that they give a balanced view.

Reviews by distinguished scientific bodies are supposed to meet such standards. Therefore, you are probably wondering how the authors of *Diet and Health* had reached their conclusion about LDL-cholesterol. I wondered too, when I started to untangle the HDL-LDL issue,[69] because extensive reading had not yet given me the answer.

The fact is that very few analyses of LDL-cholesterol have been published. For example, in the hundreds of reports from the Framingham study very little is mentioned about LDL-cholesterol. An odd fact because all participants had this cholesterol fraction measured at the start and again later in the study.

Diet and Health is the official, most authoritative and supposedly most reliable review from the National Research Council in Washington. I was confident that its highly qualified authors would have the answer. What was their evidence? Upon which observations or experiments did they base their statements about the dangers of LDL-cholesterol?

Diet and Health cites four publications. First, inn 1973 Dr. Jack Medalie and his team at the Tel Aviv University in Israel published a five-year follow-up study of 10,000 Israeli male government and municipal employees.[70] Among a large number of factors relevant to the study of coronary heart disease they had measured total and LDL-cholesterol. According to *Diet and Health* LDL cholesterol has the strongest relationship to risk of heart disease. However, the Israeli study did not support these words, because *total* cholesterol, not LDL-cholesterol, had the strongest relationship to risk of coronary disease.

The second paper claimed by the *Diet and Health* authors to support the idea about the dangerous LDL cholesterol, was a 1977 report from the Framingham Study.[71] This study concerned HDL cholesterol, however. Only logistic regression coefficients (a statistical concept unknown to most doctors) for coronary disease on LDL-cholesterol were given, and one of the conclusions of the paper was that *LDL-cholesterol… is a marginal risk factor for people of these age groups* (men and women above 50 years). Some of the coefficients were indeed low. For women above the age of 70 it was negative, which means that women at that age ran a *greater* risk of having a heart attack if their LDL-cholesterol was low than if it was high. Thus, there was no support either from that paper.

Also the third paper[72] concerned HDL-cholesterol only. Thus, no support either.

The fourth reference was to the *National Cholesterol Education Program*, which produced another large review without original data.[73] One of its conclusions was that, *"a large body of epidemiological evidence supports a direct relationship between the level of serum total and LDL-cholesterol and the rate of CHD."* I became excited, thinking, "At last, the evidence."

The large body of evidence was to be found in three references. The first one was another large review without original data, *Optimal resources for primary prevention of atherosclerotic disease*,[74] with Dr. Kannel as the first author. I shall return to their review.

The next reference was yet a large review,[75] but nothing in that review was said about the matter.

The last reference was a report from the Honolulu Heart Study.[76] The conclusion of that paper was that, *"both measures of LDL-cholesterol were related to CHD prevalence, but neither appeared to be superior to total cholesterol."*

Before I discuss Dr. Kannel's review I shall mention another conclusion in the *National Cholesterol Education program*: *"The issue of whether lowering LDL-cholesterol levels by dietary and drug interventions can reduce the incidence of CHD has been addressed in more than a dozen randomized clinical trials."* This is a most misleading statement because at that time, in 1988, only four such trials had included an LDL-cholesterol analysis,[77] and only in one of them the number of heart attacks was lowered significantly.

Let me now return to the review by Dr. Kannel and colleagues, the one used as evidence by the authors of the *National Cholesterol Education Program*, which in turn was used as evidence by the authors of *Diet and Health*. Almost nothing was written about LDL-cholesterol in Dr. Kannel's review except for the following: *"Longitudinal studies within populations show a consistent rise in the risk of CHD in relation to serum total cholesterol and LDL-cholesterol at least until late middle-age."*

A little more cautious conclusion than in *Diet and Health*, it may seem, but even for this prudent statement the evidence was weak. References to six studies were given. In two of them LDL-cholesterol was not analyzed or mentioned at all.[78] In two reports LDL-cholesterol was only correlated to the prevalence of heart disease, which means that it was not a longitudinal study.[79] In one report two tables was aimed at the subject (tables 8 and 9) and showed that the predictive power of LDL-cholesterol was statistically non-significant.[80] In one study LDL-cholesterol was predictive for heart disease, but only for men between 35 and 49 and only for women between 40 and 44.[81]

In conclusion, the "large body of evidence" can be reduced to one single study, which showed a predictive value for LDL-cholesterol but for a few age groups only. The only valid conclusion therefore is that LDL-cholesterol is *neither* centrally *nor* causally important, it has *not* the strongest and most consistent relationship to risk of CHD, it has *not* a direct relationship to the rate of CHD, and it has *not* been studied in more than a dozen randomized trials.

You can read more about the above in one of my papers.[82]

Familial hypercholesterolemia—not as risky as you may think

Many doctors believe that most patients with familial hypercholesterolemia (shortened FH) die from CHD at a young age. Obviously they do not know the surprising finding of a Scientific Steering Committee at the Department of Public Health and Primary Care at Ratcliffe Infirmary in Oxford, England.[83] For several years, these researchers followed more than 500 FH-patients between the ages of 20 and 74 for several years and compared patient mortality during this period with that of the general population.

During a three-to-four-year period, six of 214 FH-patients below age 40 died from CHD. This may not seem particularly frightening, but as it is rare to die from CHD before the age of 40, the risk for these FH patients was almost 100 times that of the general population.

During a four-to-five-year period, eight of 237 FH-patients between ages 40 and 59 died, which was five times more than in the general population. But during a similar period of time, only one of 75 FH-patients between the ages of 60 and 74 died from CHD.

If these results are typical for FH, you could say that, between ages 20 and 59, about three percent of the patients with FH died from CHD, and between ages 60 and 74, less than two percent died from CHD, fewer than in the general population.

The authors stressed that the patients had been referred because of a personal or family history of premature vascular disease and therefore were at a particularly high risk for CHD. Most patients with FH in the general population are unrecognized and untreated. Maybe the prognosis of the Oxford patients would have been even better if they had been representative for all FH patients?

Dr. Eric Sijbrands and his coworkers from various medical departments in Amsterdam and Leiden, Netherlands have the answer. The Dutch researchers screened a large number of healthy people and found three individuals with very high cholesterol. A genetic analysis confirmed the diagnosis of FH and by tracing their family members backwards they came up with a total of 412 individuals. The coronary and total mortality of these members were compared with the mortality of the general Dutch population.

The striking finding was that the FH people had a normal mortality during the nineteenth and early twentieth century; in fact, mortality was even lower than in the general population during the nineteenth century. After 1915 the mortality rose to a maximum between 1935 and 1964, but even at the peak it was less than twice as high as in the general population.[84]

Again, very high cholesterol does not lead to a heart attack by itself. High cholesterol may even be protective against other diseases. This was the conclusion of Dr. Sijbrands and his colleagues. As support they mentioned that genetically modified mice with high cholesterol are protected against severe bacterial infections.

“Don’t be afraid, doctor, but my cholesterol is very high.” These were the words of a 50-year old lawyer who visited me for the first time for a health examination. And indeed, his cholesterol was high, over 400 mg/dl (10.3 mmol/l).

“But my father’s cholesterol was even higher,” he added. “He lived happily until he died at age 79 from cancer. And his brother, who also had FH, died at age 83. None of them ever complained of any heart problems.”

My “patient” is now 53, his brother is 56 and his cousin 61. All of them have extremely high cholesterol values, but none of them has any heart troubles, and none of them has ever taken cholesterol-lowering drugs.

So, if you happen to have FH, don’t be too anxious. Your chances of surviving are pretty good, even surviving to old age.

Myth 3: High-Fat Foods Raise blood Cholesterol

Ye shall eat the fat of the land.

Genesis 45:18

Food and fat in various populations

Why do levels of cholesterol vary in different people? Because of their food! This is the answer from Ancel Keys, stated over and over again in his papers. No alternative explanations are ever mentioned; Keys's hand never trembles when he writes about the influence of diet on blood cholesterol.

One of his arguments is that the average blood cholesterol is high in countries where people eat lots of high-fat food, especially foods high in animal fat, and low in countries where people eat little fat. And, asserts Keys, if an individual with low cholesterol moves to an area where people's cholesterol is high, then his cholesterol will also rise.

In 1958 Keys illustrated his idea with a diagram demonstrating the relationship between the amount of fat in the food and the cholesterol level of the blood in various populations (fig. 3A). [86]

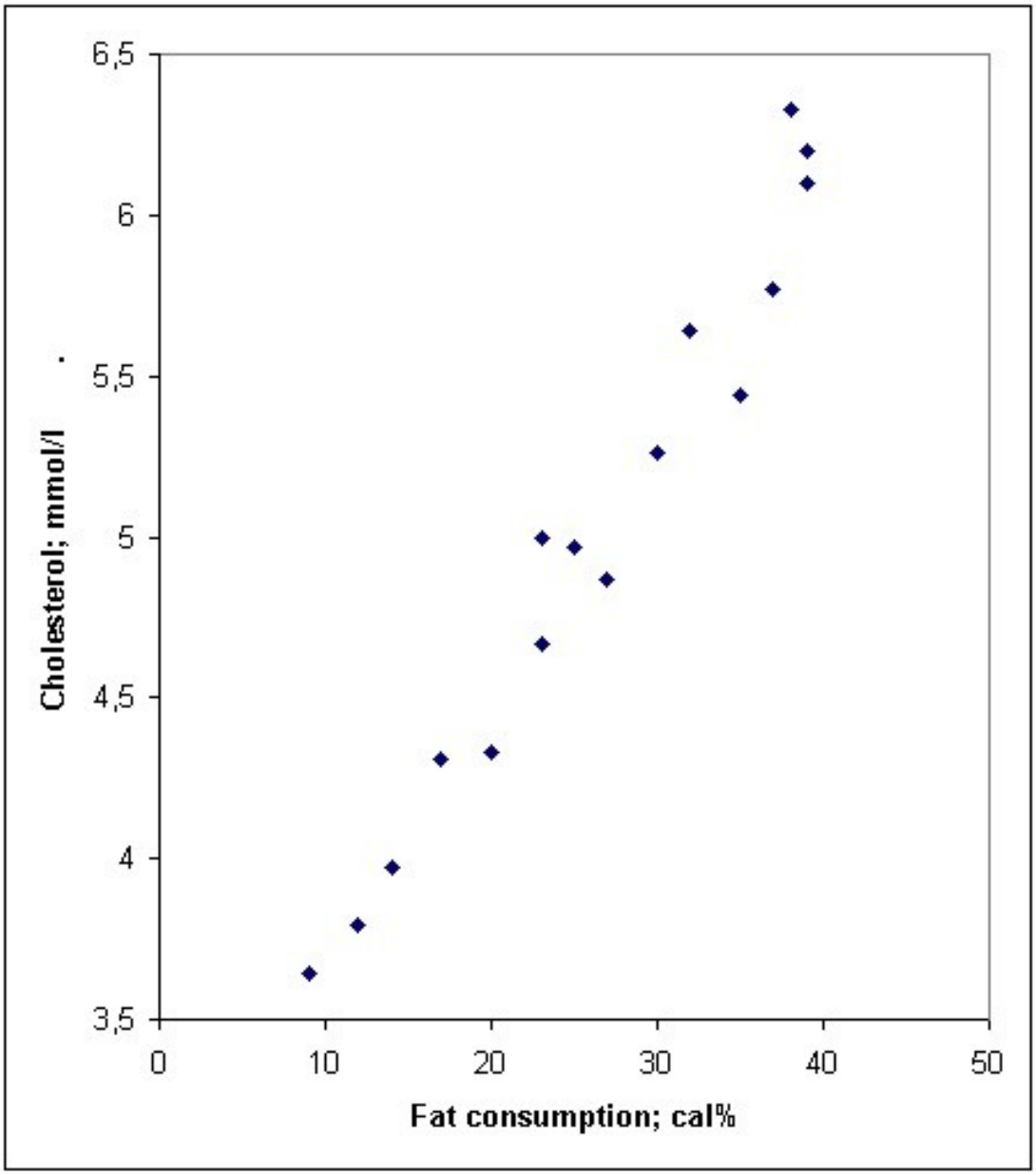

Figure 3A. Correlation between dietary fat and blood cholesterol in various populations. After Keys.

_____

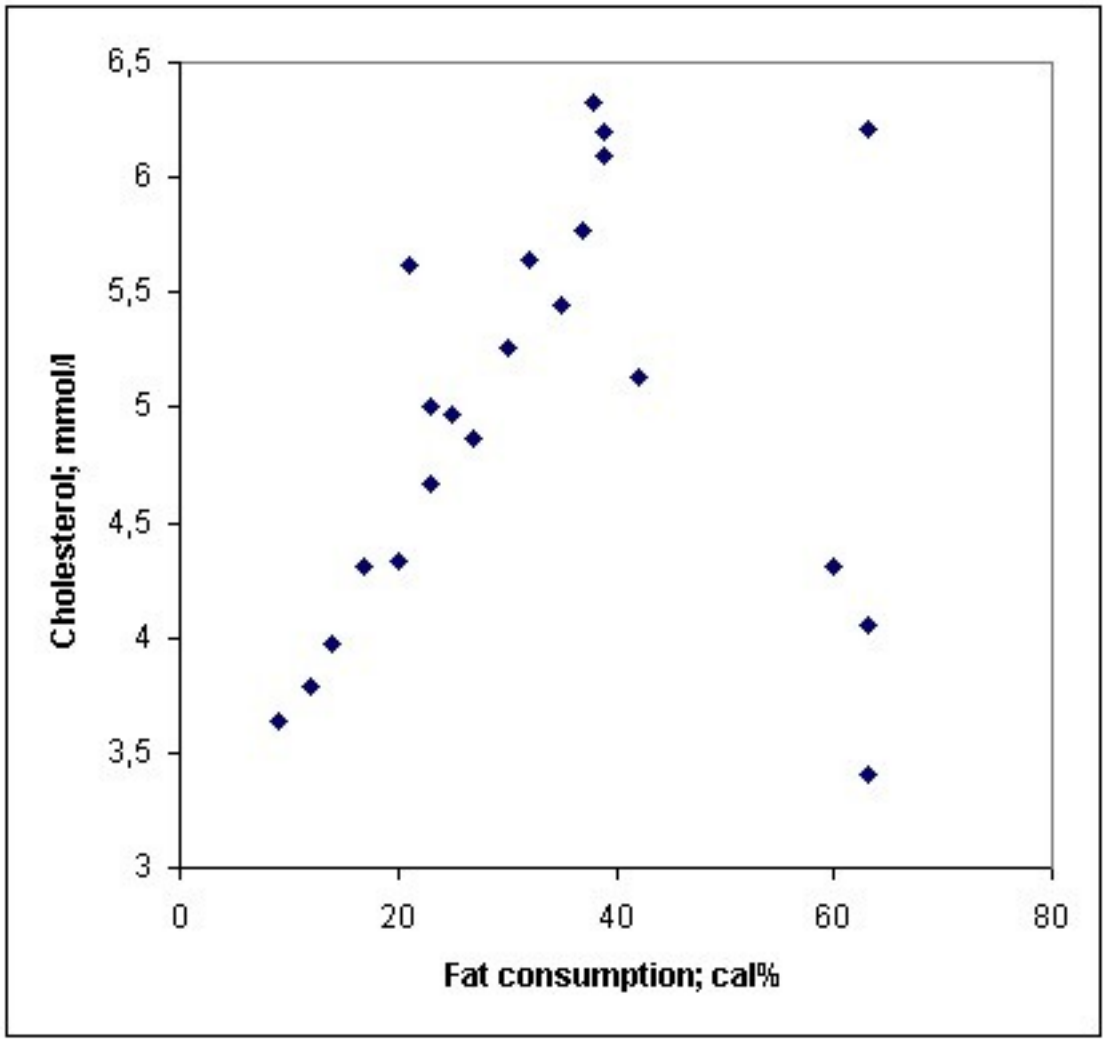

Fig. 3B. Same diagram as figure 3A, but including populations that Keys had ignored.

It is possible to draw an even curve through almost all points, an amazing result considering the uncertainties associated with the figures behind the individual points. It is highly unusual to find such a strong correlation in medical or biological science because observations of living creatures are much more imprecise than observations in physics and chemistry.

Note also that the figure gives the blood cholesterol related to the *total* amount of dietary fat. In his later study Seven Countries Professor Keys claimed that the correlation is far better if cholesterol is related to the intake of *animal* fat. Possibly you wonder how it could be better than shown in figure 3A. The reason is that in Seven Countries Keys found no correlation at all between total fat and heart mortality.

How come that in the first study Keys found a strong correlation, but in Seven Countries there was no correlation at all? The explanation is that in his first study Keys had ignored some remarkable populations.

Camels, cows and cholesterol

I have already discussed the discrepancies between the low blood cholesterol of the Masai and the Samburu cattle herders and their rich, high-fat food. Why didn't Keys include the Samburu people in his elegant diagram? Wasn't it interesting that for long periods they drank almost two gallons of milk each day. Milk from the African Zebu cattle is much fatter than our cow's milk, which means that the Samburus consume more than twice the amount of animal fat than the average American, and yet their cholesterol is much lower, about 170 mg/dl (4.36 mmol/l).[86]

Shepherds in Somalia eat almost nothing but milk from their camels. About a gallon and a half a day is normal, which amounts to almost one pound of butter fat, because camel's milk is much fatter than cow's milk.

But although more than sixty percent of their energy consumption comes from animal fat, their mean cholesterol is only about 150 mg/dl (3.85 mmol/l), far lower than that of most Western people.[87]

Cholesterol and coconuts

Dr. Ian Prior and his team from Wellington, New Zealand, studied the population of the Tokelau Islands and the Pukapuka atolls.[88] Here the main food is coconuts prepared in various ways, but seafood and chicken are also on the menu. Coconuts contain great amounts of coconut butter. Unlike most other types of vegetable fat coconut butter has a high content of saturated fatty acids, even higher than in animal fat.

On the Tokelau Islands the amount of saturated fat was almost twice that of Pukapuka and even higher than in the US, while the consumption of polyunsaturated oil was small on all islands.

The scientists confirmed that the Polynesian people really ate this great amount of saturated fatty acids by analyzing the fat beneath their skin. With a syringe they sucked out a little of this fat and found that its content of saturated fatty acids was twice that of Western people. Also, the chickens these Pacific islanders ate had a high content of saturated fatty acids in their tissue, probably because they ate a considerable amount of coconut.

The cholesterol of the Tokelauans was higher than that of the Pukapuka inhabitants as expected according to the diet-heart idea, but it was at least 20 percent lower than it should have been if Keys’s calculations were correct. Now to the most interesting point.

In 1966 a tornado pulled up a great number of coconut trees on the islands. The atolls could no longer feed their inhabitants and one thousand Tokelauans migrated to New Zealand. In New Zealand their diet changed markedly; the amount of calories from saturated fat was halved while the intake of polyunsaturated fat increased a little.[89]

Here was the perfect opportunity to prove the diet-heart hypothesis, but the results of this so-called “favorable” change n diet did not live up to expectations. Instead of going down as expected, the cholesterol of the Tokelauans increased by about 10 percent as seen in Table 3A.

———

	Tokelau	New Zealand
Proportion energy (%) from		
saturated fat	45%	21%
polyunsaturated fat	3%	4%
Blood cholesterol (mg/dl)		
men, 45-54 years	195 mg/dl	219 mg/dl
women, 45-54 years	213 mg/dl	225 mg/dl

Table 3A. Fat content of the food of Tokelau inhabitants and Tokelau emigrants in New Zealand, and their blood cholesterol level.

Thus, something in the environment or lifestyle in New Zealand had such a great impact of the Tokelauans that their cholesterol increased, although their consumption of saturated fat was reduced by half.

Experiments and reality

Another of Keys's arguments derives from the results of laboratory experiments to lower cholesterol by diet. The experiments are summarized as follows.

If energy is supplied mainly by saturated fatty acids, those dominating in animal fat and in coconut butter, blood cholesterol goes up a little.

If energy is supplied mainly by polyunsaturated fatty acids, those dominating in most vegetable fat and fat from seafood, blood cholesterol goes down a little.

Oddly, cholesterol in the diet has only a marginal influence on the cholesterol in the blood. The explanation is that we regulate our own production of cholesterol according to our needs. When we eat much cholesterol, the body's production goes down; when we eat only little, it goes up.

The fact that a suitable diet may change the blood cholesterol level has been demonstrated by the cholesterol-lowering trials. An extreme diet may lower the level by about ten percent; a more palatable diet only a few percent.[90]

Now to one of the cholesterol paradoxes. Although it is possible to change blood cholesterol a little in laboratory experiments and clinical trials by dieting, it is impossible to find any relationship between the make up of the diet and the blood cholesterol of individuals who are not

participating in a medical experiment. In other words, individuals who live as usual and eat their food without listening to doctors or dieticians show no connection between what they eat and the level of their blood cholesterol.

If the diet-heart idea were correct individuals who eat great amounts of animal fat would have higher cholesterol than those who eat small amounts; and individuals who eat small amounts of vegetable fat should have higher cholesterol than those who eat great amounts. If not, there is no reason to meddle with people's diet.

Counting money and counting food

Even in the early 1950s the Framingham study included dietary analyses. Almost one thousand individuals were questioned in detail about their eating habits. No connection was found between the composition of the food and the cholesterol level of the blood. Wrote Drs. William Kannel and Tavia Gordon, authors of the report: *"These findings suggest a cautionary note with respect to hypotheses relating diet to serum cholesterol levels. There is a considerable range of serum cholesterol levels within the Framingham Study Group. Something explains this inter-individual variation, but it is not the diet."*

For unknown reasons, their results were never published. The manuscript is still lying in a basement in Washington.[91]

In a small American town called Tecumseh, Michigan a similar study was performed by a team of researchers from the University of Michigan headed by Dr. Allen Nichols. Experienced dieticians asked in great detail more than two thousand individuals what they had eaten during a twenty-four hour period. The dieticians also asked about the ingredients of the food, analyzed the recipes of home-cooked dishes, and exerted great care to find out what kind of fat was used in the kitchen. Calculations were then performed using an elaborate list of the composition of almost 3000 American food items. Finally the participants were divided into three groups, a high, a middle, and a low level group, according to their blood cholesterol.

No difference was found between the amounts of any food item in the three groups. Of special interest was that the low-cholesterol group ate just as much saturated fat as did the high-cholesterol group.[92]

These studies concerned adults, but no association has been found in children either. At the famous Mayo Clinic in Rochester, New York, for instance, Dr. William Weidman and his team analyzed the diet of about one hundred school children. Great differences were found between the amount of various food items eaten by these children, and also great differences between their blood cholesterol values, but there wasn't the slightest connection between the two. The children who ate lots of animal fat had just as much or just as little cholesterol in their blood as the children who ate very little animal fat.[93]

A similar investigation of 185 children was performed in New Orleans with the same result.[94]

Even if no pains are spared to investigate the diet of people the information gathered is of course uncertain. Who can recall everything that he has eaten in the last twenty-four hours? And the diet of one 24-hour period may not be representative of the usual diet of the individual. A better result can be achieved by studying the diet over several days, preferably during various seasons

of the year. In London professor Jeremy Morris and his team used this method and asked ninety-nine middle-aged male bank staff members to weigh and record what they ate over two weeks.

Have you ever bargained in a bank? Maybe you will succeed in the director's office, but certainly not at the teller's counter. If anyone is scrupulous with nickels and dimes, it is those sitting behind the glass of the bank.

Ninety-nine of these honorable men were asked to sit at home with a letter balance and weigh every morsel they ate for a whole week. But again, this meticulous method revealed no connection either between the food and the blood cholesterol level.

To be certain, seventy-six of the bank men repeated the procedure for another week at another time of the year: no connection was found, once again.

To be absolutely certain the researchers selected those whose records were especially detailed and accurate. Once more, no connection was found.[95]

Another look at Finland

On average Finnish people have the highest cholesterol in the world. According to the diet-heart idea's proponents, this is due to the fat-rich Finnish food. The answer is not that simple, however. This was demonstrated by Dr. Rolf Kroneld and his team at the University of Turku.[96]

They studied all inhabitants of the village of Iniö near Turku, and twice as many randomly selected individuals of the same age and sex in North Karelia and in southwest Finland.

Apparently a health campaign had struck Iniö. There the consumption of margarine was twice as great and the consumption of butter only half as what it was in the other places. Also, the people of Iniö preferred skimmed over whole milk; the residents of the other districts did not. But the highest cholesterol values were found in Iniö.

The average value for male Iniö inhabitants was 283 mg/dl, on the two other places it was 239 and 243 mg/dl. Regarding women, the difference was even greater.

Threshold on trial

Is it really wise to meddle with people's dietary habits if their food has no influence on their cholesterol? And how do those who believe that fat food is dangerous explain all these negative results?

Most often they argue that information about dietary habits is inaccurate—and it is. But this explanation is not applied consistently. It is never used against the studies mentioned in chapter 1, those that claimed a connection between fat intake and heart mortality in various countries, although the uncertainty in these studies was much higher. The researchers did not determine dietary information by any questionnaires or surveys at all, but instead on estimates of the average intake of fat based on the highly uncertain assumption that people eat what is available. Such soft evidence should be treated with the utmost care but diet-heart supporters refuse to do more than applaud investigations that support their theories

But even information gathered through direct questioning is inaccurate. A crude relationship should appear if a sufficiently large number of individuals are meticulously questioned. If not, the influence of the diet, if any, must be so weak that it cannot possibly have any importance.

Diet-heart supporters also argue that most people in Western communities already eat great amounts of fat and cholesterol. This argument declares that we have already crossed a threshold of too much animal fat in the diet so that more fat does not make any impact on our blood cholesterol.

The argument is in conflict with the studies I have mentioned above. Dr. Nichols and his team, for instance, declared *"The distribution of daily intake of total fat, saturated fat, and cholesterol by the individuals in this study was quite broad."* And indeed it was. For about 15 percent of the men less than 12.8 percent of the calories came from animal fat, and for about 15 percent of the men more than 20 percent of the calories came from animal fat.

Consider now that it is the goal of the *National Cholesterol Education Program* to lower the intake of animal fat of all Americans to about ten percent of their caloric intake. Almost 15 percent of the participants in the Tecumseh study already ate that amount of animal fat that low, and yet it was impossible to see a difference between the blood cholesterol of those who ate small amounts of animal fat and of those who ate much more. Does it make sense to recommend this drastic reduction of animal fat if the cholesterol of those who already eat that little is just as that of the epicure?

The Mayo Clinic study also revealed a wide range of fat intake. The lowest intake of animal fat was 15 grams per day (less than 10 percent of the caloric intake); the highest was 60 grams per day. In the Bogalusa study, the range was still broader. The lowest intake of *all* fats was 17 grams per day, the highest 325 grams per day. (No information was given about the relative proportion of animal fat to vegetable oils.)

In Jerusalem a team of researchers, led by Dr. Harold Kahn studied the diet and blood cholesterol of ten thousand male Israeli civil servants. The dietary habits varied considerably between people from Israel, Eastern Europe, Central Europe, Southern Europe, Asia and Africa. The intake of animal fat varied from ten grams up to two hundred grams daily, and there were also considerable differences between their cholesterol values.[97]

If the intake of animal fat were of major importance for the cholesterol level in the blood it should be possible to find some kind of relationship from a study of so many individuals with such great variations in blood cholesterol and dietary habits. But there was no relation in this Israeli study either. Extremely low cholesterol values were seen both in those who ate small amounts of animal fat and in those who ate the most animal fat, and high cholesterol values were seen at all levels of animal fat intake.[98]

The scientists from Israel also studied the value of various ways of dietary questioning. Many studies have recorded the diet during only one 24 hour period only. Even if this information were accurate it may not be representative of the diet for the rest of the year, far less for a whole life-time. The Israeli scientists found that the best information came from a questioning over several days and during different seasons of the year, the method used in the study of the bank tellers. Using this expensive and time-consuming method in a smaller study of sixty-two individuals

they could not find a correlation either; the correlation coefficient between animal fat intake and blood cholesterol was zero point zero.

Vegetarians usually have lower cholesterol than other people and they eat little animal fat. But vegetarians differ from the rest of the human population in more than their diet. They are usually more interested in their health, they usually smoke less, they are usually thinner, and they usually exercise more often than other people. Whether it is their diet, or their other living habits, or perhaps something else that lowers their blood cholesterol is unknown.

The fact that blood cholesterol is influenced by the diet in laboratory experiments and clinical trials but not in people who live without the interference of scientists and dieticians has a simple explanation: Blood cholesterol is controlled by more powerful factors than the diet. If these factors are kept reasonably constant in a laboratory experiment or a clinical trial, it is possible to see the influence of the diet alone.

The question, however, is whether a lowering of blood cholesterol by diet is permanent. As mentioned above, the body tends to keep blood cholesterol at a fairly constant level. The dietary experiments mentioned above went on for a few months at most. The cholesterol control mechanisms of the human body probably needs more time to adapt to a fat intake that differs from the usual one. Over millions of years mammals, including homo sapiens (our kind of men), have developed effective mechanisms to counteract unfavorable changes in all blood constituents. Salt and water, for instance, are regulated rapidly within narrow limits, because even small deviations may have a strong influence on the functions of the body. Extreme variations of other substances, such as proteins and fats, have no serious consequences in the short run; the adaptation is thus slow. But in due time also these deviations may be counteracted; this has been demonstrated by the Masais, the Samburus, the Somalian shepherds, and many others.

Food and blood cholesterol

You may ask why I have written so much about fats. After all, it is blood cholesterol levels that matter, not the level of fats in the blood, and the most important thing should be how much cholesterol we eat, not how much fat. If we eat lots of cholesterol, doesn't our blood cholesterol increase? It is not that simple.

Have you limited your daily consumption of eggs, the richest source of cholesterol in our food? If so, the following statement will either make you angry or allow you to breathe a sigh of relief. The cholesterol in your food has little or no influence at all on the cholesterol in your blood.

Even the most zealous proponents of the diet-heart idea know this very well, but they keep silent, because how on earth can you promote the idea that high blood cholesterol is a threat while allowing people to eat as much cholesterol as they like? The truth is that cholesterol in your food can't influence your blood cholesterol by more than a few percent.

Numerous studies have shown that in people who eat a normal Western diet, the effect on blood cholesterol of eating two or three extra eggs per day over a long period of time can hardy be measured.[99]

To find out how eating eggs influenced my own cholesterol, I once used myself as a human guinea pig without asking for permission from the ethics committee. Before and during the experiment I analyzed my blood cholesterol. My cholesterol at the start of the experiment was 278 (7.13), close to a determination made ten years earlier. The results are shown in **Table 3B.**

Day	Number of eggs consumed	Blood cholesterol (mg/dl)
0	1	278 mg/dl
2	4	-
3	6	-
4	8	266 mg/dl
5	8	264 mg/dl
6	8	257 mg/dl
7	8	274 mg/dl
8	8	246 mg/dl

Table 3B. Egg consumption and cholesterol values in one skeptical Swedish doctor.

The data from my daring experiment showed that instead of going up, my cholesterol went down a little, even though I was eating two or three times more cholesterol than my body normally produces itself. Why didn't my cholesterol go up?

Of course, one should be careful about drawing conclusions from an experiment on a single individual. However, it is not forbidden to speculate a little; after all, eight eggs a day represents a substantial amount of cholesterol.

Most probably, no change took place at all. Cholesterol measurements can never be as exact as measurements of your weight or height. If you take a blood sample, divide it between ten test tubes and analyze the cholesterol concentration of each tube, you will probably get ten different values. The difference between the lowest and the highest can be as great as 15 percent or more, although the true concentration is, of course, identical in all nine samples. Normal day-to-day

cholesterol variations make it even more difficult to get an accurate measurement. The small decline in my cholesterol level could simply have been due to imprecise measurements.

What we do know is that when we eat large amounts of cholesterol, our cells slow down their own production of this vital substance. Part of the surplus in the blood is temporarily stored in the liver and part is excreted with the bile. In my case, this regulation was performed so efficiently that my blood cholesterol did not rise, in spite of a substantial increase in my daily cholesterol intake. Perhaps my cholesterol would have finally gone up if I had continued longer with my experiment, but even if eggs are a good and nutritious food, who wants to eat eight eggs a day?

Non-responders

Proponents of the diet-heart idea would argue that I am what they call a "non-responder." According to this view, some members of the human race are able to maintain the same blood cholesterol level even after having eaten large amounts of cholesterol. Maybe so, but in that case, most of mankind are non-responders. This can be deduced from a study performed by Dr. Martijn Katan and his group at the Agricultural University in De Dreijen, the Netherlands.[100] They gave test individuals a low-cholesterol diet for two weeks, followed by a high-cholesterol diet for another two weeks.

In some of the test individuals, called the hyper-responders, the cholesterol rose by 11 to 42 percent, whereas in others, called the hypo-responders, the cholesterol change varied from a *decrease* of 11 percent to an increase of 4 percent. These two groups, the hypo- and the hyper-responders, then participated in a second experiment, again with a high-cholesterol diet for two weeks. But this time their cholesterol levels changed very little, and the change was about the same in each group. Thus, the experiment did not support the idea about hypo and hyper-responders.

Surprised and disappointed with this unexpected result, the researchers decided to perform yet another experiment, this time with a total intake of almost one gram of cholesterol per day, and for three weeks instead of two. This time it was a little better, but there was a lot of individual variation. As the authors wrote: *"Quite a number of subjects who appeared hyper-responsive in one experiment proved to be hypo-responsive in another experiment."*

To get a significant difference between the two groups, the researchers resorted to the so-called one-tailed t-test—a less stringent parameter that is not accepted among scientists for use in research where the expected result can go in either direction—and here the result certainly went in both directions. It is not particularly scientific either to continue an experiment until you get an outcome that suits your hypothesis, because sooner or later chance will produce a suitable result. The explanation for the haphazard results is, of course, that good friend of uncritical researchers, Mr. Chance.

Obviously, cholesterol in the diet has only a marginal influence on cholesterol in the blood. Why? Because we regulate our own production of cholesterol according to our needs. When we eat large amounts of cholesterol, our body's production goes down; when we eat small amounts, it goes up.

But even if dietary saturated fat or cholesterol raises cholesterol in the blood a little, this effect is not particularly important—this is what scientists call a surrogate outcome. The crucial question is whether a high intake of saturated fat leads to cardiovascular disease, and whether you can prevent such disease by lowering the intake. In the next chapter you will see that both assumptions are false.

Myth 4: High Cholesterol Blocks Arteries

Theorists almost always become too fond of their own ideas, often simply by living with them for so long. It is difficult to believe that one's cherished theory, which really works rather nicely in some respects, may become completely false.

Francis Crick

Nobel Prize laureate together with James Watson for discovering the structure of DNA

Cholesterol: Villain or Innocent Bystander?

Although scientists should do more questioning, in cholesterol research one statement never gets questioned because it is considered just as self-evident as the law of gravity. Even many opponents of the diet-heart idea neglect to question this statement. And what is this statement? It is that, when its level is high in the blood, cholesterol passes through the vessel walls, transforming arteries from smooth canals to rocky rapids.

