ASSESSING THE HISTORY OF HEART DISEASE IN THE UNITED STATES, 1950-1990

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ABSTRACT

This thesis analyzes the history of the social theory of heart disease and its rise to prominence in the United States. The social theory, as defined by Dr. James Le Fanu in his work *The Rise and Fall of Medicine*, is society’s developed understanding of lifestyle and disease.

This work incorporates detailed analysis of this history from 1950 to 1990. From 1950 to 1961, Ancel Keys advanced his diet-heart thesis. From 1972 to 1983, the Multiple Risk Factor Intervention Trial (MRFIT) was especially influential. From 1983 to 1990, the US began the mass production of cholesterol lowering drugs and established the National Cholesterol Education Program. Each of these periods are explored in great depth in the chapters of this thesis. For each period, the thesis examines relevant articles from *The Journal of the American Medical Association*; these publications document the history of the social theory.
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Chapter 1
Introduction

For many Americans, what it means to have good cardiac health has continually changed over time. As recently as November 2017, the American Heart Association has updated the nation’s detection, prevention, management, and treatment of high blood pressure. The new guidelines state that a normal blood pressure is less than 120/80 mm Hg, and as a result of this changed definition, approximately half of the adult population is now considered to have high blood pressure, a contributing factor to heart disease.¹ So much of what we understand about our own health is determined by government guidelines that focus our efforts on sustaining longevity. However, the question of why these guidelines exist in a constant state of flux remains unanswered.

The purpose of this thesis is to investigate how our society defines medical orthodoxy and explore the specific history of changes in our understanding of heart disease and lifestyle in the second half of the twentieth century.

In the context of historical analysis, there exists a revisionist perspective on relationships between diseases of aging and lifestyle characterizations that either contribute to or inhibit the advancement of disease. The scholar behind this perspective is Dr. James Le Fanu. In his medical history, *The Rise and Fall of Medicine*, Le Fanu details what he believes has perpetuated our

modern understanding of lifestyle and disease, “the social theory”. What Le Fanu questions is the extent to which prevention practices in the United States have developed as a result of scientific evidence linking diet changes to an increased risk of death from cardiovascular disease. There is an understanding among the medical community, as well as the general public, that poor lifestyle choices will result in an increased risk of a disease of aging, such as cancer, type-II diabetes, or heart disease. However, Le Fanu argues that the modern notion that heart disease is preventable by changes in diet or other aspects of lifestyle is more a socio-economic phenomenon rather than a scientific conclusion.

Le Fanu additionally critiques the social theory by explanation that the theory does not simply encourage a healthy lifestyle in the promise of a longer life; instead the theory, “makes specific claims about the causative role of commonly consumed foods and environmental pollution as a major factor in common illnesses”. Le Fanu explains that the social theory represents society’s modern understanding of diet and lifestyle and its resulting cardiovascular consequences. *The Rise and Fall of Medicine* primarily analyzes this relationship by questioning how the science behind society’s accepted beliefs were perpetuated through media attention and government funding. The aim of this thesis is to explore the history of the social theory. My sources include a selection of articles from *The Journal of the American Medical Association*.

The social theory hypothesizes that diet is the largest contributing factor to cardiovascular complications, including heart attack (myocardial infarction) and stroke (cerebrovascular accident). Le Fanu’s analysis questions this claim. More specifically, he asks whether the modern “western” diet of the United States has had a casual role in cardiovascular disease. To contextualize

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the analysis in *The Rise and Fall of Medicine* it is also essential to consider whether or not cardiovascular disease has increased throughout the modern era. If any increase did occur on a national scale, it is important to consider when the increase occurred, the scale of the change, and the duration. To begin, it is essential to define key terms. For the purposes of this study, increased rates of heart disease will be considered direct fatalities as a result of a heart attack or stroke.

Heart disease can also be called cardiovascular disease, coronary disease, or heart and blood vessel disease. Most of the complications associated with heart disease originate from a buildup of plaque in the walls of the heart’s arteries. The blockage can slow the passage of blood through the arteries, or if a blood clot forms within the artery wall, can stop all blood flow. This process of atherosclerosis can lead directly to a fatal heart attack or stroke. Atherosclerosis can generally be defined as a slow process by which a buildup of fat, cholesterol, and other substances form plaque that reduces or completely restricts the heart’s circulation of oxygen. A heart attack and a stroke both involve atherosclerosis; however, their physiological mechanisms differ. A heart attack involves the blockage of blood flow to the heart, by way of a blood clot. When heart muscle is entirely deprived of blood, it is also deprived of oxygen, and begins to die; this process is called ischemia. Similarly, an ischemic stroke is a blockage of a blood vessel that carries oxygen to the brain. An ischemic stroke in which the brain muscle is deprived of oxygen, results in the death of that brain tissue in a similar fashion to the physiological complexities of a heart attack. A hemorrhagic stroke differs in that a blood vessel is not simply blocked but actually bursts in the

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4 "What is Cardiovascular Disease?". *American Heart Association*, May 2017. [http://www.heart.org/HEARTORG/Support/What-is-Cardiovascular-Disease_UCM_301852_Article.jsp#](http://www.heart.org/HEARTORG/Support/What-is-Cardiovascular-Disease_UCM_301852_Article.jsp#).
brain. According to the American Heart Association, uncontrolled high blood pressure, hypertension, is a likely contributor to both heart attacks and strokes.⁵

Le Fanu explains that the social theory developed as medicine’s “Golden Age of Discoveries” (ca.1940-1975) began to peter out. The accidental discoveries of antibiotics set the stage for this golden era. According to Le Fanu, in the 1930s, a doctor acted as a “therapeutic nihilist.” Both the doctor and the patient accepted the limitations of medical practice and expected little from the dozen or so remedies that the doctor had to work with.⁶ Antibiotics’ great success changed this expectation. As more antibiotics came into existence, drugs were able to target and cure specific infections, and this change saved lives. More important for the purposes of this thesis investigation, the golden age of antibiotics raised the expectations bar. People increasingly came to think that medicine could solve any health problem. As treatments for infections were established, the medical community increasingly turned its attention to diseases of aging.

One important contributor to the idea that diet might cause heart disease was the discovery of the causative role that smoking played in lung cancer development. This discovery was the first rigorous confirmation that a lifestyle choice, smoking tobacco, caused a deadly disease, lung cancer. First illustrated by Bradford Hill’s demonstration in 1950, the case of lung cancer naturally led to the question of whether the same might be true for other diseases. Perhaps mass prevention of diseases of aging was both possible and more efficient than searching for specific cures.⁷ For example, if lung cancer could easily be prevented by discouraging smoking, why spend money and time developing a cure for something that did not have to exist in the first place?

⁵ "What is Cardiovascular Disease?", American Heart Association.
There are two problems in extending the case of lung cancer to other diseases. Now we are aware that lung cancer is part of a complex causal web that includes genetic, physiological, and environmental factors in addition to smoking. More important, smoking turns out to be unique in its role as a lifestyle choice with a rigorously-verified causal link to deadly disease. For heart disease, we are now aware of genetic, physiological, and environmental factors that contribute to an increased risk of disease, in addition to whatever diet and lifestyle choices might be relevant. However, modern research relating to the causes and preventions of heart disease fails to show direct scientific evidence to suggest that diet changes alone are capable of reducing the risk of cardiac death resulting from a heart attack or stroke.

Le Fanu explains that beginning in the early 1980s, if not earlier, the social theory, became medical orthodoxy. This thesis examines the history of the social theory of heart disease and its rise to prominence. That history can be periodized as follows. From 1950 to 1961, Ancel Keys advanced his diet-heart thesis. From 1972 to 1983, the Multiple Risk Factor Intervention Trial (MRFIT) was especially influential. From 1983 to 1990, the US began the mass production of cholesterol lowering drugs and established the National Cholesterol Education Program. Each of these periods will be explored in great depth in the subsequent chapters of this thesis. For each focus and period, the thesis examines relevant articles from The Journal of the American Medical Association; these publications document the history of the social theory.

In the context of the history of links, real or imagines, between heart disease and lifestyle, the first time period of this investigation explores the origins of the diet-heart thesis and its lasting impact on the direction of future medical research and orthodoxy. The key figure is Ancel Keys, who published influential works in 1957 and 1961. This thesis examines why the American Heart Association did not originally endorse Keys’ work in 1957, but did approve the material in 1961.
Ancel Keys was an American physiologist and the Director of the Laboratory of Physiological Hygiene at the University of Minnesota. Keys had a primary interest in nutritional contributions to physiological systems and was particularly interested in cholesterol levels in an individual’s arteries as well as overall fat consumption.\(^8\) Keys was the first to pursue vigorous study of this hypothesis; however, Le Fanu suggests that Keys’ scientific process was influenced by the fact that he had identified that diet must be a contributing factor to heart disease even before his research began. According to Le Fanu, Keys failed to account for an “epidemic” pattern of heart disease in correlation to isolated diet changes, as well as for a heart attack or stroke’s defining physiological feature, a blood clot.\(^9\)

According to the American Heart Association, cholesterol is a steroid alcohol that contributes to cell building. If there is too much buildup of the substance, cholesterol can cause health problems. Cholesterol in the body comes from two primary sources; the liver and the animal products consumed. Cholesterol produced in an individual’s liver is an essential precursor for important hormones such as testosterone and estrogen. However, according to the American Heart Association, too much fat in an individual’s diet can cause the liver to make more cholesterol than is needed for a healthy individual. When too much cholesterol is circulated in the blood stream, there is a greater risk of blockage or blood clot formation that can lead to immediate death by heart attack or stroke.\(^10\) Modern physiological and nutritional understandings also separates LDL “bad” and HDL “good” forms of cholesterol. High levels of bad cholesterol and low levels of good cholesterol contribute the most to an increased risk of heart attack and stroke.

As Ancel Keys began to investigate cholesterol’s role in diet and its correlation to an increased risk of cardiovascular disease, he hypothesized that dietary cholesterol might increase the plaque in an individual’s blood vessels, thereby forcing blood through small spaces and increasing the risk of a possible heart attack. In his book, The Man Who Touched His Own Heart: True Tales of Science, Surgery, and Mystery, Bob Dunn summarized Keys’ hypothesized mechanism as follows:

The cholesterol shepherds the animal fat, which isn’t soluble in water, thorough the blood. That the levels of cholesterol in the body increase when one eats animal fats is not, in and of itself, a malfunction. It is the body’s marvelous response to a hard-to-move compound, but somehow, Keys felt sure that blood cholesterol levels must be associated with the extent to which high cholesterol leads to atherosclerosis.\(^\text{11}\)

Dunn suggests that Keys’ hypothesis was unique and perhaps an inaccurate representation of cholesterol’s physiological function.

One of Le Fanu’s major critiques of Keys was that his initial works were not published as peer-reviewed medical journals. Instead they were published as books, and this allowed the diet-heart thesis to gather social momentum. The publications were only later accepted by the medical community.\(^\text{12}\) Dunn seemed to come to a similar conclusion as he drew attention to Keys’ role in the American Heart Association’s change of position regarding the link between saturated fat, cholesterol, and atherosclerosis. Dunn suggested that Keys’ publication of his book, Eat Well, impacted the American Heart Association:

In 1959, before Eat Well, the American Heart Association took the position that the link between saturated fat, cholesterol, and atherosclerosis was not well established. In 1962, after the publication of Eat Well, and with Keys by then on its board, the American Heart Association advised Americans to avoid saturated fat and cholesterol… The American


Heart Association began to recommend a diet that bore a striking resemblance to that which the Keyses advocated in *Eat Well*.¹³

Dunn cited the American Heart Association’s change of position regarding the link between saturated fat, cholesterol, and atherosclerosis to suggest that this change was likely impacted by Keys’ work and presence on the board.

In his analysis of Keys’ work, Le Fanu summarizes that from 1920 to 1960, death rates from heart disease rose dramatically in the United States, before declining in the 1960s and 1970s (figure 1). However, he concludes that there is no evidence that this rise and fall was in direct correlation with large scale lifestyle or diet changes across the population (figure 2):

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¹³ Dunn, Rob. “The Man Who Touched His Own Heart: True Tales of Science, Surgery, and Mystery”, 213.
By the early 1980s it was quite apparent that [the rising] trend had been reversed and that the incidence of heart disease had gone into steep decline. The decline, it must be appreciated, was universal, across all ages, classes and ethnic groups, and international, occurring simultaneously in the United States, Canada, New Zealand and Australia. Thus if the ‘lifestyle’ theory of heart disease were correct, people would have had to have made substantial changes in their diet at least ten years earlier, not just in the United States but in all these other countries as well. Clearly this was impossible for, as shown in the graph on page 375 [figure 2], the precipitous rise and equally precipitous fall in heart disease occurs in different countries in parallel, while the proportion of fat in the diet hardly changes.\textsuperscript{14}

In citing the “universal” decline in incidence of heart disease, Le Fanu cites that the social theory cannot be correct. He suggests that a central weakness of Keys’ diet-heart thesis is his inability to account for this “precipitous rise and equally precipitous fall in heart disease.” Furthermore, he concludes that although diet may contribute to cardiovascular disease, the relationship is not independently causal, “a ‘high-fat’ diet along with smoking and raised blood pressure might be a contributory but not a determinant factor in the rise of heart disease.”\textsuperscript{15}

Le Fanu and others now question Keys’ conclusions, but nevertheless, by 1962, the American Heart Association supported Keys’ claims regarding the relationship between diet and cardiovascular disease. From this point forward, heart disease research focused on further investigation of the links between increased dietary cholesterol, overall fat consumption, and increased risk of death by heart attack or stroke.

As heart disease research focused on these links, the medical community was guided by the question of how best, if at all, heart disease could be prevented. Thus, the United States and Europe launched the largest and most expensive experiments in the history of medicine: The

\textsuperscript{14} Fanu, James Le. “The Rise and Fall of Modern Medicine”, 373.
\textsuperscript{15} Fanu, James Le. “The Rise and Fall of Modern Medicine”, 368.
Multiple Risk Factor Intervention Trial (MRFIT)\textsuperscript{16} and the World Health Organization (WHO) Trial\textsuperscript{17}.

