Mythbusters: Cholesterol

An Interactive Qualifying Project
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Abstract

Heart disease is a major problem in the United States, and while the generally accepted causal agent for heart disease is high levels of serum cholesterol, there are some who have suggested that the current paradigm could, in fact, be a myth. This project is focused on uncovering more information through an investigation of both what doctors and scientists believe about the cholesterol theory and the information which is being given to the public about cholesterol, heart disease, and statins.

Executive Summary

Heart disease is a major problem in the United States – it is currently the leading cause of death among Americans. Excluding cancer, the second most deadly disease among Americans, more people die of heart disease than by the number 3, 4, 5, 6, 7, 8, and 9 causes of deaths in the U.S., combined. The currently accepted malefactor of heart disease is cholesterol, in particular serum LDL cholesterol. Many studies have shown a correlation between cholesterol and heart disease, which many consider strong enough to prove the theory. There are others, however, who believe that cholesterol has been framed as the causal culprit, for some reason or another. Our project aims to examine those claims, and attempt to shed light on whether or not cholesterol causes heart disease.

In 1878, almost 130 years ago, Doctor Adam Hammer was the first person to document a heart attack. The patient had radiating chest pain, collapsed, and died. An autopsy performed later found that some of the muscle of his heart had in fact died, confirming that this was an acute myocardial infarction (AMI). This doesn't necessarily mean that there were no heart attacks before 1878, there just was no documentation prior to this report of anyone else having one. A subsequent study in 1914 by Nikolai Antischkow examined the effects of feeding high-cholesterol diets to rabbits, which are natural herbivores. The rabbits developed severe atherosclerosis and all died of cardiac arrest. The study established a long-standing belief that high-cholesterol diets cause heart disease.

Individuals such as Uffe Ravnskov and Charles McGee challenge these studies as being biased or poorly executed. In the case of Nikolai Antischkow, Ravnskov points out that it is clear the rabbits would develop atherosclerosis; since cholesterol is not normally found in their

herbivorous diets, they are not equipped with the mechanisms of cholesterol metabolism that humans are.

Even some of the most cited studies have come under fire by such individuals. The notorious Framingham Heart Study has been ongoing since 1948, and has identified numerous heart disease risk factors, including smoking, hypertension, genetic predisposition, inactivity, stress, and of course high cholesterol. What it has failed to show, however, is a causal relationship between cholesterol and heart disease, which is striking given the study's longitudinal nature.

There are also many situations and scenarios that cannot be explained by the cholesterol-theory. Familial hypercholesterolemia (FH) is a genetic disease causing severely elevated LDL levels (in excess of 500 mg/dL). An FH patient would be expected to be critically at risk of heart disease, and yet there are many cases of entire families with FH never suffering a single heart attack. Other examples logically refuting the hypothesis include tribes of nomadic peoples in Africa whose diets consist principally of fresh red meat, high in cholesterol, who have no history of heart attacks whatsoever, and the recent Vytorin study, which showed that despite a particular cholesterol-reducing drug regiment, patients on the drug developed atherosclerosis at double the rate.

It is these discrepancies and unexplained anomalies that prompted this group to do some further research into the topic. After doing some initial research on the matter the research group came up with three important research questions to be answered. First, "What do doctors and scientists believe about the Cholesterol-Heart Theory?" this question was geared toward finding out whether doctors and scientists whole-heartedly back up the current paradigm or whether there is some credence to the alternative hypotheses suggested by various authors. Our second

question, “Why do doctors prescribe statins” is an attempt to prove or disprove claims that pharmaceutical companies have a tremendous amount of sway causing doctors to prescribe one drug over another. And third, “What do scientists believe about the studies done on cholesterol” is meant to get some feedback on the validity of the studies that have already done that claim the cholesterol is the leading cause of heart disease.

In the pursuit of answering these questions, the research group concluded that directly interviewing doctors and biochemists was the best course of action. Interviews were used to gather specific perspectives of several representatives of a larger demographic. The research group came up with fourteen questions that were geared toward each representative’s specific knowledge of cholesterol, statins, and current research on the topic. All of these interviews were done face-to-face and recorded for transcribing. The responses were then collected and compared among each demographic by question.

In order to obtain some information from the two demographics of scientists and doctors in the short amount of time available to do these interviews, the research group conducted nine interviews, four with scientists and five with doctors. Given the small number of interviews planned, one can hardly say that our results are representative of respective communities, but they were enough to scratch the surface of the information we are actually trying to find. Were the study more longitudinal, it would have been more realistic to aim for a larger sample size. However, given our limited time and resources, the goal was not to attain a theoretical saturation in the interview responses, the goal of the interviews was to construct a general picture of some views and opinions held by several of the members of these more influential demographics

Responses to the interviews were initially analyzed altogether, alongside one another, according to question. Observations and general logical conclusions were made within each

question regarding the goals of the project: to assess cholesterol's role in heart disease, examine what doctors and scientists have to say about the topic, and address doctors' motives for prescribing statins. Deeper conclusions were then made based on the initial analysis; quotes and contradictions were scrutinized more closely and examined for meaning, and connections were made to the Literature Review. The nature of the demographics was also considered, insomuch as the differences and similarities in the way doctors and scientists speak, their range of knowledge, and their beliefs about cholesterol and heart disease.

In our analysis we found the presence of two social models working together. One was Thomas Kuhn's Structure of Scientific Revolutions, describing the way in which paradigms are set in place, and what it takes to change them. In the course of research on cholesterol, numerous anomalies have been uncovered, experimental results that do not agree with the cholesterol-heart theory, ones which could potentially cause a shift in the current paradigm concerning cholesterol and its link to atherosclerosis and chronic heart disease. However, it is the paradigm itself that guides the scientific process, so when these anomalies do appear the tendency has been to force them to fit the current theory, to explain them away, or to simply overlook them. The scientists we spoke to were aware of alternative theories being proposed about the link between cholesterol and heart disease, or lack thereof, and readily admitted that there is some merit to those hypotheses. However, their convictions still lay on the side of the current paradigm, as there has not yet been enough evidence to overturn it.

The other model we found was one of "nested audiences" as proposed by Keith Sawyer in his book Explaining Creativity, which depicts the way in which information flows from more specialized down to more generalized audiences. In this case, information is being passed from the scientists to the doctors, who in turn then pass it along to their patients – members of the

general public. We found that while scientists had a more nuanced understanding of the effects cholesterol has on the heart, and readily suggested the possibility of other theories about its role in heart disease, doctors were more steadfast in their decision that cholesterol is a major risk factor in the development of atherosclerosis. In fact, the doctors we interviewed had little notion that the theory was even being questioned. It appears that in the flow of information from scientists to doctors, only the current paradigm is passed along, and when that information reaches the general public, it is all they know. It is our belief that in this way the idea that cholesterol is bad has been propagated and perpetuated.

In regards to our research question of what scientists and doctors believe about cholesterol as it pertains to heart disease, we concluded that while the notion that cholesterol may not play much of a role at all has begun to take hold, overall the current cholesterol-heart theory is still the paradigm that scientists and doctors have faith in.

As for the reason doctors prescribe statins, we have found that it is not due to influence from pharmaceutical companies or pressure from health guidelines that insist on low cholesterol levels, but rather out of genuine concern for their patients. The doctors we interviewed all said that they always suggest lifestyle changes to their patients, such as diet and exercise, or quitting smoking, before they prescribe statins, and one of the scientists who happened to be on statins confirmed this procedure. The problem is with compliance: most people would rather take a pill than make changes to the lifestyle they are accustomed to, and many patients will specifically ask to be prescribed particular statins.

The answer to our final question, asking what scientists believe about the studies that have been done on cholesterol, is what one might expect: they do believe that the studies are valid, and they are invested in the current paradigm. However, that is not to say that the scientists

are blind to the theories that refute the cholesterol-heart theory – most suggested the possibility that cholesterol does not play the role it is thought to, and that perhaps it is just blamed for being in the wrong place at the wrong time.

Based on the results and conclusions made, we recommend that anyone concerned about their own heart health educate themselves about their particular risk factors and assess them with equal significance to cholesterol. If an individual does feel that cholesterol is a significant risk factor, the group must second the notion of doctors and scientists and suggest lifestyle changes before a prescription drug regimen. Finally, it is important for someone interested in any of these matters to educate themselves actively, and not rely solely on the flow of information from researchers to doctors to the public, as this will result in a more complete understanding of the issue.

Introduction

Heart disease is a major problem in the United States – it is currently the leading cause of death among Americans. In 2004 there were 652,486 deaths in the U.S. due to diseases of the heart – adjusting for age, that's a rate of 222.7 deaths per 100,000 people. Excluding cancer, the second most deadly disease among Americans, more people die of heart disease than by the number 3, 4, 5, 6, 7, 8, and 9 causes of deaths in the U.S., combined [1].

There have been many studies done that suggest high cholesterol is the culprit behind high rates of coronary heart disease (CHD) in America. There are two prominent forms of cholesterol: LDL (low density lipoproteins) and HDL (high density lipoproteins), which have been labeled as "bad" and "good" cholesterol, respectively. According to some researchers, high levels of LDL – the lipoprotein that carries cholesterol to the bloodstream – will create blockages in the arteries that will lead to atherosclerosis. HDL, on the other hand, is responsible for removing excess cholesterol from the body via the liver. Thus, lowering the "bad" LDL while keeping the "good" HDL relatively high is considered desirable [2].

For over half a century, the United States and much of the world has been living and eating under this assumption that cholesterol is a malignant chemical contributing greatly to the risk of heart disease [2]. Since the late 1960's, about a decade after the campaign to lower cholesterol was getting started, the rate of mortalities due to heart disease has been decreasing [3]. Thus, some argue that the idea of a healthy diet and exercise keeping cholesterol at bay, and in turn reducing the risk of CHD, has worked. On the other hand, this could simply be the result of better health care; furthermore, a healthy diet and exercise may reduce heart disease in and of themselves, without relation to cholesterol. All the while, however, average cholesterol intake

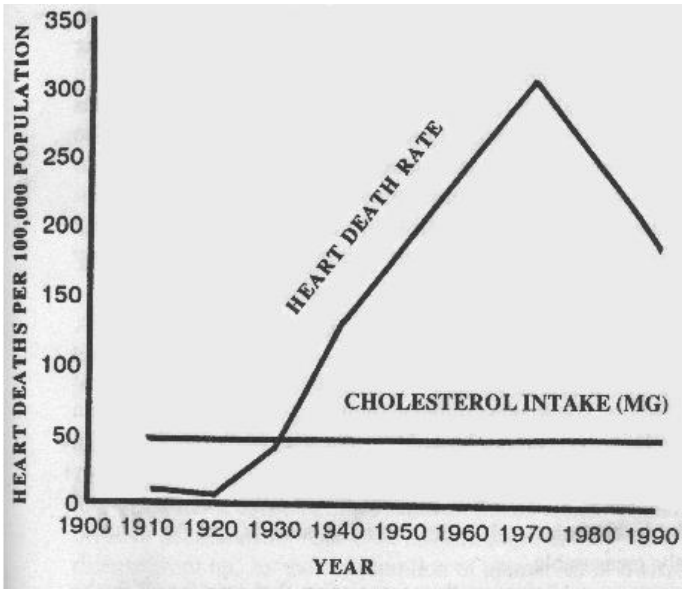

Figure 1- Incidence of heart disease deaths per 100,000 over time, alongside average cholesterol intake in milligrams over same period. Note the lack of exposure-response, indicative of causation [7].

has remained more or less constant. Figure 1 shows the heart disease trend plotted alongside that of cholesterol intake from 1910 to 1990.

At any rate, countless Americans strive to lower their cholesterol via diets and exercise programs. Altering levels of cholesterol naturally can prove to be difficult, however, as production of the substance is adjusted by the liver depending on how much or how little we consume in our diets [2]. In order to expedite the process, doctors often prescribe drugs to patients with high cholesterol levels. There are millions of Americans who take these drugs, known as statins, to reduce cholesterol. Pfizer's cholesterol-lowering drug, Lipitor, accounts for 26 million of these prescriptions alone [4]. In fact, Lipitor has been the best-selling drug in the world for several years [5].

But is cholesterol really the problem? Taking a closer look at many of the studies examining cholesterol, one finds there are several flaws in them. Some are done on samples of people who do not represent the general population, or are funded by the pharmaceutical companies themselves, posing the threat of biases in reporting results. Others are done by researchers who have questionable affiliations. Still more manipulate data to make insignificant results appear to be a big deal, perhaps on the premise that negative results are equivalent to bad, unfavorable results. Contradictory to the findings of many of these studies, other examinations

find that cholesterol is likely an important part of the immune system, working to repair damage done to arteries [6]. There is also information pointing to cholesterol as vital in the production of hormones. Thus, taking drugs to lower cholesterol, rather than making the necessary changes to live a healthier lifestyle, may prove to be detrimental.

With so many different perceptions about the role of cholesterol, surely some must be mistaken. The public is fed information from regulatory officials about daily recommended intakes for cholesterol and fats, while scientific researchers discover various facets of the role of cholesterol, many of which are contradictory. All the while doctors prescribe cholesterol-reducing drugs on the premise that lowering cholesterol will reduce the risk of heart disease. Moreover, in the face of all this cholesterol adversity, reputable scientists write books and articles professing that cholesterol is not a harmful chemical at all.

Naturally, the common citizen will take the advice of his or her doctor concerning matters of heart disease risk and cholesterol levels. It is therefore important to assess what doctors know and believe about the matter. It is also important to examine what scientists have to say about cholesterol and heart disease, since doctors, more often than not, must base their opinions on the findings of scientists. The problem this project intends to address, therefore, concerns the information which is being given to the public about cholesterol, heart disease, and statins.

Several key issues must be addressed in order to determine the scope of this problem. The knowledge of the doctors prescribing statins should be examined, as well as the opinions of the researchers who give their information to the doctors. This all leads to the question, what do doctors and scientists really think about the cholesterol theory? The answer to this question has

to be observed in order to determine whose perspectives about cholesterol are accurate, and whose are but myths.

Literature Review

In 1911, Antishkow and Ignatowsky published some of the first studies done to help determine the effects of cholesterol and how it might relate to arterial problems both of the heart and of the brain. The study analyzed the effect a high fat/cholesterol diet would have on rabbits after a few months. The result was that the rabbits' arteries were clogged with a fatty material. The problem here was that the arterial blockage observed in these animals did not resemble the same kind of obstruction observed in humans with fatty deposits in their arteries. Despite this fact, however, researchers decided that it looked close enough to the human model, and continued attempting to prove what they had already decided to accept as fact [7].

McGee goes on to say that, however unfortunate it might be, there are very many studies that have either been misquoted or have misrepresented the evidence presented and thusly, much of what we know about "bad cholesterol" may, in fact, be false. This so-called, "lipid (or cholesterol) theory" simply claims that high levels of cholesterol must be the cause of artery-related diseases such as coronary heart failure and strokes. This hypothesis, however, does not account for those "high-risk" people who never have a heart attack, or those "significantly low-risk" people who do. In fact, there seem to be so many exceptions to the rule, that there is clearly a large amount of research still to be done [7].

At the very least, there are a number of things that *are* known about cholesterol. For instance, that cholesterol is a type of sterol (steroid-alcohol) that is *absolutely* vital for life in humans. Cholesterol is a lipid that is present in the lipid bilayer of eukaryotic cells. Without cholesterol, the membrane would not be able to maintain its fluidity at different temperatures, and many cells would die because of this. On top of that, cholesterol also aids in the absorption

of certain fat-soluble vitamins (A, D, E, and K) and is transported through the system via Low Density and High Density Lipoproteins (LDL and HDL) [8].

On the other side of things, there are a number of emerging studies that are casting cholesterol in a different light than the socially accepted cholesterol hypothesis. One study, done by Bahkdi et. al., showed that LDL was capable of binding, and partially inactivating Staphylococcus aureus, the bacteria that is the main cause of staph infections [9]. Another study claims that high levels of cholesterol (even LDL cholesterol) could be better for you because it helps boost the immune system and even might help *prevent* atherosclerosis [10].

Regardless, even, of the truth – that is, whether or not cholesterol causes heart disease – there is clearly disagreement over the issue. Were this not the case, the myriad of books and articles written on the topic, this document included, would not exist. The problem is of utmost concern to the general public, which is informed by their doctors, who in turn must base their decisions and advice on the most current scientific research and health regulations. Thus, the following Literature Review will examine the history of scientific research conducted on cholesterol and heart disease, the regulatory history of cholesterol, and the pharmaceutical companies' delving into the subject. The subsequent Methodology section will seek to address questions raised in the Literature Review, followed by an analysis and conclusion of the research conducted therein.

Scientific History of Cholesterol

In 1878, almost 130 years ago, Doctor Adam Hammer was the first person to document a heart attack. The patient had radiating chest pain, collapsed, and died. An autopsy performed later found that some of the muscle of his heart had in fact died, confirming that this was an acute myocardial infarction (AMI). This doesn't necessarily mean that there were no heart

attacks before 1878, there just was no documentation prior to this report of anyone else having one. It is important to note that between 1830 and 1880, European physicians identified a large number of pathologies by performing tens of thousands of autopsies. During this time, not a single case of heart attacks was found until 1878 nor were there any reports of crushing chest pain followed by death [7].

With the newly emerging cause of death, a new study had to be done to help show *why* these deaths were occurring – what causes a heart attack? Enter the cholesterol theory. In 1910, Adolph Windaus, a German chemist, reported that plaques from atherosclerotic arteries contained 20 to 26 times more cholesterol than those in normal arteries. In 1914, Nikolai Antishkow published the results of a study which used animal models to show the correlation between fatty diets and heart attacks [11]. This study fed rabbits what was essentially pure cholesterol and performed autopsies on them post mortem. As was expected, the rabbits died of severe atherosclerosis and hypercholesterolemia. The study allowed researchers, doctors, and pathologists to accept what is now referred to as the cholesterol theory, and refocus their efforts on what was now believed the cause of heart disease [7].

The problem with the study was that rabbits are vegetarians and, as plants contain an almost non-existent amount of cholesterol, they should be expected to adapt differently to such a large amount of a new substance that they wouldn't otherwise consume. The experiment was run again and again on various different animals: guinea pigs, rats, chicken, pigeons, and rhesus monkeys – all vegetarians, all with the same result. Surprisingly enough, the experiment did not produce the same results in carnivorous dogs.

On top of all this, the arteries found in the vegetarian animals post mortem were found to be different than those found in humans with the same affliction. The atherosclerotic rabbits

were found to have plaques sticking to the inner lining of the arterial wall. In humans with hypercholesterolemia, obstructing fatty material is found to build up within the wall of the artery itself. For one reason or another, medical researchers and practitioners accepted the results of this study as "close enough," extrapolated the results to humans, and site it as proof that cholesterol kills people. This study did not show any relationship between cholesterol and heart disease, only the correlation between too much cholesterol and death in rabbits [7].

Another study was undertaken in 1953 by Dr. Ancel Keys, director of the Laboratory of Physiological Hygiene at the University of Minnesota. Keys, like Antishkow, theorized that high fat and cholesterol consumption directly increased the risk of heart disease. Rather than delve in wet-work, however, Keys gathered dietary information from six countries and charted this information against deaths by CHD. Figure 2 shows the graph Keys constructed. From his data, there appeared to be a very clear trend line, supporting his theory. There was just one problem – Dr. Keys could have used available data from 22 countries. When added to his six data points, the additional 16 points turn the trend line into a scatter plot, all but eliminating the correlation (Figure 3).

Though Keys examined calories from fat rather than cholesterol, it is now known that consuming high levels of saturated fats increases LDL in the body [12]. Keys' study jump-started the further research of fats and cholesterol, with the notion that these may actually be the factors responsible for heart disease, yet the study was clearly flawed from the start.