Doctors and scientists may debate whether cholesterol leaks in passively or is actively transported by cells. But there is a general agreement about the importance of the cholesterol level of the blood; the higher it is, the faster the arteries become sclerotic.

As early as 1953, Ancel Keys wrote: *"It is a fact that a major characteristic of the sclerotic artery is the presence of abnormal amounts of cholesterol in that artery. And he added: this cholesterol is derived from the blood."*[101]

No proofs, and no arguments, not from Keys and not from his followers. Cholesterol comes from the blood, and that's the end to it. Scientists discuss how high the cholesterol level has to be for atherosclerosis to start, but they do not discuss whether the cholesterol level by itself has any importance. The role played by cholesterol in the process of atherosclerosis is no longer under discussion; it has been settled forever, or so we are led to believe. Let us have a closer look at the facts.

Calcium and kidney stones

A finding that has convinced many scientists is the fact that when you inject cholesterol molecules made radioactive they are found at a later time in the atherosclerotic lesions. But calcium salts of kidney stones have been circulating in the blood also, once upon a time. It isn't possible, however, to prevent or eliminate kidney stones by lowering the calcium level in the blood, nor is it possible by lowering dietary calcium. And if we exclude a rare disease called hyperparathyroidism calcium stones are certainly not due to a high calcium level in the blood because the level in patients with kidney stones is not higher than normally. The calcium salts in kidney stones originate from the blood, but we simply do not know why and how they become organized in the kidneys as stones. *Any* substance in a pathological structure in our body has at some time been transported by the blood. Its presence in the structure, be it a kidney stone or a sclerotic plaque or anything else, doesn't necessarily mean that the structure is produced by a high level of this substance in the blood. That high blood cholesterol doesn't produce atherosclerosis is also evident from many studies.

If cholesterol molecules circulating in the blood tend to settle in the arterial wall and produce atherosclerosis only because the blood contains more of them than normal, then people with high blood cholesterol should on average be more sclerotic than people with low blood cholesterol, this is pure logic. The protagonists also claim that this is the case. Let me show that they are wrong.

False connections

There are many ways for scientists to find a false correlation, and false correlations can mislead both scientists and their readers. Good, sound science is difficult; false answers are all too easy, even for the scientist who means well.

Let us start with the situation where we have recorded the blood cholesterol and the degree of atherosclerosis in a large number of dead individuals. To see if blood cholesterol and degree of atherosclerosis are related we draw a diagram where blood cholesterol is read on the horizontal axis and the degree of atherosclerosis on the vertical axis. We may now obtain a false correlation if we have put together young and old individuals in our study, because in most studies old people on average have higher cholesterol and more atherosclerosis than have young people. Therefore, the young individuals with their somewhat lower cholesterol and their low degree of atherosclerosis will mainly be represented by the symbols in the lower, left part of the diagram, and the old ones with their somewhat higher cholesterol and much more pronounced atherosclerosis will probably be represented by the symbols in the upper, right part. Thus, if we do not know the age of the studied individuals we may think that there is a correlation between blood cholesterol and atherosclerosis, when in fact it is between cholesterol and age, and between atherosclerosis and age.

It is therefore necessary to study narrow age groups. For a scientifically valid answer, the question to ask is whether someone of sixty who has high blood cholesterol is more sclerotic than another sixty-year-old person whose blood cholesterol is low.

A false correlation may also appear if the study includes many participants with familial hypercholesterolemia. Such people always have very high cholesterol values and some of them have severe atherosclerosis early in life. All of them will therefore be represented by symbols in the right side of the diagram; many of them in the upper corner. If many of these people are studied together with normal people, the statistics will be skewed and will automatically produce a correlation between cholesterol and atherosclerosis. And if the written results of the study present only the mean statistical values and correlation coefficients, or if the symbols do not specify the participants with familial hypercholesterolemia, readers will not be able to see this bias or skewing effect.

I shall not discuss here whether it is the high cholesterol that causes atherosclerosis in people with familial hypercholesterolemia or not. What is certain, though, is that these people have a rare, genetic abnormality in their ability to metabolize cholesterol. And, because of that, they cannot be used as proof that high cholesterol causes atherosclerosis in the 99% or more of the normal population. Individuals with familial hypercholesterolemia should be studied separately, not mixed in with normal people, that is elementary. Nevertheless, almost all studies include both groups and in many studies people with familial hypercholesterolemia are heavily overrepresented.

Thus, many factors can prevent a scientist from arriving at valid statistical calculations. Let's keep that fact in mind as we look at some of the scientific studies that have convinced the scientific community that high cholesterol causes atherosclerosis.

Landé and Sperry

The first study of a possible correlation between blood cholesterol and degree of atherosclerosis was published by the pathologist Kurt Landé and the biochemist Warren Sperry at the Department of Forensic Medicine of New York University.[102] The year was 1936. To their surprise, they found absolutely no correlation between the amount of cholesterol in the blood and the degree of atherosclerosis in the arteries of a large group of individuals, who had died violently. In age group after age group their diagrams looked like the starry sky. Because Landé and Sperry were cautious and methodical, they should have wrecked the diet-heart idea before it ever began years later. Or, more accurately, if those who promoted the diet-heart idea had read Landé and Sperry's paper, they would probably have dropped the idea at once.

But the few who remember Landé and Sperry misquote them and claim that they *found* a connection,[103] or they ignore their results by arguing that cholesterol values in the dead are not identical with those in living people.

Veterans explained away

That problem was solved by Dr. J. C. Paterson from London, Canada and his team.[104] For many years they followed about 800 war veterans. These men were confined to a hospital because they were mentally ill or needed residential care. Over the years, Dr. Paterson and his coworkers regularly analyzed blood samples from the veterans. Because the veterans were all between the ages of sixty and seventy when they died, the scientists were informed about the cholesterol level over a large part of the time when atherosclerosis normally develops.

Blood cholesterol varied considerably from one veteran to another but for each individual it was fairly constant, so that, for example, those who had low cholesterol at the beginning of the study usually had low cholesterol just before they died.

A postmortem was performed on all the veterans who died. Changes in their degree of atherosclerosis were measured, and so was the amount of cholesterol in the walls of the arteries. Like Drs. Landé and Sperry, Dr. Paterson and his colleagues did not find any connection between the degree of atherosclerosis and the blood cholesterol level; patients with low blood cholesterol were just as sclerotic as those with high blood cholesterol.

But the studies of the veterans were also explained away. Supporters of the diet-heart idea declared that the veterans had eaten the same food and that there are much greater variations in the amount of dietary fat consumed by people living outside an institution.

Although we don't know what each individual veteran ate, it is probably safe to assume that many supplemented the hospital diet with candy bars and potato chips and other supposedly unhealthy foods. It is probably a safe assumption, too, that some of the veterans left the fatter foods untouched on their plates in the dining hall, whereas others did not. But let us assume that all these men ate approximately the same amount of fat, confined as they were to an institution. In that case, the diet-heart idea that blood cholesterol depends on the amount and type of fat we

eat must be wrong, because the blood cholesterol levels of these veterans varied considerably, just as much as in the study by Landé and Sperry.

High cholesterol and smooth arteries

In the city of Agra in India, Dr. K. S. Mathur and his coworkers have performed a similar study. [105] Their first step was to measure blood cholesterol in twenty patients shortly before death and then a varying number of hours afterwards. They found that the cholesterol values were nearly the same if sampled before death and within sixteen hours after. Thus, they showed that blood samples taken very shortly after death are reliable; an important confirmation of the study done by Drs. Landé and Sperry. Dr. Paterson's group in Canada did a similar test and with the same result.

Next, Dr. Mathur and his colleagues studied two hundred people who had died suddenly by accident without any preceding disease. Like Drs. Landé and Sperry, and like Dr. Paterson, the Indian researchers could find no connection between the level of cholesterol and the degree of atherosclerosis. Of the two hundred dead people, those with low blood cholesterol had just as much atherosclerosis as those whose cholesterol was high.

Similar studies have also been performed in Poland[106], in Guatemala[107] and in the USA, [108] all with the same result: no correlation between the level of cholesterol in the blood and the amount of atherosclerosis in the vessels.

We are the only good ones

But some studies *did* find a correlation. One of them was the famous study from Framingham, Massachusetts. The correlation in Framingham was minimal, however. In statistical terms, the correlation coefficient there was only 0.36. Such a low coefficient indicates a desperately weak relationship between variables, in this case, of course, between cholesterol and atherosclerosis. Usually, scientists demand a much higher correlation coefficient before they conclude that there is a biologically important relationship between two variables. Usually, but Framingham was not quite the usual case; it involved huge amounts of government funding.

The very low correlation coefficient was arrived at after much study. First, many of the townspeople of Framingham had their cholesterol tested several times over a period of several years. Then, Dr. Manning Feinleib of the National Heart, Lung, and Blood Institute, led a team of coworkers in studying the coronary vessels of those who had died. The researchers were eager to learn which of the many factors they had studied was most important in the development of atherosclerosis in these dead people from Framingham. Was it blood cholesterol or the number of cigarettes smoked, or something else?[109]

After carefully describing the atherosclerosis in the coronary arteries of the dead people, Dr. Feinleib and his associates concluded that it was blood cholesterol levels that best predicted the degree of atherosclerosis. Neither age nor weight nor blood pressure nor any other factor was as good as blood cholesterol. But the correlation coefficient between cholesterol and atherosclerosis was a mere 0.36.

The written report of the study offered no diagrams and no information about cholesterol and atherosclerosis of each of the individuals whose bodies had been examined. And the report did not discuss the very low correlation coefficient; it didn't even comment upon that matter.

When scientists reach a result contrary to all others, it is routine—not merely usual but routine—to provide a detailed report about the result and also to discuss any possible ways in which the study may have been biased away from accuracy and truth. In the Framingham case, there was an especially great need for this routine scientific procedure to be followed. Not only was the correlation coefficient so trivial, but this study, funded with millions of taxpayers' dollars by The National Institute of Health, could have a major impact on national health care and the American economy. If there was no connection between cholesterol and atherosclerosis, as all the previous studies had shown, then there was no reason to bother about cholesterol or the diet. And billions of taxpayers' dollars could have been spent more wisely than in lowering cholesterol of healthy people.

But the scientists conducting the Framingham study had no reservations. They were eager to stress their own excellence and to highlight the weaknesses of Dr. Paterson's study of Canadian war veterans. In their report, they did not mention the studies of Drs. Landé and Sperry at all, nor the study of Dr. Mathur in India, nor the studies in Poland or Guatemala and the USA. And when the Framingham study authors mentioned Dr. Paterson's study, it was only to criticize without putting their own cards on the table. Some of those hidden cards are fascinating to wonder about.

For example, how were the dead of Framingham chosen for postmortem examination? From 914 dead individuals the researchers examined only 281. And from the 281, they selected 127 (14 percent of all dead) who became the subjects of an autopsy program especially designed to investigate the heart and its vessels.

Thus, those chosen for autopsy in the Framingham study were not a random sampling of the population, as they had been in the previous studies. The report from Framingham said nothing about the selection criteria, although scientific studies routinely do. Usually the determining factor is age. A postmortem is seldom performed on people who have died peacefully in old age, as most of us will. Primarily, a postmortem is restricted to young and middle-aged people, who have died before their time, and so it was in the Framingham study. Almost half of those autopsied were younger than 65 years. For this reason, the autopsied subjects must have included a relatively large number with familial hypercholesterolemia. Furthermore, people with this disease are of special interest to scientists studying the cholesterol problem and were probably chosen for autopsy in a program tailored to investigate coronary disease. With only 14% of the Framingham dead chosen for autopsy, the risk of preferably selecting those with this metabolic abnormality must have been great.

The ungrateful dead

Two studies with a design similar to that of the Framingham study have been published from Japan. One, led by Dr. Noriya Okumiya, took place at the Kyushu University;[110] the other, directed by Drs. Shuichi Hatano and Toshihisa Matsuzaki, occurred at the Geriatric Hospital in Tokyo.[111] In both studies the researchers said that the level of blood cholesterol correlated with the degree of atherosclerosis.

But in the first of these studies of dead Japanese citizens, the correlation appeared only in people with a low or normal cholesterol level; in the second, it appeared only in elderly people. The reports of the studies presented no individual figures, merely correlation coefficients, and these were as small as in the Framingham study. Moreover, the researchers did not explain the fact that the small correlation coefficient between cholesterol and atherosclerosis was present only in some groups but not in others.

More remarkably, among the dead people with high cholesterol, the degree of atherosclerosis was the same, whether these people were young or old. Logically, since atherosclerosis develops more and more as people grow old, it should develop faster in people whose cholesterol is high, or it should if the diet-heart idea were true.

Perhaps you're thinking that the degree of atherosclerosis was the same in all age groups because death had consistently weeded out only the most arteriosclerotic. But all degrees of atherosclerosis were present among those who had died.

The fact that atherosclerosis was just as severe in people of all ages with high cholesterol must mean that the cholesterol level was unimportant. After all, if the cholesterol level had been of any importance, the old people should have been much more sclerotic than the younger ones, after living far longer with high cholesterol.

Similar peculiar results turned up in a study done in Oslo, Norway, where atherosclerotic diseases have been investigated for many years in a great number of the city's inhabitants. The project included a study of coronary atherosclerosis, led by Dr. Lars Solberg and his coworkers in cooperation with researchers at the Louisiana State University in New Orleans. The authors of the final report from this large study claimed that in Oslo, too, the degree of atherosclerosis correlated with the level of blood cholesterol. But, as in the previous studies, the correlation was very weak. And the correlation may have stemmed from the fact that the researchers did not consider the twenty-year age difference between the youngest and the oldest of the people whom they studied.[112]

In the investigation from Oslo, the weakness of the correlation between atherosclerosis and cholesterol appeared in many ways. For instance, many of the people who had no narrowings of the coronary vessels had cholesterol as high as in the people who had narrowings of all three coronary vessels. Furthermore, people with two narrowed coronary vessels had, on average, a lower cholesterol level than those with just one narrowed vessel. The scientific word for such results is *unsystematic*, which means that Mr. Chance and Mrs. Bias have determined their outcome.

Coronary angiography

If we take a solution of iodine atoms and inject them into a blood vessel of a living person, we can see, with X-rays, the inside of that vessel. This is the principle behind the medical technique called angiography. A narrow and flexible plastic tube is inserted into the femoral artery in the groin and pushed gently upwards through the aorta, the chief artery of the human body, until it reaches the vessel to be investigated; for instance those that provide the heart muscle with blood, the coronary vessels. When the tip of the catheter has been placed in the entrance of one of the coronary vessels, the iodine solution is slowly injected.

With the advent of bypass surgery that allow us to replace old and roughened coronary vessels with new and smooth ones, coronary angiography has gained great importance. On the x-ray pictures, the shadows show how much the coronary vessels have been narrowed.

If we know the cholesterol values of the patients studied with coronary angiography and compare these values with the angiographic pictures we can test the cholesterol hypothesis. If blood cholesterol is the most important factor in the production of atherosclerosis, as we have been told for decades, then people with rough and irregular vessel shadows should have higher cholesterol than people with smooth artery shadows.

It seems as if every specialist in coronary angiography in America has performed his own study, funded with federal tax monies awarded by the National Heart, Lung and Blood Institute. In paper after paper published in various medical journals, using almost identical words, these medical specialists emphasize the importance of the blood cholesterol level for the development of atherosclerosis.[113]

But the reports offer no individual figures, only correlation coefficients, and these are never above a minimal 0.36, usually even smaller. And they never mention any of the previous studies that found no association.

Studies based on coronary angiography are fundamentally flawed, or they are if their findings are meant to be applied to the general population. Coronary angiographies are performed mainly on young and middle-aged patients with symptoms of heart disease, which means that a great number of patients with familial hypercholesterolemia must have been included in all angiographic studies. Again, there is an obvious risk for the kind of bias that I have described earlier.

The fact that this objection is justified was demonstrated in a Swedish study performed by Dr. Kim Cramér and his coworkers in Gothenburg, Sweden. As in most other angiographic studies the patients with the highest cholesterol values had on average the most sclerotic coronary vessels.

But if those who were treated with cholesterol-lowering drugs were excluded, and almost certainly this group must have included all patients with familial hypercholesterolemia, the correlation between blood cholesterol and degree of atherosclerosis disappeared.[114]

Another Japanese paradox

You have already heard that in Japan the food is meager, blood cholesterol is low and the risk of getting a heart attack is much smaller than in any other country. Given these facts you will most probably say that in Japan atherosclerosis must be rare.

The condition of the arteries of American and Japanese people was studied in the 1950s by Professors Ira Gore and A. E. Hirst at Harvard Medical School and Professor Yahei Koseki from Sapporo, Japan.[115] At that time US people on average had blood cholesterol of 220 mg/dl whereas Japanese had about 170 mg/dl.

The aorta, the main artery of the body, from 659 American and 260 Japanese people were studied after death. Meticulously all signs of atherosclerosis were recorded and graded. As

expected atherosclerosis increased from age 40 and upward, both in Americans and in Japanese. Now to the shocking fact.

When the degree of atherosclerosis was compared in each age group there was hardly any difference between American and Japanese people. Between age forty and sixty Americans were a little more sclerotic than Japanese; between sixty and eighty there was practically no difference, and above eighty Japanese were a little more sclerotic than Americans.

A similar study was conducted by Dr JA Resch from Minneapolis and Dr's N. Okabe and K. Kimoto from Kyushu, Japan.[116] They studied the arteries of the brain in 1408 Japanese and in more than 5000 American people and found that in all age groups Japanese people were more sclerotic than Americans.

Those who want us to lower our cholesterol say that heart attacks are caused by atherosclerosis in the vessels of the heart, not in the vessels of the aorta or the vessels of the brain and they are right. Curiously, the coronary arteries of Japanese people are in fact less affected by atherosclerosis than the vessels of Americans and this may explain why Japanese people rarely get a heart attack.

But why are the aorta and the vessels of the brain just as sclerotic in Japan where cholesterol is much lower than in the US? If high cholesterol causes atherosclerosis in the vessel walls it should of course do it in any vessel because the cholesterol level is identical whether the blood comes from the heart or the brain or any other organ. Isn't it much more likely that something else causes atherosclerosis than cholesterol? Something that may vary between the vessels, for instance the blood pressure? Blood pressure may vary greatly in various arteries depending on their. For instance, the tension of the coronary vessels, but not necessarily of other vessels, increases significantly when you are mentally stressed, and mental stress varies considerably between individuals and, as Dr. Marmot argued in his Japanese migrant study, probably also between populations.

Cholesterol is innocent

That people with a low cholesterol become just as sclerotic as people with a high cholesterol is, of course, devastating for the diet-heart idea. But the names of Landé and Sperry, Paterson, and Matur do not appear in the hundreds of papers and books published every year by the proponents of this idea.

"But what about the animal experiments?" the proponents of the diet-heart idea may ask. "You cannot explain away all the animal experiments!"

What the animal experiments have taught us is the subject of the next chapter.

Myth 5: Animal Studies Prove the Diet-Heart Idea

Rabbit tricks are positive successes.

Henry Houdini

Animals eat the wrong food

Perhaps you're finding the cholesterol question in man a little complicated and it is. But it's nothing compared to the situation in the animal kingdom, although, if it will comfort you, I'll say now that cholesterol studies just don't apply to man.

None of the mammals of the world are exactly like us as regards cholesterol. They have other amounts of it in their blood, they rarely eat as we do, and most of them do not become arteriosclerotic.

Many mammals never eat food containing cholesterol. If they are force-fed a cholesterol-rich diet, the cholesterol level of their blood rises to values many times higher than ever seen in normal human beings. And since such animals cannot dispose of the cholesterol they have eaten, every organ soaks up the cholesterol as a sponge soaks up water.

If animals are so different from us, how can we use them to prove that fat food and cholesterol are dangerous to human beings? Using cholesterol-rich fodder, it is possible to induce in rhesus monkeys arterial changes that vaguely resemble human arteriosclerosis, but it is not possible in baboons. How do we know if man reacts like a rhesus monkey or like a baboon or in some very different way?

These obvious weaknesses of animal studies have not prevented thousands of scientists from thinking up numerous ways to test animals in their laboratories.

There are however, many experiments and observations that may give us food for thought. Let's start by looking at arteriosclerosis and coronary disease in wild animals. What does arteriosclerosis look like in the arteries and heart of animals living outside the laboratories?

Arteriosclerosis with an appearance similar to that in man has been found in many animals, but more rarely and less widespread, probably because many wild animals suffer a violent death as youngsters and thus rarely reach the age of arteriosclerosis. An animal with pronounced atherosclerosis may also be an easy pray.

Arteriosclerosis is found most often in birds, possibly because their blood pressure is higher than in land animals. But animal fat or cholesterol in the diet is not the cause. The seed- and grain-eating pigeons, for instance, and the fish-eating penguins become just as arteriosclerotic as the birds of prey.

There is no support for the diet-heart idea from the four-legged creatures, either. Arteriosclerosis has not been observed in beasts of prey, but it is not unusual in the vegetarian mammals that they devour. Also, sea lions and seals become arteriosclerotic; obviously it doesn't help them that their fish diet provides more polyunsaturated fat than most humans eat.[117]

Unfortunately, it is not this naturally occurring arteriosclerosis that has interested the students of cholesterol and coronary heart disease in animals. In a scientist with an open mind many relevant questions should arise. For instance, if vascular changes similar to human arteriosclerosis are found in some wild animals but not in others, why do these changes occur in the vegetarians and the sea animals and not in those feasting on animal fat? And is it possible to prevent or treat spontaneous arteriosclerosis in animals? Why have scientists studied the vascular changes created by force-feeding in laboratories and totally ignored the spontaneous arteriosclerosis?

Obviously, before they start their animal experiments, almost all scientists have concluded on their own that it is dietary fat and cholesterol that cause arteriosclerosis and coronary heart disease. So, instead of studying the animals' own arteriosclerosis they induce pathologic changes in the vessels by cholesterol-feeding and call it arteriosclerosis.

Let's have a look at some of their results.

Rabbits and cholesterol

The rabbit is a docile and placid animal. It doesn't bite, taking blood samples from its long ears is easy, and a rabbit is cheap. But the main reason that the rabbit has become the most common animal in the cholesterol laboratories is its way of reacting to cholesterol-rich fodder.

The rabbit, of course, is a vegetarian. If a rabbit is forced to eat food that it would never eat voluntarily and that it cannot digest or metabolize, its blood cholesterol rises to values 10-20 times higher than the highest values ever noted in human beings. Cholesterol percolates all through the rabbit; its liver and kidneys become fatty, its fur falls off, and its eyes become yellowish from a build-up of cholesterol that it can neither store, metabolize nor excrete. Finally, it dies, not from coronary disease but from loss of appetite and emaciation—it starves.

It is true that cholesterol is also deposited in the arteries of the rabbit, but nothing even remotely resembling human arteriosclerosis is seen. Cholesterol appears in different places in a rabbit's vessels than in man's, the microscopic changes are different, no haemorrhages or clefts appear as they do in man, no thrombus or aneurysms formation in the artery walls, and it is impossible to induce a heart attack by dietary means alone. The only effect that the rabbit shares with man is the increased cholesterol content of the arterial wall.

Overfeeding other beasts with cholesterol and animal fat produces varying results. The characteristics of the pathologic changes are similar to those in the rabbit, but the amount and location of cholesterol in the arterial walls vary. As a rule it is extremely difficult to provoke a heart attack in animals by dietary manipulations. To be successful, the scientist needs to combine diet with something else, such as a hormone injection or mechanical damage to the animal's arteries.

In rare experiments heart attacks have been seen in laboratory animals fed with cholesterol and animal fat. But this is no proof that the food is the cause, because both arteriosclerosis and coronary heart disease can also be seen in zoo animals fed their natural food. To prove that the unnatural food is causal, two groups of laboratory animals should be studied, with one group given the fat food and the other group given its natural food.[118]

Hunger-striking hearts

Those who experiment with animals often forget that the animals don't like it. This fact is crucial in studies of coronary heart disease, since frustrations and psychologic stress are considered a possible cause of the disease. In this context it may be interesting to look at some experiments performed by the American physician and scientist Dr. Bruce Taylor and his coworkers. (This is the same Dr. Taylor whom I discussed in Chapter 2.) The diet-heart proponents often cite these experiments as proof that animal fat causes arteriosclerosis and coronary heart disease in man.

Dr. Taylor and his colleagues studied wild rhesus monkeys captured from the jungle. To produce "arteriosclerosis," they gave the monkeys a fodder to which had been added a great amount of cholesterol. Throughout the experiment, the monkeys were housed individually in small dog cages, an arrangement they obviously disliked. To prevent escape the cages were reinforced with solid metal sheets.

The monkeys disliked their food perhaps more than their housing. They ate only a little and threw the rest around their cages. For long periods they went on hunger strikes.

Taking blood samples from these unhappy monkeys was difficult for all involved. To get enough blood, the groin artery of the monkey was punctured. Obviously this measure was unpleasant because at the sampling the monkeys resisted violently: they screamed, urinated and defecated. [119]

Of 27 monkeys, one had a heart attack after being experimented upon for four years in this basement laboratory in Chicago. Interestingly, this animal was hyperactive and extremely nervous, the scientists wrote.[120]

They didn't tell why it was interesting. Maybe factors other than the high blood cholesterol could have caused the heart attack in this intelligent animal isolated in a small cage for years, fed a bad-tasting diet and regularly subjected to terrifying blood samplings. Could that be? We don't know. Taylor and his colleagues, and most others who have cited their study in later papers, consider the cause to be the food and the high cholesterol level, that and nothing else.

In these experiments, the cholesterol of the monkeys climbed to values as high as ever measured in human beings. But it was not the cholesterol level that determined the outcome. This fact was demonstrated in an interesting experiment by Dr. Dieter Kramsch and his coworkers at the Evans Department of Clinical Research and the Cardiovascular Institute in Boston.

Dr. Kramsch and his colleagues studied as many monkeys as Dr. Taylor did, but Dr. Kramsch's project separated them into three groups. One group received fodder natural to monkeys, and the two others received fodder with added butter and cholesterol. The group fed the normal fodder and one of the groups fed the enriched fodder sat in their cages, inactive, throughout the experiment. The third group was allowed to exercise.

Only the inactive monkeys fed the butter and cholesterol developed coronary arteriosclerosis and coronary heart disease. But the monkeys that were allowed to exercise had wide, almost smooth coronary arteries, although their cholesterol was almost as high as that of the inactive monkeys! [121]

Unfortunately Dr. Kramsch and his team did not report what happened with the inactive monkeys fed their normal fodder. This is most curious because had these monkeys not developed atherosclerosis, it would have meant that it is the combination of inactivity and high-fat food that produces atherosclerosis. And if these inactive monkeys on normal fodder had developed atherosclerosis just as did the inactive monkeys on high-fat fodder, it would have meant that inactivity, not high-fat food, is the culprit. Both alternatives would have added most interesting information. Could it be that the study results were so controversial that the researchers dared not report them? We don't know.

Honest proponents of the diet-heart idea admit that it is by experimenting on human beings, not on animals—to prevent arteriosclerosis and coronary heart disease, not to create them—that the idea may be proved. And they think they have successfully proved it.

In the next chapter we shall see if they are right.

Cholesterol lowering in children

Zealous proponents of the cholesterol hypothesis argue that we should begin cholesterol-lowering measures in childhood. They say that atherosclerosis starts in the early years; therefore, all parents should test their children's cholesterol and teach them to eat "properly," beginning at the age of two. This age limit was chosen because, in spite of their clever persuasions, diet-heart proponents would have difficulty convincing parents that whole milk, an allegedly poisonous food for adults, is harmful to babies. So "intervention" is held off until the tender age of 24 months, when most youngsters in the US are put on skimmed milk, milk substitutes and low-fat foods.

The argument for giving growing children a draconian diet can be made by claiming that the fatty streaks, the thin layer of cholesterol-laden cells situated on the inside of most arteries, are the forerunners of atherosclerosis. These fatty streaks appear even before we are born and are found in the vessels of all children, even in populations where atherosclerosis is rare. The public has not been told that the presence of fatty streaks does not mean that atherosclerosis will develop, and that there is no evidence that these fatty streaks are due to high cholesterol, or that they will disappear if we lower cholesterol in children.

In addition, high cholesterol in childhood does not mean that cholesterol will be high later in life. Several studies have shown that about half the children with high cholesterol at age two have normal cholesterol when they reach puberty.

And even if high cholesterol in childhood remained high in adulthood and predicted cardiovascular disease later in life, how should we treat the children? The answer from the proponents is: by diet! For this reason, many children are now being fed chemically processed margarine and a variety of processed, synthetic, low-fat products instead of nutritious and natural foods like whole milk, cheese, meat and eggs.

And the effect of diet on blood cholesterol is hardly measurable, especially in children. The only way to lower cholesterol effectively is by drugs—even the proponents admit that. But even if we had evidence that cholesterol-lowering measures begun at the age of two were of benefit, we have no evidence that these measures would compensate for the side effects of an unhealthy diet or daily intake of drugs for many years because, luckily, such trials have never been carried out.

At best, emphasis on lowering cholesterol in children will create families of unhappy hypochondriacs obsessed with their diet and blood chemistry. At worst, it will have unfortunate effects on the growth of children because foods containing cholesterol and animal fats are rich in important nutrients.

Ravnskov U. Prevention of atherosclerosis in children. The Lancet 355, 69, 2000.

Myth 6: Lowering Your Cholesterol Will Lengthen your Life

But besides real diseases we are subject to many that are only imaginary, for which the physicians have invented imaginary cures; these have then several names, and so have the drugs that are proper for them.

Jonathan Swift (1667-1745)

Time for truth

As one scientific study after another has shown, people can gorge on animal fat for many years and still keep their blood cholesterol low. What we have learned also is that atherosclerosis and heart attacks may occur whether one's food is meager or fat, and most surprisingly, whether cholesterol is high or low. Given these facts, is there any reason to think that lowering blood cholesterol with diet or medicine can prevent heart attacks?

Based on what I have presented so far, the answer is no. In fairness, however, it still may be possible that high-fat food contains something other than cholesterol and saturated fatty acids that might be dangerous to the heart, or that high blood cholesterol slows the coronary circulation in some way other than by stimulating atherosclerosis. It might just be possible to reach the correct conclusion from the wrong premises.

The diet-heart idea itself is invalid, as I have already demonstrated in several ways. But the best way to know for sure if fat food and a high cholesterol level are dangerous is to use human beings as guinea pigs, to see if coronary heart disease can be induced by feeding these people animal fat or by elevating their blood cholesterol, or to see if heart attacks can be prevented by feeding the experimental subjects a low-fat diet or by lowering their blood cholesterol.

The idea to raise blood cholesterol during several years by dietary means is stillborn no matter how interesting it seems. The ethical committees that must approve all experiments on living creatures should certainly condemn the idea. Fortunately the Masais and other populations already have performed the experiment for us with well-known result.

It is much easier to get a permission to lower blood cholesterol. Many researchers have received permission and have tried although lowering blood cholesterol is possibly more dangerous than increasing it, as I shall soon explain.

To evaluate the effect of lowering blood cholesterol, all other risk factors must remain unchanged. If the test individuals also stop smoking, reduce their body weight or start exercising, or receive treatment for their elevated blood pressure, change their work or get fired, fall in love or get divorced, move to another place with a different climate and culture, or do something else that may influence the condition of their heart or blood vessels, then we do not know what we should attribute the test result to. Is it the cholesterol lowering or is it something else? And this is not the only problem.

The diet-heart proponents say that the prevention of atherosclerosis cannot start too early in life. They add that the best results may be seen if prevention start before the rougher, more rocky deposits develop in our arteries. Here comes a problem, however, because coronary heart disease

is uncommon before the age of fifty. To prove that cholesterol lowering prevents heart attacks in young and middle-aged people it is therefore necessary to study many thousands of individuals, preferably those at unusually high risk for heart attacks.

The question we ask is, if fewer heart attacks are seen among people whose cholesterol is lowered by treatment than among untreated people. A cholesterol lowering experiment must therefore include also untreated control subjects. By control subjects, we mean people who have identical risk factors for coronary heart disease, people with, on average, the same blood cholesterol, smoking habits, body weight, and so forth as the individuals who will be manipulated with treatment.

In sufficiently large studies, risk factors usually become evenly distributed by chance, provided that the test subjects and the control subjects are assigned to their two groups on the basis of some random feature such as their day of birth, or by leaving their assignment to a computer. Studies that include randomly selected control subjects are called controlled randomized studies.

As you can see, it is extremely difficult to design even the initial steps of a scientifically acceptable trial. The standards of science are high, however. In fact, they are so high that, even if we manage to select a test group and a control group with almost identical risks for heart disease, we must remember that almost identical and absolutely identical are not the same thing and that we will never know all the factors that may, or may not, stimulate the development of the disease in these people.

To these inevitable problems the trial directors themselves have added one more. If the test individuals are asked not only to lower their blood cholesterol but also to quit smoking, or to lose excess body weight, to get more exercise, or to do something else that we think may be beneficial, we do not know if a possible reduction of heart disease is caused by cholesterol lowering or by something else. Unfortunately, this method, called multiple risk factor intervention, has been used in many trials.

Sighted or blind?

Many researchers have tried to prevent coronary heart disease with diet or drugs. Some of the first trials had so many technical errors that even the diet-heart proponents ignore them when they argue for their idea in their reviews.

One of the more serious errors was that the trials were not blinded. For a trial to be blinded, the patients must not know if they belong to the treatment group or to the control group. In the best experiments, called double-blind trials, not even the doctors know which group any given patient belongs to. Blindness prevents the treated subjects from feeling better merely because they know they are being treated and the control subjects from feeling worse merely because they know they are receiving no treatment; double blindness prevents the doctors who want the treated subjects to benefit, from leaping to conclusions based more on their own hopes than on scientific facts.

Up to 1968 the results of eleven dietary trials were known. Professor Jerome Cornfield at the University of Pittsburg and Dr. Sheila Mitchell at The National Heart, Lung and Blood Institute analyzed these trials. They found that the best results were seen if the doctors knew which group the participants belonged to. In six trials, the doctors knew, and in four of these six the number of

heart attacks was reduced. In five trials, the doctors did not know, and in three of these five there was no difference between the number of new heart attacks in the control and treatment groups; in one of these five trials, even more heart attacks and more deaths occurred in the treatment group than in the control group.[122]

Unfortunately, many of the newer trials were neither single nor double-blind, as you will learn soon.

Soybeans against heart attacks

In the 1960s, in London, England, Professor Jeremy Morris led a team of physicians and scientists in an investigation to see if the use of soybean oil instead of animal fat could have some preventive effect on coronary heart disease. This oil is rich in polyunsaturated fatty acids, those that are considered protective against atherosclerosis and coronary heart disease. Enrolled in the trial were about four hundred middle-aged men who had previously been admitted to four London hospitals because of a heart attack; half of these were given a diet containing large amounts of soybean oil. (This is one of the few trials sponsored solely by a government, and not by a drug company or any other vested interest.)