Published in 1982, MRFIT was conducted in the United States. Approximately 360,000 middle-aged men were interviewed for the trial, and 12,000 men selected as high-risk patients. They were labeled as high-risk for a heart attack or stroke according to three risk factors: high blood pressure, high cholesterol, and cigarette use. These high-risk individuals were then separated into control and intervention groups. The intervention groups were encouraged to stop smoking, treated with high blood pressure medication, and educated on how to reduce their dietary intake of fat and cholesterol. The WHO Trial followed a similar protocol, and found similar results. The results illustrated that the intervention group was no less likely to suffer from a heart attack when compared to the control group that had no intervention.\textsuperscript{18}

After MRFIT’s publication in the United States, the social theory was widely established as medical orthodoxy in the 1980s. Le Fanu’s primary concern is how this came about. Independent of statistically relevant medical data, how and why did society come to accept and promote the social theory, the understanding that poor dietary lifestyle choices will result in an increased risk of a heart attack or stroke?

The social theory was initially sold as a tool for patient use; patients would have the capacity to decrease their risk of heart disease by making healthy lifestyle adjustments. Unfortunately, the reality of the social theory was that as more patients visited doctors to check their cholesterol levels, otherwise healthy individuals were placed on low-cholesterol diets and

\textsuperscript{18} Fanu, James Le. “The Rise and Fall of Modern Medicine”, 368.
treated with cholesterol lowering medications that many would take for the rest of their lives. The original appeal of the social theory as a patient tool, instead led many patients to be more dependent on their doctors and the pharmaceutical industry.

Following MRFIT, various clinical trials were run in an attempt to synthesize cholesterol lowering drugs. In 1984, the cholestyramine trial was published. Le Fanu concluded the trial was limited as it was only run on high risk patients, had serious side effects, and again showed that the number of deaths between intervention and control groups remained the same. The intervention group did experience less deaths by heart attack but ultimately succumb to other causes. Le Fanu summarizes the results of the trial to question how the public was then informed about the trial’s success:

This indeed can be interpreted as ‘reducing the chances of dying from a heart attack by 25 per cent’ (8 divided by 38 and multiplied by 100 equals almost 25). But put another way, almost 2,000 men had to take cholestyramine for seven years to increase their chances of avoiding a heart attack by less than half of 1 per cent (8 divided by 2,000 multiplied by 100).19

In order to further investigate the claims made by Le Fanu in regard to the production of cholesterol lowering drugs, this thesis will rely on articles from The Journal of the American Medical Association.

Following the cholestyramine trial in 1984, The US National Institutes held a Consensus Development Conference and launched the National Cholesterol Education Program. At the Consensus Development Conference, a panel of lipoprotein experts, cardiologists, primary care physicians, epidemiologists, biomedical scientists, biostatisticians, and experts in preventive medicine concluded that coronary heart disease, at the time, killed more individuals than all cancer variants combined. The panel was primarily concerned with both high risk patients as well as those

that may be unaware of their risk factors. They also concluded that heart disease alone cost the US $60 billion dollars a year. The panel’s conference statement draws direct attention to dietary cholesterol’s association with an increased risk of death by heart attack or stroke:

It has been established beyond a reasonable doubt that lowering definitely elevated blood cholesterol levels (specifically blood levels of low-density lipoprotein cholesterol) will reduce the risk of heart attacks due to coronary heart disease… the blood cholesterol level of most Americans is undesirably high, in large part because of our high dietary intake of calories, saturated fat, and cholesterol. In countries with diets lower in these constituents, blood cholesterol levels are lower, and coronary heart disease is less common. There is no doubt that appropriate changes in our diet will reduce blood cholesterol levels.  

This statement, and subsequent National Cholesterol Education Program, again perpetuated the cycle of more patients getting tested for high cholesterol and being placed on cholesterol lowering drugs. The pharmaceutical industry profited by the influx of new patients diagnosed with high cholesterol, and research groups were funded to further investigate the link between cholesterol and heart disease. As many Americans were now considered at risk for a heart attack or stroke, the demand for cholesterol lowering drugs continued to grow, and the social theory was established as medical orthodoxy throughout the 1980s.

The purpose of this thesis is to analyze the history of the social theory. As heart disease became the new leading cause of death in the US around 1950, society’s need to understand the disease propelled the acceptation of the social theory. Le Fanu explains that the social theory was originally contextualized by medicine's golden age, and this era changed the expectations of medical treatment. Therefore, the social theory was perpetuated and, “when this expectancy that medicine can solve any problem comes into conflict with a decline in therapeutic innovation, then

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false ideas, and claims to knowledge not possessed, are likely to flourish.”21 Through analysis of key studies and programs established from 1950 to 1990, this thesis aims to investigate the context of Le Fanu’s critiques of the social theory. This work incorporates detailed analysis of each defining study or program from 1950 to 1961, 1972 to 1983, and 1983 to 1990.

Chapter 2

Diet and the Heart, 1950-1961

From 1950 to 1961, heart disease research centered primarily around Ancel Keys’ diet-heart thesis. Keys’ thesis developed from his hypothesis that diet is a contributing factor to heart disease. Keys’ focused his research on determining if diet changes could contribute to an individual’s decreased risk of death from heart attack or stroke. This thesis chapter is driven by investigation of this claim. Using selected articles from *The Journal of the American Medical Association*, written either in this periodized time or published in retrospect, this investigation seeks to qualify the medical community’s response to this era of heart disease research. In order to determine the response to Keys’ hypothesis, it is essential to analyze published results that illustrate decreases in heart disease and whether these publications prove widespread and casual dietary changes.

Keys’ work regarding his diet-heart thesis sparked a phenomenon in this era of heart disease research that came to be known as the “cholesterol controversy”. This controversy was characterized by the sharp divide that developed among researchers at this time. Regarding the statistical significance of Keys’ publications, researchers questioned “whether the statisticians’ ‘strong associations’ could provide scientific certainty”. As the medical community became divided between those who accepted diet’s casual role in heart disease and those who called for further investigation, Keys was characterized as an interventionist researcher, “he generally has

23 “Decline in Deaths From Heart Disease and Stroke—United States, 1900-1999”, 724-725.
shunned food fads and vigorously promotes the benefits of ‘reasonably low-fat diets’.”  

As the layman public became increasingly interested in human health in the 1950s, Keys’ gained momentum for his promotion of “reasonably low-fat diets”, “from the early 1950s, Keys actively promoted his findings to an increasingly health-conscious public.” Keys’ supporters credit his interactions with the general public to have contributed to decreased rates of cardiovascular disease, “Keys’ studies and recommendations have had a substantial impact on changes in the U.S. diet and the resulting downward trend in [cardiovascular death]”. However, Keys’ critics, including Le Fanu, argue that any impact on public diet would have occurred after rates of cardiovascular disease had started to decline and that studies of the impact of low fat and low cholesterol diets remained statistically insignificant.

Throughout the 1950s, a divide occurred between supporters and critiques of the diet-heart hypothesis, “the resulting ‘cholesterol controversy’ revealed sharp divisions in post-[World War II] scientific culture over whether the statisticians’ ‘strong associations’ could provide scientific certainty.” This divide among the researchers resulted in split literature that argued significantly opposed positions:

This controversy left greater opportunity for competing food industry groups, health promotion associations, food faddists, physicians, and insurance companies to use the ambiguities and methodologic quibbles inherent in such studies to pursue their own agendas. In its simplest form, the debate over dietary fat and CVD pitted ‘interventionists’ against those calling for further studies—preferably clinical or laboratory studies.

In order to qualify the social, economic, and political entities that perpetuated these competing

24 “Decline in Deaths From Heart Disease and Stroke—United States, 1900-1999”, 725.  
25 “Decline in Deaths From Heart Disease and Stroke—United States, 1900-1999”, 725.  
26 “Decline in Deaths From Heart Disease and Stroke—United States, 1900-1999”, 725.  
27 “Decline in Deaths From Heart Disease and Stroke—United States, 1900-1999”, 725.  
28 “Decline in Deaths From Heart Disease and Stroke—United States, 1900-1999”, 725.
groups, analysis of the factors contributing to the nation’s decline in cardiovascular deaths is essential. Throughout the 1950s, how did it come to be that, “many leading cardiologists’ believe that health habits, including nutrition and exercise patterns, are important factors in the prevention and postponement of coronary disease”?  

In similar regard to the “cholesterol controversy” split among this era’s medical experts, researchers also disagreed regarding which factors would contribute to a decline in cardiovascular death. Retrospective analysis of changes in cardiovascular death rates from 1950 to 1990 generally suggest that cardiovascular deaths decreased after the 1960s; however, Keys supporters and critics offer vastly different explanations for this phenomenon. The diet-heart thesis supporters congratulate public health policies, but the critics again explain that incidences of heart disease increased and then decreased independently of widespread dietary changes.

The remaining content of this chapter will investigate these arguments through analysis of scientific literature, and the forth chapter of this thesis will investigate the public health movement of the 1980s. However, one significant example of scientific literature that opposed Keys’ theory, as early as 1961, was a population study conducted in Roseto, Pennsylvania. Assuming that low fat diets could protect individuals from arteriosclerotic heart disease, this isolated population was expected to produce death rate data from myocardial infarction that proved different from the national average but it did not. With the publication of the Roseto study, “the hypothesis that habitual diet influences the development of coronary heart disease has been challenged”.  

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to the inadequate size of the population. He continued to conduct research in support of his diet-
heart thesis.

This was not the only instance in which Keys explained his data as to diminish factors that
did not align with the hypothesis of his diet-heart thesis. Keys acknowledged that other factors did
contribute to heart disease, but he quickly clarified that these factors were linked to dietary effects:

many factors of nature and nurture may be involved in the multiple etiology of coronary heart disease, the development of the majority of cases in populations that suffer most from it, for example, the United States, is dominated by the long-time effects of a rich fatty diet and innumerable fat-loading meals.  

Keys explains that the factors of “multiple etiology” are in fact the result of “long-term effects” of
a high fat diet.

However, there were others that supported Keys’ conclusion that serum cholesterol had a
high predictive value. Keys’ based his conclusion upon the fact that no population had been found
to have a high incidence of atherosclerosis or coronary heart disease if their population was
characterized by low serum cholesterol values.  

In regard to these claims, Henry I. Russek, M.D., cited that, “the frequency of coronary heart disease in different parts of the world has been found to be related to the mode of life rather than the racial structure or age composition of the population.” He continued to cite the difficulty of separating the “cultural, social, economic, and emotional conditions” in epidemiologic studies; however, he concluded that, “there is sufficient evidence from experimental and epidemiologic studies to warrant acceptance of the view that excessive ingestion of fat is causally related to clinical coronary artery disease.”

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31 Keys, A. “Diet and the Epidemiology of Coronary Heart Disease”. JAMA. 1957;
32 Keys, A. “Diet and the Epidemiology of Coronary Heart Disease”, 1913.
33 Russek, HI. “Role of Heredity, Diet, and Emotional Stress in Coronary Heart Disease.”
34 Russek, HI. “Role of Heredity, Diet, and Emotional Stress in Coronary Heart Disease”, 92.
Supporters of the diet-heart thesis hypothesized nutrition and exercise as important lifestyle choices that could prevent and postpone the development of coronary heart disease. In 1956, Edward P. Luongo, M.D., studied one hundred cases of coronary disease and compared these cases to two hundred control cases in the same age group and occupation.\textsuperscript{35} Luongo analyzed diet and exercise patterns for his control and test groups:

The importance of dietary habits is illustrated by the finding that only 27\% of the test patients had average diets with a variety of food and an apparent balance between caloric intake and energy output, while 60\% of the [control] group had a satisfactory nutritional status.\textsuperscript{36}

Additionally, the study’s exercise results found that seventy percent of the test patients showed no regular exercise and only thirty percent of the control group failed to exercise regularly, “there is evidence that the real culprits in coronary disease are not hard work, overexercise, or occupational stress but sedentary living and poor health habits.”\textsuperscript{37} Based on his findings, Luongo concluded that the study showed how total caloric intake plays a strong role as a factor in the prevention and postponement of coronary disease. Other individuals agreed with Luongo regarding diet’s important role in the health of the US population; Frederick J. Stare, M.D., stated that, “nutrition is the most important environmental factor affecting the health of our population today.”\textsuperscript{38}

At this time, supporters of the diet-heart thesis also acknowledged other coronary risk factors that could contribute to the development of cardiovascular complications; these most significant factors included obesity, smoking behaviors, hypertension, and physical inactivity.\textsuperscript{39}

\textsuperscript{35} Luongo, EP. “Health Habits and Heart Disease – Challenge in Preventative Medicine”, 1021.
\textsuperscript{36} Luongo, EP. “Health Habits and Heart Disease – Challenge in Preventative Medicine”, 1021.
\textsuperscript{37} Luongo, EP. “Health Habits and Heart Disease – Challenge in Preventative Medicine”, 1023.
\textsuperscript{38} Luongo, EP. “Health Habits and Heart Disease – Challenge in Preventative Medicine”, 1021.
Among these factors, physical inactivity and obesity received the most attention. As both of these factors are linked to lifestyle choices and as high-fat diets directly contribute to obesity, it is logical that diet-heart thesis supporters would study these specific factors. In Luongo’s diet and exercise study, he additionally concluded that his obese test patients experience greater risk of cardiac attack, “more than two-thirds of the patients with coronary disease were overweight or obese on the average of 10 to 15 years prior to the attack, while in the control group of the same age range, only one-third were obese or overweight 10 to 15 years prior to this study.”

Therefore, the “real culprits of coronary disease” were defined as a combination of the modern American’s “sedentary living and poor health habits.”

From 1950 to 1961, researchers published conflicting studies and argued over the legitimacy of diet’s casual role in coronary heart disease. As supporters of Keys’ claims cited the influence of nutrition on an individual’s health, critics questioned if the current methods of investigation were capable of producing substantial statically significant evidence to prove, or in some cases to even suggest, that changes in diet could change cardiac health of the US population. If and how diet changes could be tested among a population, with enough certainty to make casual claims, was disputed. Most research professionals agreed that more investigation was required in order to test diet’s true role in the development of coronary heart disease. Le Fanu’s critiques of the social theory fall into this category of opposition to the connections between diet choices and cardiovascular health.

The primary relationship that most diet-heart thesis critics questioned was the relationship between high fat diets, serum cholesterol levels, and atherosclerosis. Throughout the 1950s,

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40 Luongo, EP. “Health Habits and Heart Disease – Challenge in Preventative Medicine”, 1022.
researchers established that atherosclerosis likely had many causes and no one factor alone could be its determinate; these factors included an individual’s hereditary, anatomy of the blood vessel wall, arterial blood pressure, and sex.  