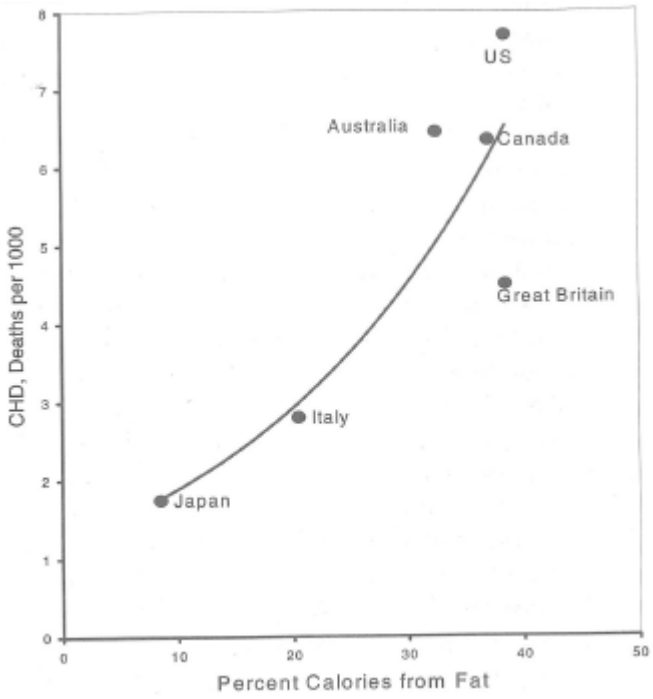

Figure 3- Correlation between the total fat consumption as a percent of total calorie consumption, and mortality from coronary heart disease in six countries

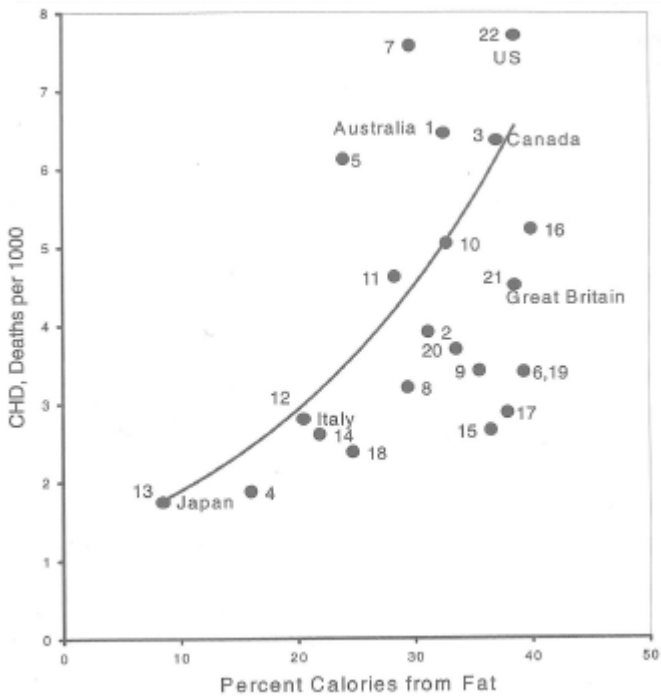

Figure 3- Same as Figure 2, but including all countries where data was available when Keys published his paper: 1. Australia 2. Austria 3. Canada 4. Ceylon 5. Chile 6. Denmark 7. Finland 8. France 9. West Germany 10. Ireland 11. Israel 12. Italy 13. Japan 14. Mexico 15. Holland 16. New Zealand 17. Norway 18. Portugal 19. Sweden 20. Switzerland 21. Great Britain 22. USA

Current and Ongoing Research

One of the most sited and longitudinal studies ever done in terms of cardiovascular research is the Framingham Heart Study (FHS). The study started in 1948 with 5,209 healthy men and women aged 30-60 (referred to as the Original Cohort) [13]. The participants went through extraordinary physical examinations and lifestyle interviews in order to collect data to look back on and analyze the development of coronary heart disease (CHD). The study picked up its second generation of participants in 1971 with 5,121 participants known as the Offspring Cohort. Currently the study is recruiting its third generation (Generation III Cohort) for further research; their goal is to get 3,500 adult grandchildren to participate.

So far, the study claims to have identified the major risk factors leading to CHD including high blood pressure, high cholesterol, smoking, and inactivity, as well as identifying a number of related factors such as age, gender, and HDL levels. The fact that this study has been ongoing for so many years should raise a few eyebrows. If cholesterol were the culprit behind heart disease, with a role in atherosclerotic development proportional to the high amounts of negative attention it has received, shouldn't several years of study produce enough data to support the claim? Such a longitudinal study would be expected to definitively show results in support of one side or the other. Regardless of the answers to these questions, the Framingham study has simply not shown that cholesterol is the definitive cause of heart disease; its ongoing nature and identification only of risk factors due to correlations, rather than a causal relationship, immediately marks the study as inconclusive in determining the cause of CHD. If the study was able to find a causal relationship, then we should see that those who lower their cholesterol should definitely have less incidence of CHD. However, the only conclusions that are drawn are merely correlations that when one lowers their cholesterol they might have less incidence of CHD. Despite this, the Framingham study is frequently cited as proof that high cholesterol does cause heart disease.

The World Health Organization (WHO) is also currently engaged in a large-scale heart disease risk factor study known as *Monitoring of trends and determinants in Cardiovascular Disease* (MONICA). Over 100 scientists and doctors in twenty-seven countries throughout North America, Europe, Asia and Australia have studied every risk factor they could possibly think related to coronary mortality, including cholesterol levels. Although the finished results of their study have not yet been published, their data has been available for some time. Figure 4 shows a scatter plot containing the data collected on serum cholesterol levels with respect to coronary

heart disease. Clearly, there is very little correlation between the two parameters, far from enough to conclude causation [14].

The studies that have founded cholesterol research have either been poorly designed (i.e. Antishkow and Keys) or do not support the cholesterol hypothesis (Framingham and MONICA). Antishkow examined herbivorous rabbits rather than some close model to humans, such as some member of the primate family. Keys failed to produce the data from 16 countries where fat consumption information was available, skewing his results. The Framingham study, despite its efforts, has yet to show a strong causal relationship between cholesterol and heart disease, and MONICA has suffered the same problem. The unifying trait is inconclusiveness in humans. Fortunately, there *is* valid information about cholesterol. The following section will examine this.

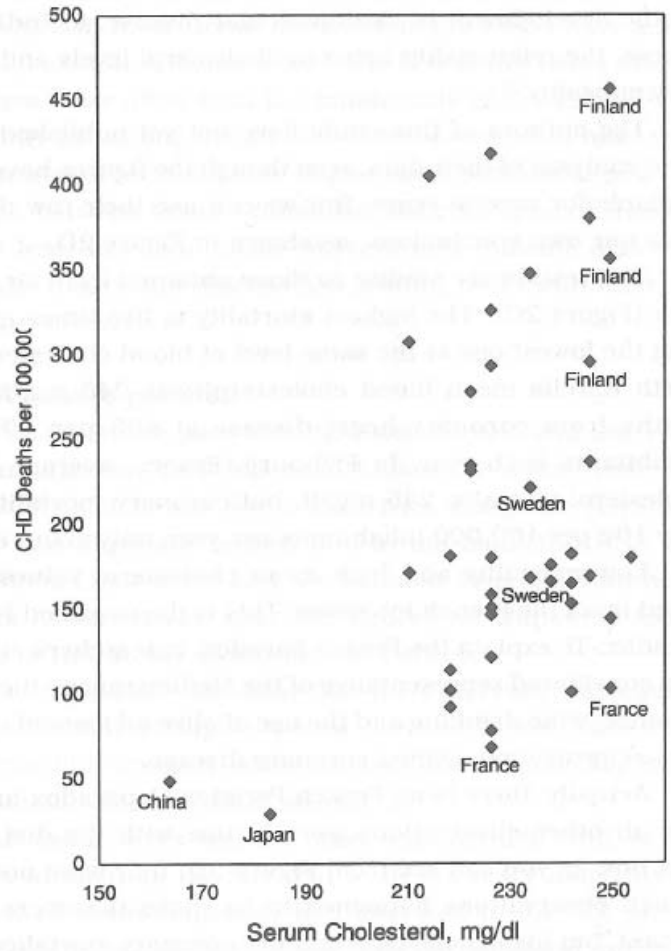

Figure 4- Plot of data from the MONICA study, showing serum cholesterol levels versus coronary heart disease deaths. Note the drastic differences in deaths, often in the same country, at identical levels of cholesterol [2].

What is Known about Cholesterol

Any analysis of the cholesterol-heart hypothesis should include a biochemical background of cholesterol itself. While some conclusions about cholesterol are controversial,

there is much information that *is* widely accepted and confirmed. The following will examine the non-controversial, accepted mechanisms behind cholesterol, as well as more questionable conclusions, and will consider several case studies on cholesterol and the heart.

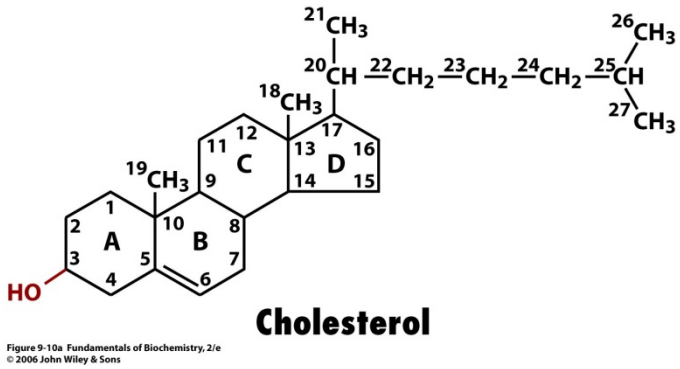

Figure 5- Structure of cholesterol.

Cholesterol (Figure 5) is a major component in animal cell plasma membranes, typically constituting 30-40% of membrane lipids by weight [8]. Without cholesterol, plasma membranes would become less resistant to temperature changes; the molecule gives membranes more durability [8]. Cholesterol's steroid backbone allows it to be used as a precursor to many other important hormones and steroids, such as testosterone [15]. If cholesterol is such a vital compound in the body, shouldn't drastically lowering cholesterol levels affect many other important factors? Wouldn't very low cholesterol, for example, result in decreased steroid production or membrane integrity? In light of this, might having very low cholesterol be a *bad* thing?

In fact, many studies *have* correlated low serum cholesterol levels (< ~185 mg/dL) to increased mortality by various causes, including cancer and suicide [16]. Some of these studies' researchers have concluded that the low cholesterol levels are not responsible for these afflictions, and that the increased moralities are the results of preclinical health problems. The preponderance of studies supporting the detrimental nature of low cholesterol speak for themselves, despite these conclusions. These studies include those conducted by JA Golier (Low serum cholesterol level and attempted suicide) and T Harris (The low cholesterol-mortality

association in a national cohort) which showed increased suicide attempts and overall mortality, respectively, with low cholesterol levels.

Though cholesterol is technically an alcohol (it has a single –OH group), it does not behave hydrophilically like an alcohol. The long hydrocarbon "tail" of cholesterol is hydrophobic, meaning it cannot interact with or dissolve in water. Thus, in order to be transported through blood vessels, cholesterol must be made water-soluble. This is done by aggregating the cholesterol, along with other lipids and fats, and wrapping the spherical aggregate in protein. These proteins hide much of the hydrophobic portions of the lipids, and are themselves soluble in the blood stream. There are many kinds of these "lipoproteins," including the most notorious high density lipoprotein (HDL) and low density lipoprotein (LDL) [8]. Considering this mechanism of cholesterol transport, the popular path by which plaques are thought to form seems counterintuitive. If cholesterol is not soluble in the bloodstream, and is only transported as lipoproteins, how can cholesterol become freed in the arteries and aggregate at specific, predictable locations on arterial walls? [17] If cholesterol *did* become freed in the bloodstream, would it not make sense that it should aggregate at "choke points" in blood vessels, such as capillaries or smaller veins? Furthermore, how is it possible that cholesterol could escape its lipoprotein coat in the bloodstream, when this is normally a process which requires the mediation of enzymes? Referring back to the Antishkow research, if atherosclerotic plaques have been found to protrude outward from within arterial walls, how does serum LDL accumulation explain this? All in all, the popular, proposed mechanism by which cholesterol aggregates on arterial walls seems a bit suspect.

The role of the lipoproteins is fairly straightforward. Cholesterol is synthesized primarily in the liver (though some is produced in reproductive organs and intestines), in very large

quantities compared to the amounts present in food. In fact, the body's own cells synthesize approximately 75% of blood cholesterol [18]. Cholesterol, once synthesized, is packaged into VLDL (very low density lipoprotein) and exported from the liver into the blood stream, where it circulates and is received by cells in need of cholesterol and other lipids. Once degraded of their constituent lipids, etc, VLDL becomes LDL, whose fate is either uptake by the liver to be turned into bile acids, or uptake by extrahepatic tissue (tissues other than the liver). Once utilized by the latter pathway, the lipoproteins return to the liver as HDL, and any remaining cholesterol is converted into bile acids [19].

Though oversimplified, this is the pathway by which cholesterol circulates in the body. The most important concept to keep in mind concerning its validity is that there has been no evidence to disprove it. In any scientific endeavor, a hypothesis is made about something, a model which attempts to describe the way something works or is. Scientists then perform experiments to test this hypothesis, continually trying to *disprove* it, since no hypothesis can ever be ultimately proven. Even the most accepted scientific laws are really only hypotheses which have stood up to test after test, and have not yet been disproved. The aforementioned cholesterol circulatory pathway is a hypothesis, which is strongly supported by X-ray crystallographic studies that have elucidated the structures of lipoproteins [20], and by other studies examining the influx and efflux of cholesterol to and from cells [19].

Another question is surely raised by anyone who has attempted to lower their cholesterol. Health experts continuously advise the public to lower dietary cholesterol intake [21], on the premise that introducing less cholesterol into the body will result in lower overall cholesterol levels, which are of course expected to lower the risk of CHD. If this is the case, why does a change in blood cholesterol levels require so much time to occur? Dietary consequences are seen

relatively quickly. The popular Atkins diet, for example, quickly reduces body weight by removing complex carbohydrates from the diet, forcing the body to burn lipid and fat reserves for energy. The simple dietary changes manifest themselves in a matter of weeks, resulting in drastically reduced body mass. Consider, now, that cholesterol is sequestered with lipids, transported alongside them. Shouldn't a diet deprived of cholesterol show lowered blood cholesterol levels in a matter of weeks, or even months? Despite this logic, it is rarely the case, as hundreds of thousands of Americans spend months to years attempting to lower their cholesterol in vain via cholesterol-free diets.

Of course, people's bodies respond differently to various stimuli. A tribe of Kenyans known as the Masai were studied for cholesterol levels in the early 1960's. What was particularly intriguing about the Masai was that their diets consisted solely of milk, blood and meat [2]. Each day, the average Masai drinks about a half gallon of milk, and on special occasions it's not uncommon to consume up to ten pounds of meat. Despite this, the Masai have never been known to die of heart disease. Furthermore, the Masai were determined to have some of the lowest recorded cholesterol levels in the world, nearly fifty percent lower than the average American's [2].

Researchers tried to attribute this to the Masai peoples' genetically superior ability to regulate their cholesterol. High dietary cholesterol, they said, caused their livers to produce less cholesterol, and vice versa. The same mechanism is present in all humans, but the Masai were supposedly genetically superior in this aspect. However, when moved to the urban setting of Nairobi, a group of 26 Masai men were observed to have cholesterol levels increased by 25 percent compared to their nomadic brethren [2].

If the Masai diet consisted of extremely high levels of cholesterol, and their low blood cholesterol was not attributable to genetic superiority, but their cholesterol levels shot up when

introduced to an urban environment, then what is different about the two settings, urban versus wilderness, that would affect such a cholesterol increase? What is it about the United States that promotes the production of plaques on arterial walls leading to heart disease, if dietary cholesterol and perhaps even high cholesterol are not factors?

It may very well be that the Masai do not naturally die of heart disease; perhaps this is because they die of other causes before reaching an age at which heart disease is a threat. Another possibility, in light of the results of the transition from wilderness to urban setting, is that stress is a major factor. Large, bustling cities are known for people running about their days, and frequently being stressed. This possibility has been raised by many others, who recognize stress' capability to elevate cholesterol levels and blood pressure, and to increase the risk of heart disease [10]. In such a scenario, cholesterol is not the cause of heart disease, but a correlated effect of the common cause, stress. As shall be explained later, a similar effect can be seen in some cholesterol-reducing drugs, where one drug may result in two effects, falsely linking the two in a cause-effect relationship.

Reflecting on this brief scientific history of cholesterol, several key points should be made. First, there has been no conclusive evidence that cholesterol causes heart disease in humans. Although much headway has been made in the research, such as tracking how cholesterol is transported and packaged, and examining correlations between levels of blood cholesterol and incidences of death, no study has shown that cholesterol is the *cause* of heart disease. It is much harder to prove causation than correlation, and while a correlation may exist, both atherosclerotic plaques and CHD may well both be the results of some other cause. Secondly, it is important to note that all current research, beliefs, regulations etc. are the result of these initial cholesterol investigations, insomuch that the "scientific" perspective of cholesterol

may be thought of as the source from which all other opinions and regulations originate. In other words, today's cholesterol regulations, prescriptions and paradigm are (purportedly) based upon scientific research, and as such should be expected to agree closely with the findings therein.

Another important point to discuss is actually a counterpoint. If several cases of patients with very high cholesterol who never develop atherosclerosis are enough to throw the cholesterol-heart hypothesis into question, shouldn't several cases of heavy smokers never developing lung cancer be enough to discard the notion that smoking causes cancer? The answer is no – and the support is in the numbers. Figure 6, courtesy the National Institute of Health, depicts the relationship between cigarettes smoked per person per year and incidence of deaths due to lung cancer. Compare this diagram to Figure 1 in the Introduction, which shows the relationship between average cholesterol intake and deaths due to heart disease. Figure 6 shows a rising number of cigarette consumption by men, followed by a corresponding rise in lung cancer deaths. In Figure 1, while the death rate due to heart disease rises and falls over time, the consumption of cholesterol remains relatively constant. There are exceptions to nearly every rule – assuming there is in fact a rule in the first place. Clearly, smoking cigarettes will very likely result in lung cancer, but this distinction is not so clear with cholesterol and heart disease; the correlation is far too weak to prove causation in the latter case.

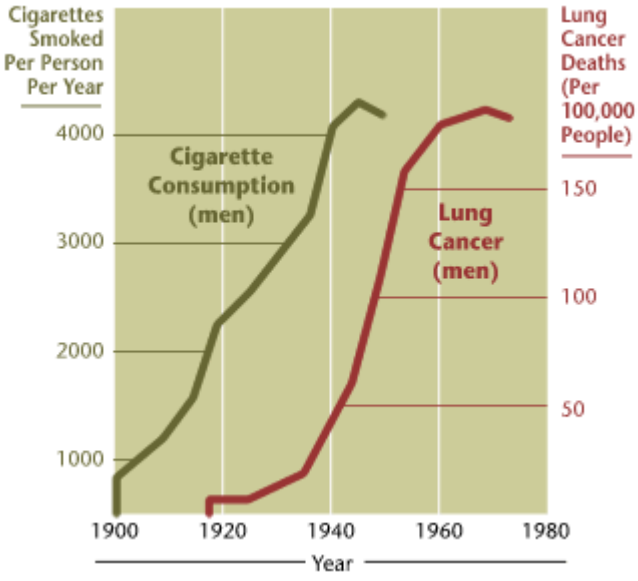

Figure 6-Correlation between cigarette consumption and lung cancer in men from 1900 to 1980.

Regulatory History of Cholesterol

Americans spend millions of tax dollars on government departments and studies for the purpose of determining optimal health recommendations and procedures. Since these are public funds, they should be apportioned to projects with a priority to public health over private or industrial interests. The public institution most relevant to cholesterol and heart health is the Department of Health and Human Services (HHS) which incorporates the National Heart, Lung, and Blood Institute (NHLBI) and the Food and Drug Administration (FDA). The HHS has worked together with the Department of Agriculture to publish Dietary Guidelines for Americans every 5 years since 1980 [21].

The 2005 Dietary Guidelines for Americans is funded by the United States Government and is based on recommendations from the Dietary Guidelines Advisory Committee. This committee is made up of fourteen scientific experts responsible for reviewing and analyzing current nutritional and dietary information, and to create recommendations understandable and applicable to the general population. The Committee served without pay and worked under the regulations of the Federal Advisory Committee Act [21]. All of this validates the recommendations and implies that these guidelines are not biased or influenced by commercial or private interests. This having been said, the recommendations concerning fat consumption put forth by this committee in this publication are as follows: “Consume less than 10 percent of calories from saturated fatty acids and less than 300 mg/day of cholesterol, and keep Trans-fatty acid consumption as low as possible” [21]. While this is an established recommendation, appearing in the Dietary Guidelines for Americans publications since 1995, there is a question as to whether or not the recommended guidelines are known by the general population, and even if so, whether the average American is able to visualize what 300mg/day of cholesterol means. Moreover, there

should be skepticism about the recommendations themselves, considering the fact that no conclusive evidence exists proving the causation of CHD by cholesterol.

The National Heart, Lung, and Blood Institute published a report on the Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults in 2004. This was a second revision of a report published in 1988. It was written by a panel of fourteen experts, eight ex-officio members, and five consultants. Of these, eight members on the panel have reported receiving recent honoraria and/or grants from top pharmaceutical companies, including Pfizer, Merck, and AstraZeneca. This raises questions about how valid the findings are, especially given conflicts of interest of the authors. Would the panel recommend treatments that benefit the drug companies in return for financial and professional security? The report officially sets LDL levels of less than 100 mg/dL as "optimal" and a total cholesterol of less than 200 mg/dL as "desirable" [22]. The report then goes on to recommend drug therapy upon consideration of the number of risk factors as determined by the Framingham Heart Study. The Framingham Heart Study, however, has already been shown to be inconclusive, requiring repeated testing and years of investigation to search for a causal relationship between cholesterol and CHD.

The regulations and recommendations, as expected, *are* based upon scientific studies; it would seem, however, that they aren't based on the true findings of these studies. The effective lobbying of the experts and consultants by pharmaceutical corporations calls the veracity of the recommendations even further into question. Even these simple observations are enough to delineate the regulatory perspective of cholesterol from the purely scientific. Though circumstantial evidence is rarely enough to prove a point, such as that the regulatory standpoint of cholesterol is significantly discrepant from the scientific research standpoint, it is weighted

enough for a closer examination to be worthwhile. Such an examination will be explained in the Methodology section.

Pharmaceutical History of Cholesterol

The 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors, also known as statins, are the most recommended therapy for high serum LDL levels [22]. There is much that is unknown about statins, though, as seen in the FDA's fact sheet for Lipitor, the best selling statin [5]: "The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown" [23]. This is disconcerting, considering the vast number of Americans currently prescribed statins.