The researchers could see no effect of the oil when the result was analyzed four years later. Although blood cholesterol had decreased considerably in the treatment group, fifteen had died of a heart attack. In the control group, fourteen had died; and the number of nonfatal heart attacks was identical for both groups.[123]

The authors of the report compared their result with a similar but unblinded experiment performed by Dr. Paul Leren, a Norwegian researcher from Oslo.[124] They concluded that, even if Dr. Leren had been more successful, the results of the two trials taken together showed that it was not possible to prevent heart attacks by eating more polyunsaturated fat.

At about the same time, Dr. Seymor Dayton and his team from the University of California in Los Angeles conducted a similar trial.[125] At a nursing home for war veterans they gave a treatment group of four hundred men a diet rich in soybean oil; the four hundred control subjects ate the institution's usual diet. Great efforts were made to prevent both patients and doctors from knowing who was treated and who was not.

Seven years later, a slightly smaller number of those who had eaten the soybean-oil diet had died from a heart attack. But the lower number of heart attack deaths was balanced by a higher number of cancer deaths.

Moreover, when the researchers analyzed the degree of atherosclerosis and the amount of cholesterol and fat in the arteries of the dead subjects, they discovered something peculiar. Although blood cholesterol had been lowered in the treatment group, there was no difference between the degree of atherosclerosis in the two groups. In fact, those who had eaten the diet laced with soybean-oil had even more cholesterol in the aorta, the chief artery of the arterial system, than those who had eaten the nursing home's standard fare.

The report from this well-performed trial did not explain why mortality from sclerotic vascular disease had decreased but atherosclerosis itself had not. The authors of the report concluded that the effect of the trial was impressive but that the trial alone was not enough to prove the diet-

heart idea; it could not be used as an argument for recommending the diet for the entire population, since only old men had been studied and total mortality hat not been lowered. The authors could also have said that the number of heavy smokers was much higher, indeed significantly higher according to the statistical tests, in the control group. Because smoking is considered a cause of coronary heart disease, the greater number of heart attacks in the control group could, logically, have resulted from smoking and not from diet.

The directors of the trials I have just referred to produced prudent reports about their efforts. It is difficult to find such balanced views from the directors of the trials that were to come.

The Coronary Drug Project

Blood cholesterol can be lowered in many ways. But which way is the most effective, and does it really help? These were the main questions when the American, government-supported National Heart, Lung and Blood Institute started the first mammoth trial to lower blood cholesterol. The year was 1967.

The trial, headed by professor Jeremiah Stamler from Chicago, was called *The Coronary Drug Project*. The drugs used were nicotinic acid, clofibrate (Atromidin®), thyroid hormone and estrogen (the female sex hormone), the latter given in two different dosages. Because these drugs and hormones lower blood cholesterol, they were considered appropriate for efforts to prevent coronary heart disease.

The subjects in The Coronary Drug Project were more than 8000 middle-aged men who had already had at least one heart attack. About 5500 of these men were randomly assigned to five treatment groups, with the rest assigned to a control group of roughly 2800. Altogether, 53 hospitals from all across the whole US contributed patients to this massive study.

The trial was well prepared. Anything of interest of coronary heart disease was studied by a large number of researchers. In the paper describing the project the list of researchers filled six pages.[126]

Within 18 months after the start of the trial, treatment for those who had received the high dosage of estrogen discontinued because the researchers found that the hormone was causing heart attacks instead of preventing them. And the patients were reluctant to take the estrogen because most of them became impotent and developed feminine-looking breasts. The investigators concluded, *"the potential value of this level of estrogen medication is probably limited."*

Those who were treated with half dose estrogen continued the treatment,[127] but a few months later even the smaller dosage was found to be unfavorable. In addition to the side effects cited above, there were also more new cases of cancer.[128]

Treatment with thyroid hormone was discontinued, as well. Although blood cholesterol was lowered, the treatment seemed to induce heart attacks instead of decreasing them, just as was the case with estrogen.[129] The remaining groups continued to the end of the trial.

The result after seven years was depressing. Those who were treated with clofibrate had died just as often as those in the control group and many of them had had serious side effects of the treatment.[130]

Even more side effects were seen after treatment with nicotinic acid. Almost all complained of flushing or skin rashes, half itched, and one in five complained of stomach pains, nausea or other symptoms pertaining to the stomach and bowels. Other common side effects of nicotinic acid were gout (a painful inflammatory disease of the joints), burning pains while urinating, excessive sweating, serious disturbances of the heart rhythm, and various skin diseases.[131] As the directors of the experiment wrote in their report: *"Great care and caution must be exercised if this drug (nicotinic acid) is to be used for treatment of persons with coronary heart disease."*

What they left unsaid, though, was how to exercise care and caution. And how can we? How are we doctors to know, before treatment begins, who will experience side effects? The drug was ineffective, anyway, to prevent fatal heart attacks. And why should we use an ineffective drug?

Nicotinic acid is still used today for prevention of coronary heart disease because of a peculiarity that appeared in a study years after The Coronary Drug Project ended.[132] Eight to nine years after all the treatment subjects stopped taking nicotinic acid, a follow-up study showed that fewer in the previously treated group had died from heart attacks and that fewer had died of any cause.

This result—no benefits from the drug during the trial, but fewer deaths years later—stimulated many speculations. One was that perhaps the nasty side effects had concealed its positive effects during the trial. The suggestion here was that perhaps it took many years before a lowering of blood cholesterol would show positive results. The books should be reopened after other trials also.

But clofibrate had lowered blood cholesterol just as much as nicotinic acid had during the trial. Yet clofibrate had prevented no deaths after many years. In fact, as the years passed, the number of fatal heart attacks in the group that had once received this drug was a little greater than in the control group. And nobody mentioned the follow-up findings of another large experiment, the WHO trial (see later). There, *more* people had died from heart attacks 4-5 years after their treatment with clofibrate ended.

It seems strange also, that a drug could help years after being discontinued, as strange as if the aspirin unsuccessfully taken to relieve a headache on Monday could prevent a headache on Friday.

It is hard to follow the logic in the conclusions from the cholesterol-lowering trials. Sometimes cholesterol lowering results in fewer deaths from heart attacks; sometimes the same degree of lowering results in more deaths. Sometimes the benefit is seen after a short time, sometimes not until years after trial's end. Or, if there is no benefit—the most common result—the trial directors declare that if the trial had continued longer, there might have been some benefit. However, when trials are sometimes beneficial and sometimes not, the more likely conclusion is that they aren't effective at all which means that their outcome depends on chance.

Primary versus secondary

The trials I have discussed so far are examples of secondary prevention. “Secondary” means that a disease—coronary heart disease in this instance—has already occurred, and that treatment is aimed at halting further spread of the disease. In contrast, a treatment aimed at preventing the disease in apparently healthy people is called primary.

There is a fundamental difference between primary and secondary prevention. Very often, people who have already had a heart attack are badly frightened and ask themselves, “Will I survive another coronary?” To prevent another heart attack, many are willing to submit to rather unpleasant kinds of treatment. Healthy people whose only defect is high cholesterol are less inclined to exercise, to renounce cigarettes and good food, and, on top of this, to take expensive drugs with unpleasant side effects. Healthy people thus make less compliant treatment subjects in a trial.

In addition, to achieve a significant result, a primary trial requires many more subjects, because the risk of a heart attack is considerably smaller for people who have never had a heart attack than for those who already have suffered one. While the subjects needed for a secondary preventive trial number in the hundreds, those needed for a primary preventive trial are many thousand. And if it is not possible to prevent a heart attack in those who have already had one, it is obviously more difficult to do so in healthy individuals. The results of the primary preventive trials have not been any more successful than those of the secondary preventive trials, even if the diet-heart proponents say otherwise. But now it is up to you, the reader, to judge for yourself.

The Upjohn trial

In the early 1970s, Dr. Albert Dorr and his coworkers at the Upjohn Company, a large pharmaceutical manufacturer in Kalamazoo, Michigan, started a trial to test Upjohn's new cholesterol-lowering drug colestipol (Lestid®).

At a large number of hospitals in the USA more than 2000 men and women with high cholesterol were selected. After the selection the local doctors consulted the directors of the Upjohn trial. In the offices at Upjohn, after being informed about certain laboratory values of the participants, the directors of the new trial decided which patients would have the drug and which would receive an ineffective sugar pill, the placebo.

To assign participants of a trial in this way obviously may introduce a bias, especially when those who assign them have vested interests. As you will see from the following the distribution of risk factors in the treatment and control groups became far from even.

Two years later the result was analyzed. No effect was seen for the women in the trial. But the effect for the men was amazing. After only two years, the number of heart attacks had been halved for the men in the treatment group. Such remarkable results have never been achieved in any trial before or since.[133]

There was a snag, however. In the control group, the number of individuals with familial hypercholesterolemia was greater than in the treatment group. As the prognosis for these people is worse than for others; some of them die young from heart attacks and lack of balance on this matter may well have biased Upjohn's result.

The WHO Trial

At the same time a similar trial was being performed under the auspices of the WHO. This trial, led by Professor Michael Oliver at the University of Edinburgh, Scotland, used clofibrate, the same drug that was used in the Coronary Drug Project.

For the WHO trial, blood cholesterol was analyzed in 30,000 healthy, middle-aged men in Edinburgh, Prague, and Budapest. The men with the highest blood cholesterol were selected for the treatment, a total of ten thousand individuals. Half of them were treated with clofibrate, the other half with an ineffective placebo.

After about five years treatment, 174 of those who had been taking the placebo had suffered a non-fatal heart attack, but only 131 of those treated with clofibrate. Apparently the drug was a success.

But the number who had *died* from heart attacks was equal. Worse yet, considerably more of those who had been treated with the drug had died from other diseases. In all three cities more men had died in the treatment group. Taken together, 128 died in the clofibrate group, 87 in the placebo group. And 4-5 years after the trial, even the number who had died from heart attacks was larger in the treatment group.[134]

Clofibrate is still recommended as a useful drug in many countries, however.

Fat food and fit Finns

One of the nations with the highest mortality from coronary heart disease is Finland. The mortality is especially high in the province of North Karelia, for reasons that no one knows. The coronary mortality rate increased year by year up to the 1960s. Of course the Finnish health authorities were concerned. To them, it was self-evident that the cause was high cholesterol, because in Finland it is higher than anywhere else, and some of the highest values are found in North Karelia.

A team of doctors and scientists at the university in Kuopio headed by Professor Pekka Puska decided to do something about the problem. They chose to start in North Karelia. To see if their efforts were beneficial, they used the district of Kuopio as their control, because people in Kuopio died just as often from heart attacks as the people of North Karelia did and their cholesterol was equally high.

In 1972, a public health campaign began throughout North Karelia. Its aim was to prevent heart disease by focusing on smoking, fat food, and high blood pressure. In the mass media, on posters, at public meetings, and through campaigns in schools and work places, the message was proclaimed. In Kuopio nothing was done; here, people were allowed to live as they had traditionally lived.

Five years later the number of heart attacks among North Karelian men had decreased from 0.77 to 0.63 percent each year. The total mortality had also decreased. Possibly this trend could improve in the future, the leaders of the campaign wrote in their report.[135]

There was a problem, however. In Kuopio, where the citizens served as control subjects, the number of heart attacks had decreased even more, among women as well as men, although the townspeople ate and smoked as they had before. In fact, heart mortality had decreased in all the provinces of Finland (figure 6a).

The disappointment of the campaign leaders is easy to imagine. All this enthusiasm and all this work were of no use. On the other hand, negative results can be and are interesting for those whose curiosity is intact and who are more interested in knowledge than in the defense of old positions.

Two conclusions may be drawn from the results of the campaign. First, it could not have been fat food or smoking or high blood pressure that caused the many heart attacks in North Karelia. If it were, the number of heart attacks should have decreased more in North Karelia than in the untreated Kuopio. Second, something had happened in the whole country to cause coronary heart disease to decrease, and it was not an improved diet, it was not reduced smoking and it was not a greater attention to blood pressure.

Unfortunately, the Finnish campaign team did not understand that they had found a track worth examining more closer. Instead, they published further papers with more analyses of their results. [136] More had died in North Karelia during the campaign than in Kuopio, they agreed, but in North Karelia there had been a greater reduction in the number of heart attacks than in all other areas of Finland. They also thought that the small irregularities of the mortality curve for North Karelia proved that their campaign had been of benefit.

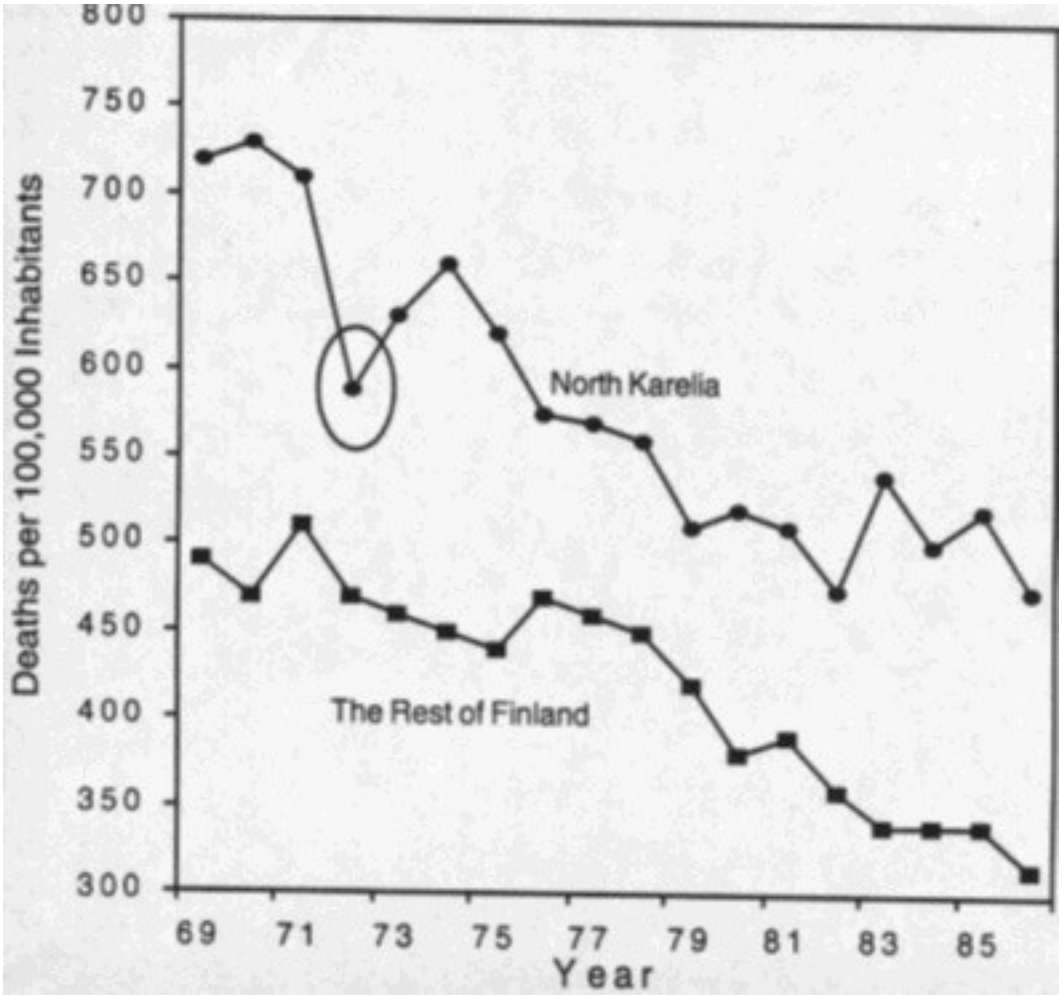

Figure 6a. Number of coronary deaths in North Karelia and in the rest of Finland.

The circle indicates the starting point of the North Karelia project. Observe that more died from heart attacks during the first three years of the project than during the year before the start, most probably a result of chance. Seen over a longer period of time, heart mortality had declined in North Karelia as well as in all of Finland and in many other countries. This decline had already started before the start of the North Karelia project. After Puska.

But what they did not mention was that the decrease in heart mortality had started several years before the start of the campaign, and that an examination of the curve over a longer period of time clearly revealed that the campaign had made no impact. In fact, if the small irregularities in the curve had any significance at all, heart mortality had *increased* during the first two years of the campaign. However, the investigators were so convinced of their success that they started similar campaigns in other parts of Finland.

One of the campaign leaders, Dr. Jukka Salonen, had a differing opinion. In a letter to the famous medical journal *The Lancet* he explained that, although he was a co-author of the North Karelia report, he had not been able to read the optimistic paper before its publication. He did not

think it possible to draw the conclusions presented in the paper and admitted that the steeper slope of the mortality curve for North Karelia could be explained in a variety of ways. For instance, he wrote, the increased heart disease seen during the previous decades had come later to North Karelia; the decrease, therefore, had come later, too. The critical factor, however, was whether the campaign had changed the trend in North Karelia (which it had not). Dr. Salonen wrote that the North Karelia project could not be used as evidence to say that the risk factors either caused or did not cause heart disease; the project had merely shown that intervention is possible and can lead to a change in risk factors.[137]

But, as Professor Michael Oliver of Edinburgh, answered: *"What was the aim of trying to change risk factors unless they were thought to have some causative role and unless positive results were expected?"*[138]

Valio

On June 23, 1988, there appeared a full-page advertisement in a great many Finnish newspapers. The ad had been paid for by Valio, a large farm cooperative that markets about 90 percent of all milk products in Finland. It presented *"five facts about dietary fat you have wished to hear about but nobody has told you."*

The five facts were as follows.

1. In Finland people eat less fat than in many Western European nations.
2. There is no direct connection between a nation's intake of animal fat and its mortality from coronary heart disease.
3. Fat intake and mortality from coronary heart disease have changed in opposite directions in many countries.
4. Mortality from coronary heart disease has decreased in Finland, despite the fact that the Finnish people has increased its consumption of animal fat.
5. Finally, a short summary of the North Karelia campaign was given.

It would be an understatement to say that the director of Valio's research department, Kari Salminen, met stormy weather; a hurricane is more like it. He was attacked in all Finnish newspapers and journals; almost every day during that summer and autumn, critical editorials, articles, and letters appeared in the Finnish press. No one could point to anything incorrect in the advertisement. Rather, it was the morality of the corporation that was rotten. The advertisement was condemned as partial, misleading, and unethical; the claim was that Valio had selected convenient statistics for a deliberate manipulation of scientific data.

As director of the North Karelia project Pekka Puska was particularly offended. He thought that the various efforts of the campaign had produced marked effects at the start (correct, but effects in the wrong direction). The connection between dietary animal fat and heart disease has been better proved than most subjects in medicine, he wrote. The facts in the advertisement, he declared, did not tell the whole truth.[139]

Kari Salminen, Valio's research director, answered that his company had merely done what the nutrition scientists had been doing for decades. Further, he replied, the advertisement had been designed as an invitation to debate and did not pretend to represent the whole truth.

The invitation was ignored. Debate was replaced by execution, and for many years Pekka Puska appeared in Finnish advertisements for margarine.

The Oslo trial

In Oslo, Norway, Dr. Ingvar Hjermann and his team thought that smoking and a high cholesterol level were the two most important causes of coronary heart disease and they wondered what would happen if smoking was stopped and blood cholesterol was lowered with an appropriate diet. To this end they studied about 1200 middle-aged men, mostly smokers, with high cholesterol. Half of these men received dietary advice and were encouraged to quit smoking. The other half received no treatment.

The result after five years appeared promising.[140] In the group given dietary and smoking advise, 19 died from a heart attack. In the control group, the number was 35; if to the latter group was added a further control participant who had died suddenly of an unknown cause, the difference between the treatment and control groups became statistically significant.

A promising result for the diet-heart supporters. But does the experiment really prove that a faulty diet causes coronary heart disease?

In their paper, the Norwegian researchers pointed to two types of intervention, diet and cessation of smoking. They admitted that if dietary advice had been the only treatment their result would not have been sufficient as evidence.

In fact they had used three types of intervention, because subjects in the treatment group were also advised to reduce their weight. Evidently, this advice was followed: at the end of the trial, the mean weight difference between the two groups was almost seven kilograms (about 15 pounds).[141] Opinions vary as to the importance of a 6-7 kilogram weight difference. It is evident that the risk of diabetes and high blood pressure is greater for overweight people, and diabetes and high blood pressure predispose for coronary heart disease. Most proponents of the diet-heart idea also recognize overweight as a problem in heart disease. Wrote Dr. William Kannel, director of the Framingham project: “Avoidance and correction of obesity deserve a high priority among measures taken to avoid coronary heart disease, since the combined effect of the risk factors it promotes on coronary heart disease incidence is formidable.”[142]

Now to the crucial question. Which of the measures had had the decisive effect in the Oslo trial? Was it lowering of cholesterol by diet, was it the reduction of smoking, or was it the weight loss? Nobody knows.

Possibly you're asking, “Why didn't the Oslo trial leaders concentrate on the diet alone?” The answer to that question lies in a previous paper.

About ten years earlier, the researcher who had performed the Norwegian soybean trial, Dr. Paul Leren, had published the latest results of that trial. Although the number of heart attacks was

reduced a little, Dr. Morris and his colleagues in England, using a similar treatment, had failed. [143]

But Dr. Leren analysed his own result and found that it might have been a good idea to change more than one risk factor, an approach called *multiple risk factor intervention*. Diet alone was unsuccessful.

Few of the diet-heart supporters rely on diet only in their trials; diet is often combined with other measures. When the LRC trial was being planned, the scientists stated frankly that diet alone was not enough, that to lower cholesterol drugs were necessary.[144]

It is laudable to try to prevent disease and premature death as effectively as possible. If all the measures are proved to be beneficial the frontier should of course be broadened. But in that case it is not possible to judge the influence of each measure individually. As no one has proved that diet alone is efficient it had perhaps been wiser to exclude the dietary advices, or to study them alone.

MR.FIT—Much ado about nothing

For many years scientists at the National Heart, Lung and Blood Institute had discussed how to prevent heart attacks. But before telling the American public what to do they needed solid proof that their advice would work.

They had rejected the idea of using diet alone. To be successful, they said, it was necessary to attack at least three of the major risk factors: high cholesterol, smoking, and elevated blood pressure. To this end the institute started a gigantic trial called the *Multiple Risk Factor Intervention Trial*—MR.FIT for short.[145] At its head was once again professor Stamler from Chicago.

The first step was to recruit more than 360,000 middle aged men from eighteen American cities. After a routine investigation the researchers selected about 12,000 men, namely those who were considered especially prone to get a heart attack.

The trial had every chance of succeeding. The test subjects had entered the trial voluntarily and they knew that their condition was considered dangerous. Although they felt hale and hearty (and, by normal standards they *were* healthy), they were overweight, their blood pressure was too high, and according to the experimenters their cholesterol scores hinted at premature death from heart disease. After the initial analyses, the men took part “with remarkably enthusiastic response.”

However, one of those initial analyses should have stopped the whole MR.FIT trial.

A decade before, a smaller, careful test study had been done. A comparison of the food eaten by the men in that study with the food consumed by the men selected for MR.FIT revealed that the MR.FIT participants had eaten more “healthfully” in all respects, more in accord with the diet-heart idea.[146]

Yet the blood cholesterol of the MR.FIT participants was higher!

Furthermore, initial surveys indicated that those MR.FIT participants who ate less saturated fat and cholesterol tended to have higher blood cholesterol! It was not exactly an encouraging finding for researchers who hoped to lower blood cholesterol by lowering just those components in the diet. But the directors of the trial responded only by declaring that, first, the odd evidence showed that cholesterol and saturated fat should be reduced more than originally planned for the MR.FIT treatment group. Second, they speculated that the fact that blood cholesterol was highest among the MR.FIT subjects who ate the most prudent diet showed that these men must have changed their diet at the last minute, right before the trial began.

Perhaps the directors were correct. The participants could have made eleventh-hour dietary changes in the days just before they were questioned about what they ate. But presented with experimental results contrary to what they have expected, scientists usually want to know "What's going on here? And why?" In accord with the long tradition of scientific inquiry, most scientist would have asked the MR.FIT participants if they really had shifted to a new diet right before the trial began. More than one hundred million dollars of taxpayers' money could have been saved if some scientists had asked. If MR.FIT participants were eating as they had always eaten, even just before the trial, they would have demonstrated that diet is unimportant for the blood cholesterol level, and this enormously costly trial could have been cancelled then and there.

But no one asked. Or did they? Perhaps it would have been too heroic for the directors to cancel a trial with all these doctors, nurses, dieticians and, not least, the trial directors themselves, lined up and assured that they would have lucrative and prestigious jobs for the next several years? If anyone asked, they didn't do it in public, and the trial continued.

The subjects were randomly assigned to two groups of equal size. Those placed in the treatment group and their families met in small groups to learn about the rationale behind the trial, and then to learn how to read food labels, to cook with minimal fat, and to change old recipes to meet new guidelines. In special sessions, the treatment subjects met for an intensive anti-smoking campaign; in selected cases, even hypnosis was used to help participants quit smoking. When necessary, individual counseling was provided by doctors, nutritionists, psychologists, nurses and other health professionals. Every four months, the treatment subjects were called in for blood sampling and to hear if they had fully understood all the new guidelines.

The dietary advice was, of course, aimed at reducing the men's intake of cholesterol and saturated fat and increasing their intake of polyunsaturated fat. High blood pressure was treated energetically, and subjects with weight problems were taught how to reduce calories and get more exercise. Dietician checked yearly to make sure that the men were really eating as prescribed.

The men in the control group received no advice, but they visited the center once a year for blood sampling and a questionnaire about their eating habits, and the results of these investigations were sent to their own doctors.

After seven years of treatment the effect was analyzed. The trial directors were satisfied that there had been major risk-factor changes. Blood pressure had been lowered considerably and many of the men had quit smoking.

But blood cholesterol had decreased by only seven percent. It had decreased in the control group, too, although the control subjects had scarcely changed their diet at all, so the difference between the two groups was only two percent.

Other risk factors had changed in the control group, as well. The one difference between the groups worth mentioning was that more of the control subjects continued to smoke.

The difference in number of deaths was small, too. In the treatment group 115 had died of coronary heart disease, in the control group 124. According to statistical precepts, such a difference could well have been due to chance. There was no statistical difference, either, in the number of deaths from all causes: 265 in the treatment group, 260 in the control group.[147]

Customarily, when a scientific experiment does not produce results supporting a hypothesis the scientists admit it straight out. But this was not an ordinary experiment. More than a decade of hard work and several hundred millions of dollars had been invested in this most ambitious medical study to date. Hundreds of doctors, professors, statisticians, dieticians, psychologists and others had been engaged. More than fifty scientific reports, most of them mammoth, had been published. And thousands of apparently healthy men, and their families, had been persuaded to take part in time-consuming investigations and to change their diet and way of life for many years. This huge effort could not possibly have been in vain.

And what had been preached for years to the American public about risk factors and heart attacks could not possibly have been wrong.

With a little statistical manipulation, the trial directors improved their results.

The participants were divided into smaller groups. Excluding from the treatment group a sub-group who did especially bad made the overall result appear better. Almost all the other sub-groups had had fewer fatal heart attacks. No great differences, and not all sub-groups, but almost all.

The trial directors concluded that the MR.FIT intervention program might have had a favorable effect for most of the participants. If some of the men had more heart attacks, it was because of the drugs used to lower blood pressure (although in another subgroup treated with such drugs, the outcome was better). It was also obvious that the outcome was favorable for those who had quit smoking, the directors wrote. In fact, the smoking habits explained the whole difference.

Within four years after the end of Mr.FIT, a total of 202 men in the treatment group and 226 in the control group had died from heart disease; again a difference that could be explained by chance (or by the smoking habits). But the investigators claimed that the figures proved the benefit of lowering blood cholesterol.[148]

More prudent diet-heart supporters admit that MR.FIT was a failure, but they usually add that the failure occurred because a two percentage lowering of blood cholesterol is too small to have any effect.

This is a reasonable objection, but with this objection diet is declared worthless as a preventive measure, because the diet had been changed as was aimed. The subjects in the treatment group had almost halved their intake of cholesterol, they had lowered their intake of saturated fat by

more than 25 percent, and they had eaten 33 percent more polyunsaturated fat. In the control group the diet was practically unchanged.[149]

If a scientific trial with almost unlimited economic and personal resources cannot lower cholesterol more than two percent over seven years, how is the over-worked general practitioner to succeed with a crammed waiting room and with no dieticians, or experts in behavior modification to hold his hand? And how is the patient to be motivated if he is not rewarded for all his trouble?

MR.FIT demonstrated that it is a good idea to quit smoking. But we already knew that, and most people can manage to quit without such costly help from society.

The final proof

Diet-heart proponents think that if we had a drug that could lower blood cholesterol sufficiently without any serious side effects, we could prevent or at least delay all diseases caused by atherosclerosis.

Here is a dream for all doctors. All that's necessary is a prescription pad and a gadget for measuring cholesterol. No time-consuming fuss with diet-counseling.

It is a dream, also, for the drug producers. A life-long lowering of cholesterol with expensive drugs in a substantial part of the population is far more profitable than for instance a brief treatment with cheap penicillin. In the offices of the drug manufacturers, the dream calculations are in the billions of dollars.

Large trials using clofibrate had not been especially encouraging, you may say. But other drugs seemed more promising. One of them was cholestyramine (Questran®).

The MR.FIT trial had excluded men with extreme cholesterol values (above 350 mg/dl), as it is considered unethical to place such “patients” in a control group without treatment. In the new jumbo trial[150] called *The Lipid Research Clinic Coronary Primary Prevention Trial* (LRC), which would use the drug cholestyramine, all individuals with high cholesterol were included. The higher cholesterol, the better.

To solve the ethical dilemma, dietary advice was given in both the LRC's treatment and control groups. Although this advice would diminish the difference in outcome between the two groups, the degree of cholesterol lowering from diet was expected to be insignificant! The great difference would be created by cholestyramine.

To find about 4000 test individuals, blood cholesterol was determined in almost half a million middle-aged men. Never in history had so many people with such high blood cholesterol levels been involved in a medical experiment. In MR.FIT the upper three percent of the cholesterol range were selected, but men with the highest values were excluded. Here in LRC, only the upper 0.8 percent participated, without exception. Consequently, the mean blood cholesterol before the dietary treatment started was about 40 mg/dl higher than in MR.FIT meaning that most of the participants must have had familial hypercholesterolemia.

All LRC participants were investigated thoroughly, as in MR.FIT. After a few weeks dietary treatment, half of the men were started on cholestyramine medication, the other half on a supposedly inactive placebo powder.

Seven to eight years later, the results were analyzed. Although blood cholesterol in the treatment group had decreased by more than eight percent, the differences in the numbers of heart attacks were so small that only chance could explain them. Of those who had taken cholestyramine, ten percent, or 190 men, had experienced a non-fatal heart attack, as against 11.1 percent, or 212, of the controls, a difference of 1.1 percentage points. As for fatal heart attacks, the figures were 1.7 and 2.3 percent, a difference of 0.6 percentage points, or twelve individuals.

But in the summary of the paper the result was given in another way. The lowering of non-fatal coronary heart attacks was said to be 19 percent and of fatal heart attacks 30 percent. These figures were arrived at by relating the percentage in the treatment group to the percentage in the control group, without any reference to the total number of men involved.

Even the exaggerated figures of the LRC report were a little too optimistic. To reach their 30 percent figure, the LRC directors included the uncertain cases, those who may or may not have died from a heart attack. But to reach their 19 percent figure, they excluded the uncertain cases. If it had been the other way around, the results would have been 24 percent rather than 30, and 15 rather than 19. In other words, they selected the most convenient figures.

Even worse, the LRC directors had lowered their own statistical demands. In a preliminary report[151] written several years before the trial ended, they had stated that, to be convincing, they would accept nothing less than the strongest statistical proof of their findings. In this case, it was a statistical level of 0.01, meaning that the trial results would be 99 percent accurate; and to ensure statistical accuracy, the researchers would use the very demanding two-tailed t-test.

Thus, the directors of the trial had begun by embracing the highest standards. Then, after the fact, when it was clear that the result of the trial did not measure up to their hopes, they shifted their demand for accuracy from 0.01 to the less stringent 0.05, and to the easy one-tailed t-test.

After their results were published, the LRC directors were severely criticized for their lowering of standards. But in response to critical letters to *The Journal of the American Medical Association*, they simply denied that they had ever declared in writing the high standards that they had originally aimed at. *"The term 'significant' was not defined in terms of a particular statistical probability level."*[152]

Diet-heart supporters look offended if you tell them that, of half a million men, twelve were rescued from death. In fact, the number rescued was even smaller. Fewer in the treatment group died from heart attacks (32 against 44), but more died by violence or suicide (11 against 4). If we calculate in the ingenious way used by the LRC leaders and other diet-heart proponents, using relative risk and not absolute rate, the excess of violent deaths was huge; after all, eleven is 175 percent greater than four.

Hyping the benefit, minimizing the risks

If all men in the USA with blood cholesterol as high as in the LRC study received the same treatment and got the same result, two hundred lives would be saved per year, provided that the

LRC result was not merely due to chance. However, in a 1990 letter to the editors of *The Atlantic* magazine, Dr. Daniel Steinberg, chairman of the conference that started the publicly funded National Cholesterol Education Campaign against cholesterol in the USA, declared that 100,000 lives could be saved each year. He further claimed that this non-fact had been demonstrated with statistical significance *"in a large number of studies."*[153]

Just a few months later, Dr. Basil Rifkind, who had been the director of the LRC study, admitted in a medical journal that the scientific trials had not reduced the number of deaths from coronary heart disease and that *"further gains in life expectancy are unlikely in developed countries."*[154]

The LRC results were so feeble that they may well have been caused by mere chance. And both the drug used in the study, cholestyramine, and the supposedly innocent placebo taken by the control group produced some extremely unpleasant side effects. Sixty-eight percent of the men taking the cholestyramine experienced gastrointestinal side effects during their first year of treatment: they had gas, heartburn, belching, bloating, abdominal pain, nausea, and vomiting, and almost fifty percent had constipation or diarrhea. In the control group during the first year, forty-three percent experienced similar side effects, a far higher rate than what occurs if the placebo is truly ineffective.

The readers of the report are reassured that the side effects were not serious and they could be neutralized by standard clinical means, and after seven years the number of these side effects had decreased to only twenty-nine percent. This was not more than after the placebo treatment. Their words suggested that the symptoms from the stomach and the guts had nothing to do with the cholestyramine treatment but was pure imagination or symptoms that the test individuals should have had also without treatment.

In controlled drug trials the control group is usually given an ineffective placebo. The reason is that symptoms considered as side effects may in fact be accidental symptoms unrelated to the treatment; symptoms which by chance appear during the treatment. Accidental symptoms may of course occur in the controls also. Therefore, the percentage of side effects in the placebo group are subtracted from the percentage of side effects in the treatment group to give the true percentage of side effects from the drug.