When considering comprehensive preventative measures of reducing an individual’s risk of atherosclerosis, there were many factors to consider that extended beyond the limited scope of diet and lifestyle. These factors included an individual’s genome and family history of disease, physiological function, and total environmental pressures. Even as researchers recognized these factors as important for maintaining overall health, the priority of heart disease research did not widely evaluate heredity or physiology. The research for environmental factors was primarily related to diet, and proceeded on the assumption that if diet did impact atherosclerosis, then total caloric intake, relative rate of caloric expenditure, exercise, and true obesity were worthy of investigation.

With specific regard to true obesity and its relation to diet, other publications countered Luongo’s conclusion that obese cardiac patients experienced a greater risk of cardiac attack. In a similar study to Luongo’s, Henry I. Russek, M.D., stated that, “no support could be found for the view that obesity is an important etiological factor in the development of coronary heart disease… manifest obesity was not significantly more prevalent in the coronary subjects than in controls.”

This example of conflicting results is indicative of the intense split of opinions that developed during this time.

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44 Russek, HI. “Role of Heredity, Diet, and Emotional Stress in Coronary Heart Disease”, 95.
Similarly, to the varied opinions regarding the relations of high fat diets, atherosclerosis, and obesity, serum cholesterol levels were also a place of contention. In 1961, Fredrick J. Stare, published three recommendations that aimed to lower serum cholesterol for obese patients through dietary restrictions. These were to “prescribe less caloric intake and more caloric output”, to “reduce the intake of saturated fats by one-half to two-thirds. Double or triple the polyunsaturated fats, keeping the total amount of fat at the usual level (40% of the total calories)”, and to “reduce the total fat intake about 25% so that fat provides approximately 30% of the total caloric intake, with a ratio of 1:2 or greater of polyunsaturated to saturated fat.”45 Although these recommendations may at first suggest that Stare supported diet’s causative role in cardiac disease, he made an additional note that spoke directly to the uncertainty of his own interpretation:

May I emphasize that this is largely an empiric suggestion with little evidence to support it… except for the first suggestion, these procedures are limited to patients who have elevated levels of serum cholesterol. They are not made for the public.46

Stare’s qualification of his own recommendations suggested that research had not yet found verified evidence of diet’s relationship to cardiac disease and that any valid nutritional recommendations could only be extended to the exact population on which they were tested and should not have been expanded to the general public without further investigation.

A major obstacle to measuring any possible relationship between heart disease and diet was the difficult task of determining dietary content from patients’ self-reported diet histories, “the diagnostic accuracy of all physicians is not equal, and standards vary from place to place. Diet histories are time-consuming and, at best, yield data which are only moderately accurate.”47 Thus

the limitations of diet histories suggested that the isolation of diet, or more specifically of nutritional components of an individual’s diet that may be related to heart disease, was very difficult to track.

Yet another obstacle to determining dietary content was the difficulty of comparing diets on an international scale, “a national diet, low in fat, is usually also low in sucrose and animal proteins; it is usually high in fiber and starch, and the vitamins and mineral content may differ from American diets.” As diets that differ in fat concentrations also differ in sucrose and animal proteins, researchers believed that conclusions should not be drawn about the impact of dietary fat concentrations unless all other nutritional elements could be controlled.

Particularly in the United States, researchers were challenged to draw conclusions about the American diet because it seemed almost impossible to isolate diets from other cultural elements, “the human diet changes according to person; religious training; social, marital, and economic status; the season; the day of the week, and the stage of life. Because of its variety, the American diet is susceptible to no more than a general kind of description.” As researchers recognized the difficulty of separating “cultural, social, economic, and emotional conditions” in epidemiologic studies, it became apparent that lifestyle factors, other than diet, likely played a significant role in developed rates of heart disease. Published summaries recognized these factors, “dietary fat may be implicated in the differing death rates from coronary disease… but other characteristics of the mode of life or environment, acting singly or in combination, may also be involved in these differences.” Instead of presenting dietary factors in the context of causation,

50 Russek, HI. “Role of Heredity, Diet, and Emotional Stress in Coronary Heart Disease”, 91.
researchers hoped for more investigation and higher scientific standards by which the research should be analyzed before its release to the public.

Among those that did attempt to take this research further, any evidence that was found seemed to suggest that diet had in fact stayed relatively consistent in the US population since the early 1900s. These publications additionally recognized the limitations of dietary analysis, but suggested that widespread changes seemed rather insignificant, "variation in dietary intake is dependent on the group and area under scrutiny. However, variation with time is not very striking". In the early 1960s, it seemed impossible to say whether or not the American diet had increased or decreased in animal fat, "Americans may or may not have increased the amount of animal fat in the diet during the past 30 years." Additionally, it was impossible to say whether any possible dietary changes would have influenced the nation’s rate of cardiovascular death:

> the proposition that the character of the American diet has so changed during the past 50 years as to increase the incidence of coronary vascular disease has not been supported... A wide variety of factors, dietary and nondietary, may be of equal or greater importance.

At this time, it seemed unlikely that a consensus could be reached regarding diet and its potential to causally impact cardiovascular heart disease.

The general trends among scientific literature at this time called for further investigation of diet’s role in the progression of cardiovascular disease. Most publications, discussed thus far in this thesis, found no evidence that diet played an insignificant role in cardiovascular disease. However, they did suggest that the current research in this area was statically insignificant and

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52 Stare, FJ. “Nutritional Challenges for Physicians”, 157.
therefore unable to illustrate a causal relationship. To make this point, researchers directly analyzed Keys’ works and called attention to his flawed methods.

In 1950, Keys first proposed the theory that quantity, but not quality, of fat was important. Before Keys’ proposal, the older, but still widely debated, understanding of dietary factors was that excessive dietary cholesterol was the causal agent of coronary heart disease. Keys displaced this older theory with his explanation that “excessive levels of dietary fat [had] caused, or at least contributed to, the development of atherosclerotic disease”. Keys additionally presented the hypothesis that total consumption of dietary fat may not only be relevant to clinical atherogenesis, but that its impact may also be proportionate to an individual’s total dietary calories contributed by food fats.

In critique of this theory, researchers believed that Keys failed to prove dietary fat’s casual role and that the discussion of fats, as a whole, was scientifically premature:

Keys replaced the idea of the stigma of cholesterol with an indictment of the total dietary fat… The response of the serum lipids and lipoproteins to restriction of dietary fat was not predictable for any patient… It seems clear that exogenous cholesterol is still a factor in the research problem. The central position of cholesterol as a suspected agent in causations may have been prematurely abandoned. Keys changed this. With a minimum of evidence, he discounted the role of cholesterol because he could not raise the serum cholesterol of 14 men fed 1gm. of supplementary crystalline cholesterol per day for 28 days. It seemed reasonable to him that these short trials were in fact decisive for a disease that requires 30 to 50 years for its usual life history.

As illustrated in this direct critique of Keys’ work, his fellow researchers established that Keys’ showed “a minimum of evidence.” Additionally, the length of Keys’ study was questioned; it seemed reasonable that more time should have been granted to monitor any potential increase in serum cholesterol.

54 Mann, GV. “Diet and Coronary Heart Disease”, 96.
55 Russek, HI. “Role of Heredity, Diet, and Emotional Stress in Coronary Heart Disease”, 91.
56 Mann, GV. “Diet and Coronary Heart Disease”, 96.
In one of his publications, Keys presented what has come to be known as the Keysian curve (figure 3). This curve illustrates fat intake, as a percentage of fat calories, and death rates assigned to cardiovascular disease. Keys’ data was widely publicized and was said to influence the diets of the American people that then followed Keys’ dietary recommendations.\(^57\) Geroge V. Mann, M.D., directly critiqued Keys’ curve to say that, “there was the uncomfortable fact, for scientists at least, that no mechanism for this relationship of dietary fat was proposed, nor was there much effort apparent to demonstrate one”.\(^58\) Mann additionally believed that Keys had prematurely made the assumption that hypercholesterolemia was somehow productive of atheroma, and that his evidence did not support this claim. Mann critiqued Keys’ results to say that, “the Keysian curve disappeared in a meaningless welter of points when not a select 6 but all 22 of the available Food and

\(^{57}\) Mann, GV. “Diet and Coronary Heart Disease”, 97.

\(^{58}\) Mann, GV. “Diet and Coronary Heart Disease”, 97.
Agricultural Organization national data were considered”. Mann leveled a serious charge against Keys, namely that Keys selected only his most desirable data to make an unwarranted conclusion.

An alternative hypothesis proposed in 1952 posited that the type of fat consumed by an individual is more important than the total quantity of fat. Advocates of this hypothesis recognized that unsaturated fats tend to lower serum cholesterol, while saturated animal fats increase serum cholesterol levels, and this would likely have more of an impact than the total amount of fat consumed. In his critique of Keys and the diet-heart thesis, Mann concluded that Keys’ results had proven insignificant; this insignificance allowed the era’s new hypothesis to gain support.

These different views led to further investigation. In 1960, the Executive Committee on Diet and Heart Disease was formed. This committee had the support of the National Heart, Lung, and Blood Institute of the US Public Health Service, the American Heart Association, the American Medical Association, and the Nutrition Foundation. Upon its recognition, the Executive Committee, “concluded that a well-controlled mass field trial was needed to test the hypothesis that, among middle-aged American men, alteration of the amount and type of fat and the amount of cholesterol in the diet would decrease the incidence of future clinical coronary heart disease.”

To test this hypothesis, the committee decided that their first logical step was to establish a smaller-scale “feasibility study” with the objective to “effect, in the several study groups, slight to moderate changes in the amount and type of dietary fat and the amount of dietary cholesterol”. With this

59 Mann, GV. “Diet and Coronary Heart Disease”, 97.
60 Russek, HI. “Role of Heredity, Diet, and Emotional Stress in Coronary Heart Disease”, 91.
61 Mann, GV. “Diet and Coronary Heart Disease”, 98.
investigative thinking, the medical community’s interest in diet and heart disease shifted primarily to trial based studies; most important was the Multiple Risk Factor Intervention Trial (MRFIT).
Chapter 3

Multiple Risk Factor Intervention Trial, 1972-1983

The Multiple Risk Factor Intervention Trial (MRFIT) was a randomized primary prevention trial that was run for seven years and was published in 1982. The trial incorporated twenty-eight research institutions and over two-hundred and fifty research investigators; it was run under the assumption that coronary heart disease is a multifactor condition. Risk factors included age, sex, high blood pressure (hypertension), elevated serum cholesterol (hyperlipemia), diabetes, and cigarette use. The trial’s early investigation established that the three major risk factors, specifically among middle-aged American men, were high blood pressure, high blood cholesterol, and cigarette use.

In the early 1980s, discrepancies among medical experts were the result of insubstantial scientific evidence to prove prevention’s success in reducing coronary heart disease. Therefore, MRFIT was designed to test the effectiveness of heart disease prevention. Investigators were also split regarding whether suggestions should be made to the public, some believed that prevention was so important that it should be recommended to the public without concrete evidence, while others wanted to conduct more research before making public claims. Leading into the 1970s,

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esteemed medical associations in the United States began to take action to move heart disease research beyond its current obstacles.

In 1961, the American Heart Association published a statement on diet and its relation to cardiovascular disease; the statement greatly emphasized the need for US public policy to focus specifically on heart disease prevention. At this time the American Heart Association also published advice for the public to improve its eating habits and to shift the serum cholesterol distribution of the entire US population downward. This advice was additionally specialized for individuals and families that were considered high risk. It is also important to note that the World Health Organization (WHO) Expert Committee of the Prevention of Coronary Heart Disease had adopted similar policies at this time and had dispensed information to the European population. The question of whether or not this advice was ready to be shared with the public, based on its disputed statistical significance, was impacted by factors of money, time, prestige, and momentum. These same factors led to MRFIT in the United States and the National Cholesterol Education Program that was created by the National Heart, Lung, and Blood Institute after MRFIT’s publication in 1982. The primary area of investigation for this thesis chapter is the analysis of how research led to these developments.

In 1970, the National Heart, Lung, and Blood Institute made two specific dietary recommendations, diet should not be studied in large-scale national diet-heart trials because of its “excessive cost and uncertain feasibility… Improvement of elevated cholesterol, hypertension, and cigarette use may reduce the risk of death due to coronary heart disease”. These

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68 “Multiple Risk Factor Intervention Trial: Risk Factor Changes and Mortality Results”, 1465.
recommendations confirmed what the earlier era of heart disease research, from 1950 to 1961, had concluded that qualitative and quantitative studies of widespread dietary changes were almost impossible to conduct. Therefore, the National Heart, Lung, and Blood Institute’s second recommendation that elevated cholesterol, hypertension, and cigarette use may reduce the risk of death due to coronary heart disease, was used as the basis for MRFIT. The ultimate goal of the trial was to test this hypothesis.

MRFIT began its seven-year investigation with patient screenings that sought to evaluate the severity of the trial’s three risk factors for each male patient. For the first screening, 361,662 men (aged thirty-five to fifty-seven years old) were recruited and 12,000 men were ultimately selected. These men were then divided into two distinct groups: the special intervention (SI) group and the usual care (UC) group. The differences between these two groups were most significant in how the patients were medicated and educated by their assigned physicians. Both groups, special intervention and usual care, received annual checkups; however, the special intervention group was provided with additional diet recommendations, drug treatment for elevated blood pressure, and support to quit smoking.69 The ultimate goal of splitting the test subjects was to, “test the effect of a multifactor intervention program on mortality from heart disease”.70

Later critiques of the trial’s design cited the ethical obstacles that MRFIT faced in its investigative design. The most simplistic issue of the controversy was that the adequacy of data relating coronary heart disease to specific risk factors was widely questioned by researchers. Additionally, researchers recognized that there was a great potential for unforeseen complications

associated with testing risk factors on a large group and then applying them to individual patients through prevention programs. Researchers feared that given the limited data available, applying programs to the public was not only unethical, but also that the prevention programs’ potential hazards and consequence remained unknown. Regarding these issues, researchers were again split between those that accepted the trial’s public publication and those that cautioned that more research was needed to inform patients and physicians alike.\(^7\)

Another ethical obstacle of the trial was the treatment of the usual care patients. The trial could not be single or double blind, as patients and physicians had to be informed of which group the patient had been placed in, special intervention or usual care. Additionally, the usual care group could not represent a true control to which the special intervention patients could be compared. Simply because the usual care patients had been randomly selected not to receive the trial’s preventative support, their physicians still had an ethical responsibility to share the best advice that they could regarding the patient’s overall health.\(^7\) MRFIT was therefore unable to truly regulate the treatment of either group, as each physician implemented individualized care.