Statins work by targeting the liver and inhibiting HMG-CoA reductase (HMGR), the enzyme responsible for converting HMG-CoA into mevalonic acid, a precursor to cholesterol. The statins compete with the normal substrate to bind to the HMGR enzyme's active site, thus preventing access by HMG-CoA. In addition, the flexibility of HMGR lets the statins alter the enzyme's structure, removing its functionality [24].

The cholesterol-heart theory would assume that statins' efficacy in lowering the risk of heart disease is due to the reduction of LDL-cholesterol. Uffe Ravnskov, an independent researcher in the field of cholesterol and heart disease, has done extensive research on this very topic, and would argue otherwise. He has found that statin treatment is effective regardless of cholesterol levels [25]. The risk of CHD is of course increased by many factors, including smoking or stress. Thus, individuals with very low cholesterol suffer heart attacks as well as those with high. Statin treatment lowers this risk in both cases, strongly suggesting that the drug acts to inhibit heart disease by some mechanism independent of HMGR inhibition [25].

Two studies done after the initial Antishkow report, examining the efficacy of statins, were the Bile Bending study and the Helsinki Trial. Neither of these studies showed a decrease in heart disease mortality. They did, however, show an increase in death by other means such as cancer. Six other studies: the Scotland, Air force, ASCOTT, MRFIT, 4S and Lipids Trials showed different results [6].

In the Scotland Trial, participants were men aged from 45 to 64 whose cholesterol was 252 or higher with an average of 272. The study, which ran for five years, was designed to assess the effects the drug Pravachol (Pravastatin – Bristol-Myers Squibb Company) has on patients with high cholesterol. After five years, the death rate from heart disease for the control group was found to be 1.6% while the experimental group was about 1.2%. This 0.4% different was found to be statistically insignificant. The death rate from any cause of death was 9.4% in the control group and 8.6% in the experimental group. Again, this difference was found to be statistically insignificant. In terms of non-fatal heart attacks, 6.2% of the control group had one, compared to 4.3% from the Pravachol group. While this result was found to be statistically significant, it is only a 1.9% difference. This essentially means that in a group of 1000 male Pravachol takers with cholesterols above 252, 19 people that have heart attacks *might* not die. An interesting fact about the study is that by the end of the study, the dropout rate of participants was nearly 30%; losing a third of the test subjects surely has some effect on the results, at the very least making the study's conclusiveness suspect [6].

The Air Force study included 997 postmenopausal women in addition to men whose average cholesterol was 221 and LDL-cholesterol was 150. This study used placebo-controlled testing to look at the effects Zocor (Lovastatin – Merck). After five years and two and a half months, the death rate from heart disease found in the control group was 2.3% while the

experimental group was 2.4%. This result was not statistically significant. The end result reported by the study was that treating 1000 people with a Lovastatin would result in 19 fewer "coronary events" – 12 of which would be heart attacks [6]. Since 19 is 1.9% of 1000, this means the drug reduces coronary events by about 2%; such a reduction could be attributed solely to chance.

One of the largest scale studies ever done was the ASCOTT Trial which studied 19,342 people with hypertension. 10,305 patients with cholesterols lower than 251 were randomly selected and assigned to either Lipitor (Atorvastatin – Pfizer) or a placebo. The study showed no statistically significant reduction of all cause deaths or cardiovascular deaths. However, Atorvastatins are used to reduce cholesterol, so why did the study start by selecting individuals with high cholesterol? The end result of the study: "the drug helped a bit" [6].

MRFIT (Multiple Risk Factor Intervention Trial), another large scale study, recruited 12,866 men between the ages of 25 and 57 that were deemed to be "high risk men". These men were randomly divided into two groups: experimental vs. control. The experimental group set out to reduce the commonly accepted risk factors such as smoking, high fat diets, high blood pressure, etc. The control group ate an average American diet and received general routine medical care. At the end of this seven-year study, the results were not in favor of cholesterol theory supporters. The heart attack death rate in the control group was slightly lower than that of the experimental group and the overall death rates for the experimental group went up due to increased cancer deaths. Only the best results were publicized. This study cost American tax payers $150,000,000 [7].

The Scandinavian Simvastatin Survival Study (4S) selected 4444 patients with angina pectoris (chronic chest pain), prior MI, and high cholesterol. The 5.4 year double-blind study was

testing the effects of simvastatins on mortality in patients with Coronary Artery Disease (CAD). The results showed that there was a 3.3% reduction in death with the experimental group. This means that 159 people have to be treated with the drug for one year in order to prevent *just one* person from having a "cardiac event" [11].

Continuing, the Lipids Research Clinics Study selected "high risk" men with cholesterols higher than 95% of the population. The purpose of the study was to examine the effects of Questran (Cholestryramine - Bristol-Myers Squibb). The participants of the study were again divided into two separate groups. This time, *both* groups went on a low fat diet as published by the American Heart Association, and one group took the drug while the other did not. The end result was that there was 19% less heart disease-related deaths in the experimental group than the control group. From data collected by researchers it was calculated that for every 1% drop in blood cholesterol, one could lower their risk of heart attack by 2% [11]. However, this is slightly misleading, as anyone who lowered their cholesterol from 400 to 200 (a 50% drop), would reduce their risk of heart attack by 100%, clearly a statistical impossibility. On top of that, someone that lowered their cholesterol by 400 to 360 (10%) would probably benefit more than someone that lowered their cholesterol from 200 to 180 (10%). Also, while the heart related death rates may have shown a decrease in the experimental group, the study did not report the overall death rates. When considering the overall death rates between the two groups, there was no improvement with the experimental group [11].

According to the National Heart, Lungs, and Blood Institute, statin drugs have dramatic effects, including lowering LDL levels by 18-55%, raising HDL levels by 5-15%, and lowering triglyceride levels by 7-30%. These numbers seem quite impressive, though as seen in the table

provided in Appendix A [26], other drug therapies show promising results with differing side effects.

A very recent study, however, has shown that the popular drug Zetia, produced by the pharmaceutical company Merck, has no benefit in preventing heart disease [27]. Patients examined in the trial took a combination of Zetia and Zocor in the form of Vytorin, and after two years of studies Merck has declared that not only is the drug ineffective in preventing atherosclerotic plaques, its intended purpose, but the plaques actually grew almost twice as fast in patients taking Zetia along with Zocor than in those taking Zocor alone. Even more shocking is this: Zetia *has* been shown to reduce cholesterol in most patients by 15-20%. If some drugs reduce cholesterol without reducing the incidence of CHD, how can cholesterol be framed as the culprit behind heart disease? This study also supports the aforementioned hypothesis that some statins may reduce heart disease incidence by a mechanism independent of HMGR inhibition. Such a correlation without causation has been seen before, in the case of stress independently causing both elevated cholesterol and heart disease incidence.

Who is Teaching the Doctors?

It is important to consider what resources doctors use to form their opinions on whether and what kind of medications they should prescribe to patients. The truth is that the pharmaceutical companies themselves provide a lot of the research materials doctors use to determine the effectiveness of various drugs.

In a survey among 3167 physicians, “A National Survey of Physician-Industry Relationships,” 28% of respondents indicated that they have received payments from pharmaceutical companies for consultation, lecturing, or enrolling patients in trials [28]. Drug companies often hire out doctors to act as representatives, paying them to give lectures at

different practices, often over lunch, about some kind of medication. There are about 200,000 physicians being paid by the pharmaceutical industry to promote their drugs. Dr. Daniel Carlat described his experience as a drug rep in a New York Times article [29]. Recruited doctors were sent to stay at lavish accommodations and were provided with dinner invitations and tickets for various forms of entertainment. They attended a conference where representatives of the pharmaceutical company provided details about research that had been done on the medication in question, and gave the physicians all the information they needed for teaching other doctors about the drug. Doctors were expected to use the research statistics and special slides provided to them; Dr. Carlat and all the other physicians hired to represent the company were valued not for their medical opinions, but for their perceived authority as doctors to determine what is good for our health.

Of those who participated in the National Survey of Physician-Industry Relationships, 94% reported that they had a relationship with pharmaceutical companies, mostly involving the receipt of food at work (83%) or drug samples (78%). Recommendations made by the American Medical Association and laws passed in some states attempt to regulate the amount of incentives provided to practices by the drug companies. However, an analysis of the reports on expenditures of pharmaceutical companies showed that the regulations are not working [30]. In Vermont, data collected by the attorney general indicates that between 2002 and 2004 drug companies spent $5.6 million on health care professionals. However, it's difficult to tell what the money was actually spent on, as information on $3.4 million of that amount was classified as trade secrets. Of payments that were listed, most were more than $100, the maximum recommended by the AMA. A lot of money went towards food for the doctors, which does not benefit the patients, another suggestion in the AMA guidelines.

Most states require certain amount of Continuing Medical Education (CME) credit hours for doctors to maintain their license. To obtain the necessary amount, physicians attend conferences and courses where the latest medical information is discussed. Over the past decade, contributions from the drug companies have been increasing. Currently, half of all CME courses are paid for by pharmaceutical companies. “Medical Education Communication Companies” are hired to create course work and find doctors to deliver the content. By sponsoring these CME courses, and charging no fee to attend, the pharmaceutical companies themselves are providing the research content for a large portion of doctors in the U.S. [31].

Lobbying

The business of statin marketing and sales is quite profitable. Lipitor brought in $12,886,000,000 in revenue for Pfizer in 2006, up from $10,862,000 in 2004 [32] and is the number one selling drug in the world [5]. The number two drug, Zocor, is also a statin drug aimed at lowering LDL cholesterol. Zocor brought in $2,803,000,000 in revenue for Merck Pharmaceuticals in 2006 [33]. With billions of dollars of revenue at stake, the pharmaceutical companies with statin drugs have a vested interest in ensuring that LDL cholesterol and statin drugs stay within the public’s knowledge base.

The pharmaceutical companies have a lot of political power. As of 2005, the industry had spent over $800 million in campaign donations and lobbying at federal and state levels during a 7 year stretch, and they continue to spend millions more each year. The large revenues of drug companies give them the ability to influence politics on a large scale. Their lobbying operation is the largest in the country, with Pfizer at the very top [34]. The producers of Lipitor spent $7.2 million to lobby the federal government in the first half of 2007 alone, persuading lawmakers in such issues as allowing easier access to less expensive generic drugs, and reducing patent

infringement lawsuits [35]. Lobbying over the years has allowed the pharmaceutical industry to get their way in legislation on price controls, patent regulations, tax breaks, freedoms in advertisement, and various other laws that would have cost the drug companies [36].

Research Questions

Looking back on the information disclosed herein, it is more than clear that there is a deviation in the view of cholesterol between pharmaceutical companies and the initial research on cholesterol. As described, even the pharmaceutical companies' own studies of various statins showed little to no improvement in death rates and coronary incidents; despite this they continue marketing their drugs under the premise that lowering cholesterol will reduce the risk of heart disease. The deeper issue at hand is that the general population, those not engaged in cholesterol studies or statin sales, must either rely on the advice of regulatory officials or educate themselves on the topic – a daunting task, as much of the information necessary to do so is difficult to gather, and even more challenging to interpret. Thus doctors, particularly primary care physicians, who are the point of interaction between the populous and the medical community, are particularly pivotal in swaying public opinion on the cholesterol-heart hypothesis. Doctors who frequently prescribe cholesterol-lowering drugs to patients with high risk of heart disease will affirm that cholesterol is the culprit behind CHD by doing so.

Furthermore, doctors and regulatory officials must back their decisions with the results of studies done by members of the scientific community. It is therefore important to know what members of the scientific community have to say concerning the cholesterol-heart hypothesis, regardless of their direct involvement, or lack thereof, in such studies. This all boils down to several key questions which will address the validity of the cholesterol-heart hypothesis, especially as it pertains to the interests of the general public: What do doctors and scientists

actually believe about the cholesterol-heart theory? Why do doctors prescribe statins and other cholesterol-lowering drugs? What do scientists have to say concerning the validity of the studies done on cholesterol?

Methodology

The three questions concluding the Literature Review were carefully selected as the target questions this methodology aims to answer. Addressing these questions aided in tackling broader questions concerning the general validity of the cholesterol-heart theory.

In the pursuit of answering these questions, the research group concluded that directly interviewing doctors and biochemists was the best course of action. Interviews were used to gather specific perspectives of several representatives of a larger demographic. Responses were analyzed and compared, and evaluated into conclusions concerning the differentiation of the perceptions of cholesterol.

While surveys would have allowed the group to obtain a broad scope of information from a larger group of demographics, including the general public, this very same information should be obtainable from the people in the medical field, since doctors are frequently the lay man's primary source of information on such matters. Furthermore, the obtainable information from a survey is largely dependent on the response rate of a very specific target audience. In addition, in the time it would take to send out and then collect a sufficient amount of data from surveys, a good deal more interviews could have been accomplished. Given the timeframe and resources, and considering the possibility of a low response rate, attempting to administer, collect, and analyze surveys would be unrealistic for the purposes of this project – it would only be possible to obtain a few surveys from a limited geographical area, which would neither be representative of the entire population, nor allow for elaborative responses to the desired questions. Based on this information, it was decided that much more useful information will be obtained by focusing our attention on completing and analyzing interviews.

It should be mentioned that in addition to the demographics that were actually interviewed, two other target audiences were considered: medical school students and “high-risk” 45-65 year old men and women. However, while these two groups could have useful information on possible questions such as “what does the general population actually believe about cholesterol?” or questions concerning public opinion of statin regiments versus lifestyle changes, both the medical and biochemical experts will be able to represent these two demographics, since, as stated above, the general public by and large believes and trusts what scientists and their doctors advise.

Interviews

Interviews targeted those whose knowledge of cholesterol and statins was anticipated to be more comprehensive than that of the average person. Primary care physicians, cardiologists, biologists and biochemists were sought for interviews. Emphasis was put on these specific demographics, with exclusion of the general public, for several reasons. Primarily, it would be difficult and time consuming to administer surveys to these groups of people, as they are relatively uncommon peoples and distribution and collection of the surveys would pose a formidable challenge. Direct interviews with representatives of the demographics proved to be simpler and more efficient, and were anticipated to be as informative as, if not more than, surveys. Furthermore, the types of questions asked during interviews were likely to be beyond the comprehension of much of the general public (e.g. what are the known side effects of statins?); public opinions are assumed to be similar to those of doctors, as shown by the flow of information in Figure 8 in the Analysis section. The diagram relates to Sawyer’s model of nested audiences, which is described further in that section.

The details of our interview process will be described in the following sections.

Sampling

As it would be impossible to interview the entire population of experts in the field of cholesterol, the researchers collected data from a subset of individuals that would represent the whole of information; this is called sampling. There are two broad forms of sampling: probability sampling and nonprobability sampling. In probability sampling, every demographic (age, gender, race, etc) of the population has an equal chance of being part of the sample. In nonprobability sampling, demographics are chosen based on their availability, ability to represent a demographic, or expertise. One side effect of a nonprobability sample is that an unknown amount of the population is not included. The effect of this is that the extent to which the sample actually does represent the whole cannot be known. [37]

In this case, a probability sample was not necessary. The research group required very specific knowledge that the general population would not be privy to, so two large demographics were chosen to be representative experts on the subject: physicians and scientists. While this means that a large amount of the population will not be represented in the sample, much more valuable information was obtained about the mechanism of cholesterol, for example, from doctors than from the randomly selected person.

In addition, we must consider exactly how many people were interviewed: this is called the sample size. As one might expect, the larger the sample size, the more representative of the general population the responses become. Herek, in his article on sampling, suggests that that any sample less than 1000 respondents, will have a larger margin of error, and thus becomes less and less representative as the number of respondents decreases. For our purposes, however, we were not looking for a large enough respondent population to be representative of the entire population. We were merely trying to scratch the surface to see what some of these two

demographics believe about the cholesterol-heart theory. On top of that, the research group was significantly limited in the amount of time available and the amount of people the group was able to contact in that amount of time.

The response rates of people contacted must be taken into consideration as well. In an ideal situation, 100% of all the people we contacted would happily interview with us and we would have an outstanding response rate. However, as can be expected, many people declined an interview for one reason or another: they were sick, busy, do not know enough, etc. Because of this, we contacted additional people than our desired number of respondents in order to make up for a non-ideal response rate.

In order to obtain some information from the two demographics of scientists and doctors in the short amount of time available to do these interviews, the research group decided to attempt to conduct six interviews from both of the demographics. Given the small number of interviews planned, one can hardly say that our results are representative of the respective communities, but they were enough to scratch the surface of the information we are actually trying to find. Were the study more longitudinal, it would have been more realistic to aim for a larger sample size. However, considering our limited time and resources, the goal was not to attain a theoretical saturation but rather to gain a general idea of some views and opinions held by various members of key communities in cholesterol research and treatment.

To set up the interviews, the research group originally planned to use email as a primary contact for scientists who teach at our college and phone calls to set up interviews with doctors. However, when contacting the doctors, receptionists suggested that faxes would be much more efficient, and so a coversheet was written up and used as a new means of contacting doctors. One problem was that while WPI professors are well aware of the WPI time frame, primary care

physicians and cardiologists are very busy people and were not privy to how quickly time goes by at WPI.

The two demographics of doctors and scientists were selected based on the Literature Review, where these two demographics were recognized as pivotal in the dissemination of information about cholesterol and heart disease. Thus, biologists and biochemists are representative of the scientific perspective while primary care physicians and cardiologists will represent the medical community.

Structure

The structure of each of the interviews was nearly identical, with particular tailoring to the demographic of which the interviewee is representative. The logic behind this is straightforward: since the problem this report intends to address is one of discrepancies of perception, those perceptions must all be subject to the same baseline analysis. As with any scientific investigation, there must be variables and constants, tests and controls. In this particular scenario, the anticipated diverse perceptions about cholesterol were the variables, and the interviews the controls or constants. Different responses to the same questions allowed for analysis as to the actual differences of opinion and perception. The “baseline” questions presented in all of the interviews can be found in Appendix B.

Interview Protocol

The preferred method of interviews was face-to-face as opposed to video or phone conversations. In this way, the research group was able to be on a more personal level with the representative and potentially tailor specific questions accordingly. Additionally, it allowed the interviewers to witness the interviewees’ reactions, body language, and emotional state when questions are asked. On top of this, the interviewers abided by a professional dress code. The

specific dress code to be adhered to is defined by Donald K. Burleson in the article Professional Dress Code [38]. The purpose for the dress code was to emanate the group's professional manor and serious attitude toward this project; it was imperative that the people being interviewed considered the group as confident individuals. The research group also wanted to ensure that the interviewees were comfortable, and that they did not feel pressured to answer questions in a way they do not agree with. Thus the interviewees were offered the choice of skipping questions they did not wish to answer, and the option of keeping their identity confidential if they wished to remain anonymous.

Transcription

Interviews were recorded using digital audio recorders. This allowed the research group to review responses given by the person interviewed, and transcribe the conversation for further analysis. Transcription of interviews began as soon as the first interview was completed, and was compiled when the last interview was finished. Transcription was done by listening to each interview, kept electronically. Transcription of the interviews allowed the group to go back and analyze a specific interview, quote certain answers, and compare multiple interviews with one another. In doing so the research group expected to find trends within each demographic, and between demographics. By understanding the differences and similarities between these demographics, the research group hoped to gain insight as to where exactly the confusions in perceptions lie, and what the causes of disagreement between the scientists, pharmaceutical corporations, regulators, and public are. The transcripts of each interview can be found in Appendix C.

Analysis Protocol

After transcribing and collecting all of the interviews, analyses must be done qualitatively. In dealing with qualitative data, rather than quantitative, comparisons must be made as analysis. The questions have been formulated such that many cross-comparisons could be made between the responses both with regards to a single interview question as well as across multiple questions. The research group used methods of condensation, categorization, and interpretation of interview responses in order to determine their meaning, as described by Steinar Kval [39]. Responses given for each question were condensed to their central themes. This allowed for the categorization of responses based on whether they were "negative," "positive," or "neutral." This categorization provided a way to look for trends among the different demographics, and a way to compare answers between individuals and demographics and interpret their meanings.

The process of analysis was a tedious one but based on clustering, pattern matching, counting, making contrasts and comparisons, and building a chain of events, as suggested by Matthew Miles [40]. Responses to our interview questions were placed in groups such that the answers to all questions in a given group could be interpreted to have a single meaning. We looked for patterns in the responses provided, counted specific types of answers to given questions, and contrasted and compared responses between individuals and paradigms to find trends in the various interviewees, and locate differences in perception. We hoped to be able to build a chain of events, or construct a narrative meaning as Kvale describes it, in order to see if the flow of information between paradigms is consistent, or if not, where it was broken. The following paragraphs will detail what type of data we collected from each interview question, how we planned to interpret that data, and what conclusions we expected to draw from them, but

we also prepared to analyze the responses in ways that were not obvious prior to having given the interviews.

Questions one and two – “Do you know your own cholesterol levels?” and “Are you concerned about your cholesterol?” – were meant to gauge how important being aware of, and keeping control of cholesterol was to each demographic. We counted the number of “yes” and “no” responses for each demographic. More positive responses to these questions reaffirm the widespread belief that cholesterol plays an important role in healthcare, while negative responses indicate a demographic is not particularly concerned with cholesterol. A negative response to the first question coupled with a positive response to the second question indicated that the interviewee simply had not had the opportunity to have their cholesterol levels diagnosed. Positive responses to the first question coupled with negative responses to the second questions indicated that either the subject is not concerned about their health, or they do not believe cholesterol is a factor in developing heart disease. The answer to question twelve – “What do you believe about cholesterol as it pertains to heart disease?” –confirmed which one.