But here they had given a placebo which certainly not was without side effects; gastrointestinal symptoms in forty-three percent is much more than is usually seen after an innocent placebo. Therefore it is not reassuring to hear that the side effects from the drug equaled the side effects from the placebo.

Neither is it reassuring to learn that, *"the side effects were treated by standard clinical means."* These words mean that more than half of these previously healthy individuals in addition to cholestyramine or placebo also took laxatives, antacids or drugs to stop diarrhea or to prevent nausea and vomiting.

A greater number in the treatment group were also admitted to hospital for operations or procedures involving the nervous system. No diagnoses or more specific information was given and as it was impossible for the experimenters to find a reliable explanation to the effect of cholestyramine on the nervous system these side effects were classified as coincidental. The

authors did not consider that it should have been the lowering of blood cholesterol and not cholestyramine itself which had given rise to the side effects.

Few people know about the many side effects, which they may get by taking cholestyramine. One reason is of course that they are rarely mentioned to the public. For instance, read another sentence from the letter in The Atlantic by Daniel Steinberg: *"The drugs in current use for lowering cholesterol levels have remarkably few side effects and, to my knowledge, no fatal side effects."*

Now we have definitely proved that it is worthwhile to lower blood cholesterol; no more trials are necessary. Now it is time for treatment. In short, this was the message from the experimenters of the LRC. And they considered treatment necessary for most people.

It is a prudent rule in clinical science to be careful with conclusions about other patient groups than those who have been studied, especially concerning a disease with large age and sex variations. If it had been shown (which indeed is questioned) that a treatment is beneficial for middle-aged men with an extremely high blood cholesterol, only this category should be treated until it has been proven that it is also beneficial for other categories of human beings.

In the LRC it was not even middle-aged men with high blood cholesterol who had been studied but to a great part men with inborn errors of cholesterol metabolism. You may probably recall that it was those with the upper 0.8 percent of the blood cholesterol values who had been selected for the trial. As almost one percent of mankind has an inborn abnormality of cholesterol metabolism most of the participants must have belonged to that category. Even if we presume that the treatment was useful it is not evident that a treatment that is useful for such individuals is useful for normal individuals as well.

But nothing was said about that in the paper, neither had the directors of the LRC trial any reservations. Not only middle-aged men should be treated but also other age groups; and not only men with a high blood cholesterol, but also those whose cholesterol was close to normal; and not only men, but also women although women were not studied and although almost all previous studies had shown that a high cholesterol is not a risk factor in women, neither is treatment of any use. The only group that was not mentioned in the report was the children, but this was repaired later.

LRC was not designed to assess directly whether cholesterol lowering by diet prevents heart attacks, they wrote, but the results from the LRC trial taken together with the large volume of evidence relating diet, plasma cholesterol levels, and coronary heart disease, its findings support the view that cholesterol lowering by diet also would be beneficial.

This is a typical argument from diet-heart supporters. Taken together one by one no study has proven that animal fat and high cholesterol is dangerous to the heart, but if you put all the studies together, they do. In the Alice-in-Wonderland atmosphere of the Lipid Research Clinics, nothing plus nothing conveniently equals something.

Science by citation

The high rate of coronary heart disease in Finland has prompted several experimenters to conduct preventive trials; Dr. Tatu Miettinen and his coworkers from Helsinki are among them.

One-half of about 1200 middle-aged, more or less overweight and hypertensive male business executives with high blood cholesterol were advised about smoking, exercise, weight reduction and diet; the other half was used as a control group. If the blood pressure and the blood cholesterol in the treatment group did not become normal they were also treated with various blood pressure and cholesterol lowering drugs.

The experimenters were quite satisfied with the effects of their efforts on risk factors. Blood cholesterol fell by 6.3 percent, the blood pressure by about 5 percent and the tobacco consumption with about 13 percent.

But improved risk factors did not lead to better end results. In the group who exercised, reduced their weight, ate less animal and more vegetable fat, and had quitted smoking, twice as many heart attacks were seen as in the control group.[155]

The investigators believed that the greater number of heart attacks probably was due to clofibrate which some of them had taken, or perhaps to the drugs against high blood pressure. (What a frightening thought that drugs which are used on millions of people to lower the blood pressure or to prevent coronary heart disease could actually cause it instead.)

Their explanation does not jibe with the results of other experiments. In two previous British trials it was said that due to clofibrate the number of heart attacks had *decreased*, and other studies have shown that the drugs used against high blood pressure *protect* against coronary heart disease.

The unfavorable result may simply have been due to the fact that the therapy is ineffective. Therefore, the outcome is determined by chance; in one trial the number of heart attacks is a little smaller, in another a little greater. But the diet-heart proponents prefer to look at the supportive studies only and ignore those that are not.

Science Citation Index was an interesting aid for scientists at that time. (Today the PubMed program on the web is even better.) Here you could see who had cited any scientific paper, how often, and where. Editors of medical journals make a point of the papers published in their journal being cited frequently. Frequent citation indicates influence and is prestigious, not only for journals but also for individual scientists. The number of those who have cited papers by Nobel Prize laureates took up many columns each year in the small-typed Science Citation Index.

It was interesting to open the Index and see how often the 1985 paper by Miettinen and colleagues had been cited. Let us compare it with the main report from the LRC trial also, published one year previously. Both papers dealt with the same subject and were published in the same journal and no one has questioned the honesty of the experimenters or the quality of the studies; at least not the Finnish one. Reasonably, they should have been cited almost equally often. That the LRC trial, at least according to its directors, was supportive, and the Miettinen trial was not, is unimportant because the aim of research is to find the truth, whether it supports the current theories or not.

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Years After Publication	Miettinen and coworkers	LRC trial
First year	6	109
Second year	5	121
Third year	3	202
Fourth year	1	180

Table 6a. Here you can see how often the two papers have been cited during the first four years after their publication.

The table shows that scientists are like the rest of us; they forget what is awkward and recall only the pleasant memories. A useful quality in private life but nothing to further knowledge.

What do you want: a gastric ulcer or a coronary?

New cholesterol-lowering drugs require new trials. That the previous results were less successful than expected was due to the side effects of the drugs. The fewer deaths from heart disease were balanced by more deaths from other reasons, it was said. Others thought that the cholesterol was not lowered sufficiently.

The new drug gemfibrozil (Lopid®) is chemically close to clofibrate, but was considered more favorable because it lowers the total amount of cholesterol in the blood and at the same time increases the “good” cholesterol. This drug was selected for a new trial in Helsinki, Finland in a project led by Professor Heikki Frick.[156]

Once again investigators chose healthy, middle-aged men with high blood cholesterol. All participants were advised to quit smoking, to exercise and to loose weight; and half of them were given gemfibrozil, the others a placebo drug.

Also in this trial the number of deaths was equal in the two groups, but for the first time a statistically significant reduction of non-fatal heart attacks was seen after cholesterol lowering only. In the Oslo-trial the participants had quitted smoking and lost weight also; in the LRC trial the effect was not significant according to the usual statistical methods; and in the WHO-trial from 1978 the smaller number of non-fatal heart attacks were outnumbered by a greater number of fatal ones.

Has science proved that high cholesterol is the killer? May we use the trial of Professor Frick and his colleagues as an argument to lower cholesterol in a large part of mankind?

According to the diet-heart idea cholesterol is dangerous because it generates atherosclerosis. If this were true then a lowering of blood cholesterol should also influence other vascular diseases caused by atherosclerosis. However, in all the trials the end points used had been fatal and non-fatal coronary heart disease only.

In all the tables of the trials the reader will find a small group of patients classified as “other cardiovascular diseases.” In most trials the number in this category is a little greater in the treatment group. No great differences, but when the effect of the trial is close to the border of statistical significance, as it usually is in the cholesterol trials (when the effect is not directly negative) the small differences between the numbers of “other cardiovascular diseases” take on great importance. If all cardiovascular diseases including coronary heart disease are put together then the result is no longer statistical significant and the result is as before: no difference which could not have been caused by chance.

In addition the treatment gave unpleasant side effects. During the first year 232 or 11.3 percent of the treated individuals had gastrointestinal symptoms. Gradually the side effects abated. The report did not tell whether the test individuals became accustomed to the drug or whether they were treated with other drugs to combat the side effects as in the LRC trial. What we know is that in the treatment group 81 were operated upon because of some gastrointestinal ailment, in the control group 53 only. Thus, if the difference in the number of heart attacks was real and not caused by chance the question is if you prefer an operation of your stomach or gall bladder, or a non-fatal heart attack, because the sum of heart attacks and operations was almost identical in the two groups.

It is a fact that even this trial failed to lower mortality from coronary heart disease and there was no difference between the total number of deaths either; if anything, more had died in the treatment group. But this is not the end of the Helsinki story.

An expedient byproduct

Parallel with the mentioned study of healthy men the Finnish researchers performed another experiment on men who already had had a heart attack. About 600 such individuals participated, all of them worked at the same companies as those in the original Helsinki study.[157]

The result after five year was disheartening. Seventeen of those who took gemfibrozil had died from a heart attack; compared to only eight in the placebo group.

Dr. Frick and his coauthors were eager to stress, that this difference was most probably a product of chance. In the summary of the paper they wrote: the number of fatal and non-fatal heart attacks did not differ significantly between the two groups.

They were right, because in contrast to their fellow-directors of the other trials they used the correct formula for determining the effect of a treatment, the two-sided t-test. If they had used the one-sided test as diet-heart supporters usually do when the allegedly positive effects are measured, significantly more had died in the treatment group.

But they had modified the result in another way. In the group “cardiac deaths” they had included a small group called “unwitnessed death.” That death is unwitnessed means that we do not know

the cause of the death. It is not self-evident that an unwitnessed death is due to a heart attack and such deaths should of course have been classified otherwise.

If they had excluded the unwitnessed deaths there were more than three times more fatal heart attacks in the treatment group; sixteen against five. And this difference was indeed statistically significant.

The directors of the study admitted that the result was not *"in accord with previous experience,"* but they had a number of explanations.

As the trial was only *"an expedient byproduct"* of the original trial the number of individuals had been too small to give reliable results, they said. They were especially concerned about the low number of heart attacks in the control group. It was unlikely that it reflected the incidence in the general population. Most probably the individuals in the control group by chance had been less affected by coronary atherosclerosis than those in the treatment group.

Short guts and long lives?

At the University of Minnesota Medical School the surgeon Dr. Henry Buchwald had a bright idea. He had noted that when the last part of the small intestine is taken away from a patient (because of cancer or another disease) his blood cholesterol level decreased sharply. The explanation is that much cholesterol and bile acid is taken up in this part of the intestine, and as cholesterol is used for the production of bile acid in the liver considerable amounts of cholesterol are lost in the stools after the operation. Could this same operation be used to treat patients with too much cholesterol in their blood?

In 1963 Dr. Buchwald and his team performed the first ileal bypass to lower cholesterol. At this operation the last third of the small intestine, the ileum, is cut and closed, and the open end of the upper two-thirds is connected with the large intestine. Many such operations have been performed since then, mainly on patients with familial hypercholesterolemia. Unfortunately, only few researchers have studied the effect of the operation in a controlled study.

Two of them were Dr. Pekka Koivisto and Dr. Tatu Miettinen from Helsinki, Finland.[158] Twenty-seven patients with familial hypercholesterolemia had this operation performed and after ten years their course was compared with twenty-seven control patients matched for a large number of the usual risk factors for coronary disease and treated with cholesterol lowering drugs only.

The ileal bypass was indeed effective, more effective than the drugs. The final level of cholesterol was 23 percent lower in the operated patients and the LDL-cholesterol was even "better." But there was no difference as regards the outcome. After ten years five of the operated patients and four of the controls had died from a coronary, and three patients in each group had had a non-fatal coronary.

In spite of this disappointing result Dr. Miettinen and his colleagues recommended ileal bypass as a treatment against high cholesterol. They saw the operation as a partial success because those who had had a coronary in the bypass group had only lowered their cholesterol by only 25 percent while those who hadn't had a coronary had lowered their cholesterol by 33 percent.

Obviously they meant that the lowering should have prevented these heart attacks had it been more pronounced.

But it is difficult to see how the cholesterol level had any importance at all, because in the control group the lowering was about ten percent both in patients who had had a coronary, and in those who had not, and cholesterol in controls who hadn't had a coronary was almost 20 percent higher than in the operated patients who had suffered one. Thus, if anything, the bypass operation had induced heart attacks instead of preventing them.

Dr. Buchwald himself, the inventor of the bypass operation, has conducted the largest trial of ileal bypass. In cooperation with 23 colleagues and 51 advisers he studied more than 800 middle-aged patients, mostly men, who had had at least one coronary. Half of them were randomized to ileal bypass, the other half were controls.[159]

After ten years 32 in the surgery group had died from coronary heart disease against 44 of the controls. In all, 49 had died in the surgery group, 62 in the control group. These differences were far from statistical significance; they could have been due to chance. But in a subgroup analysis Dr. Buchwald and his co-authors found that if only those who had suffered a less serious coronary initially were considered, the difference was almost statistically significant. (But among those who had had a *more* serious coronary initially, *more* had died in the surgery group.)

There were other bright spots. In the control group there were more non-fatal coronaries, more attacks of severe angina, and many more patients underwent an operation to get a new coronary, a so-called coronary-artery bypass grafting. If all these events were taken together the difference between the two groups was highly significant.

Apparently a success. However, a study like this is of course neither single nor double blind. It is necessary to remind you of Professor Cornfield's and Dr. Mitchell's conclusion from their early overview of cholesterol lowering trials: open trials are successful, blind trials are not. To decide whether a patient has had a coronary or something else, or whether a patient should have a coronary graft or not is of course a highly subjective matter. You must be divine to avoid irrational motives from influencing your judgment in a million-dollars trial with so much glory and prestige at stake.

The authors argued that the higher rate of coronary grafting in the control group had improved their survival and blunted the trend toward a reduction in mortality in the surgery group. However, new coronaries may eliminate your angina, but most studies have shown that they do not prolong your life. On the contrary, a net excess of two deaths in the control group could be ascribed to complications of the coronary grafting, thus a further reduction of the difference.

Other complications were produced by the ileal bypass itself. Each year four percent had a kidney stone, a total of about 135 attacks at all, 14 had their gall bladder removed, and 57 had symptoms of bowel obstruction, 15 of whom required an operation. And there was more.

Lack of the ileum means not only loss of bile acid. When bile acid is lost the fats transported with the bile are lost also and make the stools frequent and loose. Loss of fats means loss of calories. On average, ileum bypass patients had a weight loss of 5.3 kg (11.7 lbs).

You may probably recall Dr. Kannel's words about the “formidable risk” of coronary heart disease which is added by obesity. An ileal bypass is an effective treatment against obesity, and obese patients must therefore have been in great excess in the control group. It is difficult to know how many extra heart attacks among controls were due to obesity, but at least this bias should have been mentioned in the discussion and in the summary of the report.

Can atherosclerosis disappear?

Trials including thousands of individuals are laborious and of course utterly expensive. In recent years scientists have taken a shortcut. Instead of coronary deaths they have used regression of coronary artery disease as a measure of treatment effect. By regression they mean a widening or at least a less rapid narrowing of the coronary arteries as seen on coronary angiography. An increase of the mean diameter of the coronary vessels during treatment is said to be due to disappearances of atheromas, the scientific name of the vascular lipid deposits seen in atherosclerosis. Angiographic trials are much cheaper because much fewer test individuals are necessary and the result is possible to evaluate after a much shorter time.

Laboratory changes instead of number of deaths as a measure of treatment effect is called surrogate outcome. The term surrogate is used because it is not self-evident that laboratory changes can be translated to clinical effects such as lowering of mortality. It can be questioned also, if a widening of a coronary vessel seen on angiography means disappearance of atheromas and nothing else, but let me come back to this question a little later. Let us first have a look at the angiographic trials.

The National Heart, Lung and Blood Institute supports the diet-heart idea to one hundred percent. Together with the American Heart Association they administer more than 90 percent of all grants for cardiovascular research. Also on the American Heart Association they are convinced about the danger of cholesterol. In fact, most of those who have introduced the cholesterol campaign or have advocated it most vigorously are members, or have previously been members, of these institutions.

On the National Heart, Lung, and Blood Institute they decided to study the effect of cholesterol lowering directly on x-ray angiograms. To lower cholesterol they had chosen cholestyramine, the same drug that was used in the ongoing LRC trial. In five years 116 male patients with coronary heart disease and high blood cholesterol were treated; one half were given cholestyramine, the other half a placebo drug.[160]

The result was again disappointing. In the treatment group the coronary arteries widened a fraction of a millimeter in four patients, but they widened also in four of the untreated patients.

Before the trial had started the investigators had decided to analyze their results using the one-tailed t-test that is scientifically unacceptable if the outcome can be both positive and negative. On the National Heart, Lung, and Blood Institute however, they said, that it was OK to use it because the weight of laboratory and epidemiological evidence suggested that reduction of blood cholesterol would retard coronary artery disease. The result could only go in one direction.

If you haven't skipped too many chapters you will probably agree with me that the weight of laboratory and epidemiological evidence suggest nothing of the kind. Let me only mention that

when the study they initiated was published in 1984 not fewer than seven controlled cholesterol lowering trials had resulted in an *increase* of coronary mortality in the treatment groups.

By using the one-tailed t-test and by putting the figures together in different ways the fifteen directors of the study headed by Dr. John Brensike found a combination that gave statistical support for the benefit of the treatment. They admitted that the result was not exactly what they had expected, but they returned in a further paper[161] stating that the improvement was proportional with the changes of blood cholesterol they had seen in the patients independent of whether they had been treated or not. With other words, the coronary vessels had less often worsened if the cholesterol was low than if it was high.

It is easy for cholesterol researchers to get caught up in circular reasoning. We do not yet know the cause of atherosclerosis. What we do know is that high cholesterol is a risk factor. Theoretically high blood cholesterol may be the cause, but as I have said before high cholesterol may be secondary to the real cause; the causative factors may have induced atherosclerosis and at the same time it may have raised the level of cholesterol in the blood. The aim of the study was to see which of these alternatives were true by lowering blood cholesterol. Thus, the only valid finding is a possible effect of cholesterol lowering on atherosclerosis in the treated patients. If cholesterol is the bad guy a reduction in its concentration should be followed by a decrease in atherosclerosis, or at least by a halting of its progress.

If cholesterol is only an innocent bystander witnessing the crime and being influenced by it, then a reduction in its concentration would not have any effect because the unknown villain continues his activity. Crime is not prevented by killing the witnesses.

"Selective blindness"

Supported by the National Heart, Lung, and Blood Institute and the drug company Upjohn Dr. David Blankenhorn and his group started a new angiographic trial, called CLAS, the Cholesterol-Lowering Atherosclerosis Study.[162]

This study included 162 patients who had undergone coronary bypass operation. After routine laboratory tests all major arteries in the bodies were examined by angiography. The patients were then randomly assigned to two groups of equal size. One group took cholesterol-lowering drugs, the other took ineffective placebo tablets. Neither the patients nor the doctors knew which group got treatment and which did not. To be sure that cholesterol was lowered properly, two drugs were given at the same time, colestipol and nicotinic acid.

After two years of treatment an angiography was performed again. In 16 percent of those who had been given the drugs but only in two percent of the control patients the coronary arteries had widened. In 38 percent of the treated patients the diameter of the vessels had decreased, but even this finding was seen as a success as the vessels had narrowed in still more of the controls, about 56 percent.

And the differences were statistically significant according to Dr. Blankenhorn and his colleagues, but only with the one-tailed test.

It may seem petty to take exception to the details of statistical formulas, and if the authors had underlined the weakness of their study and made reservations for the questionable results

themselves no further discussion had been necessary. But the authors did not hint at any weakness. Their remarkable deviation from standard statistical practice was not even mentioned in the summary of the paper, nor when Blankenhorn's study was cited in other publications. Furthermore, there was another problem.

The side effects of nicotinic acid, one of the drugs used in the study, are so obvious that no one can have any doubt of who is taking the drug, least of all the patient. Shortly after having swallowed the tablet the patient feels his skin is burning and itching as if stung by nettles. No doubt, the patient will tell about the side effects to his surroundings, including his doctor.

If the doctors still wanted to know for certain whether the patient had treatment or not they could look into the laboratory records. To be sure that the cholesterol really went down all patients had eaten the drugs during a period of three months before the start of the trial, and those whose cholesterol did not go down as much as was anticipated were excluded.

And cholesterol went down. On average blood cholesterol decreased by 26 percent in those who took the drugs; the "bad" cholesterol decreased by as much as 43 percent. On their regular visits at their doctors the patients might as well have had a sign around their neck telling to which group they belonged.

Thus, the trial was neither single nor double blind, which the authors also admitted. They called it "selective blind"; a new, but striking description of the condition on the branch of the research tree where the cholesterol hawks are breeding.

A researcher may be utterly impartial and dedicated to the truth, but he is probably not a saint. All experience tells that if the doctors knew to which group the patients belonged, their judgement must have been influenced in at least some of the cases no matter how much they tried to avoid this bias.

But Dr. Blankenhorn's group was so certain of their results that they immediately called a press conference at the National Heart, Lung, and Blood Institute and with much fanfare announced their sensational findings.[163] Now, at last, *"for the first time"* they had shown *"a strong and consistent therapy effect from cholesterol lowering at the level of coronary arteries."*

Obviously, Dr. Blankenhorn had forgotten, that Dr. Brensike and his coworkers, claimed to have proven this several times. As you probably recall, it was Dr. Brensike's *"strong laboratory and epidemiological evidence that allowed them to use the one-tailed t-test."*

But Blankenhorn went further. He also claimed that his study demonstrated, that blood cholesterol should be lowered to a level of 185 mg/dl and this was also the limit that was set at the National Heart, Lung, and Blood Institute and the American Heart Association after Blankenhorn's study. What an amazing perspective! Remember that even the strongest supporters of the diet-heart idea do not believe that diet is sufficient to lower cholesterol as much as in Blankenhorn's trial; instead drugs must be used. How many adults have blood cholesterol above 185 mg/dl (4.85 mmol/l)? According to Dr. Basil Rifkind, one of the strongest advocates for the diet-heart idea, it probably amounts to 40 million healthy Americans. Said Robert Levy, former head of the American Heart Association, the results were "exciting" even if they were not quite unexpected. And the directors of the drug producer, Upjohn Company must have been delighted.

In a scientific report, it is customary to include discussion of the results of other investigators, especially when they deviate completely from one's own results. How did Dr. Blankenhorn and his coworkers and the brain trust at the National Heart, Lung and Blood Institute comment on the disheartening results of Drs. Bemis, Kimbiris, Shuh, Kramer and their groups, who didn't find the slightest connection between changes in cholesterol deposits in the coronary vessels and changes in cholesterol levels in the blood? How did they explain the fact that the coronary vessels improved in their own experiments, but not in the many previous studies where cholesterol went down just as much or more? Why did they place more importance on their own dubiously positive results than on the many indisputable negative ones? I cannot give you an answer because they did not comment on them at all.

Something better

Three years later, in 1990, the results from a new angiographic trial was published by Dr. Greg Brown and his team in Washington, again supported by the National Heart, Lung, and Blood Institute.[164] Obviously they were not impressed by the "strong and consistent" effect of Blankenhorn's treatment. In their paper they wrote that the lipid changes in the previous trials were small and the clinical benefits limited. Therefore Dr. Brown and his colleagues had used two drugs at the same time. Thirty-eight men received lovastatin and colestipol, 36 received nicotinic acid and colestipol and 46 received placebo, and the trial was designed as a double-blind study. Most of the men participating had familial hypercholesterolemia.

And indeed cholesterol was lowered; by 34 percent in the lovastatin-colestipol group and by 23 percent in the niacin-colestipol group. The devil himself, LDL-cholesterol was lowered even more, by 45 percent and 32 percent, respectively.

Before and after treatment the width of the coronary arteries were measured at various points, using a fivefold magnification of the x-ray pictures. Magnification was necessary, because on average, the vessel diameters in the niacin-colestipol group increased by a mere 0.04 mm only, whereas the diameters in the lovastatin-colestipol decreased by 0.002 mm and in the control group by 0.05 mm. Indeed small differences, but they were statistically significant, and Dr. Brown and his colleagues saw them as a proof of therapeutic success.

I am sure you noticed that the vessel diameters *decreased* in those treated with lovastatin-colestipol, those who had their cholesterol lowered the most. In some places of the arteries the diameter had increased, but on average, taking all measurements together, the diameters had decreased. A decrease of the diameters means of course that the coronary vessels had become narrower, which is certainly not an improvement, although the diameter in the control group decreased even more. The authors had no comments about this striking finding, neither about the fact that the only two deaths in the study, and the only heart attack, were seen in the lovastatin-colestipol group. In fact, the title of their paper said the opposite: *"Regression (improvement) of coronary artery disease as a result of intensive lipid-lowering therapy…"*

The anguish of angiography

Let us still have in mind, that a change of the coronary diameter is nothing but a surrogate outcome. It is assumed that a widening of a coronary vessel on an X-ray means less atherosclerosis and thus a better chance to avoid a heart attack, but this is only an assumption.

Artery walls are surrounded by smooth muscle cells. When such cells contract, the artery narrows. When they relax, it widens. Various factors may stimulate the smooth muscle cells of the coronary arteries. Most important, mental stress, anxiety, exposure to cold, and even a sustained handgrip may lead to contraction. The latter effect was studied six years earlier by Dr. Greg Brown, the same Dr. Brown who led the angiographic trial mentioned above.[165] He found that a handgrip sustained for a few minutes was followed by a 35 percent decrease of the vessel diameter.

Consider that the changes seen in the trials were only a few percent on average. What do you think you would do yourself if somebody were to put a long catheter all the way from your groin up to your heart and into your coronary vessels? If you are not a stuntman or an astronaut I think that you probably would have gripped the nurse's hand or something else very tightly, at least during the first examination. How, then, did the researchers know whether an increase in blood vessel diameter at the second examination was due to the patient being more relaxed or to the vessels being less atherosclerotic?

Also, drugs which relax the coronary vessels, and which are used by almost all coronary patients, may have disturbed the study. In the trial Dr. Brown and his coworkers were aware of that problem. The use of such drugs was *"duplicated as exactly as possible."* This can't have been too easy because the level of any drug in the blood depends on a large number of factors which are difficult to standardize. And Dr. Brown and his colleagues didn't write anything about duplicating possible handgrips or anxious feelings because such duplication is, of course, impossible. So, any factor which may influence the state of the smooth muscle cells in the coronary vessels may have influenced the vessel diameter much more than the possible appearance or disappearance of a tiny amount of cholesterol.

There are more uncertainties. Dr. Seymor Glagov and his colleagues from University of Chicago studied the hearts of 136 deceased individuals and found that when vessels become sclerotic, they widen to compensate for the narrowing brought about by the deposition of cholesterol in their walls. In fact, this widening overcompensates for the deposition until the cholesterol deposits occupy about 40 percent of the area beneath the muscle wall.[166] Only thereafter does the vessel become steadily narrower. In other words, an increase of vessel diameter may be due to disappearance of cholesterol in a highly sclerotic vessel, but also to a compensatory widening during the first stages of cholesterol deposition. How could the trial directors know whether the increase of vessel diameter was due to a disappearance of deposited cholesterol, or to a compensatory widening due to an appearance of deposited cholesterol?

Risk factors and coronary vessel

The fact, that a lowering of cholesterol may reverse sclerotic lesions also conflicts with the results from a number of previous, angiographic long-term studies of the coronary arteries. The aim of those studies was to explore which factors dictated the development of atherosclerosis. Were the risk factors primary or secondary? Should they be sought among the mercenary troops or were they something which followed the vestige of war as hunger and cholera? Was smoking of any importance? Did the blood pressure influence the development of atherosclerosis? Did a high blood cholesterol?

According to the conventional wisdom, atherosclerosis should increase if the cholesterol over a longer period of time is high or if it goes up, no matter why. Likewise, atherosclerosis should decrease, or at least it should not increase, if cholesterol is low or if it goes down.

One of the first who studied the inside of the coronary vessels with such questions in mind was Dr. Charles Bemis. The year was 1973. Together with his team at the Peter Bent Brigham Hospital in Boston[167] he studied about seventy patients and found that the only factor which could be connected with the degree of atherosclerosis was the level of the blood lipids at the start of the investigation. In patients with high blood cholesterol at the start, coronary atherosclerosis had increased at the following angiographic examination a couple of years later.

So far, the results were as anticipated. Once again, it was demonstrated that high blood cholesterol is a risk factor for coronary heart disease. Now to the interesting finding.

In twenty-four patients, cholesterol had decreased by more than 25 percent between the two angiographies, a lowering which was considerably greater than in most cholesterol lowering trials. Among these twenty-four patients, atherosclerosis had increased in sixteen, while it was unchanged in just eight. In twelve patients cholesterol had increased, but only in four of them had atherosclerosis increased.

Said in another way: two out of three whose cholesterol went down had become more sclerotic, while this was the case in only one out of three whose cholesterol went up. It should, of course, have been the other way around.

Dr. Bemis's result was confirmed the following year by Dr. Demetrios Kimbiris and his group in Philadelphia.[168] These investigators also found that cholesterol was unimportant. The coronary arteries of seventeen out of twenty-five patients with high cholesterol had worsened, but they had also worsened in seven out of ten patients with a low cholesterol.

Similar results were achieved at the famous Mayo Clinic by Dr. Clarence Shub and his colleagues. They found that coronary atherosclerosis had increased in all patients whose cholesterol had decreased by more than 60 mg/dl, a lowering which should have been considered more than acceptable in any cholesterol-lowering trial.[169]

In study after study the startling finding of Bemis and his colleagues was confirmed.[170] In their paper, Dr. John Kramer and his colleagues at the Departments of Cardiology and Biostatistics, The Cleveland Clinic Foundation, concluded: *"… medical treatment directed toward 'secondary prevention' may be unsuccessful in retarding or reversing the development of progressive arterial lesions and their clinical consequences."*

But nobody listened. More prudent scientists should have questioned the diet-heart idea, facing the fact that coronary atherosclerosis is worsened just as fast or faster when cholesterol goes down as when it goes up.

In a scientific report it is a rule to discuss also the results of other investigators, especially when they deviate completely from one's own results. How did Blankenhorn and his coworkers and the brain trust at the National Heart, Lung, and Blood Institute comment on these disheartening - results? How did they explain that the coronary vessels improved in their own experiments, but not in the many previous studies where cholesterol went down just as much or more? Why did

they place more importance on their own dubiously positive results than to the many indisputable negative ones?

I cannot give you an answer because nothing was said about them.

Recently, a team led by Canadian Dr. David Waters published yet another study including 335 patients.[171] They found that when the coronary vessels after a two year interval had narrowed by more than 15 percent, the risk for cardiac death or a non-fatal coronary increased considerably. Certainly not an unexpected finding. Their conclusion was that the changes seen on coronary angiography was a good substitute for cardiac events in clinical trials.

But they didn't comment that on average the cholesterol of those whose atherosclerosis had progressed did not differ significantly from the cholesterol of those whose atherosclerosis had not progressed. Remember that the cholesterol in the angiographic trials went down by 30-49 percent, but the change of the vascular diameter was much less than one percent. In Waters's study the diameter change was more than 15 percent, but the decrease of cholesterol an insignificant two percent. Such results do not suggest that the diameter changes have anything to do with the cholesterol changes.

Meta-analysis

Certain treatments are easy to assess. The right antibiotic, for instance, will cure nine out of ten women with an uncomplicated urinary infection, which means that after having treated fewer than a dozen patients and controls for a few days you already know for certain that the drug is effective. But after the many cholesterol-lowering trials, scientists still don't know whether the treatment could change mortality. Statisticians say that to prove a beneficial effect on mortality, many more test individuals are necessary, probably more than 100,000. If the beneficial effect of treatment is so difficult to prove, aren't we justified in concluding that high cholesterol cannot be that dangerous for our health?

But the problem may be solved in another way. The solution is called meta-analysis.

In a meta-analysis, data from all studies that satisfy certain standards of quality are put together in the hope that they will provide a large enough sample for statistical reliability. For medical trials, at least, three standards are mandatory. Trials should be double-blind, they should be controlled, meaning that on average, all risk factors are similar in the two groups, and the test individuals and the controls should be chosen randomly. Also, in order to use the accumulated results from many trials, it is necessary for the same kind of treatment to have been used in each trial and, of course, the result of the treatment—the outcome or the end point—should also be the same.

By now you may have realized that if all standards are to be satisfied, very few trials can qualify. Very few trials have been performed in a true double-blind fashion, and besides cholesterol-lowering, some trials have also used other kinds of intervention. Nevertheless, let us have a look at the entire body of trials that have been published before 1992, all of them performed before the introduction of the statins.

Several meta-analyses on cholesterol-lowering trials have been published. When I prepared the first edition of this book in Swedish it annoyed me that most of these analyses had excluded a

number of trials, preferably the unsupportive ones. So I decided to perform a meta-analysis myself that included all randomized and controlled trials where the aim had been to lower cholesterol, whether by diet, or by drugs, or whether they had used other kinds of intervention also.[172] I accepted open trials, since it was not possible to do a fair selection of double-blind studies because even trials that were designated double-blind were in fact more or less open for the reasons I have given above. In table 6B the raw figures from this analysis are given.

_____

	Treatment Group	Control Group
Number of individuals	59,514	53,251
Non-fatal heart attacks (percent)	2.8%	3.1%
Number of individuals	60,824	54,403
Fatal heart attacks (percent)	2.9%	2.9%
Number of individuals	60,456	53,958
Total number of deaths (percent)	6.1%	5.8%

Table 6B. Overall result of 26 controlled cholesterol-lowering trials. The number of individuals in the three calculations are not identical because a few trials did not give the number for all end points.

As you see, the number of deaths from a heart attack was equal in the treatment and in the control groups, and the total number of deaths was greater in the treatment groups. In one study total mortality had decreased significantly, in two others it had increased significantly, and in no trial was coronary mortality changed more than could be attributed to chance. More sophisticated calculations did not change the picture.

There was a small reduction in the number of non-fatal heart attacks. Calculated in the way diet-heart supporters usually do the difference was 10.4 percent; calculated the simple way, the difference was 0.3 percent. Due to the large number of individuals studied this small difference was statistically significant, but most probably it was a result of bias. Not only were the trials open and partly multifactorial; there was another finding that definitely proved that cholesterol lowering does not make any benefit.

If cholesterol lowering could reduce the risk of coronary heart disease, a pronounced and prolonged lowering should of course lower the risk more than a slight and short one. But there

was no relationship between the degree of cholesterol lowering and any of the end points, not between individuals in each trial and not between trials. And on average, total mortality was equal in short and long trials, and coronary mortality was *higher* in long trials than in short ones.

So, although some of the trials also included physical exercise, weight loss, reduction of blood pressure, and smoking advice, and although most trials were open, the number of non-fatal heart attacks was not reduced by more than 0.3 percent. And even if the doctors had been totally uninfluenced by their knowledge about the patients' group affiliation, remember that what doctors—even experienced ones—call a heart attack very often is something else.