The medical community attributed many of MRFIT’s flaws to its poor investigative design. Le Fanu highlighted these flaws in his analysis. In his critique of the social theory, he believed that there were only two possible ways to experimentally test the risk factors of heart disease. The first option was to alter the diet of a population and study its effect. Le Fanu concluded that MRFIT, as one of the nation’s most well supported public health investigations, made this attempt; however, the trial showed no causal relationship between the hypothesized

\(^7\) “The Multiple Risk Factor Intervention Trial (MRFIT): A National Study of Primary Prevention of Coronary Heart Disease”, 825.

\(^7\) “The Multiple Risk Factor Intervention Trial (MRFIT): A National Study of Primary Prevention of Coronary Heart Disease”, 825.
risk factors and death from heart disease. The second option was to analyze the changing incidence of heart disease for several decades and compare this data to dietary analyses of these populations. Le Fanu concluded that if the social theory was correct, the nation’s “universal” incidence of heart disease should have matched diet changes, but this was not illustrated (recall figure 2). As heart disease began to decrease in the United States in the 1960s, the social theory was therefore proved inaccurate. Even under the assumption that large-scale dietary change was possible, the decline of heart disease deaths began well before any large-scale preventative measures could have altered the population’s diet.

In the same year that the National Heart, Lung, and Blood Institute made two specific dietary recommendations to medical experts, 1970, the Inter-Society Commission for Heart Disease Resources recommended that, “a strategy of primary prevention of premature atherosclerotic diseases be adopted as long-term national policy for the United States.” One year later, in 1971, the National Heart, Lung, and Blood Institute established its Task Force of Atherosclerosis. This task force was primarily responsible for the MRFIT investigative design. To begin, the trial established clinical centers throughout the United States, and in November 1973, pilot testing began at the coordinating center at the University of Minnesota, School of Public Health. Whether this had a great impact on the research or not, Keys had conducted most of his cardiovascular research at this same institution.

As the trial began, the special intervention group began to receive diet recommendations while the usual care group did not. These diet recommendations emphasized an overall balanced

diet; one that was appropriate in calories and low in saturated fats. A patient’s total calories from fat were not to exceed thirty to thirty-five percent, less than ten percent from saturated fatty acids and ten to thirteen percent from polyunsaturated fatty acids. In 1976, the trial adjusted its dietary recommendations from ten percent saturated fatty acid calories to eight percent. The trial sought to educate the special intervention group through encouraging the “development of lifestyle shopping, cooking, and eating patterns”, but the patients were free to create their own diets as the trial had no structured meal plans. Special intervention patients were similarly supported for weight reduction. The trial encouraged calorie reduction and increased activity for any patient that was one-hundred and fifteen percent over their weight for optimal health, as determined by the study.

As MRFIT tracked the health of all of its patients over seven years, the trial characterized deaths into specific categories: death from coronary heart disease (the trial’s primary endpoint), death from cardiovascular disease, death from other causes, and death from combination fatal coronary heart disease and nonfatal myocardial infarction. A specific Mortality Review Committee was established in order to classify the patients’ deaths. The committee additionally used four specific qualifications to contextualize deaths from cardiovascular disease:

- myocardial infarction with death occurring within thirty days of onset of symptoms, sudden death with death occurring within twenty-four hours of onset of symptoms, congestive

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78 “Multiple Risk Factor Intervention Trial: Risk Factor Changes and Mortality Results”, 1466-1467.
79 “Multiple Risk Factor Intervention Trial: Risk Factor Changes and Mortality Results”, 1466-1467.
80 “Multiple Risk Factor Intervention Trial: Risk Factor Changes and Mortality Results”, 1467-1468.
heart failure due to coronary heart disease, or death in hospital for surgery for coronary heart disease.\textsuperscript{81}

The Mortality Review Committee was made up of three cardiologists that were unaware of the trial’s interim results or of the classification of the deceased patient, special intervention or usual care group. Retrospective analysis of MRFIT concluded that, “there was complete agreement between these classifications for 90.4% of the deaths. This assessment of agreement is an acceptable level of accuracy for cause-of-death determination as used in the report.”\textsuperscript{82}

Ultimately, MRFIT showed a decline in mortality for both the special intervention and usual care groups. The trial published its results in two distinct categories: coronary deaths and total deaths. For the special intervention group, 17.9 coronary deaths and 41.2 total deaths were reported per one-thousand patients. For the usual care group, 19.3 coronary deaths and 40.4 total deaths were reported per one-thousand patients.\textsuperscript{83} The accepted interpretation of these results was that, on average, there were more total deaths in the special intervention group over the usual care group. This difference was statistically insignificant; however, the trial had predicted the opposite result. The World Health Organization ran a very similar study, and one year after MRFIT’s publication, the WHO Trial published similarly inconclusive results regarding diet’s potentially causative impact on heart disease development. MRFIT and the WHO Trial had been the largest and most expensive scientific experiments in the history of medicine.\textsuperscript{84}

In order to explain the trials results, MRFIT suggested that, “a reduction of smoking behaviors and drug treatment for hypertension in the special intervention group resulted in

\textsuperscript{81} “Multiple Risk Factor Intervention Trial: Risk Factor Changes and Mortality Results”, 1467-1468.
\textsuperscript{83} “Multiple Risk Factor Intervention Trial: Risk Factor Changes and Mortality Results”, 1465.
\textsuperscript{84} Fanu, James Le. “The Rise and Fall of Modern Medicine”, 375
unfavorable responses”. In addition to the possibilities that it was impossible to make significant changes to a population’s lifestyle using persuasion alone or that social factors played little to no role in heart disease, other possible explanations included that the intervention program was not shown to affect cardiovascular mortality or that the intervention program did affect cardiovascular mortality, but this was not evident due to the study’s seven-year limitation. The MRFIT Research Group did not consider the last two explanations to be likely; however, critics of the trial questioned if MRFIT’s investigative design had been at all effective or if MRFIT had in fact resulted in any significant finding.

The trial had invested significant money, time, prestige, and momentum in finding a cause for heart disease, but none of these factors could change the insignificant results. MRFIT did not find its expected results in regard to coronary and total death rates of the special intervention and usual care groups; however, the study did show that “there was and is overwhelming evidence implicating the three major CHD risk factors”. As the study found highly significant differences between the special intervention and usual control groups for the three major risk factors of high blood pressure, high cholesterol, and cigarette use, the MRFIT Research Group concluded substantial success for the special intervention group in their reduction of cigarette use and decreased blood pressure (figure 4).

Given the many critiques that the trial received, the MRFIT Research group continued to suggest that the trial had left the medical community with the following lessons:

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85 “Multiple Risk Factor Intervention Trial: Risk Factor Changes and Mortality Results”, 1465.
87 “Multiple Risk Factor Intervention Trial: Risk Factor Changes and Mortality Results”, 1465.
(1) It is clear that a large, complex, multicenter trial such as this can survive phases of planning, controversy and compromise, and enter operations successfully.
(2) The trial has provided an extraordinary opportunity for a truly remarkable cooperative undertaking involving epidemiologists, biochemists, clinicians, behavioral scientists, biostatisticians, electrocardiographers, nutritionists, nurses, motivated intelligent un-specialized "people" and others.
(3) The response from the mass media and the public has been generally gratifying.
(4) The response from the medical profession has also been decidedly favorable and helpful.  

Even as the trial showed no causal relationship between the hypothesized risk factors and death from heart disease, these lessons illustrate that the MRFIT Research group valued their findings.

MRFIT was designed as an intensive long-term intervention program that hoped to successfully reduce the severity of three specific risk factors: high blood pressure, high cholesterol, high cholesterol.

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and cigarette use. The trial did show that preventative programs could be successful in reducing the severity of these risk factors; however, reducing these risks did not translate to reduced death rates as was expected.\textsuperscript{89} One possible explanation for this unexpected data, as claimed by the MRFIT Research group, was that ethical concerns prohibited the trial from using true control groups, “it may be relevant that multifactor intervention received a less than optimal test owing, in part, to unexpected declines in risk factor levels and, in part, to lower-than-expected mortality in the UC group.”\textsuperscript{90}

To summarize the trial’s results Jeremiah Stamler, M.D., cautioned that MRFIT should not be publicized to say that the trial established a “casual hypothesis”. He instead suggested that the trial should explain that a theory was established, “the general scientific conclusion that the established major risk factors are implicated in the causation of coronary epidemic, this must be - and is – based on the \textit{totality} of the data from animal-experimental, clinical pathological, and epidemiological research”.\textsuperscript{91} As not to entirely take away the debated significance of MRFIT’s findings, this caution served to warn researchers not to grant the trial too much credit as it was impacted by all previously conducted heart disease research.

Other researchers gave the trial even less credit and critiqued specific details from the research group’s publication. These researchers questioned if the results could be possible given the medical community’s assumed understanding of heart disease. Paul J. Rosch, M.D., drew specific attention to the MRFIT data that illustrated the number of cardiovascular heart disease deaths and total deaths (figure 5). Through analysis of hypertensive baseline statuses and resting

\textsuperscript{89} "Multiple Risk Factor Intervention Trial: Risk Factor Changes and Mortality Results", 1476.
\textsuperscript{90} "Multiple Risk Factor Intervention Trial: Risk Factor Changes and Mortality Results", 1476.
electrocardiogram abnormalities of the special intervention groups, the data showed that deaths from cardiovascular heart disease were reported in greater numbers in the special intervention hypertensive patients (over the usual group). Therefore, Rosch concluded that: the implications of these surprising findings are so major as to demand caution, since the results fly in the fact of current medical dogma and practice… This observation will no doubt foster sustainable debate and cause follow-up studies to test possible validity.92

Table 7.—Number of CHD and Total Deaths and Mortality Rate (per 1,000) by Hypertensive Status at Baseline and by Presence of Resting ECG Abnormalities*

<table>
<thead>
<tr>
<th></th>
<th>No. of Participants</th>
<th>CHD Deaths</th>
<th>Total Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SI</td>
<td>UC</td>
<td>SI</td>
</tr>
<tr>
<td>Nonhypertensive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>1,817</td>
<td>1,862</td>
<td>24(13.2)</td>
</tr>
<tr>
<td>Present</td>
<td>592</td>
<td>563</td>
<td>11(18.6)</td>
</tr>
<tr>
<td>Total</td>
<td>2,409</td>
<td>2,445</td>
<td>35(14.5)</td>
</tr>
<tr>
<td>Hypertensive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>2,765</td>
<td>2,808</td>
<td>44(15.8)</td>
</tr>
<tr>
<td>Present</td>
<td>1,233</td>
<td>1,185</td>
<td>36(29.2)</td>
</tr>
<tr>
<td>Total</td>
<td>4,018</td>
<td>3,993</td>
<td>80(19.9)</td>
</tr>
</tbody>
</table>

*For Multiple Risk Factor Intervention Trial Research Group participants. SI indicates special intervention; UC, usual care; MC, Minnesota Code.
1Abnormalities include high R waves in the precordial leads (MC, 3.1, 3.3, 3.4; N=1,410), negative T waves (MC, 5.1-5.3; N=511); R-R* pattern (MC, 7.8; N=488); ectopic ventricular premature beats (MC, 8.1; N=452); left axis deviation ≤−30° (N=390); incomplete RBBB (MC, 7.3; N=359); ST depression (MC, 4.1-4.3; N=237); ST elevation (MC, 9.2; N=240), major Q waves (MC, 1.1-1.3; N=184); short P-R (MC, 6.5; N=109); first degree atrioventricular block (MC, 6.3; N=85); supraventricular tachycardia (MC, 6.4; N=38); right axis deviation ≥+120° (N=17); and other rare conditions (N=39).92

Figure 5. Number of CHD and total deaths

Given these specific results, Rosch went so far as to say that the trial was likely flawed, but he did conclude that as the data showed decreased deaths for both groups, there was a possibility that lifestyle could lead to a decreased risk of cardiovascular death. However, Rosch did not believe that this possibility was supported by the MRFIT data. He stated that the trial’s only significant

impact on the medical community was that its unexpected results should have fostered further investigation.

Another implication of the MRFIT results was an increased interest in the relationship between diet, serum cholesterol levels, and cardiovascular death. Using the serum cholesterol data levels for all MRFIT screenees (figure 6), Stamler and a team of physicians concluded that:

the steady and marked decline in CHD mortality in the United States since the late 1960s – greater than for any other country in the world… is related to improvements in nutrition and serum cholesterol distribution, as well as in other major risk factors (eg, cigarette use, blood pressure).

Stamler’s team of physicians found that their investigation of the MRFIT screenees showed a strong relationship between serum cholesterol levels and cardiovascular death. They summarized their results to say that:

93 Stamler J, Wentworth D, Neaton JD. “Is Relationship Between Serum Cholesterol and Risk of Premature Death From Coronary Heart Disease Continuous and Graded? Findings in 356 222 Primary Screenees of the Multiple Risk Factor Intervention Trial (MRFIT))”, 2823.
the pattern of a continuous, graded, strong relationship between serum cholesterol and six-year age-adjusted CHD death rate prevailed for nonhypertensive nonsmokers, nonhypertensive smokers, hypertensive nonsmokers, and hypertensive smokers…. These data of high precision show that the relationship between serum cholesterol and CHD is not a threshold one, with increased risk confined to the highest quintiles, but rather is a continuously graded one that powerfully affects risks for the great majority of middle-aged American men.94

As Stamler’s team had analyzed the results of all of the MRFIT screenees in regard to serum cholesterol, and not just those that were selected for the study, they found an increased risk of cardiac death was not only limited to severely hypertensive patients, but that increased serum cholesterol levels were a threat to the cardiac health of all patients. This finding propagated even further discussion of MRFIT’s three risk factors, high blood pressure, high cholesterol, and cigarette use, and whether or not the trial had showed that these factors could impact cardiovascular death.