Questions three, four, five, and six served to reveal how much knowledge of the processes of the heart and cholesterol each demographic had, and what their theories on the matter were. The answers to questions three and five – “Do you know how atherosclerotic plaques accumulate?” and “How much cholesterol does the body/liver produce?” – gave insight into how reliable each interviewee’s ideas about heart disease and cholesterol are. Responses to these questions were divided into “knows,” “does not know,” and “some knowledge” categories. More incorrect or ‘pass’ responses among a demographic indicated a lack of fundamental knowledge about CHD and cholesterol. The research group also condensed each response to more concise explanations when possible, and saw how well they agreed within and between

demographics. The answers to questions four and six – “Why do plaques only form in arteries?” and “What effect (if any) does dietary cholesterol have on this [the cholesterol that is produced by the liver/body]?” –revealed where the theories of each demographic lie. The responses to these questions were categorized the same way as with questions three and five. Answers between demographics that were similar pointed to agreement, possibly that one relied on the other for the information, or they relied on a similar source. Different answers started to reveal some stratification in perceptions. Different answers could indicate that current research and information on cholesterol and its role in CHD is not reliable enough.

Question seven – “Do doctors or medical institutions benefit in any way from prescribing statin drugs, or a particular statin? If so, what kinds of benefits?” –revealed awareness of incentives for doctors to prescribe statins to lower cholesterol. Responses to this question were condensed and compared to determine how much doctors are affected by incentives in their prescription habits. It could reveal beliefs among demographics that doctors are manipulated into prescribing statins, and thus showed criticism of their endorsement of them.

The answers to question eight – “Is there any incentive for doctors to offer suggestions for lowering heart disease risk other than prescription meds?” –revealed awareness of any reasons doctors would suggest lifestyle changes over statins for lowering cholesterol/risk of CHD. We counted the number of “yes” and “no” responses to this question, and also kept track of what incentives interviewees suggested may exist. Negative response to this question solidify the idea that prescription medication is the best way to lower risk of heart disease, but additional comments made by the interviewee revealed beliefs about what actions should be taken to lower the risk. This question was especially significant for doctors, as it could reveal what they actually do or believe.

Question nine – “What is a doctor’s response to a patient who refuses to take drugs when prescribed?” – was asked only to doctors. Specifically, the research group asked each doctor what their personal actions would be. This question acted as a follow-up to question eight, revealing if doctors believe in any alternatives to prescription medication.

Questions ten and eleven – “Do you know and understand the mechanism by which statins work?” and “Are you aware of the side effects of cholesterol lowering prescription drugs?” –revealed how well the members of each demographic understood what statins actually do. We again divided responses to these questions into “knows,” “doesn’t know,” and “some knowledge.” Positive/negative answers indicated how important it was to understand how statins work: is it as simple as “they work so they are prescribed” or are there better alternatives? If the interviewees provided more details, we were able to compare their answers to see how much they agree.

Questions twelve and thirteen – “What do you believe about cholesterol as it pertains to heart disease?” and “Are you aware of studies which seemingly disprove the cholesterol-heart hypothesis? If so, what do you have to say about them?” –revealed what demographics believed about cholesterol and its role in CHD. Responses to question twelve were divided into “does believe” and “doesn’t believe” that cholesterol is a key factor in the development of heart disease. Different answers showed stratification between perceptions of cholesterol as it relates to heart disease. Question thirteen also revealed how popular the studies aimed at disproving the cholesterol theory are. The research group counted the number of “yes” and “no” responses to this question, and compared specific answers. Negative responses indicated that interviewees had no notion of the possibility that cholesterol is not a cause of heart disease. It was also suspected that some respondents would be aware of these studies, but would not believe their results,

indicating they are set in their ways, and do not wish to consider alternatives causes of CHD, probably because they are convinced CHD is caused by cholesterol. This could be interpreted as a source of perpetuation of the cholesterol theory.

The answers to question fourteen – “What most influenced your opinions or conclusions about cholesterol and the heart?” –helped find sources of perpetuation of the cholesterol hypothesis. Similar answers among different demographics indicated popular sources of cholesterol information, and could thus be considered causes of perpetuation of the theory.

In the end, the conclusions we extracted aim to answer larger questions about how rooted in science current beliefs about cholesterol are, and the legitimacy of the cholesterol-heart hypothesis. The data gathered therein will be compared to the hard scientific research conducted on the subject, clarifying which positions are the results of unbiased, unconcealed scientific study, and which are based on less reliable grounds, ultimately casting cholesterol in a reliable light, and providing an anchor from which conclusions about the causation of heart disease can be made.

Analysis

Responses to the interviews were initially analyzed altogether, alongside one another, according to question. Observations and general logical conclusions were made within each question regarding the goals of the project: to assess cholesterol's role in heart disease, examine what doctors and scientists have to say about the topic, and address doctors' motives for prescribing statins. Deeper conclusions were then made based on the initial analysis; quotes and contradictions were scrutinized more closely and examined for meaning, and connections were made to the Literature Review. The nature of the demographics was also considered, insomuch as the differences and similarities in the way doctors and scientists speak, their range of knowledge, and their beliefs about cholesterol and heart disease. Thus, the first section lays down general conclusions and attempts to quantify the data by reducing complex answers to digital "positive" or "negative" responses. In the more focused second section, certain data is looked at more closely, with higher regard for content and meaning, and is logically tied to prior research done by the group. Finally, the demographics themselves will be analyzed as mentioned, in attempt to paint a final picture of the cholesterol hypothesis in the Conclusion section.

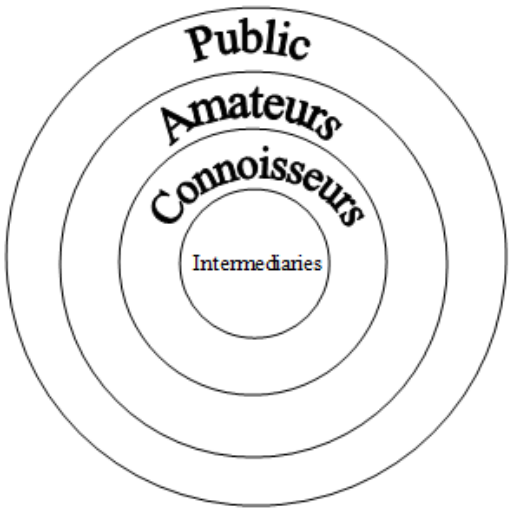

Figure 7- Sawyer's model of nested audiences

At least one social model was theorized by the research group to appear, prior to analysis. The hypothesis was that doctors, being less involved with frontier research and more with diagnosis and treatment based upon this research, would rely largely upon scientists for the reasoning behind their decisions and prescriptions. This model is based upon the model proposed by Keith Sawyer [41], in which

specialization and expertise in an area is held by a few individuals, while many more "connoisseurs" and "amateurs" exist. While information flows outward from the intermediaries to the public, it becomes less specialized and more generalized. Analogous to Figure 7 produced by Sawyer, it is theorized that such a scenario in the cholesterol field would place scientists at the center of the diagram, doctors encircling scientists, and the public comprising the corona and being the largest demographic.

Scratching the Surface

The first two questions asked in the interviews related to the interviewee's awareness of his or her own cholesterol levels and his or her concern over maintaining or obtaining lower cholesterol levels. There were many positive responses to these questions: each person interviewed responded that they have known their cholesterol levels at some point in the past few years, and all but one subject, a biochemist, were dedicated to keeping or obtaining low cholesterol. The biochemist, however, may have misinterpreted the question to mean "are you currently concerned with lowering your cholesterol?" He responded to question one with an exact cholesterol level, one generally considered to be below suggested levels. These responses reaffirm our belief that knowledge of cholesterol levels has an active role in healthcare and suggests that scientists and medical professionals see this knowledge as necessary and important for maintaining health.

Question three helped us to determine what level of specific knowledge scientists and biochemists have about cholesterol and atherosclerosis. All but one subject, a doctor, told us they know how atherosclerotic plaques accumulate. Two of the scientists and one of the doctors mentioned that they believed inflammation plays a role in this process, indicating an agreement of information between the two demographics. Furthermore, these individuals were able to

elaborate on the subject, giving rough mechanisms by which the inflammation could lead to atherosclerosis. They described a scenario in which cells beneath the endothelium, usually macrophages, take up vascular cholesterol from LDL and form foam cells, resulting in an inflammatory response, and leading to atherosclerosis. The fact that doctors and scientists were in agreement on this topic suggests that either both demographics got their information from similar sources, or that one relies on the other for information, presumably doctors upon scientists.

Question four asked interviewees to explain why atherosclerosis only occurred in the arteries, as opposed to other areas in the body. While two doctors and one biochemist simply weren't sure, the rest of the subjects gave a variety of responses. On the biochemists' side, it was claimed that nobody knows this information, that it's due to positive feedback in blood flow, or that it's because most LDL cholesterol travels to the arteries. One doctor claimed that the structure of the arterial walls, as well as the particular composition of the serum in the arterial side of the circulatory, allows for atherosclerotic plaque formation. There is obviously quite a bit of disagreement about this matter, possibly indicating that more definitive research is needed in this area.

For question five, we asked interviewees to approximate how much cholesterol the body produces internally in a given day. Only one person, a biochemist, was able to give us a definite answer: about 1000 mg/day on average. A few doctors suggested that the amount varies from person to person depending on their circumstances. The lack of details in the responses we received implies that the amount of cholesterol produced by the liver is not considered to be an important factor; and indeed in cases of familial hypercholesterolemia, it is not excess production

of cholesterol that is the problem, but a lack of receptors to remove cholesterol from the bloodstream.

We received an interesting set of responses for question six, “What effect (if any) does dietary cholesterol have on the amount of cholesterol the body/liver produce?” However, the question may have been misinterpreted by most of those interviewed. While most interviewees argued that the amount of cholesterol consumed was the most important factor in determining overall cholesterol levels in the body, very few answered in regards to the body’s response to dietary cholesterol. One biochemist argued that the type of cholesterol consumed was one of the more important factors affecting total serum cholesterol and development of atherosclerotic plaques, saying, “One of the biggest things that happens when [cholesterol is] oxidized or damaged is that you get uptake of damaged cholesterol into extracellular space around cells in your tissues.” If cholesterol is going into the extracellular space, he says, it’s not being absorbed by the cells and is contributing to serum cholesterol levels and atherosclerosis. In short, normal cholesterol (not oxidized) will traverse the bloodstream without incident and is generally not malignant, while oxidized cholesterol is prone to coagulation and will contribute to the formation of plaques. The fact that none of those interviewed answered the question as we’d expected, and rather spoke on dietary cholesterol as it pertains to atherosclerosis formation and total serum cholesterol suggests that these individuals are more concerned with atherosclerotic plaque formation than with the effects of dietary cholesterol on liver-produced cholesterol.

Concerning question number seven, most of those interviewed believe that there are kickbacks from pharmaceutical companies for doctors who prescribe their products. The Chief of Cardiovascular Medicine at UMASS Medical Center agreed that there are ways in which a doctor may benefit from prescribing drugs, though none of them are nefarious. Doctors clearly

benefit in aiding the patient and contributing to the patient's good health, but they may also gain some monetary benefit through capitated healthcare plans, in which an insurance company covers the expenses of a group of doctors up to a specified amount. If the doctors are able to treat their patients using less than that amount, they get to keep the difference. If, however, the costs of treatment are more than the insured amount, the doctors are responsible for coming up with the rest. In such a scenario, it may actually benefit the doctors to *not* prescribe expensive name-brand stains, and rather suggest lifestyle changes to patients first.

Though the majority are in agreement that there are kickbacks and compensations for some doctors and medical institutions, all the doctors avowed that they themselves had not received such benefits. "I'm not going to give out a prescription just because I got a good pen from a pharmaceutical company or because they took me out for dinner; I'm going to give whatever my patient would benefit most from," was one doctor's response. Another doctor noted that the establishment at which he works has recently restricted doctors and medical staff from receiving any kinds of benefits from pharmaceutical companies whatsoever, including dinners, free samples, and even pens.

Doctors appear to suggest lifestyle changes first to combat high cholesterol levels, and are generally reluctant to prescribe statins unless the patient presents with extremely high levels of cholesterol. However, the treatment, ultimately and after lifestyle changes, is a statin regiment. Doctors save the prescription drugs as a last effort. This is not always easy, however, as doctors are frequently pressured by patients to write prescriptions. Though doctors may delay prescribing statins until deemed necessary, in many cases it seems to be inevitable. Based on the assumption that high cholesterol levels represent an increased risk of poor health, statins are prescribed out

of concern for the patient. They are an effective means of lowering cholesterol and heart disease. This tendency will be explored in more depth later in the analysis.

Interestingly, none of those interviewed gave any account of legal or insurance ramifications in response. It was expected that a patient who contradicts a doctor's suggestions may pose a liability to the doctor. For example, a patient who refuses to take a statin then suffers a heart attack may feel inclined to blame the doctor for not pushing the statin. Based on the responses, it would seem that patients hold a great deal of power in deciding their own medical fate, if only they choose to exercise it.

The suggestions of doctors should not always be shrugged off, however. As mentioned earlier, many patients immediately seek the aid of statins in reducing their cholesterol before making necessary lifestyle changes – many of which reduce the risk of heart disease independent of cholesterol-level changes, such as quitting smoking.

Question ten asked about the mechanism by which statins actually work. Three biochemists and three doctors understood this mechanism, though only one doctor was able to provide a detailed explanation. The three biochemists and two of the doctors spoke of HMG-CoA Reductase, an enzyme responsible for the rate limiting step in cholesterol synthesis by the liver, which statins inhibit. The explanation is in accordance with primary source studies cited in the Literature Review. The scientists were able to give much more detailed responses compared to the doctors. The higher level of knowledge on this matter among the biochemists compared to the doctors indicates that the scientists are researching the drug, and doctors trust the scientists when they say that the statins will work, in line with Sawyer's social model.

Question eleven asked subjects about their awareness of the side effects of taking statins. Four doctors and one biochemist were able to explain what these side effects are. Those four

doctors prescribe statins to their patients, and the biochemist takes statins himself. They all mentioned varying degrees of muscle atrophy as one of the most common and dangerous side effects. This implies that doctors are making an effort to understand the dangers involved in taking statins, and relaying this information to their patients, rather than immediately pushing drug therapy onto uneducated patients without considering the health risks, while biochemists are more concerned with the actual mechanisms of statins and their effectiveness.

When asked what interviewees believe about cholesterol's relationship to heart disease, a wide range of answers were received. One doctor claimed that "...the data linking LDL cholesterol to heart disease in my opinion is incontrovertible and undeniable.", while another doctor simply stated that cholesterol is a bigger problem for some people and not such a big deal for others, it depends on each individual person. A biochemist, on the other hand, stated that cholesterol is not the direct cause of heart disease, but merely "a guilty bystander to the formation of plaques." Another biochemist argued that it is not just *cholesterol* that is the issue, but the *state* that the cholesterol is in when it enters your body, whether it is oxidized or not.

From this we can see that there is still no real consensus on what is the true direct cause of heart disease. There does seem to be a consensus that hypercholesterolemia depends a lot on each individual person and how they metabolize cholesterol, as well as the fact that if cholesterol does directly relate to heart disease, it is because of LDL cholesterol specifically. That said, it is clear that there is a belief that cholesterol is at least somewhat contributory to heart disease, but this causal relationship has yet to be firmly scientifically proven.

Question thirteen asks simply whether the interviewee is aware of studies claiming to disprove the cholesterol-heart hypothesis. Most of those people interviewed claim that they haven't heard this side of the story. Of those who have heard of studies refuting the hypothesis,

one biochemist says that “it is typical of any complex biological issue” to receive dissidents on both sides, while another biochemist sates that “most of [the studies] are not scientifically sound.” One doctor said that he is aware of people who don’t believe LDL cholesterol is a factor in heart disease, but that he disagrees with them. Interestingly, the two biochemists who were aware of these studies did not dismiss them completely; instead, they suggested that studies for and against cholesterol are both correct in some way, saying that while lowering cholesterol is beneficial for some, they believe that there are others who will not see significant results from lowering their cholesterol. So it would seem that scientists are researching these studies, and considering their implications. However, with respect to the responses to question ten indicating that doctors are not as aware of the actual mechanism by which statins work, but rather take the word of the scientists that they do, it appears as though doctors do not have much knowledge on studies that claim cholesterol is not a cause of heart disease because the studies have not had a large enough impact on scientists, and thus the information has not been relayed to the doctors, a characteristic indicative of Sawyer’s model.

Question fourteen inquired as to the source of information about cholesterol upon which each interviewee relies. It is interesting to note the occurrence of not only primary sources, but secondary sources and personal relationships. One biochemist responded that his opinions were largely influenced by his brother and uncle, both of whom are doctors. Conversely, another biochemist draws his conclusions from medical journals because he feels that since he has the background to understand the peer-reviewed research studies, he ought to rely on them. Other respondents indicated that they depend on alternative primary source material such as personal medical experiences. This could indicate that those interviewed form their own decisions from primary sources and are more likely to stand by their convictions.

Digging Deeper

In this section we plan to compare and contrast answers given to each of our interview questions; certain topics will be analyzed for similarities and differences between each member of the scientific community, the medical community, and between the two communities themselves. We will also bring in outside theories to rationalize the responses, including Sawyer's model of nested audiences[41] and Kuhn's Structure of Scientific Revolutions[42].

One of the most striking contradictions among those interviewed was brought forth in two of the quotes mentioned in the previous section: "The data linking LDL cholesterol to heart disease in my opinion is incontrovertible and undeniable," avowed one doctor, while one of the scientists interviewed argued that cholesterol is "absolutely not" the cause of heart disease, rather a "guilty bystander to the formation of plaques." Though the first quote does not explicitly infer that the doctor believes cholesterol to have a causal role in atherosclerosis, a later response reveals his beliefs unambiguously. When asked about his thoughts on the studies performed which seemingly disprove the cholesterol hypothesis: "I am aware that people disagree with the opinion that LDL cholesterol is a causal factor for atherosclerosis and heart disease, but I disagree with [their] opinion." It has already been pointed out that this particular doctor's means of gathering information on the topic is primarily first-hand experience and logic based, whereas the scientist at hand has relied mostly on secondary source testimony from medically practicing relatives. Such a situation would reverse the model proposed by Sawyer, in the new situation placing the doctor at the innermost circle, his knowledge based upon experience and primary source data, and placing the scientist in the peripherals. In a way, however, this situation further supports Sawyer; if the demographics are reduced to representing primary source and secondary source information, the model stands. The stipulation to applying such a model to doctors and

scientists specifically is that scientists are generally assumed to be the providers of primary sources. Doctors then rely on either these sources directly, or secondary reviews of such work.

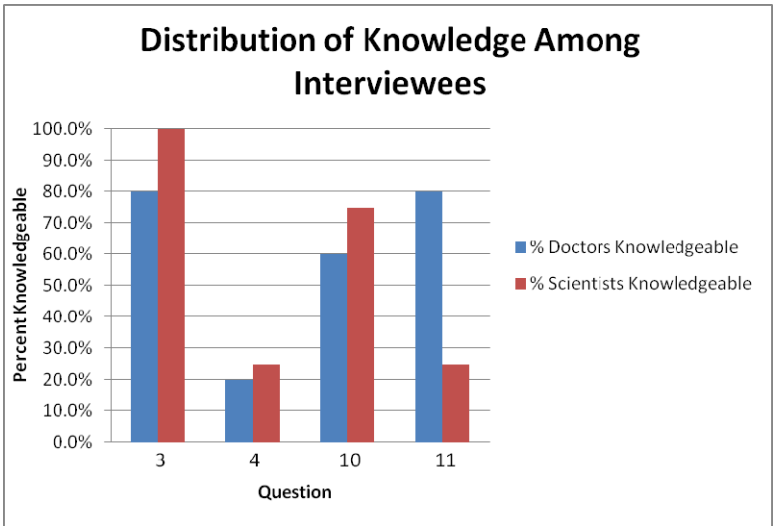

Figure 8 - Distribution of knowledge among interviewees for questions 3, 4, 10, and 11.

Analysis of answers to the right-or-wrong questions 3, 4, 10 and 11 revealed a distribution of positive and negative responses as shown in Figure 7. Contrary to expectations, the overall distribution of individuals who were able to correctly answer the questions, versus those who could not, placed doctors and scientists on level ground; neither group was clearly more knowledgeable, given the questions, than the other.

Though these findings seem to further refute the proposed model, the results may be scrutinized more deeply. Question three asked subjects if they knew the mechanism by which atherosclerotic plaques form, and invited elaboration. This question saw a 100% (4/4) positive response rate from scientists, while doctors' responses fell a bit short at 80% (4/5). Similarly for question ten, which gauged the interviewee's understanding of how statins work, the biochemists had only a slightly better grasp on the subject than did the doctors. However, responses to question eleven, "Are you aware of the side effects of cholesterol lowering prescription drugs?" showed that doctors knew much more about the side effects of statins than doctors, with an 80% (4/5) positive response rate from doctors compared to 25% (1/4) from scientists. The discrepancy may be explained by the nature of the questions. While it is the scientist's objective to elucidate

the mechanisms of the universe, atherosclerotic plaque formation included, doctors are more primarily concerned with the treatment of their patients and the well-being of individuals' health. Knowledge of the side effects of statins directly affects such patients' health, and is thus information a doctor would be expected to know, while not necessarily in the forefront of the scientist's mind.