After its publication in the *British Medical Journal*, my meta-analysis provoked harsh comments from diet-heart supporters.[173] According to my critics, the most serious mistake was to include trials using hormones, since such drugs are now considered toxic to the heart. But in one of the first controlled trials published, conducted by Professor Jeremiah Stamler, the researchers used low doses of the female sex hormone estrogen and that trial had the best result of all. High doses of estrogen are possibly harmful for men, but whether low doses are harmful is an open question. In women, at least, low doses, such as those used in post-menopausal hormone replacement therapy, seem to protect against heart attacks.[174] The results were also just as unsupportive in the subgroup calculations, even in subgroups that did not include the hormone trials.

Another objection was that I had ignored the angiographic trials, because they "can lead to regression of atheroma," as one of the critics noted. Let us therefore look at a more recent meta-analysis which included the angiographic trials.

In this analysis, Dr. George Davey Smith at the Department of Public Health, University of Glasgow, Scotland, and his coworkers excluded the multifactorial trials to study the effect of cholesterol lowering only, and they limited their analysis to total mortality.[175] They ranged the trials in order of risk according to the coronary mortality in the control groups. In high-risk trials, many control individuals had died from a heart attack, in low-risk trials relatively few.

In the high-risk trial group (including 5,115 individuals in ten trials on the uppermost part of the risk list) mortality had decreased. In the median-risk group (including 24 090 subjects in 15 trials), mortality was unchanged. In the low-risk group, the largest one (including 27,918 subjects in ten trials on the lower-most part of the list), mortality had increased. Both the decrease and the increase of total mortality was statistically significant. Overall, in trials where drugs had been used to lower cholesterol, mortality from non-coronary causes had increased significantly. The authors' conclusion was that benefits from cholesterol lowering drugs seem to be produced in only a small proportion of patients at very high risk of death from coronary heart disease. Thus, in the future cholesterol lowering should include only individuals at very high risk. But here a problem appears.

Individuals in the so-called low-risk group were only at low risk compared with individuals in the other two groups. In comparison with normal individuals, they were at high risk also. For instance, their cholesterol was 278 mg/dl (7.13 mmol/l) on average, higher than in the other two groups! Remember that at that time the lower limit for drug treatment according to the early recommendations of the National Heart, Lung, and Blood Institute was 185 mg/dl (4.75 mmol/l); according to the cholesterol campaign it was 240 mg/dl (6.15 mmol/l). Furthermore, half of the trials in the so-called low-risk group were of the secondary preventive type, which means that

they included patients who already had suffered a coronary. Such patients always have been considered as being at high risk. Many of the individuals in the low risk group were exposed to other risk factors also, so indeed this group was a sample of high-risk individuals. How should we discriminate between these high-risk individuals and the high-risk individuals who are said to prosper from cholesterol lowering? The simple fact is that we can't. Even doctors who treat high-risk individuals only may shorten the lives of their patients instead of prolonging them.

It is also questionable if mortality really was lowered in the high-risk trial group. One of the trials for instance, was in fact a multifactorial trial that had been included by mistake. The good result in that trial could therefore have been caused by something other than cholesterol lowering. The other trials were very small, and in only one of them was mortality lowered significantly. There was only one reasonably large trial in the high-risk group, but in that trial mortality had *increased*.

Anyone who has read scientific papers or official recommendations about cholesterol and the heart know that we are told another story. Listen, for instance, to the most recent recommendations of the *European Atherosclerosis Society*: *"Clinical trials of secondary prevention by lowering plasma cholesterol, when studied together by meta-analysis, show that morbidity and mortality from coronary disease are reduced; there is also a trend to lower total mortality."*[176]

This misleading statement is not unique; in fact, it is typical of diet-heart writings. Similar statements are found in numerous scientific papers from the supporters, and from the mass media.

There is more than one explanation for the inappropriately optimistic messages from doctors and scientists. Most important, scientists prefer to cite only the supportive trials. I have already told about the few citations from the unsupportive trial by Miettinen and the many citations from the allegedly supportive LRC trial. On average, I found that trials considered supportive by their directors have been cited almost six times more often than unsupportive trials.[52] The fact that a trial was cited frequently had little to do with its quality or whether it had been published in a famous or a less well-known journal. The trial directors themselves were especially unwilling to cite an unsupportive trial; since 1970 up to 1992, no trial considered unsupportive by its directors had been cited in another trial report. Even authors of meta-analyses had selected their trials according to their outcome.[54]

A successful dietary trial

The idea that a Mediterranean diet—whatever that is—would be beneficial for cardiovascular disease inspired the French researcher Dr. Michel de Lorgeril and his team from Lyon, France, to start a new dietary trial, the Lyon Diet-Heart study.[177] About 600 patients who had survived a first heart attack were included. Half of the patients were instructed to adopt the so-called Mediterranean diet by including more bread, more root and green vegetables and more fish, and by reducing consumption of animal fat and red meat. They were also instructed to eat fruit every day, to replace pork with poultry and to replace butter and cream with margarine, which was supplied free for the whole family. In contrast to the previous trials, where the dietary fat was

dominated by vegetable oils with a high content of omega-6 polyunsaturated fatty acids, these researchers used a margarine made with rapeseed oil, which has a high content of α-linolenic acid, a polyunsaturated fatty acid of the omega-3 class. This special type of margarin was supplied free for the whole family. Control group individuals were also given dietary advice, but were recommended the usual "prudent" diet.

This design was chosen because in a previous study people from Crete, the Greek island where heart attacks were rare according to the Seven Countries study, had three times more of this fatty acid in their blood than the people from Zutphen, the Netherlands. The French researchers therefore thought that α-linolenic acid might be protective because the rate of heart attacks was much higher in Zutphen than on Crete although their cholesterol levels were almost identical.

After forty months, a significant difference was found; in the control group 20 individuals had died, compared to only eight in the treatment group. Most surprising was, that in the control group eight of the patients who died from a heart attack had died suddenly, which almost always means that they have died from a disturbance of the heart rhythm. This was not seen in any of those who died in the treatment group. After four years the trial was ended because the improvement in the treatment group had continued; 24 had died in the control group but only 14 in the treatment group. And the difference between the number of nonfatal heart attacks was even larger—25 in the control group, but only eight in the treatment group—and it was therefore considered unethical to continue the trial.

For the first time a dietary trial had succeeded in lowering the risk of dying from a heart attack. Evidently it was a good idea to lower cholesterol by dietary means.

But blood cholesterol was practically identical in both groups after the trial had ended. In fact, it was a little higher in the treatment group.

If the difference couldn't be explained by the participants' cholesterol, what else could? Was it the additional α-linolenic acid or was it the extra fruit or vegetables? Or the extra bread? Or the extra fish or chicken? Or, as both fish and α-linolenic acid is rich in omega-3 polyunsaturated fatty acids, perhaps a better balance between omega-3 and omega-6 polyunsaturated fatty acids? According to the food frequency questionnaire at the end of the study the intake ratio of omega-6/omega-3 in the control group was about 20/1, in the intervention group about 4.5/1.

There is much evidence, both from animal experiments and epidemiological studies that a high ratio between omega-6 and omega-3 polyunsaturated fatty acids may predispose to heart arrhythmia, the main cause of sudden death in patients with heart disease. A few years later a new trial gave further support to that idea.

The GISSI-Prevenzione trial

One of the largest controlled, dietary trial was started in Italy, named Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico Prevenzione trial, or GISSI.[178] More than 11,000 patients who had survived a first myocardial infarction were enrolled and divided into four equally large groups. One group were treated with a capsule containing a mixture of three different omega-3 polyunsaturated fatty acids, one group a capsule with vitamin E, one group were given both capsules, and the fourth group was used as control. All of them received standard treatment for coronary patients.

On average the patients were followed for 40 months. At follow-up 3.5% in the control group had died from sudden death, 2.3% in the vitamin E group, 2.4% in the combined group, and 1.9% in the omega-3 group. Except for the result in the vitamin E group these differences were statistically different; indeed, the difference between the control and the omega-3 group was greater than in any of the following statin trials. Relatively seen, mortality due to sudden death was 46% lower than in the control group. Also the total number of deaths was significantly lower, and again, no differences were seen between the groups as regards blood cholesterol.

Interestingly, no differences were seen between the number of non-fatal heart attacks, a further argument for the idea that the omega-3 polyunsaturated fatty acids primarily protect the nerve conduction system of the heart.

Those who still believe that high cholesterol is the main villain perhaps may argue that the disappointing results from the trials I have discussed in this chapter may be because we haven't lowered cholesterol sufficiently. But to-day we have got a pharmaceutical method to lower cholesterol much more than by using any of the previous drugs; the statins. And according to the directors of the statin trial intensive cholesterol lowering by statin treatment is harmless and also an effective means to prevent cardiovascular disease.

“The most exact data base”—the screenees of MR.FIT

The figures from the MR.FIT study included both the 12,000 participating men, but also the more than 300,000 men who were excluded for various reasons. A large number of studies concerning the follow-up of these screenees has been published in well-known international medical journals, and these studies are cited again and again as the strongest proof that there is a linear association between blood cholesterol concentrations and the risk of future heart disease.

Unfortunately, the data presented in the MR.FIT reports have been carelessly produced. In a systematic search of the literature on the MR.FIT study, Professor Lars Werkö, then director of the Swedish Council on Technology Assessment in Health Care, an independent governmental agency known for its integrity, found 34 papers reporting the relationship between serum cholesterol and mortality. He asked himself whether it really was necessary to publish all these reports as their results were so similar.

“Have the editors really judged the original scientific value of each of these similar articles and deemed them worthy of publication? Or have they been impressed by the status of the research groups that authored these repetitive manuscripts, with the prestigious National Heart, Lung and Blood Institute in the background, and found that they have to succumb to the authorities?”

Worse than being repetitive, the data were inconsistent and highly questionable. For instance, the number of screenees varied greatly between the studies, from 316,099 to 361,266. In particular, Professor Werkö was critical of the studies reporting how many had died and why, because it is highly unlikely that all of 361,266 individuals could have been tracked after 6-12 years.

How the cause of death had been established was not reported but we can be rather confident that most of the reported causes were based on death certificates written by general practitioners. Not only is the information from death certificates highly unreliable, but, in many cases (between 6 and 20 percent, depending on the report), death certificates were actually missing. Yet some of the reports gave a detailed list of diagnoses for almost all deaths.

Furthermore, during the initial screening it came to light that one of the participating centers had falsified its data to increase the number of participants in the trial, possibly in order to obtain more financial support from the National Institutes of Health. This embarrassing matter received little mention in the follow-up reports, nor did the study authors mention the possibility that data falsification could have occurred in other centers as well. Instead, all discussion of the issue of quality control was studiously avoided. Wrote Professor Werkö: *“In the many publications regarding the MRFIT screenees, it is obvious that the authors are more interested in the mathematical treatment of large figures than in the quality of these figures or how they were obtained.”*

In spite of all these irregularities, the follow-up reports on the MR.FIT screenees are still cited as “the most exact database regarding the relation of risk factors to mortality in the healthy male US population.”

Werkö L. Analysis of the MRFIT screenees: a methodological study. Journal of Internal Medicine 237, 507-518, 1995.

Myth 7: The Statins – God's Gift to Mankind

It's easier to fool people than to convince them they have been fooled

Mark Twain

In the late 1980s, the pharmaceutical companies introduced a new type of cholesterol-lowering drug called the "statins." These drugs inhibit the body's production of many important substances, one of which is cholesterol.

Sold as Zocor®, Mevacor®, Pravachol®, Lipitor® and Lescol® these new drugs have received wide acclaim because of their supposed lack of serious side effects and, in particular, because of the substantial cholesterol they can achieve. Whereas the earlier drugs could lower cholesterol by 15-20 percent at most, the statins can lower it by 30-40 percent or more. As of January 2000, the results from the large controlled, randomized and double-blind studies, including more than 30,000 test individual, and numerous angiographic trials have been published. More data will come.

Most doctors believe that the outcome of these trials is a victory for the cholesterol hypothesis. However, a closer look reveals that the cholesterol lowering effects are unimportant and actually rather a drawback. Furthermore, the benefits are trivial and if present, only apply to certain patient groups. In addition, by process of statistical manipulation, ingenious criteria for selecting the test individuals, and generous limits to what are considered as normal laboratory results, the directors of the trials and the drug companies have succeeded in belittling the side effects and thus presenting the statins as harmless.

4S—The Scandinavian Simvastatin Survival Study

In 1994 the results from a large Scandinavian, multi-center trial using simvastatin (Zocor®) were published.[179] These results were noteworthy, indeed. For the first time a trial had succeeded in lowering the risk of both fatal and nonfatal coronary heart disease, and even total mortality. The results were heralded in the *British Medical Journal*: *"Lower patients' cholesterol now! There is no longer any doubt about the benefit and safety of treating hypercholesterolemia in patients who have had a myocardial infarction."*

The results of the 4S trial were published in *The Lancet* on November 19 and presented on the same day at a press conference arranged by the producer of simvastatin and sponsor of the trial, Merck Sharp & Dohme. Present at the conference were the discoverers of the deficient LDL-receptor in people with familial hypercholesterolemia, Nobel Prize winners Joseph Goldstein and Michael Brown who, according to a Merck representative, proclaimed: *"This is Christmas Eve!"*

Their excitement is understandable; they must have had many sleepless nights thinking about the many disappointing results from the previous cholesterol-lowering trials. In the vigorous marketing campaign that followed, 4S was heralded as the *milestone trial* and simvastatin as *the missing link*.

The study was performed in cooperation with 94 Scandinavian medical departments and directed by Dr. Terje Pedersen from the cardiology section at Aker Hospital, Norway. The steering

committee and monitoring staff also included employees from Merck, and all data from the trial were processed without outside supervision at Merck's laboratories in the US.

Altogether 4444 men and women with a previous heart attack were treated, half with simvastatin, half with a placebo. After 5.4 years, 8.5 percent had died from a heart attack in the control group, compared with 5 percent in the treatment group. (Table 8A.) This improvement included men only; the number of women who died from a heart attack was equal in both groups, or to be more correct, a little more women died in the statin group.

But there were other benefits. The number of nonfatal heart attacks was lowered even more, from 22.6 percent in the control group to 15.9 percent in the simvastatin group, a gain of 6.7 percent. Furthermore, the number of strokes was reduced significantly, from 4.3 percent to 2.7 percent.

Curiously, in the following, even larger HPS trial[180] the results were only half as good as in 4S although it was the same drug and the same dose that was tested on the same type of participants, and although cholesterol was lowered just as much.

However, it is the figures from the 4S trial that are used in the marketing of Zocor, and they are expressed as percentages, not as percentage points. More about that in the following.

CARE, the Cholesterol and Recurrent Events Trial

A similar study, the CARE trial, conducted by Dr. Franck Sacks and his co-workers from seven American, Canadian and British university hospitals, used pravastatin (Pravachol®) to lower cholesterol, again in patients with a previous heart attack.[181] After five years, 5.7 percent had died from heart disease in the control group, compared to only 4.6 percent in the treatment group. Considering the large number of participants, this result doesn't seem particularly impressive and, indeed, it was not statistically significant either. In fact, the reduction in heart disease deaths was offset by more deaths from other causes.

There were other benefits, however. As in the 4S trial, the number of strokes was smaller in the treatment group, and there were also fewer nonfatal heart attacks.

WOSCOPS, the West of Scotland Coronary Prevention Study

The two statin trials mentioned above studied the effect on patients who already had heart disease. Is it possible as well to prevent heart disease in healthy individuals whose only "disease" is high cholesterol? This was the question asked by Professor James Shepherd and his team from the University of Glasgow, Scotland.[182] To that end they assigned more than 6,000 middle-aged men with average cholesterol levels to receive either pravastatin (Pravachol®) or a placebo drug in a new trial, called WOSCOPS, the West of Scotland Coronary Prevention Study. Although the effect of that trial was trivial and as well could have been due to chance, no one expressed any reservations about cholesterol lowering in healthy people. If your cholesterol is high it doesn't matter how healthy you are. Lower your cholesterol!

AFCAPS/TexCAPS, the Air Force/Texan Coronary Atherosclerosis Prevention Study

Is it possible to prevent heart attacks in healthy individuals with normal cholesterol? If so, it would mean that all of us would benefit from taking a statin drug, starting at middle age and continuing for the rest of our lives. The economical ramifications are breathtaking, both for the stockholders of the drug companies and, in a less pleasant way, for the directors of health care systems all over the world, which would pay the bill.

A new statin trial called the Air Force/Texas Coronary Atherosclerosis Prevention Study, or AFCAPS/TexCAPS was organized to answer this question. It was directed by the former president of the American Heart Association Professor Antonio Gotto from Cornell University, New York, and his co-workers from various institutions and hospitals in Texas. Three of the co-workers were employees at Merck & Co., the company whose drug lovastatin (Mevacor®) was tested in this trial. More than 5,000 healthy men and almost 1,000 healthy women with no signs or symptoms of cardiovascular disease were assigned to treatment, as usual half with the drug, half with a placebo.[183]

After five years 2.4 percent had died in the treatment group, but only 2.3 percent in the control group. But as the trial directors proclaimed, the primary target in this trial was not to lower mortality, but to reduce the number of fatal and nonfatal heart attacks, and by classifying angina as a non-fatal event, the trial was indeed a success on that point.

LIPID, the Long-term Intervention with Pravastatin in Ischemic Disease study

Another pravastatin trial named LIPID included patients with previous heart disease with all ranges of cholesterol levels. This is a logical approach because the statins were found to prevent cardiovascular disease whether the cholesterol is high or low, therefore there was no reason to look at people's cholesterol at all.

This trial was conducted by Drs. Andrew Tonkin and John Simes at the University of Sydney, Australia, along with a team of 63 other researchers. Three of the co-workers came from the drug company Bristol-Myers Squibb, the sponsor of the trial.[184]

After six years 14 percent had died in the control group, but only 11 percent in the treatment group. There was also a small effect as regards heart mortality, but these effects were seen in men only. And as mentioned, the benefit was gained, whether their initial cholesterol was high or low, a finding the researchers noted with much satisfaction. Obviously they didn't realize that this finding was a serious challenge to the very idea about dangerous cholesterol.

How do you explain that cholesterol lowering is beneficial in people with normal cholesterol if normal cholesterol is not a risk factor? By changing the definition of normal, of course. Today the authorities believe that all of us have too much cholesterol in our blood and, if there are other risk factors present, that this cholesterol should be forced to its knees, even if it is already low.

Summing up

First, the statins were almost as effective for women as they were for men. Indeed in the CARE trial the effect was most pronounced for the female sex, although almost all studies have shown that high cholesterol is not a risk factor for women.

Second, in several of the trials, the effect was independent of age, although almost all studies have found that high cholesterol is not a risk factor in old people.[185]

Third, patients who had suffered a heart attack were protected even though most studies have shown that high cholesterol is a weak risk factor, if any at all, for those who have already had a heart attack.[186]

Fourth, the number of strokes was reduced after statin treatment, although all studies have shown that high cholesterol is a weak risk factor for stroke, if any at all.

Most important, there was no association between the degree of cholesterol lowering and the outcome, the benefit was independent on the degree of cholesterol lowering. Atherosclerosis is allegedly caused by high cholesterol in the blood; the higher cholesterol is, the greater is the risk, and the more we lower cholesterol, it is said, the more benefit will we achieve. The most important proof of such a hypothesis is therefore an association between the degree of cholesterol lowering in the blood and the outcome of the lowering. Such an association is called exposure-response. (A similar term is dose-response, which means that there is an association between the dose of an added factor to a medium, in this case the dose of the drug given to a patient, and the effect of that dose, in this case the outcome of the disease.)

Presence of exposure-response between degree of cholesterol-lowering and outcome doesn't prove causality, because the concentration of cholesterol may be secondary to the real cause, but absence of exposure-response definitely disproves it. Curiously, only a few of the clinical trial reports included a calculation of exposure-response.

From the CARE trial the lack of exposure-response was documented in a separate paper, and the authors' words left no doubt: "…in a multivariate analysis that included LDL concentration during follow-up, the change of LDL from baseline, expressed either as a percentage or absolute change in concentration, was not found to be significantly related to coronary events."[187] Put in plain words, benefit was seen whether cholesterol went down very much or only a little.

Many words were used to clarify this unexpected finding. The most likely explanation, that LDL has nothing to do with cardiovascular disease, wasn't mentioned, of course.

The directors of the WOSCOPS trial came to the same conclusion: *"… there was no obvious correlation between percent LDL reduction and event rate."* Their conclusion was that the statins must have other beneficial effects.[188]

It is easy to calculate exposure-response once all the trial data have been recorded and tabulated. I leave it to the reader to speculate why it hasn't been done in the many clinical trials that followed. But in conflict with these results, many authors claim that the trials did show exposure-response. Their argument is based on an association between the mean degree of cholesterol

lowering and the outcome in each trial. But presence of exposure-response demands that individual values are used in the calculation.

How come the statins are effective for individuals for whom cholesterol s not a risk factor? And how come he effect of the statins does not depend on how much they lower blood cholesterol? If the cholesterol level for these people is not a risk factor for heart disease, how could a lowering of that cholesterol improve their chance of avoiding a heart attack? If the level of our cholesterol is so important, as we have been told for many years, why doesn't it matter whether we lower it by large or small amounts?

It is obvious that the statins have other, more beneficial effects than cholesterol reduction, and this was also the conclusion of the WOSCOPS trial directors. Statins lower the risk of individuals for whom cholesterol is not a risk factor and their effect does not depend on how much they lower blood cholesterol.

When the results from the 4S trial were presented to Swedish doctors, one of the findings was the lack of exposure-response, both for total and LDL-cholesterol. I was present at two of the meetings and pointed out this striking deviation from the cholesterol hypothesis. On both occasions, it was obvious that the speaker had not recognized the implications of this phenomenon. It was not mentioned either in the first report published in *The Lancet* in 1994. Therefore I sent a manuscript to *The Lancet* presenting the above arguments and several more. The paper was rejected by the editor Robin Fox with the following words:

Dear Dr, Ravnskov

I was not surprised to hear from you about the 4S study. The article gave rise to some useful correspondence, and it is clear that the argument about cholesterol and heart disease is not yet over. We need more data, and I know that the 4S group are already investigating some of the points that you raise. Let us see, for example, whether the benefit is related to initial cholesterol concentration. I am not persuaded that publication of your hypothesis would be helpful to readers at this stage.

Yours sincerely

Robin Fox

The correspondence mentioned in Dr. Fox's letter indeed produced results. Four years later a new 4S report was published, and in that paper the authors claimed the presence of exposure-response. However, the finding concerned only the first year of the trial.[189] In a letter in Läkartidningen, the Journal of the Swedish Medical Association, I asked one of the authors, Professor Anders G. Olsson, to explain why they had published the exposure-response calculations for the first year, but not for the whole trial, in which, according to the presentations at the meetings in Sweden, there was no exposure-response. Olsson answered with the following words: *"Anyone obsessed by a particular idea is able to draw cocksure conclusions from selected subgroup analyses."*

I still wonder to whom Olsson referred.

There is strong evidence for alternative, so-called pleiotropic effects of the statins, which I pointed out in my rejected manuscript and also in a subsequent letter to *The Lancet*,[190] and the following year other researchers also published similar ideas.[191]

The statins inhibit the body's production of a substance called mevalonate, which is an early precursor to cholesterol, but also to many other substances with biological importance. The way the statins interfere in mevalonate metabolism is therefore complex and difficult to predict, like guessing what will happen if a hammer is thrown into a complicated machine. It is possible to draw a few conclusions, however.

Reduced amounts of mevalonate may explain why statin treatment has anti-inflammatory effects,[192] makes smooth muscle cells less active[193] and platelets less inclined to produce thromboxane.[194] One of the first steps in the process of atherosclerosis is the growth and migration of smooth muscle cells inside the artery walls, and thromboxane is a substance that is necessary for blood clotting. By blocking the function of smooth muscle cells and platelets, statin treatment may provide benefit for cardiovascular disease by at least two mechanisms, both of which are independent of cholesterol levels.

The protective effects of simvastatin were demonstrated in heart transplantation studies in rats.[195] Normally, the function of transplanted hearts gradually deteriorates because the coronary vessels are narrowed by an increased growth of smooth muscle cells in the vascular walls. This condition is called graft vessel disease, a condition with many similarities to early atherosclerosis. However, rats that received simvastatin had considerably less graft vessel disease than control rats that did not receive simvastatin, and this was not due to cholesterol reduction because simvastatin does not lower cholesterol in rats. In fact, LDL-cholesterol was highest in the rats receiving simvastatin.

In another experiment a flexible collar was placed around an artery in rabbits.[196] After two weeks the arteries with collars became narrow, but less so if the rabbits had received simvastatin. Again, the effect had no relation to the rabbits's cholesterol levels.

Thus, the statins in some way protect against cardiovascular disease, but their effect is not due to cholesterol reduction. The proponents of the cholesterol hypothesis have simply had incredible luck in finding a substance that prevents cardiovascular disease and at the same time lowers cholesterol. The question is, however, whether the benefits would have been even better if the statins didn't lower cholesterol.

But why bother about mechanisms? Isn't it wonderful that the statins work? Shouldn't we all take statins?

The costs

To answer that question it is necessary to look at the figures from the trials. Take a look at the figures for "number of heart disease deaths, relative risk reduction," in Table 7A. You will find that coronary mortality in these trials was lowered between 19 percent and 41 percent, most in the 4S trial and least in the CARE trial. These are the so-called relative risk figures that are used by the trial directors and by the drug companies in their ads. But let us also look at the absolute figures, the "absolute risk reduction," on the next line. Here you will find that death from a heart attack was prevented in only a small percentage of the treated individuals. This figure was

highest in the trials that included patients with heart disease, whereas it was a trivial 0.12 percent in the AFCAPS/TexCAPS trial, which included healthy individuals with normal cholesterol.

_____

m = men,women
Ctr: Control group; NS: Not significant.
*: p = 0.05; **: p = 0.01; ***:p = 0.001

Trial	**EXCEL**	**4S**	**WOSCOPS**	**CARE**	**AFCAPS/ TexCAPS**	**LIPID**
Drug	Lovastatin	Simvastatin	Pravastatin	Pravastatin	Lovastatin	Pravastatin
Length of trial; years	?	5.4 years	4.4 years	5 years	5.2 years	6.1 years
Type of participants	Healthy people with high cholesterol	Patients with CHD and high cholesterol	Healthy people with high cholesterol	Patients with CHD and normal cholesterol	Healthy people with normal cholesterol	Patients with CHD and all levels of cholesterol
Number of participants						
in drug/control group	6600/1650	2221/2223	3302/3293	2081/2078	3304/3301	4512/4502
Percent male:	59	82	100	86	85	83
Age	18-70	35-70	45-64	21-75	men 45-73 women 55-73	31-75
Cholesterol at start						

m = men,women
Ctr: Control group; NS: Not significant.
*: p = 0.05; **: p = 0.01; ***:p = 0.001

Trial	**EXCEL**	**4S**	**WOSCOPS**	**CARE**	**AFCAPS/ TexCAPS**	**LIPID**
Drug	Lovastatin	Simvastatin	Pravastatin	Pravastatin	Lovastatin	Pravastatin
LDL, mean	180	190	192	139	150	150
LDL, range	-	-	>155	115-174	131-191	-
Total cholesterol, mean	258 mg/dl	263 mg/dl	272 mg/dl	209 mg/dl	221 mg/dl	218 mg/dl
Total cholesterol, range	-	215-312 mg/dl	>252 mg/dl	<240 mg/dl	181-266 mg/dl	155-271 mg/dl
Degree of lowering						
LDL cholesterol	?	35%	26%	28%	26%	25%
Total cholesterol	?	25%	20%	20%	19%	18%
Total number of deaths						
Drug/control group; numbers	?	182/256	106/135	180/196	80/77	498/633
Percent	0.5/0.2	8.2/11.5	3.2/4.1	8.6/9.4	2.4/2.3	11/14.1

m = men,women
Ctr: Control group; NS: Not significant.
*: p = 0.05; **: p = 0.01; ***:p = 0.001

Trial	**EXCEL**	**4S**	**WOSCOPS**	**CARE**	**AFCAPS/ TexCAPS**	**LIPID**
Drug	Lovastatin	Simvastatin	Pravastatin	Pravastatin	Lovastatin	Pravastatin
Relative risk reduction; %	+150%	-29%	-21%	-8%	+3.9%	-21%
Absolute risk reduction; %	+0.3%	3.3%	-0.9%	-0.77%	+0.09%	-3%
Statistical significance	?	***	NS	NS	NS	***
Number of CHD deaths						
Drug/control, group; numbers	?	111/189	38/52	96/119	11/15	287/373
percent	?	5/8.5	1.2/1.6	4.6/5.7	0.33/0.45	6.4/8.3
Relative risk reduction; %	?	-41%	-27%	-19%	-27%	-23%
Absolute risk reduction; %	?	-3.5%	-0.42%	-1.1%	-0.12%	-1.9%
Statistical significance	?	***	NS	NS	NS	***
Number of nonfatal CHD						

m = men,women
Ctr: Control group; NS: Not significant.
*: p = 0.05; **: p = 0.01; ***:p = 0.001

Trial	**EXCEL**	**4S**	**WOSCOPS**	**CARE**	**AFCAPS/ TexCAPS**	**LIPID**
Drug	Lovastatin	Simvastatin	Pravastatin	Pravastatin	Lovastatin	Pravastatin
Drug/control group; numbers	?	353/502	143/204	135/173	116/183[a]	336/463
Percent	?	15.9/22.6	4.3/6.2	6.5/8.3	3.5/5.5	7.4/10.3
Relative risk reduction; %	?	-30%	-22%	-22%	-38%	-27%
Absolute risk reduction; %	?	-6.7%	-1.8%	-1.8%	-2%	-2.9%
Statistical significance	?	***	***	*	***	***
Similar effects in both sexes	?	No	-	yes	yes	yes
Effect in all age groups	?	yes	yes	yes	yes	yes
Effect on other cardiovascular diseases	?	yes	no	yes	-	yes

m = men,women Ctr: Control group; NS: Not significant. *: p = 0.05; **: p = 0.01; ***:p = 0.001						
Trial	**EXCEL**	**4S**	**WOSCOPS**	**CARE**	**AFCAPS/ TexCAPS**	**LIPID**
Drug	Lovastatin	Simvastatin	Pravastatin	Pravastatin	Lovastatin	Pravastatin
Effect independent of degree of cholesterol lowering	Not studied	yes	yes	yes	yes	Not studied

Table 7A. Summary of the outcome of the first six statin trials.

Put another way, the chance of not dying from a heart attack over four to six years for a patient with heart disease and high cholesterol is about 92 percent without treatment, and increases to 93 or 94 percent if he takes a statin tablet every day.

For healthy individuals, the figures are even less impressive. In the WOSCOPS trial, for instance, the chance for a healthy man with high cholesterol of not dying from a heart attack during the five years of the study was 98.4 percent without treatment and 98.8 with treatment. In the AFCAPS/TexCAPS trial, the chance of surviving was 99.55 percent without treatment and 99.67 with treatment. Most likely, no effect was seen at all because such small differences may just as well be caused by chance.

Let us compare these figures with another kind of treatment, for instance, treatment of urinary tract infections. Nine out of ten women with a urinary tract infection will recover immediately if treated with an appropriate antibiotic for a few days, at the cost of a few dollars. But in the 4S trial, for instance, they treated 28 patients for five years to prevent one fatal heart attack; in the other secondary prevention trials, they treated at least twice as many to achieve the same result. So, while one of the patients benefited from the treatment, the others took the drug in vain because they would have survived anyway.

The costs for the drug alone amounts to about $150,000 per saved life, but that was in 1994, the year for the publication of the first statin trial; to-day it is much cheaper. In the trials, all expenses are paid by the drug companies, but in real life, the patient or society must pay, not only for the costs of the drug but also for the doctors' fees, laboratory analyses and loss of income during the doctor visits. And to prevent one fatal heart attack in healthy people, if it is

possible at all, 235 individuals with high cholesterol and 826 individuals with normal cholesterol have to consume a statin drug for four to five years.

Of course, there may be other gains. Not only did statin treatment prevent coronary death, it also prevented more than twice as many nonfatal heart attacks. We should also subtract the costs for hospital care and other treatments for the patients whose heart attacks we prevent, not to mention the grief and pain associated with the loss of wives or husbands or close friends. In the most optimistic calculations, the costs to save one year of life in patients with heart disease have been estimated to be about $10,000; much more for healthy individuals.

This may not sound unreasonable. Isn't a human life worth $10,000 or more?

The implication of such reasoning is that in order to add a few more years of life for a few people, more than half of mankind should take statin drugs every day from an early age to the end of life. It is easy to calculate that the costs for such treatment would consume most of any government's health budget. And if this kind of money is spent to prolong the life of a few healthy individuals with statin treatment, what will remain for the care of those who really need it? Shouldn't health care be given primarily to the sick and the crippled?

But what is even worse, those who recommend statin treatment for healthy people ignore the fact that the treatment may produce disease instead of preventing it.

The side effects

Drugs that interfere with normal bodily functions usually have unexpected and unintended effects and so is the case with the statins. According to the drug producers and the trial directors, adverse effects from statin treatment are rare and mild, as indeed they should be, because they are aimed at life-long treatment for millions and millions of patients and healthy people. And the drug companies are of course eager to tell us that they are harmless considering the huge income they have already generated. According to Marcia Angell, former editor-in-chief of The New England Journal of Medicine, the combined profit for the ten drug companies on the magazine Fortune's list of the world's 500 most profitable companies was higher than the profit of all the other 490 put together.[197] And the statins are by far the most prescribed drugs today. In 2002, for instance, the income to Pfizer for atorvastatin was $9 billion in the US alone. Evidently, as Dr. Angell says, the drug companies' aim is "to load the dice to make sure their drugs look good." And they are clever enough to do so.

Myopathy and rhabdomyolysis

Statins block an enzyme called hydroxymethylglutaryl coenzyme A reductase, an enzyme that is necessary to produce mevalonate, and mevalonate is the building block not only for cholesterol, but also for a substance called coenzyme Q10, or simply Q10. This substance is located to the mitochondria of our cells, and the mitochondria is the cell's power plant. No energy is produced without this vital molecule and its importance is particularly great where energy is needed the most, in the muscle cells. And muscle complaints are also the most frequently reported side effect from statin treatment.

Authors of the statin trial reports claim that muscle complaints, or myopathy, occur in less than 1 percent of patients, but this is with all certainty an underestimation. Other authors, independent

of the drug companies, have found much higher frequencies. Thus, a research group lead by Helmut Sinzinger at the University of Vienna found that muscular side effects are seen in about 25% in patients who do regular exercise. They also studied this problem in 22 professional athletes with familial hypercholesterolemia who were treated with various statins. Sixteen, or three out of four, discontinued the treatment because of muscle side effects.[198] Competitive athletes may be more sensitive to muscle pain and muscle weakness than the rest of us, but even mild symptoms may have a deleterious effect on elderly people who already have muscular weakness. And considering that the best, the cheapest and the least risky way to prevent heart disease is regular exercise, muscular problems may directly counteract any possible benefit achieved by statin treatment.