Many researchers and physicians who found fault with MRFIT, expressed their opinions through responses to the MRFIT Research Group’s publication via letters to The Journal of the American Medical Association. Carl C. Stelzer, Ph.D., was among these authors, and he believed that the trial’s risk factors needed to be reevaluated. Stelzer concluded that regarding the MRFIT report “the reason for the striking failure of the trial lies in its erroneous basic assumption that reduction in CHD mortality would result from reducing the so-called major risk factors”.95 Stelzer continued to clarify what he believed to be “reason for the striking failure of the trial”:

The MRFIT program failed to achieve an anticipated greater reduction in the overall CHD mortality rate in the special intervention (SI) group than in the control group receiving usual care (UC), despite the fact that the risk factor-reduction goals were essentially met. Seltzer believed that as MRFIT’s risk factors did not perform as was expected, that the risk factors needed to be reevaluated.

Kurt A. Oster, M.D., attributed MRFIT’s faults to many different mistakes and ultimately believed that, “the fatal flaw of the MRFIT program lies in its planning.” First, he blamed the trial’s flawed manipulation of the formula from the successful Framingham Study. The Framingham Heart Study is an ongoing cardiovascular cohort study that began in 1948 and has since tracked the epidemiology of hypertensive or arteriosclerotic cardiovascular disease for three generations of patients. Oster concluded that the Framingham Study found a ten percent reduction of the serum cholesterol level of the US population, as well as a twenty-five percent decrease in cardiovascular heart disease and a fifty percent serum cholesterol reduction. Overall, the study saw an eighty-four percent reduction of cardiovascular heart disease in low risk patients. Oster claimed that MRFIT had faulted in its attempt to recreate specific parameters of this successful study. He also cited that in the early 1980s, “it should have been common knowledge that CHD is but one part of atherosclerosis symptomatology and should not be a surrogate for the entire program.” Secondly, Oster additionally explained that MRFIT’s flaw was its misunderstanding of the lipid theory. This theory is concerned with the body’s fat transport by lipoproteins and triglycerides; however, it neglects phospholipids. Oster argued that as phospholipids are physiological

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99 Oster, KA. “The Multiple Risk Factor Intervention Trial”.
“detergents”, they should have been studied in MRFIT’s cardiovascular heart disease research.

He believed that MRFIT was flawed in its planning and that diet-heart research needed to be adjusted to include all divisions of fat, including phospholipids. Oster finally concluded that MRFIT spent one-hundred and fifteen million dollars to show that it was possible to reduce serum cholesterol and that the trial’s results did not, in any way, benefit public health in the United States.

Irwin D.J. Bross, Ph.D., was yet another author that analyzed MRFIT’s results, and he questioned if the consequences of stopping smoking may have had negative consequences for patients in the special intervention group. Bross cited inconsistencies in the data, that more people in the special intervention group quit smoking in their first year, but still had the same total number of deaths. He also questioned if hypertension drugs may have had toxic side effects that could have counterbalanced the positive effects of quitting smoking. He concluded that, “there is the possibility that the ex-smokers who avoid death from coronary heart disease are the ones who go onto die of lung cancer”.

Philip R.J. Burch, M.D., critiqued MRFIT to say that the trial should have included sex and age contributions in regard to temporal trends. He suggested that some type of microorganism, such as a virus or allergen, may have been responsible for the decline in cardiovascular death in the United States around 1960. He stated that this data: “shows that a ubiquitous precipitating factor of some kind is responsible… the evidence gives no indication of any appreciable causal action by the risk factors hypertension, diabetes mellitus, cigarette smoking, hypercholesterolemia,

lack of exercise, and excess body weight. Burch suggested that the association of cardiovascular heart disease is likely entirely, or at least in large part, related to genetics. He hoped that MRFIT’s data would encourage more research in this regard, “it is to be hoped that the intense preoccupation with conventional risk factors will now diminish and that the search for the genuine precipitating agent(s) might commence.”

Weldon J. Walker, M.D., concluded that MRFIT was incomplete because potassium levels should have also been considered and researched, “the high mortality in hypertensive men receiving diuretic therapy with ECFF abnormalities in the MRFIT was most likely related to low serum K+ levels.”

As each of these authors took it upon themselves to add to the discussion of MRFIT’s shortcomings, others recognized beneficial components of the data, but suggested that these components could be easily misinterpreted. The significance of MRFIT’s cholesterol level data was particularly susceptible to misinterpretation. In 1975, it was concluded that high-density lipoproteins (HDL or good cholesterol) had a carrier function, an independent risk-lowering factor, and that additional factors influenced circulating HDL. MRFIT illustrated that plasma HDL cholesterol levels may have played a crucial role in the reduction of coronary heart disease risk; however, “conventional coronary prevention programs are unlikely to have an adverse influence on this new, risk-lowering factor.” As researchers suggested that MRFIT’s only significant data

103 Burch, PRJ. “The Multiple Risk Factor Intervention Trial”.
had been illustrated through decreased serum cholesterol levels, the notion that some other risk-lowering factor was responsible for these results lent more to the conclusion that the trial’s prevention program data showed no causal relationship between the hypothesized risk factors and death from heart disease. This notion was commonly addressed through peer reviewed publications at this time.

Paul J. Rosch, M.D., suggested that the trial was an isolated analysis of risk factors that looked only at the results of cardiovascular heart disease but not at its cause. He additionally critiqued MRFIT’s results:

The unexpected results of the [trial] should not be puzzling, given the design of the study. The fundamental error was some confusion between association and causation. An increased incidence of hypertension, elevated cholesterol level, or smoking in coronary heart disease (CHD) does not entitle one to conclude that these are causative factors. Rosch believed that determining the cause of cardiovascular heart disease was in fact more important than simply treating for the disease’s risk factors. Therefore, the most important question to ask regarding heart disease was not how can we reduce risk factor effects, but instead, why do we smoke or why do we have elevated blood pressure and cholesterol. Jeffery A. Cutler, M.D., supported Rosch’s claim, “Dr Rosch is correct in asserting that evidence of increased incidence of CHD in the presence of certain characteristics (risk factors) does not justify, in itself, the conclusion that they are causative factors.”

Additionally, Rosch claimed that, “the study failed to consider the role of stress” in the causation of cardiovascular heart disease. Although it is not well defined, stress is treated through behavioral moderation and beta blockers that prevent damage to stress educed hormone

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106 Rosch, PJ. “Risk of Coronary Artery Disease”, 1501.
107 Rosch, PJ. “Risk of Coronary Artery Disease”, 1501.
108 Cutler, JA. “Risk of Coronary Artery Disease-Reply”.
109 Rosch, PJ. “Risk of Coronary Artery Disease”, 1501.
This treatment is suggested to be the only effective strategy in preventing cardiovascular heart disease, and it seems more efficient to treat this risk factor directly instead of through other resulting risk factors such as high blood pressure, high cholesterol, or cigarette use.\textsuperscript{111}

One final flaw of the MRFIT trial was that it did not publish the participants’ causes of death that were unrelated to cardiovascular disease. Based on this shortcoming some researchers cautioned the unknown risks of treating cardiovascular heart disease through preventative means:

excess mortality from non-CHD causes at low serum cholesterol levels is sometimes attributed to the effect of disease on serum cholesterol level rather than the reverse… it is a bit surprising that the MRFIT investigators use their data to argue the case for lowering serum cholesterol when their own trial could demonstrate no benefit from reducing such factors.\textsuperscript{112}

The unknown complications of low cholesterol levels, resulting from medication, is one supporting reason for the importance of continued heart disease research.

To summarize MRFIT’s faults, the investigators underestimated the effects of the following elements: identifying and telling patients that they were high risk, telling the physician that the patients were high risk and in the control group, sharing original and annual data with physicians, not controlling for the quality of practice of the personal physicians in the usual care group, and increased knowledge and behavior changes of the public at this time.\textsuperscript{113} The suggestion was made by researchers that smaller and more well controlled projects could have been more effective and answered heart disease research’s questions at a gradual pace. Regardless of whether or not this method would have been more effective than launching the nation’s largest and most

\textsuperscript{110} Rosch, PJ. “Risk of Coronary Artery Disease”, 1501.
\textsuperscript{111} Cutler, JA. “Risk of Coronary Artery Disease-Reply”.
\textsuperscript{113} Rosch, PJ. “Risk of Coronary Artery Disease”, 1501.
expensive experiment in the history of medicine, the fact remains that MRFIT “cost millions of
dollars but in the end proved nothing or very little”. Le Fanu came to a similar conclusion in his
overall analysis of the social theory:

> [the social theory] has wasted hundreds of millions of pounds in futile research and health-
education programmes while justifying the imposition of costly regulations to reduce yet
further the minuscule levels of pollution in air and water. And to cap it all, it does not work.
The promise of the prevention of thousands of deaths a year has not been fulfilled.

As the United States approached the end of the twentieth century, the social theory continued to
persist, and contrary to what MRFIT’s many faults may have predicted, the theory gained even
more public support. As the study of this thesis shifts to the time period of 1983 to 1990, the work’s
fourth chapter will analyze the many difficulties that the social theory encountered as well as how
and why it then become established as medical orthodoxy during the 1980s.

114 Mendlowitz M. “Heart Failure: A Critical Inquiry Into American Medicine and the
Chapter 4  

Following the MRFIT publication in 1982, heart disease research continued to investigate cholesterol’s causative role in cardiovascular disease. As the evidence of this causative role was still contested, 1983-1990 saw “an explosion of interest in cholesterol and its relation to coronary heart disease.”¹¹⁶ This era of heart disease research resulted in the development of national cholesterol education programs and led to the mass production of cholesterol lowering drugs. In 1984, the Lipid Research Clinics Coronary Primary Prevention Trial was published, the Consensus Development Conference on Lowering Blood Cholesterol to Prevent Heart Disease was held, and the US the launched the National Cholesterol Education Program.

Further investigation into cholesterol’s potentially causative role drove the 1984 Lipid Research Clinics Coronary Primary Prevention Trial. This trial was “a multicenter, randomized, double-blind study that tested the efficacy of cholesterol lowering in reducing risk of coronary heart disease (CHD) in 3,806 asymptomatic middle-aged men with primary hypercholesterolemia”.¹¹⁷ Similarly to MRFIT, this cholesterol trial utilized a limited testing pool of male patients; these men were divided into control and treatment groups. The control groups were administered placebo, and the treatment groups were administered bile acid sequestrant cholestyramine resin. Bile acid sequestrant cholestyramine resin is a cholesterol reducing drug


The results of the trial illustrated reductions in the treatment group; the plasma total and low-density lipoprotein cholesterol reductions were 8.5% and 12.5% greater than the placebo group.\footnote{“The Lipid Research Clinics Coronary Primary Prevention Trial Results: Reduction in Incidence of Coronary Heart Disease”, 365.} This data suggested that the cholestyramine drug reduced total and low-density lipoprotein cholesterol. This efficacy was not criticized; however, as did MRFIT, the Lipid Research Clinics Coronary Primary Prevention Trial showed that, “risk of death from all causes was only slightly and not significantly reduced in the cholestyramine group”.\footnote{“The Lipid Research Clinics Coronary Primary Prevention Trial Results: Reduction in Incidence of Coronary Heart Disease”, 365.} Once again an expensive and large-scale heart disease research trial had not produced a treatment group, that when compared to the control group, showed a statistically significant decline in deaths from cardiovascular heart disease.

The Lipid Research Clinics Program, the group responsible for The Lipid Research Clinics Coronary Primary Prevention Trial, explained their results by stating that this insignificant magnitude was due to “a greater number of violent and accidental deaths in the cholestyramine group”; they concluded that lowering low-density lipoprotein cholesterol levels “can diminish the incidence of CHD morbidity and mortality in men at high risk for CHD because of raised LDL-C levels. This clinical trial provides strong evidence for a causal role for these lipids in the pathogenesis of CHD.”\footnote{“The Lipid Research Clinics Coronary Primary Prevention Trial Results: Reduction in Incidence of Coronary Heart Disease”, 365.} Even as the trial had not shown a significant decline in total death
between its two groups, the results were published to suggest that men with elevated plasma cholesterol levels could reduce their risk of coronary morbidity and mortality through interventionist drug therapy.

As illustrated (figure 7), the percent of total-C (plasma total cholesterol levels) and LDL-C (low-density lipoprotein cholesterol levels) were lower for cholestyramine-treated men versus placebo-treated men. Percent HDL-C (high-density lipoprotein cholesterol) and percent TG (triglyceride levels) were higher for cholestyramine-treated men versus placebo-treated men. The high-density lipoprotein cholesterol/plasma total cholesterol levels were elevated for
cholestyramine-treated men versus placebo-treated men. The Lipid Research Clinics Coronary Primary Prevention Trial was marketed to have a “19% lower incidence of coronary heart disease (CHD) in cholestyramine-treated men”. These results sparked yet another phase of the “cholesterol controversy.” Medical experts were split between those that believed the drug was ready for production and public distribution and those that believed more time and research was required.

Some medical experts found fault with the trial data. Duncan D. Adams, M.D., D.Sc., emphasized that the data between the cholestyramine-treated men and the placebo group, in regard to incidence of coronary heart disease, was not statistically significant. He summarized that, “the point to be faced is that the trial data do not establish a difference between the cholestyramine and placebo groups”, he continued to conclude the following: “1) cholestyramine lowers cholesterol levels; (2) lower cholesterol levels are associated with less CHD; and (3) cholestyramine dosage is not related to CHD frequency.” Adams suggested that although the trial had shown that cholestyramine lowered cholesterol levels, and that lower cholesterol levels were believed to decrease cardiovascular morbidity and mortality, the data did not support the expected relationship between lower cholesterol levels and decreased incidence of cardiovascular disease. Adams instead suggested that as cholestyramine does not cause a reduction in cardiovascular heart disease, there must be some other causal agent responsible for the “dual effect of lowering cholesterol levels and protecting against CHD.” Adams hypothesized that this causal agent may be

adrenaline, specifically exercise educed adrenaline, that would protect those living an active lifestyle from the progression of cardiovascular disease. The Lipid Research Clinics Program, responded to Adams’ critique to clarify that, “the study was not designed to detect the effect of treatment on fatal or nonfatal CHD events alone, and statistical tests for these subcategories were not considered appropriate.”

As further questions regarding cholesterol’s relationship to incidence of cardiovascular disease remained evident to medical experts, the Consensus Development Conference on Lowering Blood Cholesterol to Prevent Heart Disease hoped to address these issues. The questions that remained can be summarized as follows:

A large body of evidence of many kinds links elevated blood cholesterol levels to coronary heart disease. However, some doubt remains about the strength of the evidence for a cause-and-effect relationship. Questions remain regarding the exact relationship between blood cholesterol and heart attacks and the steps that should be taken to diagnose and treat elevated blood cholesterol levels.