Another intriguing contrast concerns the state of cholesterol versus the amount of cholesterol in the body. All of the people interviewed were in agreement that keeping the ratio of LDL to HDL cholesterol low is an important factor in preventing heart disease. However, one biochemist proposed a different theory involving the state of ingested cholesterol, whether or not it is "damaged." "Oxidation…changes the solubility of [cholesterol]; it changes the structure and the way that it interacts with different molecules in the body. One of the biggest things that happens when it is oxidized or damaged is that you get uptake of damaged cholesterol into extra cellular space around cells in your tissues." According to him, it is this damaged cholesterol that initiates the formation of atherosclerotic plaques. As described in the literature review, cholesterol is a hydrophobic molecule which behaves in a certain way when intact, i.e. not oxidized. When it becomes oxidized, cholesterol's properties are changed, making the molecule less hydrophobic and interact differently with other entities in the body. The source of cholesterol, he says, is an important factor in determining the state of the cholesterol. Foods such as eggs and milk consist of "intact" cholesterol, whereas overcooked foods or foods exposed to high temperatures and open to the air would be expected to contain this damaged, oxidized cholesterol, the biochemist claims. Such a scenario could explain the case of the nomadic Masai tribe, who consume only freshly killed meat, which is not cooked or exposed to open air for sufficient time to lead to oxidation. In fact, at least one study has linked oxidized cholesterol to

increased fatty streaks in the aorta. Staprans et al. found that LDL receptor-deficient rats fed oxidized cholesterol showed a 32% increase in atherosclerosis as compared to LDL receptor-deficient rats fed normal cholesterol [43].

This situation supports the theories of Thomas Kuhn, author of The Structure of Scientific Revolutions. Kuhn describes research based on a paradigm as "an attempt to force nature into the preformed and relatively inflexible box that the paradigm supplies." Researchers are not focused on finding anomalies, so when results that are contrary to what is expected to come up, they are often ignored, or go unnoticed. The explanation extends to new theories and hypotheses, as well. In this particular case, the “oxidized cholesterol” theory is a newcomer in the paradigm of “LDL/HDL cholesterol,” and is thus expected to be overlooked, especially by supporters of the current paradigm. As Staprans et al. have shown, however, an overlooked explanation is not necessarily an incorrect one.

One of the key research questions of this paper is “What do scientists believe about the validity of the studies done on cholesterol?” Out of the 9 interviewed, four individuals were able to comment on the validity of scientific studies refuting the cholesterol hypothesis. One of these individuals believed that “most of [the studies] are not scientifically sound,” claiming that “they’re not dealing with the scientific methodology to make the criticisms they make.” Another simply disagreed with the studies’ conclusions. A third individual, however, believed that both cases are accurate; that is, the studies which seem to show that cholesterol is principally responsible for heart disease as well as those that contradict this.

Sawyer has claimed that “the intermediaries in [a] field play a critical role in evaluating creative works, but after they’ve made their choices, the ultimate test for a creative work is whether or not it’s accepted by a broad audience” [41]. All of the interviewees who have

commented on the cholesterol studies have agreed that those supporting the cholesterol-heart hypothesis are scientifically sound and valid. Furthermore, these individuals are the ones who have taken it upon themselves to read primary source literature on the topic. As supporters of this primary source material, this makes these individuals intermediaries, and gives validity to the studies. Conversely, the cholesterol studies that seem to disprove the hypothesis, such as Ancel Keys' original study, have not attracted much attention from these intermediaries. Though this says nothing about the inherent correctness of either group of studies, it sheds light onto what scientists believe about their veracity: scientists by and large support the cholesterol hypothesis based on what they feel is sound research, whereas contradictory positions have not gained as much eminence. Those scientists who were aware of the contradictory studies generally shared the opinion of one of them in particular, who said that "there's some merit to some of them, and not a lot of merit to a lot of them." The others were willing to admit that the cholesterol-heart picture is a large, complicated one, and that it is likely cholesterol is not the sole culprit. This clearly illustrates Kuhn's theories of resistance to changes in scientific paradigms, as described earlier.

Figure 9- Sawyer's model of nested audiences applied to the medical community.

Digging deeper, Sawyer's theory of nested audiences may be applied as well. None of the doctors interviewed mentioned anything about the state of cholesterol in the body, let alone oxidized cholesterol. Since this theory goes against the dominant paradigm, and is not widely accepted by scientists, Sawyer's theory explains that doctors would not be familiar with the theory either, since a great deal of their information flows down from the scientific community.

Striking Similarities

One of the group's research questions is "Why do doctors prescribe statins?" As mentioned in the first section of analysis, responses to questions eight and nine ("Is there any incentive for doctors to offer suggestions for lowering heart disease risk other than prescription meds?" and "What is a doctor's response to a patient who refuses to take drugs when prescribed?" respectively) were analyzed with this question in mind. Based on the responses, it may be concluded that doctors will primarily suggest lifestyle changes, and are generally reluctant to prescribe statins. However, the responses indicate that doctors and scientists support the theory that cholesterol is responsible for heart disease, since the treatment, ultimately and after lifestyle changes, is a statin regiment.

It is unanimous among scientists and doctors interviewed that doctors will first and foremost suggest lifestyle changes. "Most doctors are taught that…one of the first things to do is to try and make suggestions and do what one can to convince patients to change their lifestyle," said Dr. Keaney. One scientist interviewed recalled that his primary care physician, a Harvard graduate with a specialty in statin drugs, would not allow him to begin a statin regiment until he had "jumped through her hoops" and made the necessary lifestyle changes.

The incentive, it would seem, is there: doctors are taught to save the prescription drugs as a last effort. This is not always easy, however, as doctors are frequently pressured by patients themselves to write prescriptions. "[Doctors are frequently at the mercy of their patients] who come in and demand these drugs, number one because they've seen it on TV, and number two they may not want to make the lifestyle changes that the doctor is also recommending for them," was the testimony of one biochemist. A doctor admitted, however, that lifestyle changes are the "least effective way for changing a number of things [followed] like lipids and diabetes, etc.

because patients only comply with recommendations on average 8% of the time." Though doctors may delay prescribing statins until deemed necessary, it is clear that there is great pressure on doctors to do otherwise.

In light of the responses to question seven, however, it may be gleaned that the reason statins are most often prescribed is out of genuine concern for the patient, based on the assumption that high cholesterol levels represent an increased risk of heart disease. Statins are prescribed, according to these testimonies, because they are the most efficacious means of lowering cholesterol, and presumably heart disease, without regard to kickbacks or benefits from pharmaceutical companies.

The doctors interviewed are in agreement that the decision is ultimately up to the patient. If a patient refuses to take a statin, the doctor would examine more closely why, and likely suggest lifestyle changes. If the doctor felt the statin was necessary, he or she may advocate on its behalf, yet remain open to the patient's decision.

Probably the most important similarity among interviewees that we discovered is that all subjects agree that cholesterol, in some form or another, plays a role in the development of heart disease. One biochemist interviewed responded to all of our questions with the baseline assumption that cholesterol is in fact contributory to heart disease, saying such things as, "Cholesterol's [bad], but you need it biologically; it's required for life. It's if you get too much of it, if you produce too much of it – that, *coupled* with an inflammatory response can lead to plaque formation." Another biochemist was more concerned with genetic elements, commenting that "people are very…different from person to person in how they metabolize cholesterol. [One person] could probably eat a pound of bacon a day and…wouldn't have bad cholesterol levels, [while another person] would be dead in two weeks if they did that, so it depends on your

personal metabolic levels." Even the most skeptical of the scientists interviewed agreed that "cholesterol monitoring is a good idea…but it *has* to be expressed in good and bad cholesterol," in accord with at least three others who stressed the importance of expressing cholesterol in LDL and HDL, where elevated LDL and/or lowered HDL levels are high risk factors for developing atherosclerosis. Other responses included such comments as "[cholesterol] is a contributing factor [to heart disease], maybe not *the* major cause, but [a factor]," and "…for some people [cholesterol] can be a major cause of heart disease." Every individual interviewed expressed some level of concern about cholesterol as contributing to atherosclerotic plaque formation.

This is a remarkable observation, especially considering that several of these individuals were aware of studies and opinions contradicting the notion that cholesterol causes heart disease, and even supported some of them, such as the recent Vytorin study. There are also significant implications to Sawyer's model of nested audiences here, as well as to Kuhn's characterizations of scientific paradigm changing. The results support Sawyer very strongly, and may be further explained by Kuhn.

According to Sawyer, the flow of information travels from the experts in a given field to the connoisseurs, then on to amateurs, etc, as described earlier. However, to continue this analysis, the nature of "knowledge" must be defined. The Oxford English Dictionary defines knowledge as "awareness or familiarity gained by experience of a fact or situation," [44] and the ancient Greek philosopher Plato described knowledge as "justified true belief." [45]In both definitions, knowledge consists of an opinion or belief which has been proven, at least to some extent by some means, true. It was once "known" that the sun and the stars revolved around the Earth, because these heavenly bodies appeared to travel across the sky. In terms of Sawyer's model, once enough experts in a field have examined a subject and gathered sufficient results to

agree that the subject has been defined accurately, the information comprising it becomes "known" in the minds of those experts. Per the nested audiences model, this description is epitomized in the case of our results that 100% of interviewees believe blood cholesterol contributes to the development of heart disease. Scientists, based on primary source research publications as well as first-hand experience, believe this to be true. Doctors, in turn, assimilate this knowledge as their own, and bolster it, in time, with their own experiences. Finally, the knowledge is relayed from doctors to the public, in various ways.

Furthermore, Kuhn's structuring of scientific paradigm shifts explains these results in a different light. Though several of the interviewed subjects expressed awareness and, in some cases, approval of studies contradicting the cholesterol-heart paradigm, they nonetheless ultimately avowed support of the currently established archetype. According to Kuhn, this is explained by the process by which observations anomalous to the expected norm affect the alteration of the current paradigm such that it accounts for previous problem-solutions as well as the anomaly. Paradigm change begins with the awareness of anomaly, a phenomenon for which the paradigm has not readied the investigator. The area of the anomaly is then explored, and once the paradigm change is complete, the result is that the scientist is able "to see nature in a different way" [42]. Since opposition to the dominant cholesterol paradigm is relatively new, as compared to the age of the established paradigm itself, any possible paradigm shift would currently be in the middle stages of development. That is, the anomaly (instances of high cholesterol individuals who never suffer a heart attack, the Masai tribe, etc.) is still being examined and new theories still being formulated. Thus, although some individuals may be aware of the anomalies, the paradigm which they have learned still holds firmly in their mind. If and when a shift does occur, the experts in the field will redefine their knowledge of this subject, and the rest of the populous

will be affected per Sawyer. Conclusions drawn from these observations will be discussed in the Conclusions section.

Response Rates

In total we contacted thirty doctors and scientists requesting interviews. Out of those contacted, we received nine responses from people offering to assist us – four biochemists and five doctors, which is a 30% response rate. We also received seven responses in which our requests were declined due to lack of sufficient knowledge or time, and there was no response from the remaining fourteen contacts. Given the small number of interviews conducted, one can hardly say that our results are representative of their respective communities. However, given our limited time and resources, the goal of this analysis was not to attain a theoretical saturation, but rather to gain a general idea of some views and opinions held by various members of a couple of key communities in cholesterol research and treatment. The results are not complete, but we believe they have led us in the right direction.

Our strategy for finding people to interview began with contacting local biochemistry professors at Worcester Polytechnic Institute through email and requesting interviews with them. It was believed that this would yield a high response rate, when in fact only three interviews were gleaned from this method. We then contacted twelve more scientists, of which one more professor, from University of Massachusetts Medical School, interviewed with us. Overall we contacted twenty scientists and received confirmation from four of them, a 20% response rate.

We had believed that obtaining interviews with doctors was going to be much more difficult than with scientists, when in fact just the opposite turned out to be true. Our initial method for contacting doctors was through fax; we sent six faxes out to various primary care physicians, and received two responses accepting our request. The next approach was to go

through personal contacts. We emailed the director of Health Services at WPI, who was able to set up two interviews with doctors for us. Also, two of our group members contacted their own physicians, of which one interviewed with us. We contacted ten doctors in all and received five responses, giving us a 50% response rate.

All seven of the people who declined to interview were biochemists, so for quite a few of the professors we contacted this subject was out of their area. We believe one reason for the low response rate for scientists compared to doctors is that scientists are often very specialized in their research, while doctors need a much more general knowledge in a wide variety of topics.

Conclusions and Implications

In the previous section, we discussed the significance of unanimity among interviewees concerning the belief that cholesterol, in some form or other, is contributory to heart disease. This was discussed in terms of Sawyer's nested audiences as well as Kuhn's structuring of paradigm shifts. It was said that a paradigm will not be completely restructured until there is an explanation of an anomaly which accounts for previous observations as well as the new one, and enough experts in a field accept the new paradigm. Thus, based on the statements of the doctors and scientists interviewed, we may conclude that they do believe cholesterol plays a role in the development of atherosclerosis, and that elevated LDL cholesterol is a risk factor for heart disease for many, though not all, individuals, which is a reasonable assertion and likely could be the case.

According to the responses received during interviews, the reason statins are most often prescribed is out of genuine concern for the patient, based on the assumption that high cholesterol levels represent an increased risk of heart disease. Doctors recommend diet and exercise first and consider what would be best for the patients, which appears to be the only bias in their decisions to prescribe statins or not. Doctors take the information that they get from science, which is the current, accepted paradigm, and use this paradigm to steer medical practices and treat patients. If doctors are stuck in the accepted paradigm, however, how readily could they change their views and practices if the paradigm is proven incorrect in favor of new theories? Though a future paradigm shift based on new research, discoveries, and anomalies may better and more universally define cholesterol's role in heart disease, the act of restructuring the way cholesterol is conceptualized is still underway.

The biochemists we interviewed do believe that the studies done in support of the cholesterol theory are scientifically sound, and that their results are scientifically valid. However, scientists are constantly changing hypotheses based on the information available, and the biochemists seem generally more open to alternative possibilities while doctors seemed very firm in their opinions about the current theory. This must be due to the flow of information. Biochemists and doctors alike generally agree that cholesterol is a contributing factor leading to heart disease, which implies that the information has successfully passed from one demographic to the other.

There is no panacea when it comes to heart disease. Prescription drugs are merely tools that can be used in combination with overall lifestyle changes to reduce risk of heart disease. No single approach is applicable to everyone, at least not without careful attention to detail and individual adjustments.

Those most knowledgeable about statin drugs told us they get a lot of their research information from primary sources, such as medical journals, patient interaction, and scientific studies. The interviewees who were unable to describe the mechanism by which statins work stated that they obtain their information on cholesterol from secondary sources. By going out of their way to seek and study primary source materials, knowledgeable interviewees took the effort to better understand the mechanisms and side effects of statin drugs. This implies that they care enough about the issue, either in a positive or negative light, to put forth the effort to find information on the topic. Considering the flow of information discussed earlier, using primary sources is the best way to get the whole picture when it comes to cholesterol and heart disease.

Finally, cholesterol is only one risk factor among a long list of correlated conditions, including smoking, high blood pressure, and genetic predisposition. It is valuable to take all

these risk factors into account, and not put all your cholesterol-laden eggs in one basket. Leading a healthy lifestyle, eating right, and exercising can help with maintaining a healthy heart, as well as having many other positive effects on the body.

Appendix A

Table of Drugs Affecting Lipoprotein Metabolism

Drugs Affecting Lipoprotein Metabolism

Drug Class, Agents and Daily Doses	Lipid/Lipoprotein Effects		Side Effects	Contraindications	Clinical Trial Results
HMG CoA reductase inhibitors (statins)*	LDL HDL TG	↓18-55% ↑5-15% ↓7-30%	Myopathy Increased liver enzymes	Absolute: • Active or chronic liver disease Relative: • Concomitant use of certain drugs†	Reduced major coronary events, CHD deaths, need for coronary procedures, stroke, and total mortality
Bile acid Sequestrants‡	LDL HDL TG	↓15-30% ↑3-5% No change or increase	Gastrointestinal distress Constipation Decreased absorption of other drugs	Absolute: • dysbeta-lipoproteinemia • TG >400 mg/dL Relative: • TG >200 mg/dL	Reduced major coronary events and CHD deaths
Nicotinic acid¥	LDL HDL TG	↓ 5-25% ↑15-35% ↓20-50%	Flushing Hyperglycemia Hyperuricemia (or gout) Upper GI distress Hepatotoxicity	Absolute: • Chronic liver disease • Severe gout Relative: • Diabetes • Hyperuricemia • Peptic ulcer disease	Reduced major coronary events, and possibly total mortality
Fibric acids§	LDL *(may be increased in patients with high TG)* HDL TG	↓5-20% ↑10-20% ↓20-50%	Dyspepsia Gallstones Myopathy Unexplained non-CHD deaths in WHO study	Absolute: • Severe renal disease • Severe hepatic disease	Reduced major coronary events

* *Lovastatin (20-80 mg), pravastatin (20-40 mg), simvastatin (20-80 mg), fluvastatin (20-80 mg), atorvastatin (10-80 mg), cerivastatin (0.4-0.8 mg).*

† *Cyclosporine, macrolide antibiotics, various antifungal agents and cytochrome P-450 inhibitors (fibrates and niacin should be used with appropriate caution).*

‡ *Cholestyramine (4-16 g), colestipol (5-20 g), colesevelam (2.6-3.8 g).*

¥ *Immediate release (crystalline) nicotinic acid (1.5-3 g), extended release nicotinic acid (Niaspan ®) (1-2 g), sustained release nicotinic acid (1-2 g).*

§ *Gemfibrozil (600 mg BID), fenofibrate (200 mg), clofibrate (1000 mg BID).*

Appendix B

Interview Questions

The following is a list of questions pertaining to cholesterol, the heart, and prescription drugs. If you are uncomfortable with a question, do not know the answer, or do not wish to respond, feel free to say 'pass' and we will move on.

1. A strictly yes or no response is all that is asked for in this question: do you know your own cholesterol level?
2. Are you concerned about keeping or obtaining low cholesterol?
3. Do you know how atherosclerotic plaques accumulate?
4. Why do plaques only form in arteries?
5. How much cholesterol does the body/liver produce?
6. What effect (if any) does dietary cholesterol have on this?
7. Do doctors or medical institutions benefit in any way from prescribing statin drugs, or a particular statin? If so, what kinds of benefits?
8. Is there any incentive for doctors to offer suggestions for lowering heart disease risk other than prescription meds?
9. What is a doctor's response to a patient who refuses to take drugs when prescribed? (doctors only)
10. Do you know and understand the mechanism by which statins work?
11. Are you aware of the side effects of cholesterol lowering prescription drugs?
12. What do you believe about cholesterol as it pertains to heart disease?
13. Are you aware of studies which seemingly disprove the cholesterol-heart hypothesis? If so, what do they have to say about them?
14. What most influenced your opinions or conclusions about cholesterol and the heart?

Appendix C

Interview Transcripts

Scientists

Scientist Interview #1

Teacher, Cell Biology
1/29/08

Q1: Do you know your own cholesterol level?
A1: Yes

Q2: Are you concerned about keeping or obtaining low cholesterol?
A2: Yes

Q3: Do you know how atherosclerotic plaques accumulate?
A3: Yes, sort of, it's not my area, but I do know that there are a variety of proteins that lead to an inflammation, it's an inflammatory response. *Why it forms in this spot versus that spot, if you could figure that out you'd be a billionaire, so no one knows the answer to that. But in general it's an inflammatory response, and cholesterol's only a part of it, it's a small part of it, but it's very complex. There are different things that lead to the formation of plaques. All this stuff you read about in the newspapers regarding cholesterol – it's part of it, not all of it, it's certainly not the entire story. Triglycerides, fats, etc. and other proteins that we're still discovering [are involved], it's a very interesting story. We don't understand it completely.

Q4: Why do plaques only form in arteries?
A4: See * in A3

Q5: How much cholesterol does the body/liver produce?
A5: I have no idea. We need it though; you need it for membrane production. You need it also for forming hormones, certain hormones require steroids in cholesterol, and cholesterol is a key component of the lipid bilayer. It has this bad rap, right? Cholesterol's "bad," but you need it biologically, it's required for life. It's if you get too much of it, if you produce too much of it – that, *coupled* with an inflammatory response can lead to plaque formation.

Q6: What effect (if any) does dietary cholesterol have on this?
A6: It certainly *can*, not always, but it can elevate serum cholesterol, meaning if I eat a ton of saturated fats, things that are extremely high in cholesterol – if you couple that with the genetics, which predisposes you to it – it's a combination, meaning you don't process it well – then that can lead to elevated serum cholesterol. You go on a diet that's completely animal fat-free, I guarantee you your cholesterol's going to go down. So some of those things we understand, but it's not only diet, it's also genetics, because you can have two people on the same diet, and their cholesterol levels are not going to be identical – so it's both what you are consuming and what are you manufacturing on your own, and how you

process what you're consuming – and all that's different between individuals. So you have to factor in the whole story, and that dictates what your total cholesterol levels are. It's very multi-variable, it's not just what you eat – two or three people could be on the same diet and have different cholesterol levels. But diet can affect serum cholesterol.