Now compare these figures with those given in table 6A. Whereas at least 20 percent suffered from muscular problems, only a few percent gained benefit from statin treatment.

When muscles are damaged, the concentration of an enzyme called creatine kinase, or CK, becomes elevated in the blood. Elevated CK is thus an early sign of muscle damage, both of the skeletal muscles and the heart. We are told that elevated CK is seen in less than one percent of patients treated with statins as well. But trial directors insist on a CK elevation ten times higher than the normal upper limit and taken at two successive determinations before they call it elevated.

Similarly, liver damage, another side effect, is only reported if the liver enzymes in the blood are more than three times higher than the normal upper limit, and again, only if it has been reported twice.

I have never heard or read about anyone questioning this practice. No one seems to be asking what happens to the liver after ten or twenty years of statin treatment in those whose liver enzymes are only 2.5 times higher. And what happens to the muscles of those whose CK is only nine times higher?

The habit of diagnosing muscle damage only if CK is elevated, whether just a little or quite a lot, is also questionable, because microscopic examinations of muscle tissue from statin-treated patients have shown signs of damage in patients with a normal CK.[199] And even patients on statin treatment, but without muscular symptoms, may be damaged. In a study of muscle tissue using electron microscopy, the structural integrity of skeletal muscle fibres was compromised in 10 of 14 statin-treated patients without any subjective complaints, but in only one of eight control individuals.[200]

In rare cases, myopathy progresses to the destruction of muscle tissue, a condition called rhabdomyolysis. Large amounts of a muscle protein called myoglobin are liberated into the blood, and too much myoglobin in the blood clogs the kidneys leading to renal failure. A few years after the introduction of Bayer's statin drug Baycol, fifty patients receiving Baycol were reported to have died from renal failure, and Bayer was therefore forced to withdraw the drug from the market. According to a more recent report from Bayer, more than 100 patients had died from kidney failure. The number of patients who needed dialysis or a kidney transplant as a result of Baycol treatment is unknown. This number must be much higher because to-day treatment of end-stage renal failure is highly effective, in particular in young and middle-age people.

Rhabdomyolysis is seen after treatment with other statins also, but less frequently. In a recent review of statin side effects the authors found 4.4 cases of rhabdomyolysis per 100 000 patient years after pravastatin, simvastatin and atorvastatin treatment. But there is obviously something wrong with such figures. In the TNT trial (see later), where statin doses up to eight times higher than normal were used, five non-fatal cases of rhabdomyolysis were reported, four of them during the treatment period. However, the authors claimed, that these cases had nothing to do with the treatment because they were not dose-dependent.

But if the four cases observed in the TNT trial were not due to treatment, and if the figure for rhabdomyolysis mentioned above is true, it means that rhabdomyolysis should be twice as common in untreated people as in those treated with statins. This is obviously not true. Rhabdomyolysis is rarely seen spontaneously; it always occurs secondarily to something else, for instance severe muscle injuries as a result of arterial occlusion or deep venous thrombosis in the legs, or to exposure to toxic chemicals or drugs. The odds are that arterial thrombosis may have been the cause in one of the cases. But even so it is highly unlikely that none of the cases were associated with statin treatment. Obviously, trial directors try to cover up the truth about statin side effects. And this is only part of the evidence.

Heart failure

The heart is also a muscle and therefore should be affected by a decrease in Q10. As early as 1990, the biochemist Karl Folkers, who first described the molecular structure of Q10, reported that lovastatin lowered the concentration of Q10. What he also found was that the function of the heart went downhill whereas Q10 treatment was able to improve it.[201] Several recent trials have confirmed the beneficial effect of Q10 treatment in patients with heart failure.[202]

Heart failure is not reported as a side effect of statin treatment according to the trial reports, probably because patients with heart failure are routinely excluded from statin trials, but also because heart failure may be seen as the result of the primary disease rather than an adverse effect. This is most likely what the practicing doctor will think as well, because heart failure is not mentioned as a potential side effect on the drug labels.

Brain problems

Apart from the adrenal glands, the highest cholesterol concentration is present in the brain. The brain cells themselves produce practically all of this cholesterol because in the brain, little or no LDL-cholesterol is taken up from the blood. The rate of cholesterol synthesis is extremely high in the central nervous system of the fetus and the newborn, probably explaining the severe malformations and dysfunctions of the brain seen in children with Smith-Lemli-Opitz syndrome, an inborn error of cholesterol metabolism that leads to extremely low cholesterol values. Cholesterol is used as a component in the membranes of the brain cells and the nerve fibres and is also vital for proper function of the synapses, the connections between the nerve cells. It is therefore not too farfetched to assume that low cholesterol levels may adversely affect brain function in normal people. Indeed, we have much evidence to support this idea.

In several of the trials a larger number of the treated individuals died from violence or suicide. In none of them was the difference statistically significant, but all studies pointed in the same direction. Most diet-heart proponents belittle this problem. It must be coincidental, they say. It is

out of the question to conclude that lowering cholesterol makes people more likely to die from violence or suicide.

Matthew Muldoon and his team from the University of Pittsburgh, Pennsylvania, were the first to point out this phenomenon.[203] Their conclusion was that if all the trial results were added up in a meta-analysis, the increased number who died from violence and suicide was, in fact, statistically significant. Fewer died from a heart attack, but more from violent and sudden deaths. The authors also stressed that low blood cholesterol levels are seen more often in criminals, in people with diagnoses of violent or aggressive-conduct disorders, in homicidal offenders with histories of violence and suicide attempts related to alcohol, and in people with poorly internalized social norms and low self-control.

In a comment on the paper, David Horrobin, the editor of *Medical Hypotheses*, wrote that the most serious consequence of cholesterol-lowering measures is invisible. If low cholesterol levels cause violence and depression, then intervention to reduce cholesterol on a large scale could lead to a general shift to more violent patterns of behavior. Most of this increased violence would not result in death but in more aggression at work and in the family, more child abuse, more wife-beating and generally more unhappiness. Such events are not recorded in the trials—no one asks about them—and they are therefore never detected.[204]

In other words, we are told about the number surviving a heart attack, but not about the number surviving violence or suicide attempts.

The conclusions of Muldoon and co-workers were strengthened by a large investigation in Sweden by Dr. Gunnar Lindberg and his team. They measured cholesterol in more than 50,000 men and women and kept track of them for 20 years. During the first six years, five times more had committed suicide among those with low cholesterol compared with those whose cholesterol was high.[205]

The increased risk of suicide disappeared with time. The authors therefore concluded that the increased risk may be associated with a concentration of cholesterol below a subject's habitual value, which means that the risk of suicide is greater if low cholesterol is induced by diet or drugs.

Several others have confirmed the association between low cholesterol and depression, suicide and suicidal attempts.[206] Not unexpectedly, relapse in cocaine addiction is also seen more often in people with low cholesterol,[207] and cholesterol levels in monkeys, dogs, and human beings with a violent behavior patterns fall most often in the lower end of the scale.[208]

Beatrice Golomb, a professor of medicine at the University of California in San Diego, has devoted much of her research on the side effects of statins and she is today the most knowledgeable researcher in this area. In a meticulous analysis of all studies published since 1965 that looked at the association between low or lowered cholesterol levels and violence, she concluded that the association is causal, and that the risk of creating violent behavior should be taken into consideration before doctors advise their patients cholesterol lowering measures.[209] Together with her co-workers she reported about patients with severe irritability and short temper on statin treatment. All of them recovered after discontinuation. A strong argument for a

causal role of the statin treatment is that re-challenge with the drug in four of the patients led to reappearance of their anti-social behavior.[210]

There is no medical term for irritability and shortness of temper, so therefore the statin trials do not record these changes in behavior. As far as the trial directors are concerned, these effects are not on their radar screen. But they are in full view of the family members and friends who must cope with the personality changes in the patient taking statins, as well as hugely present with the patients themselves, whose golden years may suddenly become overcast with a bleak and grumpy outlook on world… all for the presumed benefit of adding a few months of life to the human carcass.

Progressive dementia in two patients on atorvastatin was described by Dr. Deborah King at the University of Mississippi. After discontinuation of the drug a dramatic improvement was observed in both patients.[211]

Leslie Wagstaff, and his team at Duke University searched the FDA's MedWatch surveillance system for reports of statin-associated memory loss and found 60 cases. The symptoms varied between short-term memory loss, and total amnesia. Usually the symptoms appeared after several months of treatment and disappeared after its withdrawal.[212]

The influence of cholesterol on memory was studied in hundreds of women by Professor V. W. Henderson and his team at the University of Arkansas. They found that LDL-cholesterol, but no other lipids, was strongly associated with the memory score, just as was the case in Professor Muldoon's study. Women with high cholesterol scored better than women with medium cholesterol, and women with medium cholesterol scored better than women with low cholesterol. They also compared the score with changes in LDL-cholesterol levels over several years and found that women whose cholesterol increased had a better score than women whose cholesterol went down.[213]

Memory loss, or amnesia is a common and entertaining theme in the movies. In real life it is very rare, at least before the statins were introduced. One of the victims of this scary condition was Dr. Duane Graveline, astronaut, aerospace medical researcher, flight surgeon and family doctor. In his book Lipitor, Thief of Memory, Graveline described how he himself became a victim of temporary but total memory loss.

Six weeks after his annual astronaut physical, where he had been prescribed Lipitor because of high cholesterol, he was found by his wife aimlessly walking around close to their home. He didn't recognize her and refused to go into their house, and it took her much time and persuasion before he, utterly reluctantly, got into their car so they could go to their family doctor. He was finally examined by a neurologist who, after a thorough examination couldn't find anything wrong except for the amnesia. No recommendations were given and shortly after the examination he felt completely normal. Eventually, however, Graveline began suspecting that the cause of the amnesia might have been his treatment with Lipitor and he therefore stopped taking it.

At the next physical Dr. Graveline was again prescribed Lipitor. Neither the NASA doctors, nor any of the many doctors or pharmacists whom he had consulted, had ever heard about this side effect, so he followed their advice. Six weeks later he experienced a second episode of amnesia

that lasted for twelve hours. This time he couldn't recall anything that had happened after high school. His years on college, his training at medical school, his time as a USAF flight surgeon, his marriage and his four children, his selection by NASA as a scientist astronaut, his twenty years as a family doctor, his busy retirement and his eight books, all of it had disappeared, and also all that he had learned. Afterwards he realized that he would not even have been able to treat a common cold.

Again, everyone denied any possibility of a Lipitor association. But this time Dr. Graveline himself was convinced that the drug was the villain. He wrote a letter about his experience that was published in the nationally syndicated column, The People's Pharmacy.

Graveline was referred to a statin drug study at UCSD College of Medicine, where the principal investigator, Dr. Beatrice Golomb told him that she knew of several similar cases, and after publication of his letter, hundreds of distraught patients and relatives and even a few doctors contacted him. They told about a full array of cognitive side effects, from amnesia and severe memory loss to confusion and disorientation, and all of them were associated with statin treatment.

Similar stories are still reported to and filed by the Federal Drug Administration. However, to date the agency has taken no action—not even issued a warning. "The subject is still being reviewed," was their most recent response according to Dr. Graveline, if they bothered to reply at all.

Anyone who has been prescribed a statin drug is urged to read his book and its follow-up, Statin Drugs Side Effects and The Misguided War on Cholesterol, or at least go to his website, where he summarizes what he has learned from thousands of victims who have contacted him after the publication of his first book. Here are his words about amnesia:

"For every reported case of transient global amnesia there are hundreds of case reports of impaired memory, disorientation and confusion among an older group of patients that rarely, if ever, get mentioned. All too frequently, this group is willing to accept old age, 'senior moments' or incipient senility as the cause, particularly when their physicians are also ignorant about this side effect."

Meanwhile, pilots taking statins still fly planes, truck drivers taking statins still drive trucks and parents and grandparents taking statins still drive their children and grandchildren in cars. Is anyone safe with such a large proportion of the population on statins?

Peripheral polyneuropathy

If low cholesterol is bad for the brain, it is reasonable to assume that it is bad for the peripheral nerves also. A reasonable guess and, unfortunately, it seems to be true. Damage to the peripheral nerves is called polyneuropathy. This is a most disturbing and painful condition that starts in the feet and legs and may spread to other parts of the body. Pain, burning, tingling and even total loss of sensation are common symptoms. Polyneuropathy may lead to muscular weakness and difficulty walking as well.

In Denmark all residents have a civil registration number that is used in discharge prescription registries, so that it is possible to find all residents with a particular disorder and find out which

drugs they have been taking. In one of Denmark's counties with a population of 465,000, Dr. David Gaist and his team at Odense University Hospital asked all patients who had polyneuropathy of unknown cause to see how many were on statin treatment compared with the general population in the county. They calculated that the risk for definite polyneuropathy was 16 times higher for statin users than for non-users, and even higher for those who had used statins for more than two years.[214]

The authors stressed that the frequency of polyneuropathy was very small, but they also pointed out that it increased over time. The question is, of course, how many statin-treated individuals may have polyneuropathy after 20 or 30 years of treatment? Nobody knows. The problem is particularly serious for patients with diabetes, because even without statin treatment diabetics run a much greater risk to develop polyneuropathy than other people. Polyneuropathy in statin users has been seen by other researchers as well. For example, Elias Ragi, consultant clinical neurophysiologist at Royal Devon and Exeter Hospital, Exeter, reported about 16 patients with statin-induced polyneuropathy in just one year, and many of them had severe symptoms.[215]

Impotency

There are many reports about erectile dysfunction after statin treatment. To get an impression of its frequency, Dr. Anthony Wierbicki and his team at St. Thomas Hospital, London asked 82 patients who were gong to start on statin therapy about their sexual functions. Six months later 20% of the patients had become more or less impotent.[216]

Again, drug labels provide no mention of this embarrassing side effect, and from my clinical experience I know that few men would dream of bringing it up with their doctors.

It is also worth mentioning that Dr Wierbicki's study was sponsored by Pfizer. However, nothing is mentioned about this potential side effect on the official Lipitor site. And why should they? Just take a Viagra pill, another bestseller from Pfizer.

Worse than thalidomide

On the drug labels pregnant women are warned against statin treatment. But how many read the fine print? Furthermore, about half of all pregnancies are unplanned, and any adverse effects on the fetus occur already within the first two months.

To learn more about these effects, Drs. Robin Edison and Maximilian Muenke at the National Institutes of Health reviewed 178 cases of statin exposure reported to the FDA. After having excluded those with spontaneous and voluntary abortions they ended up with 52 cases considered valuable. Almost half of them had serious malformations of the brain or the limbs. [217]

But that is not all. At the Oncogenetic Laboratory of the Tel Aviv University, Dr. Tartakover-Matalon and his team studied living placental tissue retrieved from normal pregnancies that had been terminated legally. They found that if they added small doses of simvastatin to the culture medium, several vital functions of the placental cells were inhibited. They concluded that these toxic effects might have caused the higher abortion rate and malformations seen in previous studies of animals given statins during pregnancy.[218]

There is reason to believe that the many cases of spontaneous abortions reported by Drs. Edison and Muenke also were caused by the statins.

Cancer

Statins produce cancer. This was the conclusion of University of California researchers Thomas Newman and Stephen Hulley after having analysed all studies of what happened when laboratory animals were treated with statins.[219]

They asked themselves why these drugs had been approved by the Food and Drug Administration at all. The answer was that the doses used in the animal experiments were much higher than those recommended for clinical use. But as Newman and Hulley commented, it is more relevant to compare blood levels of the drug. Their review showed that the blood levels that caused cancer in rodents were close to those seen in patients on statin drugs.

Because the latent period between exposure to a carcinogen and the incidence of clinical cancer in humans may be 10 to 20 years or more, the absence of any controlled trials of this duration means that we do not know whether statin treatment will lead to an increased rate of cancer in coming decades. Thus, millions of healthy people are being treated with medications the ultimate effects of which are not yet known. Newman and Hulley therefore recommended that the statins should be used only for patients at very high risk for coronary disease, not for people with life expectancies of more than ten years. Healthy people with high cholesterol as their only risk factor belong to the latter category. Yet these are the very people targeted for cholesterol-lowering drugs in the current trend toward mass medication. There is good reason to exercise caution in the use of the statin drugs because there is already much evidence that statin treatment may lead to cancer in humans as well.[220]

If statin treatment is cancer-provoking, cancer is likely to show up first in people with the highest risk of cancer, for instance in old people. There are also great differences between the incubation period for different cancers. Those that appear the earliest are, of course, those that are easy to detect. The results from the statin trials are therefore disquieting.

In the first two simvastatin trials, 4S and HPS, more patients in the treatment group got non-melanoma skin cancer. However, although these figures appeared in the tables, the authors did not mention this alarming finding in the discussion or in the summary of the reports. The reason may be that the difference was not significant in each trial. However, if the numbers from both trials are added together, the difference becomes statistically significant, meaning that it is highly unlikely that the result was due to chance.

Non-melanoma skin cancer is considered unimportant because it is easy to treat; nobody dies from non-melanoma skin cancer today. However, a cancer is a cancer. If statin treatment or low cholesterol are able to create various types of cancer as in the animal experiments, the first type we should expect to see is, of course, skin cancer, simply because it is easily detected and at an early stage. Besides, there is evidence that non-melanoma skin cancer may be a harbinger of more vicious types of cancers later on.[221] But by unknown reasons the trial directors of all studies published after HPS haven't bothered to report the number of skin cancers.

No significant increase of cancer was seen in a ten-year follow-up of the participants in the 4S trial and the authors therefore concluded that ten years of statin treatment does not induce cancer.

Neither does ten years smoking.

Another easily detectable malignancy is breast cancer. In the CARE study, breast cancer was more common among those who took the drug than in the control group. In the treatment group 12 women got breast cancer during the trial, whereas there was only one case in the control group, a difference that is highly statistically significant.

The authors of the CARE report were eager to explain away the increased frequency of breast cancer. “These findings could be an anomaly,” they wrote. It is possible that they are right because the expected number of breast cancer cases in the control group, calculated from the frequency normally seen in the population, should have been five cases. Nevertheless, thirteen is more than twice as many as five.

Breast cancer has not been reported in any of the more recent trials, but after the publication of the CARE trial, all patients with cancer, including those who have underwent cancer treatment, have been excluded from the trials. This is a most curious decision because supporters of statin treatment claim that statins are able to prevent cancer.

In the package insert for Pravachol, you can read about the risk of various less dangerous side effects, although none of these was reported significantly more often in the treatment group. But nothing is mentioned about the possible risk of breast cancer, the only side effect that was seen significantly more often.

And there is more evidence that statin treatment may cause cancer. Let us take a look at PROSPER, a large trial involving elderly people.[222] This trial was directed by Professor James Shepherd, the director of the WOSCOPS trial. In PROSPER, men and women aged 70-82 were included only. All of them had either vascular disease or had a raised risk of such disease. At follow-up, 4.2 percent had died from a heart attack in the control group, but only 3.3 percent in the treatment group. This small benefit was neutralized by a higher risk of dying from cancer. Indeed, there were 28 fewer deaths from heart disease in the pravastatin group, but 24 more deaths from cancer. If we include non-fatal cancer in the calculation, the cancer difference between the two groups became statistically significant; 199 in the control group and 245 in the pravastatin group. Furthermore the difference between the two groups increased year for year.

To put this finding in context, as they wrote, they counted the number of new cancers in all pravastatin trials together and found that there was no significant increase of cancer. However, in this calculation they did not include the number of skin cancers.

What they also forgot to mention was that in the previous trials the participants were 20-25 year younger than in their own trial. Cancer is primarily a disease of old age and cancer is a frequent finding at post-mortem of old people who have died from something else. Cancer in the elderly is often dormant or it grows so slowly that it never becomes a problem during their lifetime—unless of course the growth is stimulated by something like statin treatment.

If cancer appears within a mere three or four years in the elderly, isn’t it likely that cancer will become a problem in young people, those who have been told to take a statin drug every day the rest of their life?

There is another way to determine whether statin treatment is able to produce cancer. At five hospitals in Tokyo a group of Japanese researchers studied whether cancer patients had been treated with statins more often than other people. To that end they selected patients with various forms of lymphoid cancers and control individuals of the same age and sex without cancer admitted to other departments at the same hospitals during the same period. A total of 13.3 percent of the cancer patients, but only 7.3 percent of the control individuals were or had been on statin treatment.[223] Again, just as with skin and breast cancer, lymphoid cancer is easily detectable, at least compared with cancers in the internal organs. Had the Japanese researchers chosen patients with pancreatic cancers for instance they might not have found any difference, because this cancer type may go undetected for many years.

Effect and side effect

As you can see from Table 6C, the gain in the number of fatal heart attacks in the CARE trial was 1.1 percent whereas the loss in numbers of breast cancers was 4.2 percent. Calculated in the way trial directors usually do, as relative rather than absolute risk, the difference was even more striking, with 12 percent fewer heart attacks but 1500 percent more breast cancers. However, you will never see side effects calculated in this way—only positive effects. (Unfortunately, the authors did not give the number of fatal heart attacks for each sex. The figures in the table relate to both sexes.)

How to minimize side effects

Patients chosen for the statin trials do not look like the typical patient sitting in the doctor's waiting room. To be included they must satisfy a long list of criteria. As an example I shall tell about how the participants were selected for the TNT trial, but the principles used in that trial are similar to those of the others.[224]

At the start, the researchers screened 18,469 patients with evident coronary heart disease. Of these, 15,464 were deemed eligible. We are not told why the other 3,005 patients were not eligible, but from the many previous trials we know that patients with all kinds of pre-existent conditions or frailty are disqualified. As mentioned above, cancer is one of the exclusion criteria, but any serious condition, such as kidney and liver disease, heart failure, uncontrolled diabetes, hormonal dysfunction, and gastrointestinal disorders belong to that category—including, of course, any patient who has previously shown intolerance to statin therapy.

After that the 15,464 potential participants were given a small dose of atorvastatin, the drug to be tested. This procedure led to the exclusion of a further 5,462 patients. According to the authors, most of them were excluded because they did not meet the randomization criteria, a most curious argument as these criteria were already defined from the beginning. Why weren't they excluded in the first round? Others were excluded because they experienced adverse effects from atorvastatin, or they died, or had a vascular event during the test, or they showed lack of compliance.

Thus, from the original group of 18,469 patients only 10,001 patients, or 54 percent were included in the trial. It is obvious that the participants in the trial represented a selection of unusually strong and healthy patients. Taken together with the unwillingness to record obvious

signs of organ dysfunction as side effects, the figures for statin side effects are obviously completely unreliable.

Another note of caution

To test a drug on many thousands of patients is extremely costly and laborious. The only groups willing to spend several hundred million dollars for such trials are the drug companies because the potential profit is gigantic. Consequently, all statin trials are sponsored by the company whose drug is tested in the trial. Not only do the companies pay for the necessary meetings, workshops, conferences, authors' and speakers' fees and travel expenses for the many hundreds of participating doctors and researchers in each trial, they also prepare the trial, take part in the selection of patients and control individuals, design and produce the protocols, participate in monitoring of the results, analyze blood cholesterol and are responsible for the complicated statistical calculations. The companies may even hire professional writers to prepare the reports. Can we be totally confident that their vested interests have no influence at all on the outcome of these trials? Can the wolf play the role of shepherd?

And are the results really blinded as we are told? In most of the trials the lipid analyses are performed at the drug company laboratories, and these results are not released to the doctors and patients throughout the whole trial. But what about the lipid analyses that were performed at the individual clinics and departments—were they blinded also? When the first favorable results from the trial are announced in the press, for example, how do you think the participants would react? Wouldn't they want to know whether they were taking the new wonder drug or whether they were taking an ineffective placebo? An easy way to find out is to take a cholesterol test. Almost certainly, all of them knew their cholesterol level at the beginning of the trial. A new cholesterol test would in most cases have told them to which group they belonged, and even if their trial doctor hadn't analyzed their cholesterol, it would have been easy to have it done somewhere else.

So it is not unreasonable to assume that a substantial proportion of the patients and their doctors knew to which group the participant belonged and such information might have unintentionally influenced the results.

But let us assume that the doctors and the patients were not influenced at all. What about the trial directors? By now you are familiar with the tendency of the previous directors to exaggerate the trivial effects of their treatment and minimize the side effects. In fact, many of these reports do not appear to have been written by scientists in search of the truth and nothing but the truth.

Consider also that positive results are much more financially rewarding for researchers than negative ones. Researchers, who come up with positive results, in particular positive results from drug trials, are more often invited as speakers to meetings and congresses and more often chosen for further lucrative research projects.

Should we, therefore, be confident that statin research results have been presented in a nonpartisan manner? And why haven't we heard about the outcome of the first statin trial, the EXCEL study?

EXCEL, the Expanded Clinical Evaluation of Lovastatin

This trial was performed by Dr. Reagan H. Bradford and his team from a large number of American clinics and research institutions, including the Merck Sharp & Dohme Research Laboratories at West Point, NY, where the drug was produced where the drug was produced. More than 8,000 healthy individuals (called "patients" in the trial reports) with cholesterol levels between 240 and 300 mg/dl (6.2-7.7 mmol/l) received one of four different doses of lovastatin (Mevacor®) or a placebo.[225]

With a view to reporting on possible adverse effects of the treatment, preliminary study results were published after only one year of the trial. No significant side effects were reported, but in the fine print the authors were obliged to mention that death due to all causes was 0.5 percent in the four lovastatin groups combined (32 or 33 individuals out of a group of about 6,600—no exact figures were given in the report) compared to 0.2 percent in the placebo group (three or four individuals out of a group of 1,650). By taking all the lovastatin groups together, the difference would have been statistically significant if the number of deaths in the treatment groups were 33, but not if it were 32. Even if the difference wasn't statistically significant after one year, it would certainly have become significant if the tendency to a higher mortality in the treatment groups had continued throughout the trial. In any case, the aim of the treatment was to lower mortality and most certainly no lowering was achieved.

Today at least 20 reports from the EXCEL trial have been published in various medical journals. These reports tell us how well lovastatin is tolerated and how effective it is in lowering blood cholesterol levels in various populations, but not one of them has reported the final outcome of the trial, although more than ten years have passed since it began. Therefore, we do not know whether the increased mortality, seen after just one year of treatment, has continued throughout the trial.

Why have we never heard about this outcome of the first statin trial, which was one of the largest? I asked that question in a letter to Merck, Sharp & Dohme. They answered that, "the trial was not designed to measure the clinical outcome, only to test whether the drug was tolerable and did not produce any serious side effects."

New guidelines

On May 16, 2001, an expert panel from the National Cholesterol Education Program published new guidelines for "the detection, evaluation and treatment of high blood cholesterol."[226] The guidelines introduced new risk factors that demand preventive measures (or "risk-reduction therapy," as they call it) and widened the limits for the old ones.

The main target is LDL-cholesterol, they said, because *"research from experimental animals, laboratory investigations, epidemiology and genetic forms of hypercholesterolemia indicate that elevated LDL-cholesterol is a major cause of heart disease."* (If you have read this book from the beginning you will probably agree with me that such research has indicated nothing of the kind.) The optimal values should be 150 mg/dl (3.8 mmol/l) for LDL and 200 mg/dl (6.1 mmol/l) for total cholesterol. But if there were any risk factors present, the optimal cholesterol level should be even lower. The more risk factors, the lower cholesterol should be.

In the highest risk category were patients with heart disease because, according to the statistics from Framingham, they run a more than 20 percent risk of having a new heart attack in ten years. (The report did not tell us where to find these figures, however.) Other atherosclerotic diseases were said to be just as risky, such as is diabetes from the age of twenty. And the presence of two or more other serious risk factors was said to put the patient at a similar risk.

The new guidelines provided an intricate scoring system showing how the different risk factors were graded. Men with an accumulated score of 15 or more belonged to the highest risk category. And it was easy to get a high score. For instance, if you were seventy years old, you were automatically given 12 points. A cholesterol level above 275 mg/dl (7.05 mmol/l) at age 39 gave you 11 points, less with increasing age. An untreated systolic blood pressure reading of 130 mm Hg (which is completely normal) got one point, two if you were on antihypertensive treatment.

Smokers below age 40 got eight points, and you are a smoker if you have smoked at least one cigarette during the previous month. Women needed a higher score to be placed in the highest risk category, but they got more points for their risk factors.

The guidelines recommended that everybody over age 20 had his or her cholesterol level tested every fifth year. If you were in the highest risk category and your LDL-cholesterol was above 100 mg/dl (2.6 mmol/l), you should change your life habits; if your LDL was above 130 mg/dl, (3.3 mmol/l) you should immediately start cholesterol-lowering treatment. But you might as well start with both measures, said the guidelines, because few people succeeded in lowering their cholesterol by life-habit intervention alone—although in another place in the paper the authors claimed that life-habit intervention was an effective way of lowering cholesterol!

Emerging risk factors

The indications for treatment were stronger if there were other risk factors than those mentioned above, for instance if you were overweight, if you exercised too little or if you ate too much animal fat. Even “emerging” risk factors should be taken into consideration, and by emerging risk factors the authors included almost all laboratory tests that, on average, had been found higher in patients with heart disease. According to the authors, “the emerging risk factors do not categorically modify LDL-cholesterol goals; however, they appear to contribute to CHD risk to varying degrees and can have utility in selected persons to guide intensity of risk-reduction therapy.” (In other words, take a bunch of laboratory tests and most of us become candidates for statin treatment.)

Subclinical atherosclerosis

One of the emerging risk factors was called “subclinical atherosclerotic disease.” The guidelines gave no explanation for this new concept. The term comes from a new technique called electron beam tomography that is a method for depicting calcifications without putting a catheter up into the coronary arteries. The degree of calcification is said to reflect the degree of atherosclerosis and is therefore a much better predictor of future heart attack than high blood cholesterol or, for that matter, any other risk factor. According to an advertisement for one of those huge health centers that have become popular in the US, *“The electron beam tomography scan gives*

individuals who have risk factors for heart disease a painless, non-invasive way to obtain peace of mind knowing that early indications of heart disease are or are not present."

Whether you obtain peace of mind is questionable because in the most recent study using electron beam tomography, sixty percent of a group of healthy women over age 55 had "subclinical atherosclerosis," yet, according to the new guidelines, half of these women belonged to the low-risk category.[227] In other words, with one blow this new technique has landed many further millions of healthy people into the high-risk category.

The most surprising finding, at least for those who have not read this book, was the lack of an association between degree of calcification and total or LDL-cholesterol or any other lipid fraction. The authors of the study had no comments about this finding—which of course is totally devastating to the cholesterol hypothesis—except to say that they considered the new guidelines insufficient and suggested regular electron beam tomography for the whole population. I sent a short letter to William W. Parmley, the editor of the journal (*JAMA*) where I told about the many other studies with similar results and asked him, why the authors did not question the cholesterol hypothesis. He answered: "Because of space limitations we are able to publish only a few letters addressing controversial issues."

More new risk factors

The guidelines stated officially for the first time that high triglycerides should be lowered and low HDL-cholesterol should be raised. True enough, admitted the authors, no study has proven that raising HDL-cholesterol provides any benefit. (There is no evidence that lowering triglycerides provides any benefit either.) Nevertheless, they recommend treatment with clofibrate (Atromid-S® Abitrate®) or nicotinic acid (niacin®). Obviously, the many unsuccessful trials with these drugs and their many harmful side effects had been completely forgotten.

As an argument for using cholesterol-lowering drugs, the supporters claim that 20 percent of patients with coronary heart disease have a heart attack within ten years. But that number is obtained by including minor symptoms without any clinical significance. Many people survive even a major heart attack with few or no symptoms after recovery.

Heart attacks may even appear without any symptoms. I have seen many patients myself with indisputable ECG indications of a recent myocardial infarction, but who recall no more than slight discomfort, if any symptoms at all, during the preceding weeks. What matters is how many die and this is much less than 20 percent.

Lower and lower

New guidelines have appeared regularly for at least 40 years. In 2004, new trials inspired the National Heart, Lung, and Blood Institute to publish a set of updated guidelines, according to which, cholesterol should be lowered even more aggressively than before.[228] This advice was based on three trials.

In two of them, REVERSAL[229] and PROVE-IT,[230] half of the patients were treated with 40 mg pravastatin, half with 80 mg atorvastatin. The "best" effect was seen in the high-dose groups, where LDL-cholesterol was lowered by 46 and 51 percent respectively, whereas in the

pravastatin groups it was lowered by 25 and 22 percent respectively. Therefore, the authors argued that we should take cholesterol down to much lower levels than previously recommended. They also considered their result as proof of exposure-response.

But you cannot study exposure-response with two different drugs, because there are large differences between the other, the so-called pleiotropic effects of the various statins. Furthermore, the eight times higher dose of atorvastatin (the usual dose is 10 mg) only cut cholesterol marginally more than the usual dose. In a previous atorvastatin trial named ASCOT for instance, 10 mg atorvastatin lowered LDL-cholesterol by 35 percent whereas the eight-times-higher dose in the two trials mentioned above lowered it only by a further 12 percent and 16 percent respectively.

In a third trial, named TNT (Treatment to New Targets),[231] about 10,000 patients with stable heart disease were treated with atorvastatin for five years; half of them with 10 mg and half with 80 mg. Again, the "best" effect was seen after 80 mg and the authors claimed that their study was a further support to the new guidelines. Some curious things emerged from that trial, however.

First, total mortality was almost identical in the two groups; 5.6 percent in the low-dose group, 5.7 percent in the high-dose group. The reason was that the fewer who died from cardiovascular disease was outnumbered by a larger number dying from other causes. These causes were not given, however, and our request for more details was ignored.[232]

Second, heart mortality was significantly lower in the high-dose group, but the report only provided the number of "non-procedure-related myocardial infarctions." By non-procedure-related infarctions is meant heart attacks that have not occurred during operations or diagnostic investigations at the hospital. The latter infarctions should, of course, have been included as they have been in all other trials. There can only be one explanation why the researchers have omitted them—their number was higher in the high-dose group. Had more occurred in the low-dose group, the authors with all certainty would have reported them.

Benefits and risks

The fact that the number of side effects was larger than the number of patients that benefited from treatment should have given the authors great concern, all of whom have strong financial ties to Pfizer, the sponsor of the trial. If doctors recommend a high statin dose to their patients, they should be able to tell them whether the benefit of such treatment counterbalance possible harmful side effects, but no such useful information emerges from this trial report.

Patients with non-fatal cardiovascular diseases such as a myocardial infarction and stroke often recover completely. It is therefore not self-evident that the many side effects are balanced by the lower incidence of cardiovascular events. A relevant question to a patient with heart disease is whether he prefers memory loss (which with all certainty was not regarded as a side effect, as nothing about that is mentioned anywhere in the official reports or on the drug labels) instead of a non-fatal heart attack, which often heals without serious sequels. Or ask whether he prefers polyneuropathy, which may become permanent as an invalidating and very unpleasant condition, or a minor stroke, which may heal without any sequels.