In the hopes of resolving these issues that continued to divide medical experts, the National Heart, Lung, and Blood Institute and the National Institutes of Health Office of Medical Applications of Research convened a Consensus Development Conference on Lowering Blood Cholesterol to Prevent Heart Disease from December 10th to 12th, 1984. At this conference a panel of lipoprotein experts, cardiologists, primary care physicians, epidemiologists, biomedical scientists, biostatisticians, experts in preventive medicine, and lay representatives came together to watch a series of expert presentations and review all of the available data regarding heart

disease research at this time. The panel agreed upon five overarching questions that they hoped to answer:

1. Is the relationship between blood cholesterol levels and coronary heart disease causal?
2. Will reduction of blood cholesterol levels help prevent coronary heart disease?
3. Under what circumstances and at what level of blood cholesterol should dietary or drug treatment be started?
4. Should an attempt be made to reduce the blood cholesterol levels of the general population?
5. What research directions should be pursued regarding the relationship between blood cholesterol and coronary heart disease?  

In attempting to answer these questions, the panel hoped to unify researchers regarding the relationship between cholesterol and cardiovascular heart disease. They came to the following conclusion:

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elevation of blood cholesterol levels is a major cause of coronary artery disease. It has been established beyond a reasonable doubt that lowering definitely elevated blood cholesterol levels (specifically, blood levels of low-density lipoprotein [LDL] cholesterol) will reduce the risk of heart attacks caused by coronary heart disease.
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This statement additionally summarized that this reduced risk, “has been demonstrated most conclusively in men with elevated blood cholesterol levels, but much evidence justifies the conclusion that similar protection will be afforded to women with elevated levels.”  

This conclusion was criticized by those who questioned if this “evidence” should have been extended to the wider public, including women, children, and the elderly. This criticism will be further investigated throughout this chapter.

Additionally, the panel made suggestions regarding who should receive cholesterol lowering treatment:

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127 “Lowering Blood Cholesterol to Prevent Heart Disease”, 2080.
128 “Lowering Blood Cholesterol to Prevent Heart Disease”, 2080.
129 “Lowering Blood Cholesterol to Prevent Heart Disease”, 2080.
After careful review of genetic, experimental, epidemiologic, and clinical trial evidence, we recommend treatment of individuals with blood cholesterol levels above the 75th percentile (upper 25% of values). Furthermore, we are persuaded that the blood cholesterol levels of most Americans are undesirably high, in large part because of our high dietary intake of calories, saturated fat, and cholesterol.  

In order to make this claim that those above the 75th percentile should receive treatment, the panel sighted evidence form countries with diets lower in total calories, saturated fat, and cholesterol. They suggested that these countries experienced less coronary heart disease, and that, “there is no doubt that our appropriate changes in our diet will reduce blood cholesterol levels.” However, isolating and controlling for diet in investigative research still remained an obstacle to heart disease research at this time.

According to the panel’s new treatment recommendations, about half of the adult population in the United States was then considered to be at risk for developing premature coronary heart disease (cholesterol levels above 200 to 230 mg/dL). In 1986, the American Medical Association published a statement cautioning that, “factors such as age, sex, family history, other risk factors, accompanying disease, prognosis and anticipated compliance may all influence the clinical decision to treat the hyperlipidemia”; however, medical professional still worried about the dangers of too low cholesterol due to overtreatment.

Gerald M. Reaven, M.D., argued that the dangers of over treating the American population could lead to a problematic loss of HDL for individuals not at imminent risk of cardiovascular heart disease:

131 “Lowering Blood Cholesterol to Prevent Heart Disease”, 2080.
132 “Lowering Blood Cholesterol to Prevent Heart Disease”, 2080.
133 Marwick, C. “Campaign seeks to increase US ’Cholesterol Consciousness’”, 1097.
we know that low-fat, high-carbohydrate diets tend to increase serum levels of very low density lipoprotein triglycerides [VLDL-TG] in normal people. There is a strong relationship between VLDL and high density lipoprotein [HDL] metabolism. When VLDL-TG concentration rises, HDL concentration goes down, so the protective effect of HDLs is diminished.135

Similarly, Donald McNamara, Ph.D., argued that in patient trials for cholesterol treatment or prevention, no concrete evidence existed at this time to prove a decrease in overall number of deaths, “if this holds true in the population, it means that those in the 90th percentile will remain at elevated risk. And there is no indication that the rest of the population will gain any benefit whatsoever”.136

McNamara felt uneasy that the National Heart, Lung and Blood Institute’s dietary recommendations were available to the public; he felt that individuals were thus encouraged to make diet changes without physician involvement or oversight. McNamara argued that national programs should instead focus on individual screenings, “no cholesterol reduction program—even the adoption of the prudent diet—should be undertaken without a screening program to identify those at risk. Such programs, though expensive, are not beyond consideration.”137 McNamara suggested an alternative public-health approach; to first screen the population to identify serum cholesterol levels high enough to be at risk and to then set those patients up with a physician that could individually monitor their diet changes or drug use.138

135 Merz, B. “Low-Fat Diet May Be Imprudent for Some, Say Opponents of Population-Based Cholesterol Control”, 2279.
136 Merz, B. “Low-Fat Diet May Be Imprudent for Some, Say Opponents of Population-Based Cholesterol Control”, 2280.
137 Merz, B. “Low-Fat Diet May Be Imprudent for Some, Say Opponents of Population-Based Cholesterol Control”, 2280.
138 Merz, B. “Low-Fat Diet May Be Imprudent for Some, Say Opponents of Population-Based Cholesterol Control”, 2280.
These concerns fostered discussions regarding the appropriateness of a national cholesterol education program and how the program should be run, if at all. Supporters of the program cited the success of the High Blood Pressure Education Program that began in the 1970s, “that hypertension education program, many say, is at least one of the reasons why, over the 20 years prior to 1983, the death rate from cardiovascular disease declined by 36%.” Critics, however, argued that “there are major differences between diagnosing and managing high blood pressure and diagnosing and managing serum cholesterol.” These differences cite that blood pressure is easier to take and interpret than serum cholesterol levels; therefore, elevated hypertension level thresholds are more widely accepted.

The efficacy of cholesterol lowering drugs, versus hypertensive drug therapy, was also questioned, “increasingly effective antihypertensive agents are available. And, suggests Stephen B. Hulley, MD, most of them are better tolerated than are cholesterol-lowering drugs….In contrast with hypertension, Hulley says, measurements of serum cholesterol by current methods are less accurate.” Regarding treatment by cholesterol lowering drugs, there was argument regarding whether the drugs should be used at all, and if used, when treatment for elevated serum cholesterol should begin:

many physicians seem less convinced of the impact on heart disease of elevated serum cholesterol levels than they are of the adverse effects of high blood pressure… there's a big difference in attitudes between blood pressure and cholesterol. We all know this. High blood pressure gets treated vigorously, but not cholesterol. It is measured much less consistently and often the primary care physician will refer the patient who has high levels elsewhere or do nothing.

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139 Marwick, C. “Campaign seeks to increase US 'Cholesterol Consciousness'”, 1097.
140 Marwick, C. “Campaign seeks to increase US 'Cholesterol Consciousness'”, 1097.
141 Marwick, C. “Campaign seeks to increase US 'Cholesterol Consciousness'”, 1098.
142 Marwick, C. “Campaign seeks to increase US 'Cholesterol Consciousness'”, 1098.
These differences in opinion regarding cholesterol lowering drugs illustrated, that regardless of the efforts made by researchers to answer cholesterol’s remaining questions, the issues continued to persist. More importantly, the persisting issues influenced differing opinions of medical experts regarding the appropriateness of a national cholesterol education program.

Among those that did support a national campaign, education remained the priority. William R. Harlan, M.D., and Jeoffrey K. Stross, M.D., cited that “an important and critical dimension would be education, both of the public and of health professionals. The pertinent educational issues are identified in the categories of knowledge, attitudes, and skills.” They also concluded that evidence suggested that both a public health and medical approach would be effective in lowering incidence of cardiovascular disease in the United States; however, economic considerations remained of great importance when implementing a national initiative that required a great amount of attention in order to develop the program.

Conversely, opponents of a national campaign summarized that lowering serum cholesterol on a national was inappropriate. Beverly Merz stated that “several clinical investigators are contending that lowering serum cholesterol is not a public health matter. They would like to see cholesterol- lowering programs tailored to the individual rather than presented as an edict to the population at large.” Merz additionally argued that the recommendations of the National Heart, Lung and Blood Institute’s were unnecessary:

None of the naysayers is challenging the notion that hyperlipidemia should be treated. Nor does any of them doubt that excessive dietary cholesterol is often associated with coronary disease. What they are taking issue with is the NHLBI's recommendation that all

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145 Merz, B. “Low-Fat Diet May Be Imprudent for Some, Say Opponents of Population-Based Cholesterol Control”, 2279.
Americans above the age of 2 years reduce their intake of dietary fats to 30% of calories and of saturated fats to 10% of calories. They contend that cholesterol education programs should not be designed around this dietary dictum.¹⁴⁶

Yet another controversy between the supporters and critics of the education program developed regarding the role of the Food and Nutrition Board of the National Academy of Sciences/National Research Council. This board faced an ethical controversy driven by researchers’ split opinions regarding the publication of dietary guidelines. In response, the Food and Nutrition Board published the following statement:

Any public official considering a new public health program for disease prevention must evaluate the potential effectiveness of the proposed action before recommending its adoption. If there is uncertainty about its effectiveness, there must be clear evidence that the proposed intervention will not be harmful or detrimental in other ways. In the case of diseases with multiple and poorly understood etiology, such as cancer and cardiovascular disease, the assumption that dietary change will be effective as a preventive measure is controversial.¹⁴⁷

Drawing specific attention to the “cholesterol controversy,” The Food and Nutrition Board made clear its concerns with supporting the national cholesterol education programming.

The response of the public also contributed to the growing controversy. In 1983 and 1986, the National Heart, Lung, and Blood Institute sponsored national probability telephone surveys to determine the country’s attitudes and knowledge regarding heart disease risk from high blood cholesterol levels and whether or not the public was making efforts to lower blood cholesterol levels. Between these two surveys, the results of the Lipid Research Clinics Coronary Primary Prevention Trial were released, and as a result:

the percentage of adults who believed that reducing high blood cholesterol levels would have a large effect on heart disease increased from 64% in 1983 to 72% in 1986… In 1983, 35% of adults reported that they had their cholesterol level checked vs 46% in 1986… By

¹⁴⁶ Merz, B. “Low-Fat Diet May Be Imprudent for Some, Say Opponents of Population-Based Cholesterol Control”, 2279.
¹⁴⁷ Merz, B. “Low-Fat Diet May Be Imprudent for Some, Say Opponents of Population-Based Cholesterol Control”, 2280.
1986, 23% of adults reported that they made dietary changes specifically to lower their blood cholesterol level, up from 14% in 1983.148

This data suggested that public awareness regarding the publicized relationship between cholesterol levels and coronary heart disease was recognized and individuals were acting upon this information. This data was thus used to develop national cholesterol education programs.

In 1984, the National Heart, Lung, and Blood Institute sponsored the country’s National Cholesterol Education Program. Within the medical community, the education program sought primarily to help physicians deal with the overwhelming and confusing task of treating patients for elevated cholesterol. The education program took the following steps to facilitate information to physicians. The campaign was titled Physician First and was designed to recognize practicing physicians as the primary audience for new information concerning the relationship between cholesterol levels and coronary heart disease.149 To begin, the National Heart, Lung, and Blood Institute created the Cholesterol Counts booklet to guide physicians on how to manage high serum cholesterol levels and to illustrate the link between high blood cholesterol levels and the risk of coronary heart disease; this booklet was widely distributed to practicing physicians and could be requested via inquiry. Next, the program formed a panel of heart disease research experts, “to develop more definitive guidelines that may be even more helpful to physicians in the diagnosis, evaluation, and treatment of elevated blood cholesterol levels.”150 Medical education curriculums were additionally encouraged to incorporate these updated guidelines into their teachings. And finally, the program sought to improve the quality and effectiveness of the standardized methods

149 Marwick, C. “Campaign seeks to increase US ’Cholesterol Consciousness’”, 1098.
150 Marwick, C. “Campaign seeks to increase US ’Cholesterol Consciousness’”, 1098.
of measuring and reporting serum cholesterol levels that were available to physicians at this time.\textsuperscript{151}

In response to this campaign, the American Heart Association Task Force was generally supportive. The Task Force recommended, "support of programs, within and without the American Heart Association, for physician education in the area of hypercholesterolemia, coupled with existing risk reduction programs." \textsuperscript{152} However, five members of the Task Force urged further research into the safety and efficacy of plasma cholesterol-lowering diets. These members, "found no compelling reasons for the American Heart Association to dissent in principle from the conclusions of the [1984] consensus development conference statement." \textsuperscript{153} Perhaps a contributing factor to the conflicting opinions regarding the relationship between cholesterol and cardiovascular disease was the many ruling bodies of heart disease research that continually published updated guidelines and at times conflicted with other authoritative groups.