Q7: Do doctors or medical institutions benefit in any way from prescribing statin drugs, or a particular statin?

A7: Yeah, they get kickbacks. Statins are some of the best-selling drugs in history. More billions have been made off the statins than any other drug in history, and that includes aspirin, it's amazing.

Q8: Is there any incentive for doctors to offer suggestions for lowering heart disease risk other than prescription meds?

A8: My primary doctor does [offer suggestions other than meds], she got her PhD from MIT on statins, she's extremely knowledgeable on statins. And she, for the first two years when I met her, refused to prescribe me any statins – she talked only about exercise, that's all she talked about. (I'm on a statin, for the record.) But she wouldn't put me on one, until I went through her hoops. I had to go through her diet, and then I had to increase my exercise levels, etc., and only when I did not respond – we followed my blood-cholesterol constantly, 2 or 3 times a year I had it checked – and after 2 years when she brought it down, but she still wasn't quite happy, then she prescribed the statins. So I'm currently on a statin, *lowest dose*, but I'm currently on a statin – it's Lipitor. And oh my god, I started at 250 total serum cholesterol – milligrams per deciliter they call it – and with the statin at the lowest prescribed dose, I dropped to like 150. It was unbelievable, man, it was like gold. But do I think that all doctors prescribe low diets and exercise first before jumping to the statins? No. But I can tell you mine did.

When he said he was on the lowest dose of Lipitor, he put his hands up and said it in a way as if he was guilty of a crime, but that it wasn't too bad since he's only on the lowest dose.

Q10: Do you know and understand the mechanism by which statins work?

A10: Yeah. They lower the production of cholesterol in the liver, and they do so by blocking a terpine pathway, they block HG-co reductase [*sic*]. It's an enzyme that synthesizes cholesterol in the liver, so if you block that enzyme, then it lowers the production of cholesterol in the liver, so less of it is released in the blood stream.

Q11: Are you aware of the side effects of cholesterol lowering prescription drugs?

A11: Yeah, oh man, I'm an expert on them. The worst you have to watch for is muscle pain, because if your dose is too high – a low entry level dose would be 10mg, 10mg/day is the lowest dose to be good for patients – when you start getting up around 40mg/day, and certainly around 50, you start worrying terribly about muscle soreness, and if so that is potentially extremely harmful. I don't want to quite say "fatal," but potentially fatal. Yeah, it's serious; it's not just stuff you want to play with. Now, at the dose I'm on at 10mg, the percent of patients that show serious side effects are extremely small, .1% or something, very small. But at the high doses you have to watch it. So I am aware, muscle weakness is an extremely serious side effect, seen at the high doses. Others are mild and include things

like nausea, head ache, diarrhea. I personally haven't had any of the above, but I knew to watch for them, real quick, because what's the tradeoff? OK, so I lower my cholesterol, but then you pick up all these other side effects, so why bother? Plus you're paying for the darn thing, so why would I want to pay for someone to give me a headache? But I haven't experienced any of the side effects that I've been warned about, and those are headaches, diarrhea, bloating, constipation for some, but I haven't seen any GI problems whatsoever, so thank goodness. To me, its quality of life, you know? If I did [experience side effects], particularly like a headache or something, then it lowers the overall quality of life. With the statin, you're really talking about trying to benefit yourself 20 years from now, and so this is going to be a subtle effect. I myself was pleased to see it go from 250 down to 150. If it went from 250 to 230, then what have you gained? But on the lowest dose, from 250 to 150… 200 was the overall recommended level, approximately. It used to be 220 by the way, but we lowered it to 200, now I think they're saying the recommended level's 190, so they keep lowering it each year. I blew the socks off all of the above at 150, so this is a huge drop for the lowest dose with no side effects whatsoever, that I can see anyway. But yeah, but if I picked up muscle weakness you'd see me stop it that same day. Headaches, I would complain to my doctor about it and see if they can switch me to something else, but then I would say probably not, because it's quality of life. What am I going to do, live with 20 years with headaches to hope that I have less of a chance of a heart attack in the future? It's a tradeoff, so I would probably drop it.

Q12: What do you believe about cholesterol as it pertains to heart disease?
A12: *This question wasn't asked, but it can be inferred that the interviewee does believe cholesterol is a risk factor for heart disease.*

Q13: Are you aware of studies which seemingly disprove the cholesterol-heart hypothesis? If so, what do they have to say about them?
A13: I've seen some of them. I think it's typical of any complex biological issue. It's not a simple story, it's a complex story, so you can always find opposite data. From my point of view as a biology teacher, and also as a patient (I'm on Lipitor) I look for the big picture. So what's the big picture? The big picture is that we have very clearly established patients, we call them FAC – familiar hypercholesterolemia – it's genetic, it runs in families – familial. Hyper means elevated, and cholesterolemia means "pertaining to cholesterol." These are individuals where high cholesterol runs in their family, and you're talking way up there. If I was at 250, they're at 650. And these are individuals that were dying of heart attacks and plaque buildup at the age of 21, 25, and so those patients, FAC patients, were the ones that first pointed us years back, that cholesterol might be a player in heart disease. You take someone who's at 650, who has already has heart attacks, and verify that the heart attacks are due to plaque buildup, which you can do using echocardiograms. Now come in and ask the question "What if I lower the cholesterol in that individual?" With either drugs, or in some cases we use gene therapy – my area. These patients were missing the receptors that bind cholesterol in the blood to take it out of the blood, so if you're missing the receptors to take it out of the blood, the cholesterol builds up in the blood, and you can't remove it from the blood. What if you do gene therapy to restore the receptors? We saw the cholesterol levels, through studies, goes from 650 back down to 200. Then the question is "Does that individual show less plaque buildup 2 years from then, 3 years from

then?" Because it's not instantaneous, and that's a problem that frustrates us, the public wants to see instantaneous results, but it takes years. So now the question is "If you took someone who was at 650 and had plaque buildup young, and lowered it to 200, several years from now do you see lower plaque buildup by echocardiogram?" And the answer is "Yes, on average." Do all patients show less plaque? No. Alright, there's your story, so the question is "What does the vast majority show – not the statistical deviants, but the average?" If 99 times out of 100, the lowering of the cholesterol shows, by echocardiogram, less plaque buildup, then probably – not always, but probably – the two are related to each other. Does the one guy over here who didn't benefit have a story? Yeah probably, because he's probably saying something interesting, like his plaque buildup's due to something else. Now that's an interesting story biologically. Does that disprove the fact that the others where you did lower the cholesterol [had less plaque buildup due to lowering cholesterol]? What else would cause their lowering? Because you're assuming diets remained the same, the only thing that happened was you took the lovastatin or the Lipitor, and are now back to lower cholesterol, and you can show physically, by echocardiogram, less plaque formation. Well what would be responsible for it unless you're lowering the cholesterol? So anyways, do I believe the guy, the 1 in 100 – or let's say it's even 20 in 100, that still have the same plaques when you've lowered their cholesterol? Yes. Do I think it disproves the 80%? No, I think they're both correct. The 80% are saying that the cholesterol was the main reason for their plaque formation, and when we reversed it, so goes away their plaques. The 20% are saying cholesterol was not the main reason for their plaque formation, you see what I mean? I believe both of them.

Q14: What most influences your opinions or conclusions about cholesterol and the heart?
A14: Textbooks, I teach this, so textbooks, and also medical journals, myself – like I said, I'm a patient – from my doctor, and also newspapers. I'm aware of the people who claim that they've had their cholesterol lowered, but it did not affect plaque production, I'm aware of those studies and I agree with them. [Otherwise] I would have to tell you I'm part of the medical establishment, you know what I mean? You know, if you're representing [the people who claim] "The medical establishment is all out to make money, and they're all out to bilk the consumer for this damn Lipitor," you know, then "Yeah man, because they're milkin' *me*, man!" So I'm for that, I'm pro you, if that's what you think. I'm for lowering the cost, because I'm getting hammered, man. But do I think that Lipitor is *only* a ploy placed on the masses to earn the physicians money? No. I think in some cases it is, but I think in some cases it's been over-prescribed. But do I think that for the vast majority that it's merely physicians making money? No. I think that, in my opinion, the majority are going to benefit. I don't think everyone benefits from it. So anyways, I get my information from textbooks, talking to physicians, talking to other professors, debating – as you can see it's a complex topic.

Additional comments: I like your IQP, it's an interesting topic. I'm just hoping that the IQP team doesn't jump too quick to the conclusion that all MDs are bad, and all MDs are out *only* to make money for themselves by bilking the public, getting them to buy into Lipitor when there's no supporting evidence whatsoever that Lipitor works, that it's just making money for the physicians. Because if I really thought that, I would be joining your IQP team, and you and I would be out there publishing papers and screaming at the HMOs and

that sort of thing. I think it's like any other story in the real world – complicated. And in my opinion, I think that both camps are correct, it's just that in the majority of cases the plaque formation is in part because of their elevated cholesterol, and that camp will benefit from the Lipitor treatment. The others I think also are telling a very good story, they're not going to benefit, and as soon as the physicians see they're not benefitting, they should take them off, quit making them pay for that drug. So I think you're on an interesting topic, it's just I'm hoping you don't jump to one side over the other. If you were one of these that thinks all physicians are out only to make money, you'll have trouble supporting that clause, when you see that some physicians refuse to take the kickbacks. That might surprise you, and I know a few that are that way at UMass med. They've told me they're approached by the sales reps, and that they are not taking their kickbacks, so that might surprise you, but some are not doing so. I think it's a fascinating topic you've got going.

Scientist Interview #2

Assistant Professor, Biology & Biotechnology
WPI
2/15/08

Q1: Do you know your own cholesterol level?
A1: Yes

Q2: Are you concerned about keeping or obtaining low cholesterol?
A2: Yes

Q3: Do you know how atherosclerotic plaques accumulate?
A3: Yes

Q3.1: Would you care to elaborate?
A3.1: One of the more recent suggestions about the initiation is inflammation. It seems to be the major problem, but if there is adherence of cholesterol or any other obstruction to the walls of the artery then there can be invasion of the middle tunic through the endothelium into the middle layer, either the muscle cells there convert into what are called palm cells and then accumulate cholesterol, or it could be that it these are invading white blood cells – that the plaque then is essentially accumulating around an irregularity in the vessel wall and definitely cholesterol is found In the plaque

Q4: Why do plaques only form in arteries and not in veins?
A4: Well there's sort of positive feedback to turbulence, so if anything adheres to the wall, you'd disrupt the laminar flow and then more comes along. But beyond that I hadn't really thought of it so I don't really have any real reasons why that might be.

Q5: Do you know how much cholesterol does the body/liver produce?
A5: I don't know the absolute amount, but it is about 30 times more than dietary. That is after assuming that giving the nod to drugs like Zetia that keep it from being absorbed, it doesn't

matter if you've got Zetia or not – if you have a normal metabolism, you can ONLY absorb a certain amount of cholesterol in a day, and that amount is about 2 eggs worth.

Q6: What effect (if any) does dietary cholesterol have on the body's cholesterol level?
A6: Dietary cholesterol is a minor player, but for years it was presumed that because they found so much cholesterol in the plaques and because people on a low cholesterol diet seem to do better in terms of heart disease and so on, it was assumed cholesterol was the culprit. But now it appears that it's the low density lipoproteins that accompany high cholesterol foods that is the real problem, and with a big load of low density lipoproteins cholesterol may get elevated, but they [low density lipoproteins] are the signal, they are the problem. The LDL and the HDL receptors, once characterized, were the basis for giving someone the Nobel Prize, though I don't remember his name.

Q7: Do doctors or medical institutions benefit in any way from prescribing statin drugs, or a particular statin? If so, what kinds of benefits?
A7: Well, there are, did you say doctors or hospitals? (*yes, both*) You've got your most blatant case of abuse with the privilege of having a soapbox in doctor Jarvick who pushes Lipitor like it's the best thing since night baseball. And because he invented the artificial heart, because he takes Lipitor himself, he probably does believe in it, and so there are financial benefits for anyone who would shill for it, that's one thing. Hospitals don't go around and advertise this stuff, but it's my belief that they get kickbacks from the drug companies – various drug companies, this isn't just cholesterol drugs. They'll sponsor seminars in places like San Juan or Hawaii, where people go and learn about the specific drugs. I think that all said, the medical community gets some spillover from what the drug companies make.

Q8: Is there any incentive for doctors to offer suggestions for lowering heart disease risk other than prescription meds?
A8: Well I have to interject that the poor doctors, in this day of pervasive television advertizing, are at the mercy of their patients quite often, that the people come in and demand these drugs because #1: they've seen it on TV and #2: they may not want to make the lifestyle changes that the doctor is also recommending for them. Are there benefits to the doctor? I would say that in general, every doctor will do it [offer suggestions for heart disease risk other than prescription medication], the incentive is actual concern to keep his patients healthy, and unless he is a vascular surgeon, he is not necessarily benefiting directly. If he is a vascular surgeon, he can always say "well you need a bypass," and bypasses seem to be an overused and undermanaged operation in this country.

Q10: Do you know and understand the mechanism by which statins work?
A10: Statin Drugs, like Lipitor? No, actually, I don't. I'd have to look it up.

Q11: Are you aware of the side effects of cholesterol lowering prescription drugs?
A11: No, something about libido in there, but I don't really know them or have a good grasp. Obviously, I don't take them or I would've read the pamphlet and I'd be able to tell you more. My mother is on Lipitor, I know, and I guess you're not supposed to eat grapefruit, because, now get this, grapefruit itself contains statin-like compounds. I say "Why not prescribe the grapefruit instead of the drugs?" but no one asked me.

Q12: What do you believe about cholesterol as it pertains to heart disease?
A12: The crux of the issue… I think that cholesterol monitoring is a good idea, but it HAS to be expressed in good and bad cholesterol. The high density lipoproteins which are carrying the cholesterol for cell membranes, and so on, are an important part of metabolism and membrane health and steroid hormone production in the body, so I think you can get your cholesterol level too low. You really can't get your LDLs too low. And is cholesterol the direct cause of heart disease? Absolutely not. It is, let's say, a guilty bystander to the formation of plaques.

Q13: Are you aware of studies which seemingly disprove the cholesterol-heart hypothesis? If so, what do they have to say about them?
A13: I couldn't cite a particular study. I am aware that this is being questioned, and one of the people who question it is my brother, who is a vascular surgeon. He has reamed out his share of arteries that have plaques in them. He doesn't do bypass surgery or work on hearts, but blood vessel occlusion is a big problem and it has as much to do with A) inflammation and B) sedentary lifestyle as it does lowering cholesterol. There are perfectly healthy people walking around with cholesterol counts above 300 that are just tolerant of it. The medications spectrum is not one-size fits all, you've got to look at family history and if there's ever been a heart attack in the family, ease up on all of these drugs and focus on lifestyle.

Q14: What most influences your opinions or conclusions about cholesterol and the heart?
A14: The two physicians in my family. One, an uncle of mine, not a blood relative, but since the 1950s he put himself on a cholesterol restrictive diet and always touted the benefits of it. In the end he died of a stroke, but he was 92 years old at the time, and all of his kin, his blood relatives, had croaked before the age of 60. So, he definitely was a case for a Low "something" diet, and he thought it was low cholesterol. But my brother, who has helped me form my opinions even more strongly than my uncle, suggests why it was so useful for my uncle to be on that regime, and it was the low LDLs which then did not provoke cholesterol and plaque formation. So you asked me what influenced my opinion, well those are it. And, more recently, reading about the calcium and vitamin D and inflammation all seem to play critical roles. There's as good a correlation between tooth decay and heart disease now that people have been looking at it. What might be the trigger is the inflammation, which is ever present if you've got cavities and problem teeth.

Additional comments: Well, I would comment that I do some horseshoe crab research with a guy, and he is a medical doctor. He is a blood specialist, particularly blood clotting, and he maintains that there is not a scintilla of evidence that exercise is of any benefit to the vascular system. Now he is a very smart guy, but I disagree with him, mainly on the basis of common sense, and the fact that exercise can reset your blood pressure and lower your blood lipids, so I'm all for that – I think people should exercise as long as their joints hold out. I don't think there have been any lawsuits yet, but clinical trials have been stopped and I think Zetia is going to be yanked off the market. Here is an inhibitor of dietary uptake of cholesterol which is, from other things that I've said, such a piddling problem for the person with hypercholesterolemia. The dietary angle is just NOT even an issue, and Zetia is

prescribed for so many people, I believe, because concerned, mainly 'worried well' people, go to their doctors and insist on taking it. And the doctor in this case has probably said "Oh well, it's not going to hurt them," so he'll prescribe it, but it probably in fact has side effects, none of which I can quote at the moment, but it is the management of cholesterol by low fat diet, low saturated fat diet – I don't think I ever mentioned this before, but it is all SATURATED fat that seems to boost cholesterol, not unsaturated. And so I think that that's about it. I feel a little smug, because my family doesn't have a history of heart disease or stroke though my mother's cholesterol is quite high. She's doing ok, she's 91, 92 today in fact!

Scientist Interview #3

Assistant Professor, Biochemistry and Molecular Biology
WPI
2/15/08

Q1: Do you know your own cholesterol level?
A1: Yes, as of 8 months ago.

Q2: Are you concerned about keeping or obtaining low cholesterol?
A2: Not really, I tend to not have problems with it. My cholesterol is something like 114.

Given subsequent answers, it can be inferred that the subject would likely be concerned about his cholesterol if it were higher.

Q3: Do you know how atherosclerotic plaques accumulate?
A3: Yes

Q4: Why do plaques only form in arteries?
A4: It has a lot to do with what we consider "vascular" cholesterol levels. There's cholesterol in all different places in the body – cell membranes, the liver, and different organs and tissues – but it's the excess of low density cholesterol particles in the bloodstream that lead to accumulation of plaques in the arteries, almost exclusively just because of location. So you get a lot of cholesterol transfer between the liver and the bloodstream, and if you get too much of that stuff in the vascular system you end up getting plaque formation.

Q5: Do you know how much cholesterol does the body/liver produce?
A5: No

Q6: What effect (if any) does dietary cholesterol have on the body's cholesterol level?
A6: In general, it has a fair amount of effect. A lot of the body's cholesterol is produced de novo, so we make this stuff in our liver and it gets shipped out, and in the process sent around the body. But a fair amount of dietary cholesterol that we intake enters that same system, that same metabolic pathway. Then it just becomes a question of "What's the source of that cholesterol, and is it a good source of a bad source?"

Q7: Do doctors or medical institutions benefit in any way from prescribing statin drugs, or a particular statin?
A7: Yeah.

Q8.1: Is there any incentive for doctors to offer suggestions for lowering heart disease risk other than prescription meds?
A8.1: I'd hate to think so. Are there, out there? I'm sure there are, I'm sure there are doctors out there that are taking some type of kickback somewhere, but I hope that it's a rare thing. It certainly would be highly illegal. In these pharmaceutical companies, they send MDs these pamphlets and flyers and samples and things like that, things to really push. It's almost a marketing gimmick, the more they make the doctors aware of their drugs, they hope the more they prescribe them, that the doctors will hopefully gain more trust in these drugs. But in my personal experience with myself and my family, it seems as if most of the doctors I've heard about or encountered are pretty reluctant to prescribe statins unless they absolutely feel it's necessary – they always try dietary stuff first.

The interviewee may have misunderstood the question, so we tried to present it in a different way:

Q8.2: Do you think there are advantages to doing dietary things before taking the statins?
A8.2: Oh yeah, absolutely, if it can be controlled dietarily, that's certainly the way that you'd want to go. I think it really just depends on the severity and the nature of the disease. If you are overweight and you have inordinately high LDL levels in your bloodstream, and you don't eat very well, obviously it's something that diet could probably correct. If you've got some hereditary condition, like familial hypercholesterolemia or something like that, where you've actually got genetic mutations that are responsible for the increase in danger of cardiovascular disease and that kind of thing, then that's obviously something that diet won't be able to correct, and that statins would be useful for. A lot of people, even in my family, have chronically higher cholesterol levels, but the most important thing – with atherosclerosis and cardiovascular disease and heart attacks, and that kind of stuff – with cholesterol is the ratio between your high density and low density lipoproteins. All your cholesterols get packed into these little particles, almost exclusively because they're not soluble in water – so you can't have them running around your bloodstream as free cholesterols, they'd form huge clumps and kill you in seconds. There's a protein called an apoprotein that wraps them in these clusters that keeps them soluble and in little packets to be transferred throughout the bloodstream. You've got two different flavors of those – high density and low density – and basically the only major difference is the amount of cholesterol in the particles: high densities have really low amounts of cholesterol and they tend to be smaller particles; low densities have a lot of cholesterol and they tend to be really big particles. The ratio of those two in the bloodstream is what's most important for preventing disease. Just because you have high LDL levels – which people coincide with the "bad stuff," but I hate the nomenclature – doesn't mean you're going to have heart disease, it's really the ratio of the two. It's most important because the LDL molecules are responsible primarily for shunting cholesterol, shedding that cholesterol in the particles into your tissues. And the HDLs are responsible for taking it out, so they have this inverse

relationship. So it's kind of obvious why too much LDL would lead to accumulation of cholesterol in the arteries. But it's at least pretty firmly rooted now that you need to have a ratio that's off, so too little HDL, too high LDL, as well as the size of the particles – if your LDL particles are nice and big and plump, and you have very little of them, that's the best situation. The worst situation is if you have a lot of LDL and the particle size is small, because they just clump and shed cholesterol like crazy. So if the doctors have enough information about what they're looking at, then I think they could prescribe it pretty well. They should be able to anyway.