An alarming report

After the publication of the new guidelines, yet another trial comparing normal and high-dose was published, the IDEAL trial.[233] In this trial, where usual-dose simvastatin was compared with 80 mg atorvastatin, no significant difference was seen either as regards the major endpoints. Even worse, the number of adverse effects was far higher. Almost 90 percent had side effects and almost half of these were recorded as serious. No, this isn't a printing error: almost half of them!

The authors did not comment on this alarming finding except by mentioning that, "there was no difference between the groups in the frequency of adverse events that were rated as serious." Nor did they inform the reader about the nature of these events. In their answer to our request[234] the authors responded as follows:

"The numbers do not represent only drug-related adverse effects. In accordance with good clinical trial practice, the study protocol required that all observed or volunteered adverse events, whether or not considered drug-related, should be recorded during the trial. This included worsening or increase in severity or frequency of preexisting conditions as well as minor and serious new signs, symptoms, or laboratory findings. In a population of middle-aged or elderly coronary disease patients aged up to 80 years, it is rare that anyone does not have at least an episode of common cold or a minor musculoskeletal injury over a period of 5 years. The frequency of all adverse events in the IDEAL study was therefore as expected. Adverse events considered definitely or possibly drug-related were few, and significant differences between the two treatment groups were presented in the article. The frequency was not greater than in comparable trials."[235]

How could the authors know whether the frequency of all adverse events was "as expected?" The number of common colds and minor injuries has never been reported in any previous trial; neither can they be classified as serious. And why didn't they tell us about which adverse effects they considered drug-related?

The large number of side effects may have another explanation. As mentioned above, almost half of the patients originally selected for the TNT trial were excluded because of various types of weaknesses or diseases or because they didn't tolerate the drug. In the IDEAL trial, only eight percent were excluded. These patients may therefore have been more similar to patients in real life, and many of the "new signs, symptoms, or laboratory findings" may have been due to the drugs.

Why are trial directors always so eager to sweep all disadvantageous observations under the rug? Aren't they concerned about future patients? Shouldn't they follow the words of Hippocrates: *"First, do no harm."*

Is the explanation to be found at the end of their letter, which states as follows:

"Financial Disclosures: Dr. Pedersen has reported receiving consultation fees and speaker's honoraria from Pfizer, Merck, Merck AG, and AstraZeneca and research grants and steering committee fees from Pfizer and Merck. Dr. Kastelein has reported receiving research grants from Pfizer. Drs. Olsson and Holme have reported receiving honoraria from Pfizer as steering

committee members. Dr. Bendiksen was previously employed by Pfizer Norway and has reported receiving honoraria from Pfizer as a steering committee member."

Can we trust the drug companies?

In his book "The Whistleblower," Peter Rost, a former top executive in Pfizer, reveals a company riddled with corruption. According to Rost, Pfizer and other drug companies spend huge amounts of money to promote their trials. One way is to pay renowned researchers for putting their name on the final trial report, when, in fact, the reports are written by PR firms. Also, according to Richard Smith, former editor at the British Medical Journal, many medical journals are packed with articles ghostwritten by pharmaceutical companies.[236]

The FDA recently cited Pfizer for publishing the results of a Valdecoxib trial in a manner that obscured the risks and the drug now has a black box warning. Pfizer has also pleaded guilty to numerous charges of false advertisements and agreed to pay billions of dollars to satisfy criminal and civil penalties. Pfizer funded the TNT trial, paid its directors and authors, analyzed the data, and assigned one of their employees as co-author of the trial report. There were thus numerous opportunities to have influenced the results, knowingly or unknowingly.

The new guidelines may possibly prevent cardiovascular death in a small minority of patients with cardiovascular disease. But at the same time they may increase mortality from other diseases, transform healthy individuals into unhappy hypochondriacs obsessed with the chemical composition of their food and their blood, reduce the income of ranchers and dairy farmers, undermine the art of cuisine, destroy the joy of eating, and divert health care money from the sick and the poor to the rich and the healthy. The only winners are the drug companies and imitation food industry—and the researchers that they support.

And there are more problems with the advice we receive from the authorities. Read on!

False safety

Many side effects from new drugs do not appear before they are used in greater scale. Doctors are told to report all new, unexpected side effects, but there is a great risk that they are underreported. Most drugs have side effects either because they are toxic or because the patient is hypersensitive to the drug. Therefore, the side effects appear very soon after the start of the treatment and the patient therefore easily recognize the symptoms as a result of the treatment. The statins are not directly toxic and they do not result in hypersensitivity reactions. The statins disturb the normal synthesis of several important substances in our body. It may therefore take a long time before these substances are totally depleted and symptoms of deficiency appear. Both the patient and the doctor may therefore overlook that late symptoms may be caused by the drug. Statins are used mostly in old people. Cancer, loss of memory, weak muscles, impotency and heart failure are common in old people and may therefore be considered as natural effects of old age. Furthermore, old people are often treated with many different drugs. In Sweden, for example, old people discharged from a medical or cardiology department are often prescribed a dozen or more different drugs. So, even if doctors should suspect that the patient's symptom were caused by the medicine, how can someone determine which of the medicines is to blame?

That side effects are underreported is obvious from a study in Rhode Island, USA. A questionnaire sent to all practicing doctors and answered by 74% showed that the serious side effects reported to the FDA during the previous year corresponded to only one percent of the numbers actually seen.[237]

It is comforting to learn that many patients realize themselves that the statins are toxic. In Ontario, Canada researchers studied how many people had continued their statin treatment. A total of more than 140,000 old people were included in the investigation. Two years after the first statin prescription two thirds of those who already had a heart disease, and three fourth of those whose only "disease" was high cholesterol had discontinued.[238]

The alleged omnipotence of statin drugs

You may probably have read in the newspapers about the many other allegedly positive effects of the wonder drugs, the cholesterol-lowering statins. Carefully placed articles now claim that statins can prevent cancer, ankylosing spondylitis, chronic obstructive pulmonary disease, severe sepsis, heart failure, hip fractures, and much more. The way the researchers have studied these allegedly beneficial effects is confounded with a serious bias, however. As an example I shall analyse one of these claims, the idea that statin treatment prevents Alzheimer's disease.

First, studies claiming that statin treatment is good for almost any disease do not come from trials where the control individuals have cholesterol levels just as high as those in the treatment group. Instead, comparisons are made between people treated with statins and control people selected from the same community, but who are not treated with statins.

Obviously these people's cholesterol is lower than those treated with statins, at least lower than their cholesterol before treatment, which means that the researchers have compared the outcome of low-cholesterol people with high-cholesterol people, and there are many studies showing that people with high cholesterol are healthier in many aspects compared to people with low cholesterol.

For starters, most studies have found that old people with high cholesterol live longer than old people with low cholesterol. But we have also some specific data about brain function and cholesterol. For instance, Bianca Schalk and her team at the University Medical Center in Amsterdam, Holland followed more than 1,000 people age 55-85 for three years and found that those whose cholesterol was lower than 200 mg/dl (5.1 mmol/l) were more likely to decline in functional performance tests such as walking, turning around, dressing themselves and standing up and down from a kitchen chair with folded arms.[239]

Another Dutch study showed that among more than 6,000 people above age 55 and followed for nine years, women with high cholesterol developed Parkinson's disease less often than women with low cholesterol; the higher the cholesterol, the lower was the risk.[240]

Researchers at the Johns Hopkins University, Baltimore and Göteborgs University, Sweden followed 382 old people for ten years. Among those with the highest cholesterol values much fewer had dementia at follow-up than the others.[241] In accordance with these findings is a study from the Framingham Heart study. Here Penelope Elias and her team followed about 2,000 individuals for 16-18 years. A detailed record of their ability to learn, to reason, to concentrate

and to organize showed that there was a direct association with these mental performances and cholesterol; the higher cholesterol, the smarter they were.[242]

Let us have a look at Alzheimer's disease itself. The allegation that low cholesterol prevents Alzheimer comes from comparisons between people on statin treatment and people who are not, and obviously there are unavoidable errors associated with such a comparison. A better way to get an answer is to compare initial cholesterol in people who develop Alzheimer and in those who do not. This was done by Dr. G. Li and others at the University of Washington, Seattle. After five to six years, about 13% of more than 2000 old people had developed Alzheimer's disease or all-cause dementia and on average, their cholesterol did not differ from the others. [243]

People who take lipid-lowering agents might also be wealthier than those who do not, because statin treatment is expensive and wealthy people are healthier than poor people. The only way to decide whether statin treatment prevents Alzheimer's or any other disease is a controlled clinical trial. Let us see what they have to tell us about this subject.

The protocol for PROSPER, the trial where old people were treated with pravastatin (Pravachol), included psychometric tests and a mental examination every year. At the end of the study, the directors concluded that their mental functions declined at the same rate in the treatment as in the control group. Similar findings were reported in the WOSCOPS trial. Thus, no evidence either that the statins other effects are able to prevent Alzheimer.

To study the effect of cholesterol lowering on memory, Professor Matthew F. Muldoon assigned 192 healthy adults to a six-month double-blind trial. Half of the participants were treated with Lovastatin and half of them with placebo. At the start and at the end of the trial a large number of tests were performed to assess neuropsychological performance, depression, hostility and quality of life.[244]

Normally, when such tests are performed repeatedly, the test subjects improve because of learning or practice, and this was indeed seen in the control group. But tests of attention and psychomotor speed, which are not subject to this type of error, gave significantly lower scores in the Lovastatin group. The change in performance was unrelated to the percent change in LDL-cholesterol but was significantly related to the level achieved after treatment with Lovastatin; the lower the cholesterol, the worse was the memory.

Thus, the claim that statin treatment or low cholesterol levels protect against Alzheimer's disease has no scientific basis; if anything these results rather suggest the opposite.

Those who pay

Financial disclosures for the authors of the NCEP guidelines 2004 were not given in the original publication. After a critical letter from Merrill Goozner of Center for Science in the Public Interest (CSPI) who questioned the scientific basis and objectivity of the guidelines, the financial disclosures were published on the web:

Financial Disclosure[245]

Dr Grundy has received honoraria from Merck, Pfizer, Sankyo, Bayer, and Bristol-Myers Squibb.

Dr Hunninghake has current grants from Merck, Pfizer, Kos Pharmaceuticals, Schering Plough, Wyeth Ayerst, Sankyo, Bayer, AstraZeneca, Bristol-Myers Squibb, and G. D. Searle; he has also received consulting honoraria from Merck, Pfizer, Kos Pharmaceuticals, Sankyo, AstraZeneca, and Bayer.

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Myth 8: Polyunsaturated Oils are Good for You

Intervening is a way of causing trouble.

Lewis Thomas

Risk at both ends of the scale

The smaller number of heart deaths in the soybean trial of Dr. Dayton and his team, mentioned in chapter 6, was offset by a larger number of cancer deaths. Does it mean that soybean oil causes cancer?

Diet-heart proponents would argue that Dr. Dayton's soybean trial was an anomaly, and that other trials with polyunsaturated fat have not resulted in more cancer. However, never before had such huge amounts of polyunsaturated fat been eaten over such a long period of time. Dr. Dayton's patients were also much older than in the other trials, and thus more susceptible to cancer, which means that a possible cancer-provoking effect could be detected more easily.

Another disquieting fact is that many studies have reported a low cholesterol to be a risk factor for cancer. The purpose of these studies was to follow a great number of individuals for many years to see if the Framingham researchers were right when they claimed that high cholesterol means a high risk of a heart attack. Surprisingly, these more recent studies revealed that it was just as dangerous to have a very low cholesterol level, as it was to have a very high one. Those who had very low cholesterol levels had a greater incidence of cancer while those with very high cholesterol suffered more heart attacks.

Most investigators thought that low cholesterol levels were not the cause but the *result* of the cancer since cancer cells need cholesterol, just as any other cells do. Perhaps their rapid growth and greater need for cholesterol reduced the cholesterol levels in the blood?

It is interesting that the diet-heart proponents immediately relegate low cholesterol to a secondary and thus an innocent phenomenon in the etiology of cancer, but never admit that *high* cholesterol might be a secondary and thus innocent phenomenon in the etiology of heart disease. No, say the diet-heart proponents, high cholesterol is always dangerous and should be lowered by any means.

A great number of studies also found that cholesterol was low many years before the cancer was discovered. [246] If the low cholesterol was a consequence of rapid cancer growth, then the level should decrease when the cancer started to grow. But in some patients cholesterol was low eighteen years before the cancer appeared.

Of course, this fact was a serious drawback for those who planned cholesterol-lowering measures of most of the population, and the diet-heart proponents therefore met in 1981 to discuss the problem.[247]

The meeting was of sufficient importance to attract most of the leading American cholesterol researchers, including Jeremiah Stamler, director of two major cholesterol-lowering trials and author of a large number of papers that expanded on the dangers of high cholesterol; Basil Rifkind, head of the Lipid Metabolism Branch at the National Heart, Lung and Blood Institute,

and later head of the LRC trial; Robert Levy from Columbia University, chairman of the meeting and previously director of The National Heart, Lung, and Blood Institute; Antonio Gotto, director of the American Heart Association; Ancel Keys, and many more of those who made up the anti-cholesterol army.

Predictably, the participants concluded that low cholesterol did not cause cancer, but they were unable to explain the phenomenon. It was a subject for future research, they noted, but not a threat to public health.

The published report from the meeting stated: *"It was an unanimous opinion of the panelists that the data did not preclude, countermand, or contradict the current public health message which recommends that those with elevated cholesterol levels seek to lower them. There is evidence of a possible increase in cancer risk at very low cholesterol levels (but) the risk is generally modest."*[248]

These were their words. By "very low levels" the panel meant less than 4.7 mmol/l (183 mg/dl). But diet-heart proponents do not consider 4.7 mmol/l (183 mg/dl) too low when it comes to treatment of *high* cholesterol. A couple of years later for instance members of the National Heart, Lung, and Blood Institute and the American Heart Association (many of whom participated in the meeting) recommended that people should bring their cholesterol levels down to at least 4.85 mmol/l (188 mg/dl).

It is not certain that low cholesterol levels provoke cancer: the fact that cancer is seen more often in individuals with low cholesterol is no proof of cause and effect. Low cholesterol level is a *risk factor* for cancer, precisely as high cholesterol is a risk factor for heart disease.

Again, a risk factor is not necessarily the cause. Something may produce cancer and at the same time lower blood cholesterol. Chemical compounds with such a potential do exist.

Burglars among molecules

"*Somewhere, on some remote planet… on the other side of our galaxy, there is at this moment a committee nearing the end of a year-long study of our own tiny, provincial solar system. The intelligent beings of that place are putting their signatures… to a paper, which asserts, with finality, that life is out of the question here and the place is not worth an expedition. Their instruments have detected the presence of that most lethal of all gases, oxygen, and that is the end of that."*

With these words Lewis Thomas, the famous essayist and professor of medicine opened one of his speeches to his new students. Thomas's story is not pure fantasy—oxygen can be dangerous.

A civil war rages inside us from the sweet second of fecundation until we end as dust or ashes. Atoms and molecules are fighting for the tiny elements that are surrounding them, the electrons. The haze of electrons gives identity and character to each atom and molecule; if the number of electrons is altered, a valuable molecular citizen may, in a split second, be turned into a useless and even destructive hoodlum.

Electrons prefer to be present as couples. Paired electrons furnish the atom or molecule with stability and resistance against harassment, but some pairs are more stable than others.

The main part of a fatty acids is composed of a core of carbon atoms to which hydrogen atoms are attached. When the number of hydrogen atoms is optimal their electrons form stable pairs with those of the carbon atoms. Examples of stable molecules are the saturated fatty acids, those said to be dangerous to the heart and the vessels. They are called saturated because they are saturated with hydrogen.

Unsaturated fatty acids are short of hydrogen atoms. Monounsaturated fatty acids are missing two, polyunsaturated fatty acids are missing four or more. This means that instead of sharing one pair of electrons with each other, some of the carbon atoms are sharing two pairs of electrons with his neighbor carbon instead of one pair, forming the so-called double bond.

A double bond is less stable than a single bond. The hydrogen sitting close to the double bond is easily snatched by a free radical, a process called oxidation. Free radicals snatch hydrogen atoms because one or more of their electrons lack their partner; they are unpaired.

Combustion fumes, such as cigarette smoke and diesel exhaust, are especially rich in free radicals, but even the oxygen molecule is a free radical. It is especially active when heated. If the temperature is high enough, all its neighbors are oxidized—they burn. But what we are interested in here is oxidation at body temperature.

Inside the cells of our body oxidation is vital to cell function and life as long as this process is controlled by hormones and enzymes. Step by step sugar and other fuel molecules are oxidized to water and carbon dioxide, a process that releases energy for the cell machinery. So far, so good.

But if oxidation occurs without control, as it may do if we are exposed to free radicals, molecules other than sugar may be oxidized. Among these others are the unstable polyunsaturated fatty acids. Loss of hydrogen atoms is disastrous to a polyunsaturated fatty acid (as to other molecules as well), because its stability is ruined and it is split into lesser molecules with nasty qualities.

Usually the human body is protected against oxidation thanks to many various antioxidants, kind molecules that donate hydrogen atoms to the free radicals thus protecting us against uncontrolled oxidation. Vitamin E, for example, is a well-known and important antioxidant that protects the polyunsaturated fatty aids in our cell membranes. There are many others.

But if too many polyunsaturated fatty acids are present, or if too many free radicals are available, or if the amount of antioxidants is insufficient, then protection from the antioxidants may fail.

Nobody knows the limit between harmless and harmful amounts of polyunsaturated fatty acids. Cholesterol campaigners now recommend no more than 10 percent of our calories from polyunsaturated oils, but give no reasons for the limit. They don’t tell us about the evidence that an excess of dietary polyunsaturated fatty acids may be dangerous.

Does polyunsaturated oil produce cancer?

When too much polyunsaturated oil is given to laboratory animals their white blood cells are damaged so that the animals die more easily from infectious diseases and cancer. We do not know for sure whether the same is valid for human beings, but we do know that our immune system is sensitive to a surplus of polyunsaturated fatty acids. If a preparation of such oils is

added to the diet of patients who have received a kidney graft the function of their white blood cells is hampered resulting in a better acceptance of foreign material, including the transplanted kidney.[249]

But other foreign and less useful material, such as bacteria and virus, may be accepted also. One of the great problems with transplant patients is that their immunosuppressive treatment makes them more vulnerable to infection. It is a general rule that any substance which harms the white blood cells also stimulates infections. Some of these substances may even stimulate cancer.

It has never been proved that polyunsaturated fatty acids stimulate cancer, but proof may come in time. By analogy, cigarette smoke may produce cancer, but only after many years of exposure.

Do polyunsaturated oils make you age faster?

It is commonly accepted that aging is partly a result of the eternal fight of free radicals for electrons. If laboratory animals are exposed to free radicals, or to substances highly sensitive to free radicals—if, for instance, these animals eat great amounts of polyunsaturated oils—yellowish pigments are stored in many organs. The same pigments develop in most creatures including man, and accumulates with age.

The fact that polyunsaturated oils may accelerate aging was demonstrated by Dr. Edward Pinckney. In collaboration with a plastic surgeon he asked a large number of patients how much polyunsaturated oil they usually consumed.

Fifty-four percent of the patients said that they had increased their intake considerably. Of those patients 78 percent showed marked clinical signs of premature aging, and 60 percent had required the removal of one or more skin lesions because of suspected malignancy. Of the patients who had made no special efforts to consume polyunsaturated oils the figures were 18 and 8 percent respectively.[250]

Today most deep-frying is done in vegetable oils. Very few know that if polyunsaturated oils are kept hot over many hours, its ability to produce cancer in laboratory animals increases.[251]

Do polyunsaturated oils make you stupid?

Polyunsaturates have other nasty effects. Premature children have only small amounts of vitamin E in their bodies. Dr. Joshua Ritchie and his team in San Francisco studied seven premature babies who were admitted to the hospital with widespread edema, anemia, disturbances of the blood cells and lack of vitamin E. The researchers found that the most plausible cause was the food; these children had all received commercial formulas composed of skim milk and vegetable oils with a high content of polyunsaturated fatty acids.[252]

The brain has low levels of vitamin E. This fact may explain why chickens fed polyunsaturated fat develop brain damage very quickly.[253]

Do polyunsaturated oils cause atherosclerosis?

A new theory about the origin of atherosclerosis is that it is not normal cholesterol, but oxidized cholesterol that is dangerous.[254] And oxidized cholesterol means cholesterol that has been damaged by free radicals.

Even in the fetus the walls of the arteries are speckled with fat. The microscope shows that these speckles or fatty streaks are composed of white blood cells filled with tiny bubbles. These cells are called foam cells. But the substance is not foam; it is cholesterol.

Patients with homozygous familial hypercholesterolemia have foam cells also. This fact was a stumbling block to the Nobel prize winners Michael Brown and Joseph Goldstein. What they discovered was that in individuals with the rare genetic error called familial hypercholesterolemia, cholesterol molecules in the blood do not enter the cells as they do in normal individuals. The reason is that their key to the cell, the so-called LDL-receptor, is defective. Individuals who have inherited the disease from one parent (heterozygous form) have too few receptors; those who have inherited the disease from both parents (homozygous form) have no receptors at all. The lack of LDL-receptors explains why patients with familial hypercholesterolemia have a high blood cholesterol level.

But how can cholesterol enter the foam cells in patients with the homozygous form of familial hypercholesterolemia if, as Brown and Goldstein suggested, the cholesterol door to the cell is closed? This is certainly a crucial question because diet-heart proponents consider these foam cells the forerunner of atherosclerosis.

Recent studies have shown that it is not normal cholesterol which accumulates in the foam cells. Instead, it is oxidized cholesterol. And oxidized cholesterol has no problem entering the cells; it takes another route. The problem seemed solved. But how has cholesterol been oxidized?

There is much evidence that free radicals are the cause of the oxidation, and the source of free radicals is most probably the polyunsaturated fatty acids. For example, scientists can reduce the fatty streaks (called *atherosclerosis* by the proponents) in rabbits with familial hypercholesterolemia[255] (named Watanabe rabbits) with the drug probucol, without lowering blood cholesterol.[256] The explanation may be that probucol, just like vitamin E, is an antioxidant that hampers the attacks of free radicals.

On the other hand, lowering cholesterol in Watanabe rabbits does not reduce the fatty streaks.[257]

If polyunsaturated fatty acids promote oxidation of cholesterol and thus atherosclerosis we should avoid eating too much of them. But diet-heart proponents continue to insist that it is more important to lower cholesterol by avoiding saturated fat and continue to recommend polyunsaturates as a substitute.

It is difficult to follow the proponents line of thought. The depositing of cholesterol in the artery walls of Watanabe rabbits was not reduced by lowering the blood cholesterol but by preventing its oxidation. Then, does it make sense to lower cholesterol with polyunsaturated oils if too much of it stimulates oxidation?

One of the scientists introducing the new theory about oxidized cholesterol is Dr. Daniel Steinberg, from the University of California in La Jolla. He was the chairman of the consensus committee that started the American cholesterol campaign. This campaign has recommended that all Americans eat polyunsaturated vegetable oils instead of saturated fat. The committee recommended an upper limit of 10% for the consumption of polyunsaturated oil (now the reader

know why). However, the committee did not call attention to the fact that the food they had previously called a protection against atherosclerosis was now seen as its cause.

It has not been proved, however, that oxidized cholesterol is the forerunner of atherosclerosis. A link is missing.

What has been demonstrated is that oxidized cholesterol is accumulated as fatty streaks, but the presence of fatty streaks is not the same as atherosclerosis. And the accumulation of cholesterol in fatty streaks has been shown in Watanabe rabbits, not in common rabbits. Because Watanabe rabbits inherit the same defect in cholesterol metabolism as people with familial hyper-cholesterolemia, the correct conclusion from the rabbit experiments is perhaps that fatty streaks in individuals with familial hypercholesterolemia may be induced by oxidized cholesterol.

However, there are observations that do suggest an adverse effect of polyunsaturated oil. In the worldwide epidemiological study of atherosclerosis the investigators found a connection between the degree of atherosclerosis and the total intake of fat. As there was no association between the intake of saturated fat and degree of atherosclerosis, the association obviously concerned unsaturated fats.

What we know for certain is that polyunsaturated fatty acids may produce a great many unfortunate things, none of them pleasant for human beings. We need polyunsaturated oils in small amounts to keep us healthy; some of them are even essential to life. Thanks to their lack of electrons, polyunsaturated fatty acids are soft and flexible. If our cell walls had only saturated fats, we would probably become as stiff as candles. But to have too many polyunsaturated fatty acids is undesirable. After all, who would like his home to be occupied by terrorists?[258]

Trans fat

The fact that polyunsaturated fats such as corn, soybean, and sunflower oils are liquid, even at cold temperatures, has been a problem for the oil manufacturers in countries where butter and lard, not oil, are used in the diet. However, early in this century, French and German food technologists invented a method for converting vegetable oil into solid fat. They heated the oil to 150-200^{o} Celsius in large reactors, mixed the oil with nickel powder that acted as a catalyst, and then forced hydrogen through this unappetizing soup. This method, still used today, changes the chemical structure of the polyunsaturated fatty acids and creates something called trans fatty acids. Trans fatty acids are also unsaturated, but the hydrogen molecules in the double bonds have been arranged so that the resulting molecules behave like the more solid saturated fatty acids. The final product, which is a mixture of various polyunsaturated, saturated, and trans fatty acids, is called partially hydrogenated oil and is used as an ingredient in many food products including margarine, crackers, cookies, doughnuts, french fries, potato chips, pastries and sweets.

Tiny amounts of certain trans fatty acids are also found in animal fats. However, the kinds of trans fatty acids that are produced by industrial hydrogenation have another chemical structure and are rarely found in natural food. By mistaking them for naturally occurring fatty acids, the human body may place them in the cell walls and other parts of human cells and because these trans fatty acids differ chemically there is a risk that we may suffer disturbances in cellular function if we eat too much of them.[259]

Some fatty acids are vital just as vitamins are. This means that we cannot synthesize them ourselves, but need a small amount of them in our food. Normally, the risk is very small that we should suffer from lack of these fatty acids, because they are found naturally in most fats. However, when experimental animals are fed with trans fatty acids from hydrogenation, they develop symptoms similar to those that occur after a shortage of the vital fatty acids, either because the trans fatty acids are toxic by themselves or because they in some way inhibit the usage of the vital fatty acids. The most serious effects concern reproduction. The testicles of rats are damaged, and the rats become sterile;[260] in mice, the fat content of the milk decreases.[261]

In human beings, trans fatty acids in the mother's blood pass over to the fetus. Whether it has any importance is uncertain, but a study by Dr. B. Koletzko at the Pediatric Department at Ludwig-Maximilians University in Munich on premature infants is suggestive. He found that a low birth weight in these children was associated with a higher proportion of trans fatty acids in the blood.[262] Of course, this is no proof that the low birth weight of these children was due to the excess of trans fatty acids, but the finding certainly gives rise to concern, because there is experimental evidence that trans fatty acids may inhibit growth, for instance from a study by Dr. Atal and his coworkers at various institutions at the University of Maryland and at the National Institutes of Health.[263] They gave young mice two different diets. The only difference between the diets was that a tiny amount of normal fatty acids (not of the vital ones) was substituted with the same amount of trans fatty acids. After two years the body weight of the mice fed with trans fatty acids was 20-25% lower than the weight of the control mice. Thus, although the mice had been given exactly the same amount of calories, those which ate trans fatty acids instead of other fatty acids did not grow as they should have done.

Too much dietary trans fat makes the blood cholesterol level rise.[264] Not that this effect matters in itself; if you haven't skipped Chapter 4 you may recall that atherosclerosis has nothing to do with the blood cholesterol level, and from Chapter 2 you may remember that most heart attacks are seen in people with normal cholesterol levels. But people who think that the cholesterol level is important should know, that by following the official recommendations and eating margarine rather than animal fats, they might raise their cholesterol instead of lowering it.

Trans fat is present in considerable amounts in solid margarine and in bakery shortenings. The consumption of trans fat has increased substantially in most Western countries during the last century. In the United States, it has increased from 12 grams per day and person before World War I to about 40 grams in 1985. This is the average figure; some people may eat more, especially if they have followed the recommendations of the National Cholesterol Education Program, because very often fat that is called polyunsaturated on the food labels may be trans fat. Even the few people who prefer butter over margarine consume trans fat if they eat processed food products such as those mentioned above.

Many researchers, in particular those who advocate for the diet-heart idea, argue that the evidence is weak that trans fat is harmful to human beings. However, the mere suspicion that reproduction and growth may be hampered by an artificial nutrient, or that the same component may stimulate cancer growth, demands careful studies before it is distributed as food to most of mankind.

Dr. Ornish and The Lifestyle Heart trial

Coronary heart disease is a multifactorial disease that requires multifactorial intervention. This is the view of Dr. Dean Ornish and his group at the Preventive Medicine Research Institute, Sausalito, California, a view they share with many other doctors and researchers. Dr. Ornish and his group chose to intervene with a low-fat, low-cholesterol vegetarian diet, smoking cessation, stress-management training and moderate exercise. They selected 94 patients with a diagnosis of coronary artery disease according to a previous coronary angiogram. Fifty-three were randomly assigned to the experimental group and 43 to the control group, but when told about the design of the study only 28 and 20, respectively, agreed to participate.

A new angiogram was performed after one year, but one of the angiograms disappeared; in three patients the second angiogram could not be evaluated; one patient was not studied because of unpaid bills; one died during heavy exercise; and one dropped out because of alcohol misuse. Thus, only 22 patients in the experimental group and nineteen in the control group were available for analysis.

The result seemed promising. In the treatment group the total cholesterol fell by an average of 24 percent and LDL-cholesterol by 37 percent; mean body weight had decreased by ten kilograms; less severe chest pains were reported; and the coronary arteries had widened a little, whereas they had become a little more narrow in the control group. These improvements were strongly related to the degree of adherence to the intervention program in a "dose-response" manner, as the authors wrote in their report. The vascular improvements were still there after a prolongation of the study by five years, but now the difference was calculated using the less-demanding one-tailed t-test. Unfortunately, there was no difference in frequency, duration or severity of angina between the groups, but this unexpected finding was *"most likely"* due to bypass operations performed in the control group. Nothing was mentioned about how many operations had been performed, however, and no comparison was made between those who had not had an operation. In addition, a further six individuals were unavailable for follow-up study.

And there were more flaws. Not only was it an unblinded study, (although in the latest publication it was called blinded!), the low number of participants also resulted in a most uneven distribution of the risk factors. For instance, at the start the mean age was four years higher, mean total cholesterol 8 percent higher and mean LDL-cholesterol 10 percent higher in the control group; but mean body weight was almost 25 pounds higher in the treatment group. Such large differences between risk factors obviously complicate the evaluation of the treatment effect.

But let us assume that the improvement of the treated individuals was true and a result of the intervention—and this may well be possible—which of the intervention measures had a beneficial effect? Was it a weight reduction of more than 25 pounds? Was it a difference in smoking habits? (One in the experimental group smoked and stopped; nothing was mentioned about the number of smokers in the control group.) Was it the exercise? Was it the inner sense of peace and well-being produced by the stress-management education? Or was it a combination of these factors?

That the diet had any importance is unlikely because there is no evidence that vegetarians have a lower risk of coronary disease than other people. It is also unlikely that it was the change of LDL-cholesterol because at the end of the study there were no significant differences between these values in the two groups. The latter also contradicts the statement that the changes of coronary atherosclerosis and the diet were strongly correlated in a dose-response manner. To the pertinent question *"Precisely how strong were the correlations?"* asked by Elaine R. Monsen, editor of *Journal of the American Dietetic Association*, Dr. Ornish answered that *the study wasn't really set up to do these kinds of analyses, so when we get beyond saying they're correlated, we're on shaky ground.*

It is laudable to try prevention without drugs, and we already know that it may be health-promoting to avoid being overweight, to exercise a little and to avoid smoking and mental stress, but with such weak evidence, why inflict a diet that only rabbits may find tolerable on millions of people? Perhaps the results would have been better if the patients inner sense of peace and well-being had been strengthened even further by allowing them to eat more satisfying and nutritious foods.

Ornish D and others. Can lifestyle changes reverse coronary heart disease? The Lifestyle Heart Trial. The Lancet 336, 129-133, 1990.

Ornish D. Reversing heart disease through diet, exercise and stress management: An interview with Dean Ornish. Journal of the American Dietetic Association 91, 162-165, 1991.

Gould KL, Ornish D and others. Changes in myocardial perfusion abnormalities by positron emission tomography after long-term, intense risk factor modification. Journal of the American Medical Association 274, 894-901, 1995.

Myth 9: The Cholesterol Campaign is Based on Good Science

… the fourth and last wrong measure of probability I shall take notice of, and which keeps in ignorance or error more people than all the other together, is… the giving up our assent to the common received opinions, either of our friends or party, neighbourhood or country. How many men have no other ground for their tenets than the supposed honesty, or learning, or number of those of the same profession? As if honest or bookish men could not err, or truth were to be established by the vote of the multitude; yet this with most men serves the turn. If we could but see the secret motives that influenced the men of name and learning in the world, we should not always find that it was the embracing of truth for its own sake, that made them espouse the doctrines they owned, and maintained.

John Locke (1632-1704)

When two people share responsibility, they will each carry only one percent of the burden, at most.

Piet Hein

(1906-1996; Danish poet and physicist)

The proofs

"It has been established beyond a reasonable doubt that lowering definitely elevated blood cholesterol levels...will reduce the risk of heart attacks caused by coronary heart disease."

If you have read this book, you probably wonder if I just quoted a drug advertisement, and if the drug company got taken to court for misleading advertising practices. The statement, however, is quoted, word for word, from the summary of a consensus conference held at the National Institutes of Health in 1984[265]. The aim of this conference was to discuss how the results of the LRC trial should be translated into general recommendations for the American people.

The conference was headed by Basil Rifkind, who had been the director of the trial. Rifkind also determined who would be invited to join the panel that formulated the final recommendations.

Consensus is Latin for accord or unanimity. There were no such feelings in the audience, however. Among the many critical voices, Professor Michael Oliver from Scotland, the director of the early WHO trial, stressed that the trend towards an increased mortality from other causes was as strong as the trend towards a reduced mortality from coronary heart disease. "Why explain these results away?" he asked.

A British epidemiologist named Richard Peto admitted that in every trial "something ridiculous" had happened. But, he said, while no single trial was convincing, the trial evidence was impressive when analyzed together. (Does this sound familiar?).

Biostatistician Paul Meier from the University of Chicago opposed Rifkind's presentation of the LRC trial. He remarked: *"To call 'conclusive' a study which showed no difference in total mortality, and by the usual statistical criteria, an entirely non-significant difference in coronary incidents, seems to me a substantial misuse of the term."*

There was no unanimity, either, about the treatment that was going to be introduced. One speaker at the conference advised lowering dietary cholesterol; another advised lowering dietary fat of animal origin and did not think that dietary cholesterol had any importance; a third member recommended lowering the caloric intake, no matter how.