Individuals physician also saw fault with the changing guidelines for what should constitute high cholesterol. Robert E. Olson, M.D., concluded that:

there seems to be no dissent about lowering cholesterol levels in those in whom it is elevated… I think telling people to have their cholesterol levels measured, particularly high-density lipoprotein levels because total cholesterol doesn't tell you everything, is useful public health education. But telling everybody, from two years of age onward, to go on modified diets, reducing their consumption of saturated fats and cholesterol with the idea that this will reduce their chances of getting coronary heart disease, is totally unnecessary.\textsuperscript{154}

Olson suggested that those with dangerously high cholesterol levels should receive individual treatment; however, he was uncomfortable making a jump to treating the greater population. Olson

\textsuperscript{151} Marwick, C. “Campaign seeks to increase US 'Cholesterol Consciousness’”, 1098-1099.
\textsuperscript{152} Marwick, C. “Campaign seeks to increase US 'Cholesterol Consciousness’”, 1098-1099.
\textsuperscript{153} Marwick, C. “Campaign seeks to increase US 'Cholesterol Consciousness’”, 1099.
\textsuperscript{154} Marwick, C. “Campaign seeks to increase US 'Cholesterol Consciousness’”, 1099, 1101.
additionally cited that more research regarding the treatment of children and the elderly had become increasingly necessary.\textsuperscript{155}

Similarly, Thomas Chalmers, M.D., concluded that the treatment of cholesterol had been severely overcomplicated. He agreed with Olson to say that those in danger of developing coronary heart disease should seek treatment, while individuals with lower levels should be continually monitored by their physicians but do not need immediate intervention. Chalmers concluded that, "It's simple. If you're going to die of heart disease, you ought to lower your cholesterol. If you're not, you shouldn't bother. All you have to do is figure out how to tell."\textsuperscript{156} This call to “figure out how to tell” seemed to reference the medical community’s need to develop one overarching model by which to establish the threshold level at which high cholesterol was life threatening. In summary of the argument made by those that opposed the National Heart, Lung, and Blood Institute’s National Cholesterol Education Program, “the evidence of benefit from treating very high blood cholesterol levels is pretty clear, among those who have lower levels it's more debatable. There is also some uncertainty involved in extrapolating the policy to older and younger patients, and to women.”\textsuperscript{157}

As heart disease research continued to progress, the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol made yet another statement regarding cholesterol levels in 1988. These guidelines defined the following categories of total cholesterol levels: under 200 mg/dL as desirable blood cholesterol; 200 to 239

\textsuperscript{155} Marwick, C. “Campaign seeks to increase US 'Cholesterol Consciousness’”, 1099, 1101.
\textsuperscript{156} Marwick, C. “Campaign seeks to increase US 'Cholesterol Consciousness’”, 1101-1102.
\textsuperscript{157} Marwick, C. “Campaign seeks to increase US 'Cholesterol Consciousness’”, 1102.
mg/dL as borderline-high cholesterol and 240mg/dL or over as high blood cholesterol. In order to establish these guidelines, the panel cited MRFIT evidence.

Using the relationship of serum cholesterol to coronary heart disease that was presented in MRFIT’s data (figure 8), the following was included in the statement regarding the above guidelines established by the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol:

Because the relationship between serum cholesterol level and CHD is a continuous and steadily increasing one (Fig 1), these cutpoints are necessarily somewhat arbitrary. However, this is also true of other risk factors, such as blood pressure, and the success of basing clinical decisions on whether or not a patient is classified as hypertensive indicates the value of establishing cutpoints for clinical decisions.

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The expert panel recognized that these guidelines, or cutpoints, may be somewhat arbitrary, but that they were nevertheless just as essential as the guidelines relating to other risk factors of cardiovascular disease.

Based on the initial patient classifications of total cholesterol (figure 9), the panel’s statement recommended that all American adults with greater than 6.21 mmol/L (240 mg/dL) seek treatment to lower their cholesterol levels. One recognized consequence of this recommendation was the number of patients that would now seek medical intervention. Medical experts became increasingly concerned in this regard:

Whether or not one agrees with the new recommendations, they will have a big impact on medical practice. Instead of just dealing with the occasional patient with severe hyperlipidemia, physicians will face increasing numbers of purportedly "normal" adults

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who now are being told that their blood cholesterol value is too high. These patients will
descend on a medical profession that generally agrees that lowering elevated blood
cholesterol levels is important but, as a whole, is admittedly poor in effecting such changes.
The challenge is to develop effective and practical approaches for reducing blood
cholesterol level among free-living American adults, and to do so very soon.\textsuperscript{161}

Developing these effective and practical approaches seemed to remain the largest obstacle to the
country’s new public health movement at this time.

The National Cholesterol Education Program Expert Panel on Detection, Evaluation, and
Treatment of High Blood Cholesterol additionally gave specific dietary guidelines and established
“diet therapy as the primary cholesterol-lowering treatment”. \textsuperscript{162} The expert panel gave dietary
recommendations in two distinct categories: step-one diets and step-two diets. The diets differed
in that step-one called for a reduction of major and obvious sources of saturated fatty acids and
cholesterol in the diet, but step-two was a more radical redesign of the diet as a whole that sought
to reduce dietary saturated fatty acids and cholesterol to a minimal level of compliance with
adequate nutrition. \textsuperscript{163} The rationale of these diets was explained as follows:

Saturated fatty acids and cholesterol are not essential nutrients, and neither is required in
the diet. The body can make these lipids in abundance, and they can be transported from
one tissue to another to assure that any local shortage is supplied by lipids produced
elsewhere in the body. The real need then is to reduce dietary saturated fatty acids and
cholesterol to the levels required to achieve the goals of LDL-cholesterol lowering and still
provide a diet that is nutritious and palatable. The fat-modified diets proposed in this report
are designed to achieve these aims. \textsuperscript{164}

\textsuperscript{161} Ellison, RC. “Give Diet a Chance in Lowering Cholesterol Levels”, 1017.
\textsuperscript{162} Goodman DS, Hulley SB, Clark LT, et al. “Report of the National Cholesterol Education
Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in
Adults”, 36.
\textsuperscript{163} Goodman DS, Hulley SB, Clark LT, et al. “Report of the National Cholesterol Education
Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in
Adults”, 47.
\textsuperscript{164} Goodman DS, Hulley SB, Clark LT, et al. “Report of the National Cholesterol Education
Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in
Adults”, 47.
If these dietary changes failed to decrease a patient’s cholesterol level, via step-1 and then step-2 restrictions, the next recommended step was drug treatment. The panel recommended the following drugs for consideration, “bile acid sequestrants cholestyramine, colestipol); nicotinic acid; HMG CoA reductase inhibitors (lovastatin); gemfibrozil; and probucol,” and outlined the treatment protocol (figure 10).

Medical experts generally concluded that diet recommendations should precede direct intervention through cholesterol lowering drugs, especially for children. However, drug therapy was accompanied by economic benefit. Physicians cited feeling pressured to prescribe cholesterol lowering drugs:

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166 Ellison, RC. “Give Diet a Chance in Lowering Cholesterol Levels”, 1018.
while the cost-benefit aspects of using [lovastatin] or any drug for hyperlipidemia are favorable for individuals with markedly elevated levels of cholesterol, for the child or young adult with modest increases in cholesterol level the answer is less clear. The general rule should be always to give diet a very good chance before adding any drug.\textsuperscript{167}

Le Fanu believed that the social theory’s drug therapy movement was primarily driven by economic interest; he cited this conclusion as follows:

The pharmaceutical industry has metamorphosed into the powerful and sinister ‘Big Pharma’ which, Marcia Angell alleges, ‘has moved very far from its original high purpose of discovering and producing useful new drugs. Now principally a marketing machine to sell drugs of dubious benefit, it uses its wealth and power to co-opt every institution that might stand in its way, including the US Congress, the Food and Drug Administration, Academic Medical Centers – and the medical profession itself.’\textsuperscript{168}

Le Fanu suggested that the “Big Pharma” seemed to have tremendous power in influencing physicians to recommend drug treatment for at risk patients. In the 1980s, drug companies began to mass produce cholesterol lowering drugs at the same time that national cholesterol guidelines continued to lower what cholesterol levels qualified a patient as high risk.

Additionally, physicians still found fault with the recommendations made by the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol. Robert E. Olson, M.D., was again a critique of the new public movement. He objected to “the arbitrariness of recommendations for the identification, evaluation, and treatment of "hypercholesterolemic" adults”.\textsuperscript{169} Olson found fault with how the committee defined its guidelines based on current research. He questioned why research had not illustrated higher

\textsuperscript{168} Fanu, James Le. “The Rise and Fall of Modern Medicine”, 466.
incidence of heart disease for patients with elevated cholesterol, and specifically cited MRFIT data (figure 11); he concluded that:

> in all prospective studies that have been conducted thus far, except for the study of Multiple Risk Factor Intervention Trial (MRFIT) screenees in which there were 350,000 persons in the cohort, there has been no evidence that the CHD mortality is greater in persons with serum cholesterol levels from 5.17 to 6.18 mmol/L than in those with levels below 5.17 mmol/L.\(^\text{170}\)

![Figure 11. MRFIT CHD and total mortality](image)

Olson’s concern with the current direction of the nation’s new public health movement was that authoritative bodies, such as the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol, had been too quick to assume

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cholesterol’s causative role in cardiovascular disease. He posed the question that if cholesterol was causative, how and why had research since MRFIT not produced similar results?

Around the time that the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol released its guidelines in late 1988, the American Medical Associations’ Campaign Against Cholesterol released similar recommendations. This announcement was criticized by Frederick J. Stare, M.D. The second chapter of this thesis discussed Stare’s opinion that research had not yet found verified evidence of diet’s relationship to cardiac disease. In 1989, Stare addressed the announcement by the American Medical Association's Campaign Against Cholesterol to say that:

Thus, it seems as though the current "cholesterol hype" will be accelerated. The cholesterol factor is of minor importance as a risk factor in cardiovascular disease. Of far more importance are smoking, hypertension, obesity, diabetes, insufficient physical activity, and stress. The cholesterol content of the diet has only a minor effect on the total cholesterol content of the blood…Thus, the clamor for labeling foods for cholesterol content is a waste of time and money.

In this analysis, Stare labeled cholesterol as a minor factor in cardiovascular disease’s much more complicated trajectory, and he claimed that this minor factor had become too important and taken control of heart disease research. Stare additionally critiqued that for the past thirty years of scientific evidence had recognized that redacting total caloric intake and increasing in total caloric expenditure, so as to reach and maintain a reasonable body weight, was of much greater importance than limiting fatty acids in the diet to lower blood cholesterol. Stare was disappointed by the work of the National Cholesterol Education Program of the Department of Health and Human Services, the American Heart Association, and the American Medical Association, because he argued that

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172 Stare, FJ. “The AMA's Campaign Against Cholesterol”, 3240.
the nation’s cholesterol education campaigns gave, “undue emphasis to a minor risk factor in cardiovascular disease and thus a false hope to millions of individuals”. Stare continued to conclude that the medical community needed to reevaluate the emphasis that it placed on various risk factors of cardiovascular disease:

How much better if the above three organizations would have sponsored a National Health Education Program with an emphasis on no smoking, consuming fewer total calories (particularly from saturated fats and alcohol), increasing caloric expenditure so as to reach and maintain a reasonable weight, consuming a variety of foods from among and within the major food groups so as to obtain adequate amounts of the 50 or so known nutrients (and no doubt others still to be discovered), and emphasizing that eating is one of the pleasures of life and that it can remain so.”

Stare’s argument called attention to the neglected, but still very relevant, risk factors of cardiovascular disease that had been less emphasized as the “cholesterol hype” took control of heart disease research. Perhaps, these risk factors were even more relevant to incidence of cardiovascular disease than cholesterol, but that remained uncertain at this time.

In direct response to Stare’s damning critique, Steven V. Seekins of the American Medical Association and Arthur Ulene, M.D., of Feeling Fine Programs Inc, answered with their own explanations. Seekins responded to say:

That cholesterol is of minor importance as a risk factor for cardiovascular disease is a subjective opinion… The AMA clearly supports a total, healthy life-style approach to cardiovascular and other disease prevention that includes, as Dr Stare points out, smoking cessation, decreased alcohol and caloric intake (particularly from saturated fats), increased exercise, weight control, and a balanced diet.

This response was that of the American Medical Association clarifying that their program did indeed promote a healthy lifestyle through recommendations to decrease the impact all of

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173 Stare, FJ. “The AMA's Campaign Against Cholesterol”, 3240-3241.
174 Stare, FJ. “The AMA's Campaign Against Cholesterol”, 3240-3241.
cardiovascular disease’s recognized risk factors. Ulene supported Seekins’ summary that these facts were clearly communicated in the materials developed for the campaign. Additionally, Ulene was disheartened by Stare’s critique of the for-profit organizations that assisted groups like the American Medical Association with their campaign distribution, “I resent Dr Stare's implication that we are "hyping" the cholesterol issue for profit opinion… We make no apology for the fact that Feeling Fine Programs Inc, which is responsible for developing and operating the Campaign Against Cholesterol, is organized as a for-profit company.” This conflicting discourse among medical experts at this time illustrates the great extent to which the “cholesterol controversy” had persisted to the last decade of the twentieth century. The influential factors of money, time, prestige, and momentum, were still obvious in the work of heart disease research.

As heart disease research approached 1990, the following passage summarized the progress and areas of further required study regarding diet and cardiovascular disease:

The importance of high serum cholesterol levels as a risk factor for coronary heart disease and the benefit of lowering cholesterol levels for reducing risk are being increasingly accepted. A broad consensus to this effect has led to the establishment of the National Cholesterol Education Program. Although the available evidence fully justifies this program, its practical application to the American public has generated a series of new questions that must be explored. For example, it can be questioned whether reduction in coronary risk through lowering cholesterol levels extends to both sexes and all age groups. For people with high cholesterol levels, dietary modification is undoubtedly the first step of management, but the fraction of people responding adequately to dietary change remains to be determined. Finally, indications for drug therapy and choice of drugs need further exploration, particularly in the area of cost vs benefit. Thus, continuing research must be carried out in parallel with clinical and public health application of cholesterol education.

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177 Ulene, A. “The AMA's Campaign Against Cholesterol-Reply”, 3241.
178 Grundy SM, Goodman DS, Rifkind BM, Cleeman JI. “The Place of HDL in Cholesterol Management: A Perspective From the National Cholesterol Education Program”, 3053.
Cholesterol’s relationship with incidence of cardiovascular disease remained controversial and medical professionals still questioned the evidence that had led to this acceptance. However, in the late 1980s, recognition of the cholesterol risk factor and the benefit of lowering its levels was “being increasingly accepted”. This change had been drive by the National Cholesterol Education Program and the mass production and availability of cholesterol lowering drugs.

The impact of this new wave of heart disease research brought new questions. Most importantly the question of whether evidence based trials run on high risk middle-aged men should be extended to all men, women, and children. This was both a question of method as well as of ethics. Cholesterol’s treatment protocol via diet and or drug therapy was also debated. Overall, cholesterol’s new public health movement suggested that further research was required to address its remaining unknowns. Nevertheless, the 1980s defined cholesterol lowering treatments as medical orthodoxy for cardiovascular disease.
Chapter 5
Conclusion

The purpose of this thesis was to analyze the history of the social theory of heart disease and its rise to prominence in the United States. Through analysis of this history from 1950 to 1990, the work has detailed major developments that established the social theory as medical orthodoxy. Considering the many difficulties that the social theory encountered, it nevertheless dominated heart disease research and patient treatment. This thesis was designed to study how and why this the social theory was established.