Q10: Do you know and understand the mechanism by which statins work?
A10: Yes. Statins are really, really effective at controlling cholesterol because they specifically target an enzyme call HMG-CoA reductase. It's an enzyme involved in metablosim of cholesterol – synthesis of cholesterol. Hydroxy-methyl-glutaryl-CoA reductase, or something like that. But it's one of the core enzymes in synthesis of cholesterol in the liver, and these drugs very specifically inhibit that. What happens is you basically shut down liver synthesis of cholesterol, and your body responds to that, in need of cholesterol now, by inducing your cells to uptake cholesterol from the bloodstream in the form of LDL, because that's where you get your cholesterol into the tissues from, the LDL particles. So indirectly, it lowers the LDL levels in the bloodstream, which is good for preventing heart disease. They're extremely effective; they work really well to rapidly correct cholesterol. The nice thing is that once you bring LDL levels down, your HDL automatically goes up. So you can correct the ratios, you can dose it to people, and it's this nice pathway in that your low density lipoproteins, your LDL receptors, which gobble up this stuff out of the bloodstream, are all the ones that are connected to a lot of the familiar diseases. That's why there's this kind of dichotomy in the field as to whether the statins are effective with familial cases, because their receptors aren't pulling the stuff out of the bloodstream anyway. But they work really well, it's been one of the most successful drugs out there in a long time.

Q11: Are you aware of the side effects of cholesterol lowering prescription drugs?
A11: I know there are some, but I don't know that I'm aware of the specifics, no.

Q12: What do you believe about cholesterol as it pertains to heart disease?
A12: I guess my opinion varies according to the particular place that I'm analyzing. If I look at the link between cholesterol in the body and heart disease, as in having higher LDL levels in the bloodstream, ratios being off, things like that leading directly to plaque formation, the evidence for that is pretty solid. Some of the best evidence for that, in my opinion, has come from more recent studies with these familial genetic cases, where they've actually genetically mapped the mutations. They call them single nucleotide polymorphisms in the DNA, in the LDL receptor, the receptor that docks the LDL and pulls it out of the bloodstream. These people have a direct defect in doing that, so their LDL levels are always high in the bloodstream because they can't pull them out into the tissues, and there's a dramatic correlation between people that have those mutations and heart disease and vascular disease, they almost always have it. So at least the link there, as far as I'm concerned, is solid. I think the stuff that gets really murky is dietary stuff. You know, people tell you "You can't eat this, you can't eat that, you've got to have so much of this,

and so much of that." There are basically two aspects of it. One is genetic diversity – people are very, very, very different from person to person in how they metabolize cholesterol. Take a person like me, I could probably eat a pound of bacon a day and I probably still wouldn't have bad cholesterol levels, but that's just because I have a more rapid cholesterol metabolism. The person next to me would be dead in two weeks if they did that, so it depends on your personal metabolic levels for that stuff. But it also depends on the state of the cholesterol in your diet. Cholesterol's kind of a funny molecule in that it is very hydrophobic, and so it's not soluble with water at all – that's why it clumps together if we put it in, like how oil and water won't mix, the oil kind of clumps together. It does the same thing, but if it's compromised in some way, if the molecule is damaged – oxidation is one of the biggest things that does this – it changes the solubility of the molecule; it changes the structure and the way that it interacts with different molecules in the body. One of the biggest things that happen when it's oxidized or damaged is that you get uptake of damaged cholesterol into extracellular space around cells in your tissues. It goes into that space very readily if it's been damaged, but not necessarily if it's intact. So one of the big things that's being investigated still, in terms of ingesting dietary cholesterol, is "What's the source, where is it coming from?" Is it fully intact, biochemically sound cholesterol, or is it oxidized, damaged cholesterol, that if you eat then perhaps – we don't know for sure – it's going to go directly into your extracellular spaces, and could contribute to higher incidences of heart disease. Those things we're not entirely sure of. What we are sure of is that there are sources for good and bad cholesterol. For example, if you're drinking whole milk or you're eating eggs – those are sources of cholesterol, but it should be intact. As long as you're not completely oxidizing it, or overcooking it, things like that, it should be fine. There's always this big thing about eggs, how many eggs should you eat, because they're full of cholesterol – it could be the case that you can eat as many as you want because it's just fine. It shunts right into your metabolic pathways and your body handles it just fine. However, if you're dealing with fried food and all kinds of trans-fat and things like that, you're going to be looking at a lot of damaged cholesterol, and that's probably bad. But it's certainly not locked up on that side of things, because we don't know precisely that bad cholesterol goes right to plaques, or leads to plaque formation, so that's a little up in the air.

Q13: Are you aware of studies which seemingly disprove the cholesterol-heart hypothesis? If so, what do they have to say about them?

A13: Yes. There are different flavors of them. Most of the ones that are out there in these campaigns against all the current thinking about cholesterol being bad, saying that the big pharmo's are just trying to suck up money, and the statins are a joke and all that stuff – most of them are not scientifically sound. They're not dealing with the scientific methodology to make the criticisms that they make. There are some that do though; there are a lot of refereed scientific papers and scientific studies that talk about what's the real effectiveness of changing your diet as far as cholesterol goes, what's the real effectiveness of using the statins in patients. Those are very well executed studies, and I've read some of them. As far as the statins go, there's a big debate into whether they should be administered or not, but I think what it comes down to is that some of the best studies in those areas that have been done say that it depends on the patient. Some patients with familial diseases, you're just not going to be able to treat at all with the statins. Some patients that are at very

high risk for heart disease are not really going to benefit from it either. You don't see a difference when you treat them unless you give them this whopping amount of the statins, which could contribute to advanced side effects. Probably the best patients to do it [are the ones] with intermediate risk; you get the best outcome with those. Those are the best kinds of studies because that's almost what you'd expect – it's not going to work the same for everyone, there are populations of people whom it works better for. I think the ones to avoid are these studies that are put out there by interest groups and things like that, that talk about "Well, if you just take a B vitamin, and change your diet, you'll never develop heart disease," and that type of thing. Global stereotypes for biochemistry are dangerous in that respect, because certain people can do that, they can control it with their diet. Other people simply can't, and they're going to need some help with drugs or they're going to develop a heart attack at 4 years old. I think there's some merit to some of them, and not a lot of merit to a lot of them.

Q14: What most influences your opinions or conclusions about cholesterol and the heart?
A14: I have the background to read the peer-reviewed journals, so I try to get my research information from a lot of scientific studies. I tend to avoid more public publications, if that makes sense. So I tend to stick to that stuff because I can. I tend to avoid the news, and Time Magazine, things like that.

Scientist Interview #4

Professor, Biochemistry and Molecular Pharmacology
UMass Medical School
4/8/08

Q1: Do you know your own cholesterol level?
A1: Yes

Q2: Are you concerned about keeping or obtaining low cholesterol?
A2: I'm borderline high on baseline cholesterol, about 205 I think, but I am concerned about keeping my HDL high and keep saturated fat out of my diet. I'm aware of what's going on, and that I don't have much time left.

Q3: Do you know how atherosclerotic plaques accumulate?
A3: I think so, to the extent that anyone knows, we know that when there's an increase in LDL in the serum, that these particles are accumulated at the walls of blood vessels, and macrophages are attracted to that region, and it ends up creating waxy plaques that block the vessels, but I think actually the real physical mechanism is surmised at, it's hard to say that anything is specifically understood.

Q4: Do you know why plaques only form in arteries?
A4: No

Q5: How much cholesterol does the body/liver produce?

A3: About 1000 milligrams per day.

Q6: What effect (if any) does dietary cholesterol have on this?
A6: Zero, as far as I know.

Q7: Do doctors or medical institutions benefit in any way from prescribing statin drugs, or a particular statin?
A7: Well I think statins have been pretty widely agreed to reduce cardiovascular disease, or certain forms of it atleast, by as much as 30%. So hospitals and doctors benefit from having a healthier population. They may not benefit because they don't have more people in the hospital, I don't know, but I think society benefits and hospitals should consider that a benefit, too.

Q8: Is there any incentive for doctors to offer suggestions for lowering heart disease risk other than prescription meds?
A8: I think before they prescribe drugs they should insist that the patient, provided that they're healthy enough to, undertake exercise and dietary fat reduction. I think that should be the first step always.

Q10: Do you know and understand the mechanism by which statins work?
A10: Well I thought I did, but I'm not sure I do. Do they inhibit HMG-CoA reductase? *Yes.* What's really interesting is that ends up, surprisingly, in I think either an upregulation in HDL receptors, or downregulation in the other one, so it's a counter-intuitive result, and it's an upregulation, I think, of HDL that might benefit the patient. It's something like that. It wasn't just because it's inhibiting a specific enzyme in the cholesterol metabolism pathway. That's how biology works most of the time, you think you're going to get one effect and you get another one.

Q11: Are you aware of the side effects of cholesterol lowering prescription drugs?
A11: No I'm not, but if I were taking them I'd read up on it.

Q12: What do you believe about cholesterol as it pertains to heart disease?
A12: I think it's certainly clear that people with highly elevated LDL levels are really prone to coronary heart disease and atherosclerosis and strokes. I actually believe that it's a myth that you can control your cholesterol levels by just controlling cholesterol intake – we make way too much, actually it's essential, it's as high as 40 mol % in our cell membranes. So it could actually be very dangerous to reduce cholesterol, whether by production or intake. I think there probably is a link between saturated fat consumption and coronary heart disease, and it probably interferes with LDL metabolism and HDL metabolism. But when I do experiments I expect to see a "yes" or "no" answer. When you see a 20% or 30% effect, epidemiologists say that's significant. To me those are small effects, but if I were one of the 30% I would be very happy I suppose. I still think we can gain more from lifestyle changes, like diet and exercise, than from pharmacologic intervention, unless the individual isn't healthy enough to undertake those exercise regimes. That's my view, but I'm not a physician.

Q13: Are you aware of studies which seemingly disprove the cholesterol-heart hypothesis? If so, what do they have to say about them?

A13: I've seen people reinterpret the Framingham Heart study to say there's no link between cholesterol intake and body cholesterol levels, but we know that anyways. I'm not certain what the motivation for those studies are, whether it's just scientific integrity, or whether they're maybe being paid by the cattle industry, or whatever, to introduce alternative views. I would actually need to look at the studies directly themselves to make a decision, but I know there are people out there who are trying to push counter opinions.

Q14: What most influences your opinions or conclusions about cholesterol and the heart?

A14: I think it was the original work of Brown and Goldstein where they identified individuals with a genetic disease, and showing that hypercholesterolemia is very bad for the heart and for the circulation. But that is a really extreme scenario relative to what we normally experience. But there's no question in that extreme case, there's a very severe deficit in cardiovascular physiology. The rest, I'm just playing it safe, I'm not going to go counter to accepted practice, unless I see the evidence is really bad. Epidemiology is a very interesting field, in that it takes large numbers of patients with very carefully controlled studies in order for reasonable conclusions to be drawn. And even then it's a statistical conclusion. It's like the insurance actuary tables, or the bookies out in Las Vegas who are betting that they're going to win. So unless there's a really profound impact from a particular type of treatment, where everyone who's treated in a certain way experiences benefits, I think there's a possibility that you won't be in the group of beneficiaries of that particular treatment. But you hope you are, that's why you take it. I think exercise is the key thing, it's something I wish I had more of.

Additional comments: There have been people who will say "There's no link between cholesterol and heart disease, but it's like people denying there's global warming, or that DDT is bad for birds.

Doctors

Doctor Interview #1

Pediatrician
WPI Health Services
1/28/08

Q1: Do you know your own cholesterol level?
A1: I got it checked a couple years ago, and I know it was normal, but I don't have the exact number off the top of my head, no.

Q2: Are you concerned about keeping or obtaining low cholesterol?
A2: I try to eat healthy, yeah.

Q3: Do you know how atherosclerotic plaques accumulate?
A3: I believe it has to do with cholesterol – that it's still because it binds to blood vessels.

Q4: Do you know why plaques form only in arteries?
A4: No.

Q5: Do you know how much cholesterol the body/liver produces?
A5: No.

Q6: What effect, if any, does dietary cholesterol have on this?
A6: Well I know that you can have high cholesterol for a couple of different reasons. One would be dietary, one would be genetic; your body just makes more cholesterol. The dietary – if you have too much in your diet, then that's just going to add to the cholesterol you're body is already making.

Q7: Do doctors or medical institutions benefit in any way from prescribing statin drugs, or a particular statin? If so, what kinds of benefits?
A7: They will in the fact that their patients will most likely become healthier from them. But as far as monetary [benefits], if that's what you mean, no, unless some doctor in particular is doing a research project on statins, and they are getting paid to try a certain statin. Otherwise I don't believe so, I think doctors would prescribe a drug they feel is going to help a patient the most.

A lot of times pharmaceutical companies will take doctors out for dinner, or push their drug, like advertisement.

Right, right. I don't know how much that really has an effect on doctors. Like for me, I'm not going to give out a prescription just because I got a good pen from a pharmaceutical company or because they took me out for dinner; I'm going to give whatever my patient would benefit most from.

Q8: Is there any incentive for doctors to offer suggestions for lowering heart disease risk other than prescription meds?

A8: Yeah, definitely. The first line of treatment, depending on what their cholesterol level is, first of all would be exercise and diet to try to get the cholesterol lowered, and if that doesn't work, *then* you can start medication. But, yeah, I think definitely you need to look at the whole picture and not just let the patient eat whatever they want and not exercise.

Why wouldn't you want to push statins right away, and just get the cholesterol lowered?

I'd rather try the non-pharmaceutical treatment first, if their cholesterol isn't too high.

Q9: What would your response be to a patient who refuses to take a suggested statin?

A9: I would counsel them and let them know the risks and benefits, and explain to them why I think they should be on the statin, and hear their side, why they don't want to be on the statin. But in the end I can only give my opinion, and they can make the decision on what they want to do. If they were really persistent about not being on the statin, like I said, I would try counseling them on diet and exercise, but I wouldn't force them, I would just give them my opinion, tell them what I think is best for them, and then they can make the decision.

Q10: Do you know how statins work?

A10: I don't remember… like I said, I'm a pediatrician, I haven't written a prescription for a statin in probably five years.

Q11: Do you know the side effects of statins?

A11: Kind of in the fact that you have to be checking liver enzymes, but, once again, I'm not too familiar.

Q12: Do you believe that cholesterol is the major cause of heart disease?

A12: It's a contributing factor, maybe not *the* major cause, but yeah.

Q13: Are you aware of the studies refuting this?

A13: No.

A lot of people think that cholesterol really doesn't have anything to do with it, and they go through all the studies done on statins and whatnot, and just kinda finding all these flaws.

Well, you have to see who it is that's critiquing these studies. Are they biased in any way, and who did the statin studies – were they drug companies?

Q14: What most influenced your opinions on cholesterol?

A14: Medical school, you know, my training, from my teachers and my colleagues. And, not that I get really influenced by this, but you know, just commercials and the media out there – that's not where I get my education, but it's out there, and you use it.

Doctor Interview #2

Nurse Practitioner
WPI Health Services
1/29/08

Q1: Do you know your own cholesterol level?
A1: I do, it's a couple years old, but I know it. I think my total cholesterol is like, 180, I don't know, under 200 I know that.

Q2: Are you concerned about keeping or obtaining low cholesterol?
A2: I try to, I try to make a conscious effort. I have a really strong family history, my sister's already on medication. I try to exercise.

Q3: Do you know how atherosclerotic plaques accumulate?
A3: I do, a little bit. Through platelet aggregation I believe, so it's buildup against the walls of the platelets over time, and it causes narrowing of the vessels. The plaques form through buildup of basically fats, and it causes narrowing of the vessels which can cause a heart attack, or it could cause spasms, which is not always exactly a heart attack but it can cause tissue damage.

Q4: Why do plaques only form in arteries?
A4: Are you talking specifically about the heart vessels versus other areas? I think you can get atherosclerosis in other areas, too, like in your carotid arteries and your femoral arteries. So no, I don't think I can answer that.

Q5: How much cholesterol does the body/liver produce?
A5: I wonder if that's specific to each person, it's probably specific to what they're personal intake is, what their family history is. I don't know an average number, sorry.

Q6: What effect (if any) does dietary cholesterol have on this?
A6: I think it depends on what your cholesterol is, and how much cholesterol you put into your body. So if you're conscious about what you eat, and if your body able to break down fats, and in your liver and your gut, too, can get rid of the extra fats, I think it depends.

Q7: Do doctors or medical institutions benefit in any way from prescribing statin drugs, or a particular statin?
A7: When I worked in that particular office [as a physician] there were drug reps there always hounding me; drug rep lunches, breakfasts, whatever, trying to sell us a new medication for diabetes, a new medication for birth control, a new medication for cholesterol. So yeah, I think there are a small number of them wanting to make money, obviously. They give you tons of samples, and it's great to have the samples, but if I give them a 30-day supply of Lipitor and then their insurance won't cover it for the next month and I put them on something else then what good have I done them? Now their cholesterol's looking great because they're on Lipitor, but they can't afford their medication because it's $500 a month for a 30-day supply of Lipitor, and that's a lot of money to expect of elderly people that are probably living only on their social security which may or may not cover what they need. I

don't know about any of those pharmaceutical lunches where they kind of push me to prescribe or not to prescribe because for different people it's not always appropriate to be on the medication. Unfortunately the goal of pharmaceutical companies is to make money in America, it shouldn't be like that but it is, and they're making a lot of money off Lipitor, I can tell you that. It's very expensive per pill, per patient. Even Vytorin's very expensive. My sister's on Vytorin and her insurance without prior authorization is, for a 30-day supply, about $200. I think that's a lot to ask of people, and she has the genetic component, she has the gene, we have a gene in our family. I'm OK, but she's not, so she has to be on these medications; she sees a cardiologist already and she's 28 years old, so she's been strength training, trying therapeutic lifestyle changes, and needs to be on medication. The medication worked for her, the good deal is she was able to try the fish oil first, diet and exercise, they put her on the red rye yeast, that didn't help.

Q8: Is there any incentive for doctors to offer suggestions for lowering heart disease risk other than prescription meds?

A8: Absolutely. Definitely, if you don't have that gene you can lower your cholesterol with increasing fiber in your diet, cardiovascular exercise – bring your heart rate up to the max heart rate for your weight and age and height and your sex – and using over-the-counter stuff that's been proven, that they do recommend to help, like omega-3, fish oil pills, and red rye yeast. So there's definitely good reasons that you should try everything else first, especially because the medications are expensive, once they start doing the job most people have to stay on them long-term, and they have lots of side-effects, too. As far as prescribing goes, I think the guidelines still are: the first six months is called TLC for "Therapeutic Lifestyle Changes." You should be doing diet therapy, lowering cholesterol, increasing the fiber in your diet, starting a true exercise regimen. The guidelines now are like 60 minutes a day, 3 days a week, which is a lot to ask of people, but it was 30 minutes which [is ok], as long as their increasing their exercise. There are some over-the-counters, not really considered alternative therapy, but there's over-the-counters that you can try – fish oil, some of the omega-3's, red rye yeast actually is something you can use to help lower your cholesterol. Typically, I think that initially prescribing isn't the first thing they do, I think you're allowed six months – if you don't have a lot of risk factors – to try to get your cholesterol better, and if it's not [getting better], statins are the best things to help lower your cholesterol. I did work in primary care a little bit, and from what I noticed you could have a patient on 3 different generics, and it would not have the same effect as being on a higher dose of Lipitor, statins. And it's hard because your insurance coverage is kind of hard on that area, so for someone elderly, or other people, it's difficult for them to afford brand name Lipitor, it's very expensive. Sometimes you have to go through the route of trying a few different types of the generics first, and then getting prior authorization to go ahead and prescribe Lipitor medication, and that way the insurance company will cover it. It's kind of a process to do it. As far as nurse practitioners go, we try to think of the whole picture, try to be more holistic, and think about what we can do to get the patient better. When I saw patients in primary care that weren't diabetic, weren't severely obese, things like that, I really tried to push them to set goals – to try to exercise, to try to diet, give them a sample diet for two weeks and see what they can do, give them a book to read, and just really encourage them to not go on the medications because a) they're expensive and b)

they have tons of side effects, and not everybody likes to take a pill every day, so if you're not going to be good about taking a pill every day then what's the point?

Q9: What is a doctor's response to a patient who refuses to take drugs when prescribed?
A9: I think I would examine why they don't want to be on the statin. Is it the cost? Is it compliance for someone who's not good about taking a pill every day? Side effects? Maybe they heard from their friends, a lot of older people especially that kind of talk and they have knitting circles about "well I was on this medication and I peed every five minutes," "I was on this one and I liked it." So I may just ask a little bit about what their bias is, but I think if they truly needed it then I would have to find a reason why they would want it and then kind of adapt their care around it

Q10: Do you know and understand the mechanism by which statins work?
A10: I did, I can give you a good guess. It works in your gut I believe, unless that's the other ones. I think it works on the cholesterol in your gut, and then you actually lose it that way.