The final statement from the conference resolved the disagreements by recommending all three dietary measures. Criticism from the audience was simply swept under the rug. Some of the critics were cut off by the panel chairman, Daniel Steinberg, who cited a lack of time. Requests to write a minority report were denied as inconsistent with the conference's goal of consensus. [266]

Let us now look at the findings, which the panel considered as the scientific support for their recommendations. Here they are at last, all the proofs, which, added to each other, supposedly speak overwhelmingly for the diet-heart idea. Knowing the radical measures, which followed, we can be confident that the panel members included all available arguments. Here they come, all the strong proofs.

Proof #1

The inherited disorders prove that high blood cholesterol by itself can induce coronary heart disease.

This is pure speculation. What we do know is that people with inherited disorders have high cholesterol because the passage of cholesterol from blood to cell is slowed down. What we also know is that atherosclerosis is more widespread and more severe in these individuals. But is it true atherosclerosis? And is it really caused by t heir high cholesterol?

What is special for individuals with familial hypercholesterolemia is best seen in the rare homozygous form, the form that appears when both parents have the deficient gene for the LDL-receptor. Autopsy studies of such individuals show that cholesterol deposition is increased, not only in their vessels, but generally, throughout their bodies. Many other organs are impregnated with cholesterol, just as is seen in cholesterol-fed rabbits.

The vascular changes seen in people with the more common heterozygous form of familial hypercholesterolemia are more difficult to analyze because these changes must partly be due to the metabolic error and partly to common atherosclerosis. And how do we know if possible effects of treatment stem from reduction of the changes caused by the inborn error or from reduction of atherosclerosis? Thus, any conclusion, which may be true for individuals with familial hypercholesterolemia, cannot possibly be valid for the rest of mankind.

Proof #2

Animals become atherosclerotic when they are fed diets that raise their blood cholesterol, and the atherosclerosis disappears when their cholesterol is lowered again with diet or drugs.

What the animal experiments are worth as evidence is seen in chapter 5. The fact that vascular changes, produced by an extremely unnatural diet, disappear when the diet is terminated cannot prove anything about human atherosclerosis. The fact that vascular changes produced by an extremely unnatural diet forced down in a stressed rabbit’s stomach by catheter disappear when

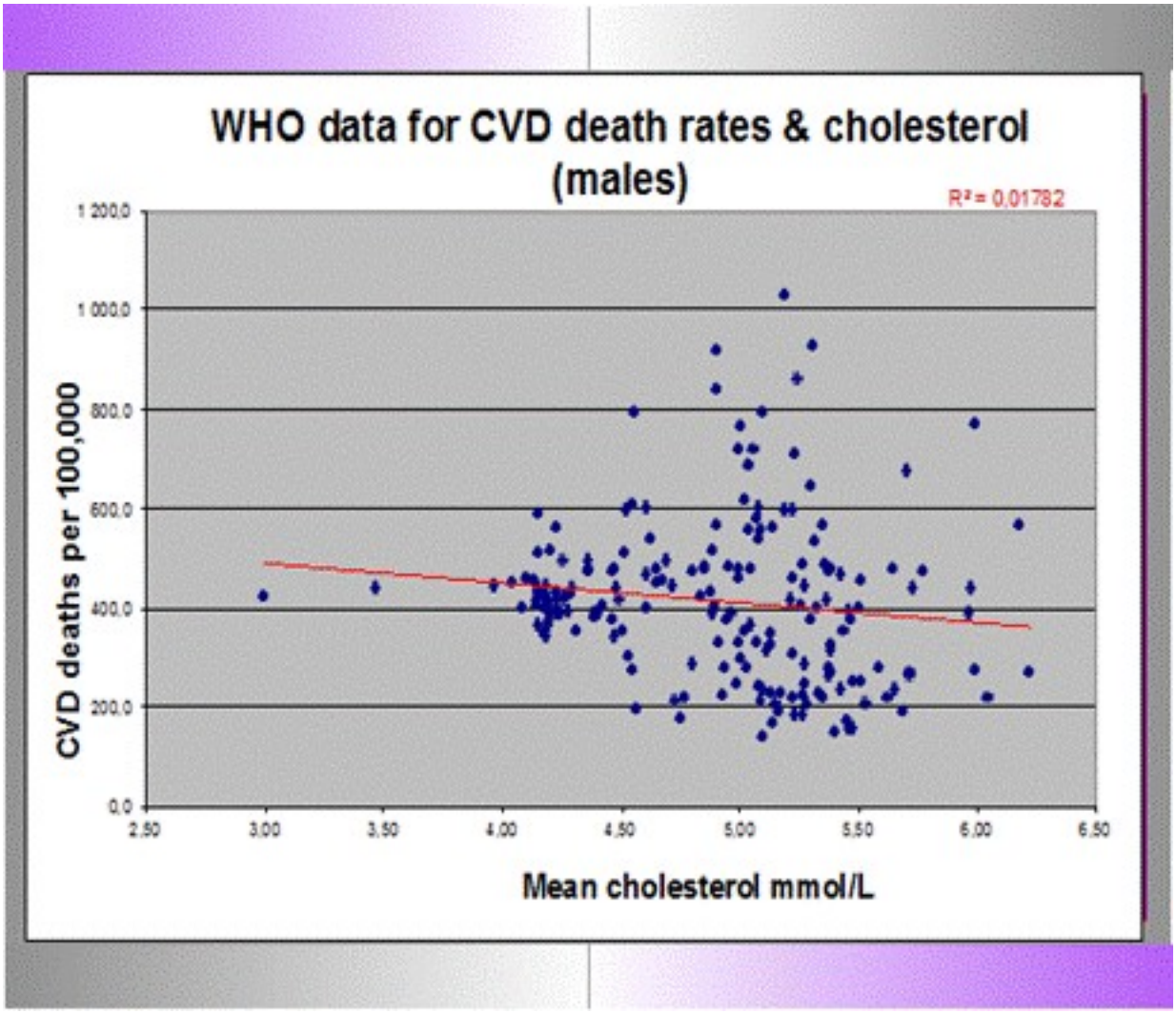
the diet is terminated cannot prove anything about human atherosclerosis. Weird John's gastric ulcer, caused by his swallowing iron nails, disappeared when John ceased eating hardware. But this is no proof that other patients' gastric ulcers are caused from eating building materials.

Wisely, nothing was said in the report about coronary heart disease, because it is not possible to produce this disease in animals only by increasing blood cholesterol.

Proof #3

There is a direct connection between blood cholesterol and the occurrence of coronary heart disease in various populations.

Look at this diagram. It is based on data from WHO and FAO and shows the association between cardiovascular mortality and serum cholesterol in various countries. If anything, low mortality is seen more often in countries where mean cholesterol is highest.



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Proof #4

People who have emigrated to another country with a higher average blood cholesterol level gradually acquire the dietary habits, blood cholesterol concentrations, and CHD rates of their new country of residence.

The Masai people, the Polynesians and many more were ignored; nothing was said either about Marmot's studies of the Japanese emigrants.

Proof #5

Severity and frequency of raised plaques in the aorta and coronary arteries are strongly correlated with blood cholesterol levels.

Amazing, isn't it? Maintain any delusion again and again, no matter how far from reality it may be, and it may finally be taken for the truth. See chapter 5 for the facts.

Proof #6

Populations experiencing severe dietary (especially fat) limitations and weight loss have been shown to have less atherosclerosis and CHD and fewer heart attacks.

Many other factors than lack of dietary fat are different in severely deprived people; no conclusions can be drawn from such observations.

Proof #7

Epidemiological studies have shown that elevated blood cholesterol levels in healthy people predict the future occurrence of coronary heart disease.

… except for Maoris, Stockholmers, Greeks, Finns and Canadians, except for women and men after forty-seven, and except for those who already have had a coronary.

Proof #8

Evidence emerging from multiple clinical trials clearly indicates that lowering blood cholesterol levels in patients with a high blood cholesterol level decreases the likelihood of fatal and nonfatal coronary heart disease.

A few lines after the above statement, the consensus report said that none of the previous dietary trials had proven that a lowering of blood cholesterol can diminish the incidence of coronary heart disease. In both the "proving" trials (LRC and CLAS), cholesterol had been lowered with drugs because diet was considered insufficient. Thus, the panel admitted, that no trial with diet had proven beneficial. At that time no drug trial either had lowered fatal coronary heart disease with statistical significance.

Proof #9

Thus, the evidence obtained from genetic, experimental, epidemiological, and clinical intervention investigations overwhelmingly supports a causal relationship between blood cholesterol levels and coronary heart disease.

This was all of it. This is the scientific foundation of the cholesterol campaign, the numerous proofs that do not suffice one by one but that, taken together, are so "overwhelming."

The panel considered the conclusive power so great that they had no doubts when it came to recommendations.

Recommendation #1

More than a dozen randomized trials of the effects of fat-controlled diets or drugs permit the conclusion that reduction of blood cholesterol levels in people with relatively high initial levels will reduce the rate of coronary heart disease. This has been shown most convincingly in men with a high cholesterol level, but although direct intervention studies have not been conducted in women, there is no reason to propose a separate treatment schedule for women.

Nothing was said about the fact that most trials did *not* demonstrate any benefit (in fact both the number of deaths and the number of heart attacks had *increased* in some of them); or that in most studies high cholesterol has not been associated with an increased coronary mortality for women.

Recommendation #2

Individuals in the high-risk group (above 6.2 mmol/l (242 mg/dl) at an age of 30-39; above 6.7 mmol/l (261 mg/dl) at an age above 40) should primarily have intensive dietary treatment requiring a major effort on the part of physicians, nutritionists, dieticians, and other health professionals. If this treatment does not work, drug therapy should be used.

Thus, only in the United States, tens of millions of healthy individuals should be on a diet. Let's hope that there are enough health professionals to carry out this daring project.

The drug producers and their stock holders should be happy, because, as you now know, it is extremely difficult to lower blood cholesterol with diet alone. The panel also knew it: after all, the control individuals in the LRC trial had eaten the recommended diet, and their cholesterol decreased less than one percent. No doubt about it—drugs would be necessary.

Recommendation #3

Individuals with moderate-risk blood cholesterol (above 5.7 mmol/l (220 mg/dl) at an age of 30-39; above 6.2 mmol/l (240 mg/dl) at an age above 40), — the upper 25 percent on the cholesterol scale — should also have intensive dietary treatment, and if other risk factors were present, drug therapy should be considered.

Further tens of millions of Americans on drab diet and dangerous drugs! In the LRC trial those from the upper 0.8 percent on the cholesterol scale were treated, and with drugs. And only after enormous effort could the trial directors come up with a result that nobody but a statistical incompetent could see as positive.

If it is that difficult with drugs to improve the prognosis for people with the most extreme cholesterol levels, how can diet alone produce a benefit for those with no more than a moderately high cholesterol?

Recommendation #4

Blood cholesterol is too high in most Americans because they eat too much saturated fat, too many calories, and too much cholesterol.

To avoid conflicts between the proponents, the recommendations included *all* the suggested diets.

Recommendation #5

Therefore, all Americans except children below the age of two are recommended a diet with no more than 250-300 mg cholesterol per day, and a reduction of total saturated fat intake to 10% or less of total calories, and an increase of polyunsaturated fat intake but to no more than 10% of total calories. The goal is to reduce blood cholesterol in the entire population to less than 5.0 mmol/l (195 mg/dl).

Here everybody is urged to eat what was originally advised for the high-risk group, except that people with normal cholesterol do not get help from health professionals. These people, the majority, have to judge for themselves when the magical ten per cent limit for polyunsaturated fat has been reached, the limit between harmless and dangerous amount. Nobody knows how the panel members found just that limit as crucial; nor why they chose a cholesterol limit of 195 mg/dl (5 mmol/l). (Every authority sees to have his own limit; the chosen value was probably determined by a vote).

Recommendation #6

There is no direct evidence of the benefit to be expected in the elderly, but dietary treatment may still be helpful.

Apart from the fact that there is no evidence either for the rest of mankind, why should we sour the lives of the elderly with an unpleasant diet if its benefit has never been proven? And remember you belong to the elderly as soon as you reach the age of forty-seven.

Recommendation #7

Also children should have treatment but not before the age of two. If blood cholesterol is above 4.4 mmol/l (172 mg/dl) diet is recommended; if it is above 5.2 mmol/l (203 mg/dl), drugs should be given, for instance, cholestyramine.

Poor kids! Remember that two out of three trial subjects given cholestyramine had gas, heartburn, belching, bloating, abdominal pain, nausea, vomiting, constipation or diarrhea.

Recommendation #8

If the American population follow the recommendations of the National Cholesterol Education Program, substantial improvements are in sight. For instance, if the cholesterol is lowered by five percent, the risk of having a heart attack will be reduced by ten percent.

These figures, which are cited in all official papers on cholesterol and diet, are grossly misleading. The risk of having a heart attack in the LRC trial was lowered from 9.8 to 8.1 percent, a difference of only 1.7 percentage point. This equals 0.2 percentage point for each percent of cholesterol lowering, which means a total of only one percentage point if blood cholesterol is lowered by 5 percent. But this whole line of reasoning is absurd because, after all, the LRC trial did not lower the number of heart attacks more than could be explained by chance.

Recommendation #9

The absolute magnitude of this benefit should be greater in patients at high risk from existing coronary heart disease or the presence of other risk factors such as cigarette smoking and hypertension.

This statement is preposterous. The calculations mentioned above were based on the figures from the LRC trial which studied no one but high risk individuals.

No reservations

The panel had no reservations except to say that a number of problems should be investigated in the future (thus ensuring huge amounts of future government welfare for scientists and research doctors). They suggested for instance, that more information should be gained about the possible danger of eating great amounts of polyunsaturated fat. Let us hope that a diet, very high in polyunsaturated fatty acids is not harmful, but it would have been wise to perform such studies before launching a campaign to reform everyone's diet.

The document prompted protests from many scientists, but, as we know, without any impact whatsoever. The cholesterol campaign has flourished ever since then and has spread to many other countries. Rumors are circulating that Ancel Keys has been suggested as a candidate for the Nobel prize.

Nothing was mentioned in the consensus report about the numerous unsupportive studies I have discussed in this book. And contrary to the initial statement of the consensus report many scientists have not agreed about the dangers of fat food and cholesterol. In the next chapter I shall present some of the critics and their objections.

Insider Insight

From a George Lymann Duff memorial lecture:

“A final lesson worth noting is that the current cholesterol campaign represents a rare concordance of interests on the part of many constituencies. The health professions, the pharmaceutical industry, government, the public—all should benefit from efforts to promote and implement the recommendations and guidelines in the Adult Treatment Panel report. Physicians will benefit because they will be providing better medical care to their patients and incidentally will have available a new and expanded market of patients for preventive medical care. The pharmaceutical industry will benefit from the greatly expanded market for cholesterol-lowering drugs that will result from even the most careful application of the guidelines on a national scale. The public will benefit from reductions in coronary risk and disease. And government will benefit from better health of its citizens and from reduced national expenditures that should result from reductions in coronary risk and disease.

“Moreover, this concordance of interests should promote cooperation—even collaboration—on the part of these various constituencies, something that is indeed occurring in part in quite a gratifying way.

“In closing, I’d like to acknowledge the pleasure I’ve had in playing an active role in the national cholesterol campaign. It has been a most exciting year—and a great pleasure this evening to be able to share some of my thoughts with friends and colleagues in the cholesterol and cardiovascular communities.”

Myth 10: All Scientists Support the Diet-Heart Idea

Only dead fishes go downstream.

Polish proverb

At this point you may probably wonder why you haven't heard about all this controversy before and why not even your doctor knows anything.

Criticism has been raised—a great deal of criticism. But it has been presented in journals and books that are not easily accessible to the layman, and critical voices have been drowned out in a flood of papers from the proponents. And the media, supported in large part by advertising revenues from pharmaceuticals and a food industry that has found it extremely profitable to use vegetable oils instead of animal fats, has consistently ignored the voices of dissent while hyping the recommendations for expensive drugs and dietary change.

Furthermore, as I have exemplified here and there in the previous chapters, the pontiffs of the cholesterol crusade systematically ignore the contradictory findings. And the same people are brilliant in finding the few studies that apparently are in support, and if they are not, a magic spell may change the picture. And don't forget that if your research is in accord with the wizards view, financial support from the drug and the food industry is almost endless. If not, you may risk both your funding and your position. Let me just remind you about Kilmer McCully, the American researcher who discovered the association between homocysteine and atherosclerosis. When he published his observation that the homocysteine, not the cholesterol concentration in the blood was associated with degree of atherosclerosis, he lost his position at Harvard Medical School and Massachusetts General Hospital and for two years he wasn't able to get a new one anywhere.[268]

And there are more brave researchers. Presented here, in alphabetic order, are a few of those who have had the courage to swim against the current. All of them have produced a large number of scientific studies of which I shall mention only the most important.

Mary Enig[269]

is an international expert in the field of lipid biochemistry, a nutritionist and a consulting editor to a number of scientific publications, including the Journal of the American College of Nutrition. She is also President of the Maryland Nutritionists Association. Her main research has concerned the hazards associated with consumption of trans fatty acids. She has published many scientific papers on the subject of food, nutrition, and food fats and oils; several chapters on nutrition for text books; and a primer for laymen and professionals on fats, oils and cholesterol. When asked whether saturated fats cause heart disease, she replied:

"The idea that saturated fats cause heart disease is completely wrong, but the statement has been 'published' so many times over the last three or more decades that it is very difficult to convince people otherwise unless they are willing to take the time to read and learn what all the economic and political factors were that produced the anti-saturated-fat agenda."

Michael Gurr[270]

was previously an associate professor of biochemistry at the School of Biological & Molecular Sciences in Oxford, previously editor-in-chief of *Nutrition Research Reviews* and editor of three other scientific journals. In a recent 50-page review published in *Progress in Lipid Research,* he presented the arguments of the cholesterol hypothesis in a thorough and honest way along with all the weaknesses of the theory. His main objections were the insufficient correspondence in vascular pathology between animal models and man and between familial hypercholesterolemia and atherosclerosis; the flaws and selection bias in the epidemiological evidence; the lack of correspondence between trends in coronary mortality and fat consumption patterns; the weak prediction achieved by measuring blood cholesterol; and the lack of improvement in mortality after dietary and pharmacological lowering of blood cholesterol. Professor Gurr's final words provide a fitting summary of everything that we have discussed in this book:

"The arguments and discussion of the scientific evidence presented in this review will not convince those 'experts' who have already made up their minds, for whatever reason, be it truly scientific or political, that a fatty diet is the cause of CHD. However, I hope that some readers, who were, perhaps, unaware that the lipid hypothesis had any shortcomings, will have been persuaded that the relationships between the fats we eat and the likelihood that we may die from a heart attack is by no means as simple as these simplistic statements imply."

George Mann[271]

was previously a professor in medicine and biochemistry at Vanderbilt University in Tennessee. From his studies of the Masai, he realized that animal fat could not possibly be the main cause of high cholesterol and coronary heart disease. As long ago as 1977, in the *New England Journal of Medicine,* he presented his main arguments against the diet-heart idea:

"the lack of relationship between dietary habits and blood cholesterol, the lack of correlation between this century's trends in fat consumption and death rates in the United States, and the disappointing outcome of the cholesterol-lowering trials."

Eight years later, when the cholesterol education campaign was getting into gear, Professor Mann summarized his criticism of the diet-heart idea in *Nutrition Today*. *"The diet-heart idea is the greatest scientific deception of our times, perhaps of any time,"* he said. Mann is especially critical of the cholesterol-lowering trials. *"Never in the history of science have so many costly experiments failed so consistently, he declared."*

Professor Mann severely criticized the LRC directors. The unsupportive results from the LRC study have not prevented them from *bragging about this cataclysmic breakthrough*. And he continued:

"The managers at the National Institutes of Health have used Madison Avenue hype to sell this failed trial in the way the media people sell an underarm deodorant. The Bethesda Consensus Panel… has failed to acknowledge that the LRC trial, like so many before it, is saying firmly and loudly:

'No, the diet you used is not an effective way to manage cholesterolemia or prevent coronary heart disease and the drug you so generously tested for a pharmaceutical house does not work either.'"

People who are faced with the many distorted facts about diet, cholesterol and heart disease often ask me why almost all scientists unquestioningly accept the diet-heart idea. And you may have asked the same question after reading this book. Here is Professor Mann's comment:

"Fearing to loose their soft money funding, the academicians who should speak up and stop this wasteful antiscience are strangely quiet. Their silence has delayed a solution for coronary heart disease by a generation."

Professor Mann offers a little glimpse of hope at the end of his article in *Nutrition Today*:

"Those who manipulate data do not appreciate that understanding the nature of things cannot be permanently distorted—the true explanations cannot be permanently ignored. Inexorably, truth is revealed and deception is exposed… In due time truth will come out. This is the relieving grace in this sorry sequence."

Edward Pinckney

was previously an editor of four medical journals and former co-editor of the *Journal of the American Medical Association*. In 1973, he published a book called *The Cholesterol Controversy*, which summarized all the inconsistencies in the cholesterol idea.[272] It seems impossible that any sensible and honest doctor who has read this book could continue to teach his patients about the dangers of cholesterol.

Pinckney describes all the factors that influence blood cholesterol in healthy people and how difficult it is to get a reliable measure of the cholesterol level due to uncertainties of the analysis:

"The level of one's blood cholesterol is, at best, nothing more than an extremely rough indication of a great many different disease conditions. At worst, it can be more the cause of stress and the diseases that stress brings on. To alter one's life-style as a consequence of this particular laboratory test may well cause more trouble than it could relieve."

Pinckney thoroughly describes the dangers of lowering one's cholesterol and devotes an entire chapter to the political drama preceding the cholesterol campaign. He had long wondered about the dairy industry's passive acceptance of the slurs against its products. The explanation he found was that many dairy distributors also distributed polyunsaturated products at an even greater profit. And the dairy farmer does not protest because the federal government uses taxpayer money to buy the farmer's surplus butter at a price far higher than what he could make by competing on the open market.

The beginning of Chapter 1 in Pinckney's book is worth citing:

"Your fear of dying—if you happen to be one of the great many people who suffer from this morbid preoccupation—may well have made you a victim of the cholesterol controversy. For, if you have come to believe that you can ward off death from heart disease by altering the amount of cholesterol in your blood, whether by diet or by drugs, you are following a regime that still

has no basis in fact. Rather, you as a consumer have been taken in by certain commercial interests and health groups who are more interested in your money than your life."

Raymond Reiser[273]

was a professor of biochemistry at Texas A & M University. In 1973 he criticized the recommendations for dietary treatment of high cholesterol by declaring:

"The authority quoted by these authors for the recommendation is not a primary source but another review similar to their own. It is this practice of referring to secondary or tertiary sources, each taking the last on faith, which has led to the matter-of-fact acceptance of a phenomenon that may not exist."

In his paper, Reiser continued with a thorough 30-page review of almost all experiments on the influence of dietary fatty acids on blood cholesterol levels. His main conclusions were that most experiments are biased by serious faults, that limited time frames and too few test individuals have been used, and that the diet studied has been too extreme to allow conclusions that are valid for ordinary people…

"One must be bold indeed to attempt to persuade large segments of the populations of the world to change their accustomed diets and to threaten important branches of agriculture and agribusiness with the results of such uncontrolled, primitive, trial-and-error type explorations. Certainly modern science is capable of better research when so much is at stake."

More recently, Reiser analyzed the references used as support by the American Heart Association in its rationale for its dietary recommendations. He could not find any supportive studies. In fact, some of the studies had results that contradicted the diet-heart idea:

"Thus the rationale is not a logical explanation of the dietary recommendations but an assemblage of obsolete and misquoted references. Since rational explanations for the recommendations are essential for their acceptance, the public to whom they are addressed is justified in remaining skeptical of them."

Paul Rosch[274]

is President of the American Institute of Stress, Clinical Professor of Medicine and Psychiatry at New York Medical College, Honorary Vice President of the International Stress Management Association and Chairman of its US branch. He is the editor or subeditor of three well-known medical journals, and he has served on the board of several other journals. He has served as President of the New York State Society of Internal Medicine, as Chairman of the International Foundation for Biopsychosocial Development and Human Health and has been an Expert Consultant on Stress to the United States Centers for Disease Control. He has written extensively over the past forty-five years on the role of stress in health and illness, with particular reference to cardiovascular disease and cancer. He has appeared on numerous national and international television programs such as *The Today Show, Good Morning America, 60 Minutes, Nova* and on *CBS, NBC, PBS, BBC* and *CBC* network presentations. His editorials and comments have been published in every major medical journal, and he has also been interviewed and widely quoted in numerous major American newspapers and magazines.

As the author of the *Newsletter of the American Institute of Stress*, Professor Rosch has published several articles about the cholesterol hypothesis and the diet-heart idea. His conclusions are close to those presented in this book:

"A massive crusade has been conceived to 'lower your cholesterol count' by rigidly restricting dietary fat, coupled with aggressive drug treatment. Much of the impetus for this comes from speculation, rather than any solid scientific proof."

"The result is well-known. The public is so brainwashed, that many people believe that the lower your cholesterol, the healthier you will be or the longer you will live. Nothing could be further from the truth."

How can this go on year after year? Professor Rosch has several explanations:

"The cholesterol cartel of drug companies, manufacturers of low-fat foods, blood-testing devices and others with huge vested financial interests have waged a highly successful promotional campaign. Their power is so great that they have infiltrated medical and governmental regulatory agencies that would normally protect us from such unsubstantiated dogma."

Rosch reminds us that practicing physicians get most of their information from the drug companies. But… *"compared to their peers a half century ago, most doctors don't have the time or skills to critically evaluate reports, very few know anything about research, nor did the generation that taught them."*

Now in his eighties, Rosch is still active and his critical voice appears now and then in the scientific press.

Ray Rosenman[275]

is the retired Director of Cardiovascular Research in the Health Sciences Program at SRI International in Menlo Park, California, and previously associate Chief of Medicine, Mt. Zion Hospital and Medical Center in San Francisco. He has been a cardiologist and a researcher since 1950. He has published four books, many textbook chapters and numerous journal articles about cardiovascular diseases. His main interest has been the influence of neurogenic and psychological factors on the blood lipids, but he has also written reviews critical of the diet-heart idea. Here is the conclusion from his most recent review:

"These data lead to a conclusion that neither diet, serum lipids, nor their changes can explain wide national and regional differences of CHD [coronary heart disease] rates, nor the variable 20th century rises and declines of CHD mortality."

"This conclusion is supported by the results of many clinical trials which fail to provide adequate evidence that lowering serum cholesterol, particularly by dietary changes, is associated with a significant reduction of CHD mortality or improved longevity. It is variously stated that the preventive effects of dietary and drug treatments have been exaggerated by a tendency in trial reports, reviews, and other papers to cite and inflate supportive results, while suppressing discordant data, and many such examples are cited."

Russell Smith[276]

was an American experimental psychologist with a strong background in physiology, mathematics and engineering. In cooperation with Edward Pinckney, he studied all aspects of the diet-cholesterol-heart issue with extreme thoroughness and presented his findings in two large scientific reviews of the literature containing more than 700 pages with more than 3000 references, as well as in a popular book. No review written by the proponents of the diet-heart idea can compare with Russell Smith's books when it comes to completeness and scientific depth. Volume 1 of his review is an overview of the entire issue. Smith's summation is devastating for the diet-heart proponents:

"Although the public generally perceives medical research as the highest order of precision, much of the epidemiologic research is, in fact, rather imprecise and understandably so because it has been conducted principally by individuals with no formal education and little on-the-job training in the scientific method. Consequently, studies are often poorly designed and data are often inappropriately analyzed and interpreted. Moreover, biases are so commonplace, they appear to be the rule, rather than the exception. It is virtually impossible not to recognize that many researchers routinely manipulate and/or interpret their data to fit preconceived hypotheses, rather than manipulate hypotheses to fit their data. Much of the literature, therefore, is nothing less than an affront to the discipline of science."

Russell Smith concluded:

"The current campaign to convince every American to change his or her diet and, in many cases, to initiate drug "therapy" for life is based on fabrications, erroneous interpretations and/or gross exaggerations of findings and, very importantly, the ignoring of massive amounts of unsupportive data… It does not seem possible that objective scientists without vested interests could ever interpret the literature as supportive."

In his books and papers Russell Smith criticized a large number of leading scientists from the National Heart, Lung and Blood Institute and the American Heart Association, which he calls the alliance. He considered their work incompetent and sloppy:

"The fraud is so blatant and so pervasive that it was considered necessary to take some liberties with the usual staid rhetoric of a scientific review and inject stronger language to emphasize the problem."

Russell Smith was aware that he was up against some extremely powerful institutions:

"The political and financial power of the NHLBI and AHA team… is enormous and without equal. And because the alliance has substantial credibility in the eyes of the public and most practicing physicians, it has become a juggernaut, able to use its power and prestige to suppress a great body of unsupportive evidence and even defy the most fundamental tool of scientists, logic."

The scientists who have produced the misleading papers and reviews are, of course, the first with whom Russell Smith finds fault. But he added:

"Equally culpable are the editors of the many journals who publish articles without regard to their quality or scientific import. It is depressing to know that billions of dollars and a highly sophisticated medical research system are being wasted chasing windmills."

William Stehbens[277]

a former professor at the Department of Pathology, Wellington School of Medicine, and director of the Malaghan Institute of Medical Research in Wellington, New Zealand, is another articulate critic. Based on his own studies and on extensive reviews of the literature, he has effectively demonstrated the many fallacies of the diet-heart idea. In a thorough review of the experimental studies he concluded:

"Upon examination of this evidence and consideration of the specific criteria for the experimental production of atherosclerosis, any pathologist of independent mind and free from preconceived ideas would conclude that human atherosclerosis and the lesions induced by the dietary overload of cholesterol and fats are not one and the same disease."

Stehbens has also pointed out the weaknesses of the epidemiological studies that have used mortality statistics as proof for causality:

Continued, unquestioned use of unreliable data has led to premature conclusions and the sacrifice of truth. The degree of inaccuracy of vital statistics for CHD is of such uncertain magnitude that, when superimposed on other deficiencies already indicated, the concept of an epidemic rise and decline of CHD in many countries must be regarded as unproven, and governmental or health policies based on unreliable data become completely untenable.

According to Stehbens, atherosclerosis is due to wear and tear of the arteries, and not to high cholesterol levels in the blood, an idea he supports with many good arguments.

The following words from a 1988 paper summarize Stehbens's view on the diet-heart idea:

The perpetuation of the cholesterol myth and the alleged preventive measures are doing the dairy and meat industries of this and other countries much harm quite apart from their potential to endanger optimum nutrition levels and the health of the populace at large…. It is essential to adhere to hard scientific facts and logic. Scientific evidence for the role of dietary fat and hypercholesterolemia in the causation of atherosclerosis is seriously lacking… The lipid hypothesis has enjoyed undeserved longevity and respectability. Readers should be aware of the unscientific nature of claims used to support it and see it as little more than a pernicious bum steer.

Lars Werkö[278]

was previously a professor of medicine at Sahlgren's Hospital, Gothenburg, Sweden, scientific director at the Astra Company, and then head of the Swedish Council on Technology Assessment in Health Care, a governmental agency. Professor Werkö has been an opponent of the diet-heart idea for many years. In 1976 he criticized the design of the large epidemiological studies aimed at preventing coronary heart disease, most of all the Framingham study.

According to Werkö, the dogma is based on questionable “facts” rooted in hopes, wishful thinking and studies using selected materials.

“No studies have proved anything, but instead of formulating new hypotheses, diet-heart supporters call the current one the most probable truth, and they have intervened in people’s lives because they will not wait for the final proof.”

In another paper, he pointed to a number of inaccuracies and sloppy data gathering in the MR.FIT trial.

At the age of 90 Werkö is still active. Recently he was awarded by the Swedish medical journal *Dagens Medicin* for his many critical contributions to today’s debate around Swedish health care.

Epilogue

After a lecture, a journalist asked me how she could be certain that my information was not just as biased as that of the cholesterol campaign. At first I did not know what to say. Afterwards I found the answer.

She could not be certain. Everyone must gain the truth in an active way. If you want to know something you must look at all the premises yourself, listen to all the arguments yourself, and then decide for yourself what sees to be the most likely answer. You may be easily led astray if you ask the authorities to do this work for you.

This is also the answer to those who wonder why even honest scientists are misled. And it is also the answer to those who after reading this book, ask the same question.

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[266] According to Moore, the communiqué had been written before the meeting.

[267] Some of the many critical voices are listed here:

Palumbo PJ. National cholesterol education program: does the emperor have any clothes? Mayo Clinic Proceedings 63, 88-90, 1988.

Oliver MF. Consensus or nonsensus conferences on coronary heart disease. The Lancet 1, 1087-1089, 1985.

Merz B. Low-fat diet may be imprudent for some, say opponents of population-based cholesterol control. JAMA 256, 2779-2780, 1986.

Pinckney ER, Smith RL. Statistical analysis of lipid research clinic's program. The Lancet 1, 503, 1987. Pinckney and Smith concluded that “the US government via the NHLBI has launched a nationwide program to alter the diet of Americans, based on a study (costing $150 million of public money) that had a faulty statistical analysis. What is more, the statistical defects were known to the trial's organisers and to the journal that published the results.”

Patel C. The lipid research clinic's trial. The Lancet 1, 633-634, 1984. Patel has calculated that if the result of the LRC trial is transferred to England and Wales one of every 400 coronary deaths could be saved each year, amounting to the cost of about £140 million a year and of gastrointestinal side effects in more than 130 000 healthy individuals.

Editorial. The Lancet 1, 333-334, 1988. The author stressed the fact that there is little correlation between dietary fat intake and cholesterol level; that no convincing dietary prevention study had been published; and that the increase in deaths from other causes in the drug trials "cannot be ignored simply because it did not form part of the hypothesis that these trials were designed to test."

[268] The full story about Kilmer McCully was published in New York Times on August 10, 1997. Go to www.thincs.org, click on "Members," look for his name and click on "Interview."

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Enig MG. Know Your Fats: The Complete Primer for Understanding the Nutrition of Fats, Oils, and Cholesterol. Bethesda Press, Silver Spring, MD, 2000.

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[274] Paul Rosch's view on the cholesterol campaign is available in Health and Stress. The Newsletter of The American Institute of Stress, 1995, nr 1; 1998, nr 1; 1999, nr 8; 2001, nr 2,4,7.

Read also:

Rosch, PJ. Statins don't work by lowering lipids. Electronic response in BMJ 17. Nov 2001.

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Smith RL. The Cholesterol Conspiracy. Warren H. Green, Inc. St. Louis, 1991. (c) Smith RL. Am Clin Lab November, p. 26-33, 1989.

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Werkö L. Prevention of heart attacks. Ann Clin Res 11, 71-9, 1979.

Werkö L. Diet, lipids and heart attacks. Acta Med Scand 206, 435-9, 1979.

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