To study this establishment, the thesis was divided into investigative chapters that analyzed a landmark study or turning point that was crucial to the history of the social theory. From 1950 to 1961, Ancel Keys advanced his diet-heart thesis. From 1972 to 1983, the Multiple Risk Factor Intervention Trial (MRFIT) was especially influential. From 1983 to 1990, the US began the mass production of cholesterol lowering drugs and established the National Cholesterol Education Program. Each of these periods were explored in great depth in the chapters of this thesis. For each period, the thesis examined relevant articles from *The Journal of the American Medical Association*; these publications documented the history of the social theory.

In order to introduce, and now to reflect upon, the establishment of the social theory it was essential to contextualize the definition of this term. Le Fanu defined the social theory as our modern understanding of lifestyle and disease; he argued that the modern notion that heart disease is preventable by changes in diet or other aspects of lifestyle is a socio-economic phenomenon more than a conclusion driven by scientific evidence.

Le Fanu made specific claims regarding the impact of the social theory on patient care:
The Social Theory is synonymous with victim blaming because its logic requires that patients have only themselves to blame for persisting with their unhealthy habits and not heeding helpful advice. It has made people much more, rather than less, concerned about their health and an infinite variety of hidden dangers in their lives. The reality that now most people live out their natural lifespans to succumb from complex diseases determined by ageing is transformed into the illusion that illness is ubiquitous, and its causes lie in the way that people lead their lives, and thus can be readily prevented. The Social Theory simultaneously manages to overemphasise the role of illness in people’s lives while at the same time trivialising it. It generates the myth that the practice of medicine is futile, because the allegedly important factors in health are outside its control.\(^\text{179}\)

Le Fanu cited that the social theory placed prevention above the capabilities of all other medical care. For heart disease, Le Fanu believed that claims regarding the causative role of certain risk factors led to the strong emphasis on disease prevention that developed from 1950-1990. He additionally questioned how the science behind society’s accepted beliefs were perpetuated through media attention and government funding.

Most importantly, Le Fanu explained that from 1920 to 1960, death rates from heart disease rose dramatically in the United States, before declining in the 1960s and 1970s. However, there was no evidence that this rise and fall was in direct correlation with large-scale lifestyle or diet changes across the population (recall figures 1 and 2). Citing a “universal” decline in incidence of heart disease, Le Fanu concluded that the social theory could not be correct.\(^\text{180}\) In specific regard to diet, he believed that although diet may contribute to cardiovascular disease, the relationship was not independently causal, “a ‘high-fat’ diet along with smoking and raised blood pressure might be a contributory but not a determinant factor in the rise of heart disease.”\(^\text{181}\) This association of “a high-fat” diet, along with smoking, and raised blood pressure”, as well as later discussion of high cholesterol, drove heart disease research from 1950-1990. Research in this period sought to

determine the relationship between these lifestyle driven risk factors and the incidence of cardiovascular disease.

From 1950 to 1961, heart disease research was dominated by Ancel Key’s diet-heart thesis. Keys hypothesized that diet was a contributing factor to heart disease, and focused his research on determining if diet changes could contribute to an individual’s decreased risk of death from heart attack or stroke. Keys was particularly interested in an individual’s cholesterol levels as well as their overall fat consumption. The “cholesterol controversy” began as medical experts questioned if Keys’ “‘strong associations’ could provide scientific certainty.”

Other researchers at this time concurred with Keys’ hypothesis linking diet and incidence of cardiovascular disease. Edward P. Luongo, M.D and Frederick J. Stare, M.D., agreed that nutrition was among the most, if not the most, important risk factor of disease. Other significant factors included obesity, smoking behaviors, hypertension, and physical inactivity. As research explored these relationships, some experts were led to conclude that the “real culprits of coronary disease” were a combination of the modern American’s “sedentary living and poor health habits.”

However, critics of Keys’ hypothesis questioned it claims. Henry I. Russek, M.D., performed a similar research study to Luongo, but found very different results. This example of conflicting results was indicative of the intense split of opinions that developed during this time. Researchers cautioned that even as medical experts found fault with Keys’ work, he had greatly

183 “Decline in Deaths From Heart Disease and Stroke—United States, 1900-1999”, 724-725.
influenced heart disease research. In retrospect, Robert Dunn, Ph.D., cited that after Keys’ publication of his book, *Eat Well*, the American Heart Association changed its position regarding the link between saturated fat, cholesterol, and atherosclerosis. Dunn suggested that this change was likely impacted by Keys’ work and presence on the board.

During the 1950s, research primarily focused on evaluating diet as a risk factor for heart disease; however, evidence seemed to suggest that diet had in fact stayed relatively consistent in the US population since the early 1900s. Diet studies were severely limited as it became apparent to researchers that, “the human diet changes according to person; religious training; social, marital, and economic status; the season; the day of the week, and the stage of life. Because of its variety, the American diet is susceptible to no more than a general kind of description.”186 This challenge led to incomplete conclusions. In the early 1960s, it seemed impossible to say whether or not the American diet had increased or decreased in animal fat, “Americans may or may not have increased the amount of animal fat in the diet during the past 30 years.”187

Despite the challenge of qualifying diet, Keys’ research progressed and was continually critiqued. George V. Mann, M.D., established that Keys’ data showed “a minimum of evidence.”188 Mann leveled a serious charge against Keys, namely that Keys selected only his most desirable data to make an unwarranted conclusion (recall figure 3). He additionally concluded that Keys’ results had proven insignificant; this insignificance thus allowed a new hypothesis to gain support. In 1952, this alternative hypothesis posited that the type of fat consumed by an individual was more important than the total quantity of fat.

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186 Mann, GV. “Diet and Coronary Heart Disease”, 96.
188 Mann, GV. “Diet and Coronary Heart Disease”, 96.
The early stages of the “cholesterol controversy” led to further investigation. In 1960, the Executive Committee on Diet and Heart Disease was formed to address the questions facing the relationship between lifestyle risk factors and the incidence of coronary heart disease. This led to the development of various research trials; MRFIT was the most important.

MRFIT was published in 1982, and the randomized primary prevention trial directed the next era of heart disease research as well as the “cholesterol controversy.” The trial established that the three major risk factors of cardiovascular disease were high blood pressure, high blood cholesterol, and cigarette use. Based on their high-risk categorization, out of the 361,662 middle-aged American men that were screened, 12,000 men were selected for the trial. After being randomly selected for a treatment or control group, the trial followed these men for seven years. Both groups, special intervention and usual care, received annual checkups; however, the special intervention group was provided with additional diet recommendations, drug treatment for elevated blood pressure, and support to quit smoking. The ultimate goal of splitting the test subjects was to, “test the effect of a multifactor intervention program on mortality from heart disease”.

In the United States, MRFIT was the largest and most expensive scientific experiment in the history of medicine. Medical experts criticized the trial’s design for various reasons. Critics questioned the adequacy of data relating coronary heart disease to specific risk factors, the great potential for unforeseen complications associated with testing risk factors on a large group and

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189 Rosch, PJ. “Risk of Coronary Artery Disease”, 1501.
thus applying them to individual patients through prevention programs, and the ethical obstacle of treating the usual care patients.\textsuperscript{193}

The trial results showed a decline in mortality for both the special intervention and usual care groups. As heart disease was seen to decline “universally” as early as the 1960s, this evidence did not prove causation of the trial’s risk factors. Ultimately, MRFIT showed no causal relationship between the hypothesized risk factors and death from heart disease. This result seemed to suggest that lifestyle factors were likely impervious to significant modification or insignificant to heart disease. At this same time, Europe’s World Health Organization Trial published similarly inconclusive results regarding diet’s potentially causative impact on heart disease development.\textsuperscript{194}

Various researchers and medical professionals expressed their concerns with the trial. Some made damning claims that “the reason for the striking failure of the trial lies in its erroneous basic assumption that reduction in CHD mortality would result from reducing the so-called major risk factors”\textsuperscript{195} or that, “the fundamental error was some confusion between association and causation. An increased incidence of hypertension, elevated cholesterol level, or smoking in coronary heart disease (CHD) does not entitle one to conclude that these are causative factors.”\textsuperscript{196} Others cited potential dangers of the prevention protocols, “there is the possibility that the ex-smokers who avoid death from coronary heart disease are the ones who go onto die of lung cancer”.\textsuperscript{197} These critiques of the trial ultimately suggested that continued research was necessary,

\textsuperscript{193} “The Multiple Risk Factor Intervention Trial (MRFIT): A National Study of Primary Prevention of Coronary Heart Disease”, 825.
\textsuperscript{194} Fanu, James Le. “The Rise and Fall of Modern Medicine”, 368.
\textsuperscript{195} Seltzer, CC. “The Multiple Risk Factor Intervention Trial”.
\textsuperscript{196} Rosch, PJ. “Risk of Coronary Artery Disease”, 1501.
\textsuperscript{197} Bross, IDJ. “The Multiple Risk Factor Intervention Trial”.
and this led to the trials of cholesterol lowering drugs that dominated heart disease treatment beginning in the 1980s.

1984 was an extremely influential year in the history of heart disease research; the Lipid Research Clinics Coronary Primary Prevention Trial was published, the Consensus Development Conference on Lowering Blood Cholesterol to Prevent Heart Disease was held, and the US launched the National Cholesterol Education Program. This education program, coupled with the mass production and availability of cholesterol lowering drugs, resulted from “an explosion of interest in cholesterol and its relation to coronary heart disease.”198 The Lipid Research Clinics Coronary Primary Prevention Trial was, “a multicenter, randomized, double-blind study that tested the efficacy of cholesterol lowering in reducing risk of coronary heart disease (CHD) in 3,806 asymptomatic middle-aged men with primary hypercholesterolemia”.199 The trial had a similar method to MRFIT, and when compared to the control group, the cholestyramine treatment group did not show a statistically significant decline in deaths from cardiovascular heart disease. However, the trial did show that cholestyramine was effective in lowering low-density lipoprotein cholesterol levels. Duncan D. Adams, M.D., D.Sc., summarized the trial’s results to say that although the trial had shown that cholestyramine lowered cholesterol levels, and that lower cholesterol levels were believed to decrease cardiovascular morbidity and mortality, the data did not support the expected relationship between lower cholesterol levels and decreased incidence of cardiovascular disease.200

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198 Grundy SM, Goodman DS, Rifkind BM, Cleeman JI. “The Place of HDL in Cholesterol Management: A Perspective From the National Cholesterol Education Program”, 3053.
199 “The Lipid Research Clinics Coronary Primary Prevention Trial Results: Reduction in Incidence of Coronary Heart Disease”, 365.
200 Adams, DD. “Lowering Cholesterol and the Incidence of Coronary Heart Disease”, 3090.
The National Heart, Lung, and Blood Institute and the National Institutes of Health Office of Medical Applications of Research convened a Consensus Development Conference on Lowering Blood Cholesterol to Prevent Heart Disease in December 1984. As a result of the conference, new treatment recommendations stated that treatment for high-risk cholesterol levels should begin at levels above 200 to 230 mg/dL. In this same year, the National Heart, Lung, and Blood Institute launched the National Cholesterol Education Program.

Some medical experts and physicians felt uneasy about these recommendations and the education campaign. They hoped instead for individualized treatment plans, “no cholesterol reduction program—even the adoption of the prudent diet—should be undertaken without a screening program to identify those at risk. Such programs, though expensive, are not beyond consideration.” In 1988, the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol made yet another statement regarding cholesterol levels. These guidelines defined the following categories of total cholesterol levels: under 200 mg/dL was a desirable blood cholesterol; 200 to 239 mg/dL was a borderline-high cholesterol and 240 mg/dL or over was a high blood cholesterol.

The changing guidelines and competing authoritative bodies that presented such recommendations likely contributed to conflicting opinions regarding the relationship between cholesterol and cardiovascular disease. Thomas Chalmers, M.D., summarized these conflicting opinions, "It's simple. If you're going to

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201 Marwick, C. “Campaign seeks to increase US 'Cholesterol Consciousness’”, 1097.
202 “Lowering Blood Cholesterol to Prevent Heart Disease”, 2080.
203 Merz, B. “Low-Fat Diet May Be Imprudent for Some, Say Opponents of Population-Based Cholesterol Control”, 2280.
die of heart disease, you ought to lower your cholesterol. If you're not, you shouldn't bother. All you have to do is figure out how to tell.”

While the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol also gave specific dietary guidelines and established “diet therapy as the primary cholesterol-lowering treatment,” drug treatment was additionally recommended if diet changes alone were not effective in reducing a patient’s cholesterol level. Le Fanu believed that the social theory’s drug therapy movement was primarily driven by economic interest; he cited that the “Big Pharma” had tremendous power in influencing physicians to recommend drug treatment for at risk patients. Physicians additionally cited the cost benefits of drug therapy but cautioned that “using [lovastatin] or any drug for hyperlipidemia are favorable for individuals with markedly elevated levels of cholesterol, for the child or young adult with modest increases in cholesterol level the answer is less clear.” Questions remained regarding whether evidence based trials run on high risk middle-aged men should be extended to all men, women, and children, but at this time, drug companies had already begun to mass produce cholesterol lowering drugs.

Other medical experts still questioned the overall importance of cholesterol in heart disease research. Frederick J. Stare, M.D., argued that the cholesterol education program gave, “undue emphasis to a minor risk factor in cardiovascular disease and thus a false hope to millions of individuals”. As heart disease research progressed into the late 1980s, it was clear that although

205 Marwick, C. “Campaign seeks to increase US ’Cholesterol Consciousness’”, 1101-1102.
207 Ellison, RC. “Give Diet a Chance in Lowering Cholesterol Levels”, 1018.
208 Stare, FJ. “The AMA’s Campaign Against Cholesterol”, 3240-3241.
the contested material had evolved over time, the “cholesterol controversy” still inspired debate among researchers and medical experts. Nevertheless, “the importance of high serum cholesterol levels as a risk factor for coronary heart disease and the benefit of lowering cholesterol levels for reducing risk [were] being increasingly accepted.” During the 1980s, the mass production and availability of cholesterol lowering drugs was coupled with national guidelines that continued to lower the high-risk threshold for cholesterol levels. Thus, the social theory was established as medical orthodoxy.

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