Q11: Are you aware of the side effects of cholesterol lowering prescription drugs?
A11: There are a lot of side effects to Lipitor, there's myalgia – muscle pain, muscle breakdown, so you have to monitor them closely for that. And it can be life-threatening for some people, so when you actually start them on statin therapy you have to check their blood levels for muscle breakdown, and their liver function has to be tested before, and I think three to six months after, starting the medication, because that muscle breakdown can actually cause long-term damage or death from liver disease. So there's lots of side effects, you have to be careful. People with liver disease, they can't be on the medication. It can cause other damage, too, so it's not always appropriate for some people, so it's good to try to push them to do diet and exercise and things like that.

Q12.1: What do you believe about cholesterol as it pertains to heart disease?
A12.1: I think that for some people it can be a major cause of heart disease. If you play in a combination of some people who are diabetic with high cholesterol that live a sedentary lifestyle with a strong family history of heart disease, they are probably at the highest risk. Smoking is still your number one modifiable risk factor to prevent heart disease. So that could mean in that case that there needs to be more push on smoking cessation versus cholesterol treatment therapy, but there is a major relationship between high cholesterol levels and heart disease, absolutely. I think it ranks pretty high up there with the risk factors. [There is something] called familial hypercholesterolemia, so there's a genetic component to it where, just in general by age 20 you should have at least one test of cholesterol if you don't have a family history, and if it's normal you should repeat it every five years basically. But if it's abnormal, obviously, if there's a strong family history, you should be starting screening a lot sooner than that because if you have that genetic component you do need strict therapy whether it's diet versus statin therapy, just because you need to prevent heart disease. If it's cholesterol, smoking, obesity, it's a major risk factor for heart disease, atherosclerosis.

Q12.2: So you would suggest trying to quit smoking before going on statins?

A12.2: Yeah, because it's a sort of lifestyle change, absolutely. Some people can't change the fact that they have diabetes; that's what you have, it's not going to change. But as far as obesity, exercising, things like that that are lifestyle modifications, the number one thing you can change that causes heart disease is smoking. So I think that that's pertinent. If somebody comes in and says that they smoke cigarettes and they have high cholesterol with no other risk factors, I'd still get them on smoking cessation along with diet and exercise for the first six months, and if that didn't work then we'd probably have to start medication.

Q13: Are you aware of studies which seemingly disprove the cholesterol-heart hypothesis? If so, what do you have to say about them?

A13: No, I did do a quick search online though and there was one person, I don't know if he's a physician or not, I don't know how trustworthy he is, but he's from England and he was talking about whether there's a real relationship or not between cholesterol and heart disease, or if it's just a push for meds. But I think there is, I don't think I'm aware of any studies that there is no relationship between cholesterol and heart disease. The only study I know of that targets a certain statin is the Vytorin study that just came out. There's that research that just came out on Vytorin, which is Zetia and Zocor combined, and you wonder how good of a combination they really are, if they're effective versus taking one of them, taking Zetia or Zocor, so it's kind of concerning.

Q14: What most influences your opinions or conclusions about cholesterol and the heart?

A14: I try to stay with the American Heart Association guidelines, and the NIH, National Institute of Health, puts out there clinical practice guidelines on what you should be doing. They kind of take a look at all the studies that are out there, and they say "OK, from these studies, what Is really real?" So I try to stay with the American Heart Association guidelines, the National Institute of Health, and the National Parent Health guidelines, those are my three gold standards for cholesterol.

Additional comments: *A large portion of this interview did not flow in a question and answer format. The comments made during the interview were matched to the questions that would have been asked as shown above, and we asked for clarification on any questions that were not answered.*

Doctor Interview #3

Primary Care Physician
Middlesex Family Physicians
3/5/08

Q1: Do you know your own cholesterol level?

A1: Yes

Q2: Are you concerned about keeping or obtaining low cholesterol?

A2: Well, I do try to keep my LDL levels pretty low, it's on the high side of normal right now, and my HDL could be better. So yes, I guess I do.

Q3: Do you know how atherosclerotic plaques accumulate?
A3: Well, basically, when cholesterol gets through the wall of an artery, the body's immune system responds by sending specialized white blood cells to absorb the cholesterol. These white blood cells trigger your body's inflammatory response and form plaques, and cholesterol plaque causes the muscle cells form a hard cover over the area. This hard cover is what narrows the artery and increases blood pressure

Q4: Why do plaques only form in arteries?
A4: I guess it could have to do with different proportions of different components of the blood, but I really don't know.

Q5: How much cholesterol does the body/liver produce?
A5: I find it varies between patients

Q6: What effect (if any) does dietary cholesterol have on this?
A6: Not much. Your body is good at keeping a level balance of things like cholesterol levels, so it's hard to change that. Usually it takes a long stretch of lifestyle changes, usually 6 months or more.

Q7: Do doctors or medical institutions benefit in any way from prescribing statin drugs, or a particular statin?
A7: Well, I think I have a Lipitor pen from somewhere, but I don't prescribe patients Lipitor because of it… there aren't financial kickbacks or anything, though the reps sometimes drop off office supplies with their name on it, which I suppose saves me from buying a pen. When actually writing prescriptions, though, I take into account what the patient needs, and what is best for them. I always suggest diet and exercise first. Now, whether they follow that is up to them. After six months or so, if I don't see the improvement I hoped for, I might suggest a statin regiment. I guess my main benefit is to continue to have patients… if they all kick from heart attacks, who will I see every day? (Laughs)

Q10: Do you know and understand the mechanism by which statins work?
A10: They inhibit HMG-CoA reductase, an enzyme used to make cholesterol. If your body can't make the cholesterol, you'll have lower levels in your blood.

Q11: Are you aware of the side effects of cholesterol lowering prescription drugs?
A11: The common side effects could be headaches, nausea, and fever. Occasionally you find muscle cramping or atrophy, in which case we'll generally go an alternate route.

Q12: What do you believe about cholesterol as it pertains to heart disease?
A12: I think that people with elevated LDL levels are prone to atherosclerosis and coronary heart disease. I think that people walking around with cholesterol levels out of control are in huge risk of having a heart attack, just because they don't even realize there's a problem

that they could fix just by eating a little better and exercising. Patients gain a lot from diet and exercise, if they actually follow it, which often isn't the case.

Q13: Are you aware of studies which seemingly disprove the cholesterol-heart hypothesis? If so, what do they have to say about them?
A13: Well, I think I would have to look at the particular studies. I don't have any opinions on the idea right now, just that I haven't really looked into it.

Q14: What most influences your opinions or conclusions about cholesterol and the heart?
A14: Well, I'd have to say medical school, and just kind of logic. I've had patients with elevated LDL levels go on to have heart attacks, and while that isn't always the case, it follows with what I was taught. I also go to conferences where I see other doctors or researchers give lectures, and I suppose if they had a compelling argument that might pique my interest.

Doctor Interview #4

Primary Care Physician
UMass Memorial Medical Center
3/12/08

Q1: Do you know your own cholesterol level?
A1: Yes

Q2: Are you concerned about keeping or obtaining low cholesterol?
A2: Yes

Q3: Do you know how atherosclerotic plaques accumulate?
A3: Yes, now I can elaborate… so in normal arteries components of the blood traverse the endothelial cell layer – which is the innermost layer of the artery – on a routine basis, and also exit the arterial wall and become part of the circulation again. It is a way of providing substrates and nutrients to different part of the arterial wall. For reasons that we are still trying to elucidate, in certain parts of the arterial tree lipoproteins in particular appear to be retained in the arterial wall for longer periods of time. And under those circumstances those retained lipoproteins become a substrate for inflammatory cells, particularly monocyte-derived macrophages, where they're taken up by those cells in an unregulated manner, in a manner that does not involve the classic LDL receptor, and form foam cells. The continued formation of foam cells results in the activation of inflammatory pathways. Changes in the overlying endothelium that facilitate accumulation of lipoproteins and inflammatory cells in the arterial cell wall, and through an autocatalytic process that occurs over time, the atherosclerotic plaques begin to form, and then there is a process of maturation in which the collections of cholesterol coalesce, form crysatals and a variety of physical alterations that, for a lack of a better term, take on the appearance to biological systems of an abscess, an area or collection of material that is not supposed to be there. And in the process of walling off the collection of cholesterol, that is part of the maturation of atherosclerotic plaque formation. You have a core that has inflammatory cells and cholesterol, you have a

cap that involves some smooth muscle cells and some extra cellular matrix, and then you have an endothelium that overlies that, and usually the endothelium overlying the plaque has dysfunctional characteristics that don't support the normal processes that maintain the latency of blood vessels. It's through those processes that one develops a plaque, and ultimately the plaque can rupture and facilitate a cardiovascular event.

Q4: Why do plaques only form in arteries?
A4: Plaques in only form in arteries because the structure of the arterial wall is such that the types of cells needed to form the plaque are more abundant in arteries that in veins and the number of the injurious stimuli to arteries only exist on the arterial side of circulation. And the evidence to support that is derived from observation that if one performs a transplant and puts a vein on the arterial side of the circulation it will develop atherosclerotic plaques.

Q5: Do you know how much cholesterol does the body/liver produce?
A5: It depends on the individual and circumstances… I wouldn't know with certainty.

Q6: What effect (if any) does dietary cholesterol have on the body's cholesterol level?
A6: In the short term it has a relatively modest effect. You often don't change your circulating total cholesterol levels by short term dietary changes. Over the long term it has a significant effect through two pathways. One involves the actual addition of cholesterol to the blood stream through what is absorbed through the gut, and the other involves sending signals to the liver that actually prompts it to generate more cholesterol in particles known as VLDL [Very Low Density Lipoproteins] that better metabolize in the body through a number of more constitutive processes that generate LDL cholesterol.

Q7: Do doctors or medical institutions benefit in any way from prescribing statin drugs, or a particular statin? If so, what kinds of benefits?
A7: The answer is yes, in a few different ways. One is that by taking better care of your patients and lowering their cholesterol one gives the impression to the patients, deservedly so, that they are being well cared for, reaching their target, and that their overall healthcare is improved. The reason why statins would be used has a lot to do with the fact that they are the most efficacious class of drugs we have in reducing levels of cholesterol. In terms of individual statins, I personally don't benefit from any individual statin I might prescribe. There is no way to increase one's income by prescribing one statin versus another. There are occasionally constraints from insurances that might impact a physician's income, based on what statin they prescribe, in what is known as a capitated healthcare plan. One way health insurance [is provided] to individuals is to say "OK, your insurance company will pay a group of doctors $5000 a year for taking care of you." If the cost is less than $5000, they keep the difference; if it costs more, it's their problem. So if they find less expensive drugs to treat your problems with, it costs less to treat you, and they might have a little more money at the end of the year. Depending upon the area, one statin might cost more or less than another, and that might be a particular benefit.

Q8: Is there any incentive for doctors to offer suggestions for lowering heart disease risk other than prescription meds?

A8: There's ample evidence that if patients CAN change their lifestyle that they'll do better and have less heart disease. Most doctors are taught that that is one of the first things to do – to try and make suggestions and do what one can to convince patients to change their lifestyle. It is however, the least effective way for changing a number of things we follow like lipids and diabetes, etc., because patients only comply with recommendations on average 8% of the time. One contrasts that sharply with the compliance rate of statins which don't have a lot of side effects, in excess of 80-90%. For 100 patients, one set treated with lifestyle only, one set treated with statins, at the end of the day there will be more patients in the statin group that respond than the lifestyle group. In the lifestyle group, of the people that respond and are very serious, they'll get a lot of benefit, but that's a smaller fraction of the patients. It's a product of what people will do.

Q9: What is a doctor's response to a patient who refuses to take drugs when prescribed?
A9: One could use different drugs other than statins, or one could focus solely on lifestyle changes, but we don't get mad at patients or yell at them or call them stupid or that sort of thing. That's not professional.

Q10: Do you know and understand the mechanism by which statins work?
A10: Yes. The rate limiting step in cholesterol synthesis is an enzyme known as HMG CoA Reductase (hydroxyl methyl gluteral CoA) and inhibiting that enzyme prevents production of melovonate, which is first building block for cholesterol. So when you give an animal or individual a HMG CoA Reductase inhibitor, also known as a statin, you essentially are poisoning the liver's ability to make cholesterol. As a consequence, the liver perceives that you are in a state of cholesterol deficit and up-regulates its receptors on the surface to attach to circulating particles of cholesterol in the blood and grab them because it needs them, but it can't use them to make more cholesterol so it excretes them in the bile. That's where more cholesterol exits. One of the other things statins do is they tell the body that it's cholesterol poor, so your intestines reabsorb a lot of the bile to make more cholesterol. That's actually a break on the efficacy, how much you reabsorb, but far and far away HMG CoA Reductase inhibitors are the most potent way of lowering the patient's cholesterol with a drug. There are other ways you can do it that are not as patient friendly as a statin.

Q11: Are you aware of the side effects of cholesterol lowering prescription drugs?
A11: Yes, they differ based on type of drug. Statins have side effects that some are common with other cholesterol lowering drugs and some are distinct. Most common side effect from statins are what are called myalgias, which is a fancy medical term for muscle aches, and this happens in up to 15% of patients who take statins, about half of that 15% will discontinue the statins because of the muscle aches. One can also have a more severe form of the muscle aches, which can actually cause a breakdown of the muscle tissue, which is known as rhabdomyosins and that's a very serious side effect. Other common side effects include evidence of minor liver dysfunction based on tests we can obtain from the blood and also evidence of mild muscle dysfunction and then there's a host of less common side effects that actually don't really differ from placebo in trials.

Q12: What do you believe about cholesterol as it pertains to heart disease?

A12: Cholesterol is a little bit of an imprecise term; the data linking LDL cholesterol to heart disease in my opinion is incontrovertible and undeniable.

Q13: Are you aware of studies which seemingly disprove the cholesterol-heart hypothesis? If so, what do they have to say about them?
A13: I would have to review the study you're talking about in particular. I am aware that people disagree with the opinion that LDL cholesterol is a causal factor for atherosclerosis and heart disease, but I disagree with that opinion.

Q14: What most influences your opinions or conclusions about cholesterol and the heart?
A14: The fact that the entire of circle of evidence exists for the link between LDL cholesterol and cholesterol. Back in the day when infectious diseases were a big problem, a guy named Koch developed what's called Koch's postulants. So there was a time that people didn't believe that bacteria caused disease, so he developed a method of proving an organism caused a particular disease. The postulants were: in every instance of the disease you should be able to isolate the offending organism; the offending organism should be able to be cultured after you isolate it, and then you should be able to inject the organism back into a person and prove that it recapitulates diseases. So that's how we got to the concept of the circle of evidence. So what is the circle of evidence for LDL cholesterol? People who have higher LDL cholesterols have higher heart disease levels. People who have a genetic defect in their LDL cholesterol metabolism, notably a defect in the LDL receptor in the liver, have very high levels of LDL, and also have a very precocious level of heart disease. Patients whose LDL cholesterol is reduced by a multiple of mechanisms, statins being only one, demonstrate reduced levels of heart disease, and if you give experimental animals high levels of LDL cholesterols, they'll develop heart disease, so the entire circle exists for LDL cholesterol.

Doctor Interview #5

Primary Care Physician
UMASS Memorial Medical Center
4/3/08

Q1: A strictly yes or no response is all that is asked for in this question: do you know your own cholesterol level?
A1: Yes.

Q2: Are you concerned about keeping or obtaining low cholesterol?
A2: Yes. I'm on a medication for it.

Q3: Do you know how atherosclerotic plaques accumulate?
A3: I know about as well as anybody else. Do you want the explanation? Well, it's thought that the cholesterol penetrates the endothelial arteries and builds up as a plaque underneath the surface.

Q4: Why do plaques only form in arteries?
A4: Good question, I don't think anybody knows.

Q5: How much cholesterol does the body/liver produce?
A5: Like how many grams per day? I have no idea. It does manufacture cholesterol and recycles it through the bile, but I don't know how many grams.

Q6: What effect (if any) does dietary cholesterol have on this?
A6: I think your body just produces whatever it's going to produce, and how much you eat *adds* to that. But it doesn't influence what your liver does, in terms of making the cholesterol.

Q7: Do doctors or medical institutions benefit in any way from prescribing statin drugs, or a particular statin? If so, what kinds of benefits?
A7: The days when we used to get – I never got – kickbacks from the pharmaceutical companies – free vacations if you write a hundred prescriptions for their drug – those days are long gone… So I don't think in terms of the medical profession there's any benefit for doctors or hospitals to prescribe their statin.

Q8: Is there any incentive for doctors to offer suggestions for lowering heart disease risk other than prescription meds?
A8: No… but there used to be. You'd have your own program and you'd refer people to that. But nowadays, with all the ethical concerns – UMass, they just passed a rule here that we can't take dinners. It used to be we'd go out to dinners, they'd want to sell a statin, or they'd have a new statin. They'd be able to rent a restaurant room, and all the doctors who would want could go there, and there'd be a lecture and they'd provide the meal, and that was kind of a standard all over the country. UMass physicians can't go to the drug-sponsored dinners anymore. We're not even supposed to take pens that say, you know, have a statin on them. Two weeks ago they introduced a bill on Beacon Hill to make it a law in Massachusetts that doctors can't go to these. But, there's no ulterior motive for doctors to prescribe statins, or to promote one form of reducing heart disease over another.

Q9: What is a doctor's response to a patient who refuses to take drugs when prescribed? (doctors only)

If a patient came to you with high-risk cholesterol levels, what would you recommend to them, and your reasoning behind it?

A9: Well, yeah, part of it is genetics, and part of it is diet. It's always cheaper to change your diet than to take a drug. Most, not everybody, but most people would rather – well I don't know, maybe half and half – some people would just like to take a pill and eat whatever they want, but other people would rather make a change in their diet rather than have to take a pill every day, so it really depends on the patient's philosophy, but I always try to take the cheapest route to keep medical costs down, which is change your diet first, depending on how high the cholesterol is. If it's just a little bit high, I'll tell you to watch what you eat and have them check it again next year and see what it is. If something needs to be done immediately then I refer you to a nutritionist, because really, it takes an hour to

sit down with somebody to explain what to eat and what not to eat, and really tailor the diet so that they'll like to eat it, and I don't have time to do that in a 15-minute visit. So we have a nutrition clinic and we just send them all off to there. We usually give that about 3 months to a year, depending on how bad their cholesterol is, and then check the cholesterol again, and see how they're doing. So some people who have horrible diets – and good genetics – are able to bring their cholesterol down to a desirable level just by changing what they eat. Nowadays there aren't that many of my patients that really eat that badly. So most of the time there's not much room for improvement in their diet, so they can do this or that, and it doesn't affect their cholesterol that much. Then I'll start them on a statin usually – that's the least side effects of all the medications we have available for lowering cholesterol.

Would you say that as a rule you would reserve statin treatment as a last resort?

It's my first *prescribed* resort, but yeah, I usually try other things first. I also use a high cholesterol level to motivate people to quit smoking. Now, they may be on the fence about quitting smoking – I just did this about 10 minutes before you came here – somebody's cholesterol level was really bad, and I said, "You need to quit smoking." Or it could be that a high cholesterol level would make me more aggressive about bringing the blood pressure down – if someone has a blood pressure that's really on the border line and then they come back with really high cholesterol, then I'm going to be more aggressive about reducing their other risk factors. Losing weight can help; it doesn't help that much with cholesterol, but it can help, so that's another risk factor for heart disease. I usually do all of those other things, then as a last resort would be medication.

Q10: Do you know and understand the mechanism by which statins work?
A10: I think I do – I haven't thought about it in a while. I think it reduces production of cholesterol in the liver.

Q11: Are you aware of the side effects of cholesterol lowering prescription drugs?
A11: They don't have very many… if I can think of how many… Well, the famous ones are rabdomyalysis, or muscle breakdown. Serious cases of that are fewer than 1 in 10,000. Elevated liver enzymes – when they first came out we would check everybody's liver before you started and do it again, but there's never been a fatal case of hepatitis from a statin. So there's no real need to be on the lookout for that. If they have a problem you just stop it. They're very well tolerated, it's much better than blood pressure medicine or medication for diabetes, they don't make you sleep or stay awake, or give you diarrhea. I've met occasional patients who have had an allergic reaction, but you can have that with any medication, or food for that matter.

Q12: What do you believe about cholesterol as it pertains to heart disease?
A12: Well, I think it's an important risk factor, but it's not the only one. Probably high blood pressure's the worst, and then smoking and diabetes, lack of activity, obesity, genetics – these are all cardiac risk factors, and cholesterol is one of the many. For some people it's their only risk factor, and for other people it's just one out of the whole gang of risk factors they have. It's not always the most important.

Do you think, in general, people need to put more emphasis on other risk factors?

Well I think they all get hit pretty hard. Yeah, we don't make people go exercise, as a general rule. I don't think cholesterol's overemphasized.

Q13: Are you aware of studies which seemingly disprove the cholesterol-heart hypothesis? If so, what do they have to say about them?
A13: Hmm… I haven't seen any of them.

Q14: What most influenced your opinions or conclusions about cholesterol and the heart?
A14: Well these big decade-long studies with hundreds of thousands of people in them where they actually measure the cholesterol. I can give you the little graphs if you want. I have little bar graphs showing if your cholesterol's 100, this is how many people died, and the ones at 150, this is how many people died, and you just see that the higher the cholesterol goes up, in a very nice pattern, the more deaths there were in that group. And now they have it divided up according to your good cholesterol and your bad cholesterol, so I find that very convincing.

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