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Leslie S. Leighton Date

Explaining the decline of coronary heart disease mortality in the United States in the 1960s: An historical analysis

By

Leslie Steven Leighton

Doctor of Philosophy

The Graduate Institute of the Liberal Arts

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Howard I. Kushner, PhD

Advisor and Dissertation Committee Chairman

_____

Arri Eisen, PhD

Committee Member

_____

William McClellan, MD, MPH

Committee Member

_____

Barry D. Silverman, MD

Committee Member

Accepted:

_____

Lisa A. Tedesco, Ph.D.

Dean of the James T. Laney School of Graduate Studies

_____ Date

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An abstract of

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Abstract

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Coronary heart disease (CHD) as a chronic disease came to attention in the United States and other countries in the early 20th century. Over the course of the 20th century its incidence rose to epidemic proportions and it became the leading cause of death in this country as well as most industrialized nations. Prevention and treatment of the disease evolved over the century and mortality plateaued in the U.S. in the 1960s and by all accounts began to decline by the end of the decade. The reason for the decline has been speculated and investigated since the 1970s, when it was first fully recognized, but has never been adequately explained. This dissertation takes a critical look at CHD and its evolution as a disease and major cause of death over the course of the twentieth century. More pointedly it attempts to explain the reason or reasons for the abrupt initial decline in its mortality which began in 1968 and has continued to date. As a result of archival research and oral histories, as well as statistical analysis, it is clear that there is no one single explanation for the initial decline in disease mortality. After 1974 it appears that both prevention and treatment played important roles in reducing the mortality of CHD but the initial decline in 1968 appears to have been the result of a number of factors, the least of which seems to be prevention. By the data amassed in this dissertation it is unlikely that mitigation of what are considered the major risk factors for CHD, including elevated serum cholesterol, hypertension and smoking, resulted in an initial reduction in mortality. Much more likely it was a number of incremental changes that occurred in the treatment of the disease, including the cardiac chair (an end to prolonged bed rest as treatment), the advent of the coronary care unit, the professionalization of the specialty of cardiology, Medicare and Medicaid that together led to a reduction in CHD mortality.

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I would like to acknowledge the outstanding support and help rendered to me in the completion of this dissertation by Dr. Howard I. Kushner who believed enough in me to allow me to come to Emory and the Graduate Institute of the Liberal Arts to study with him. He was the individual who suggested the topic of this dissertation to me very early on in my studies at Emory University. I have transformed as a result of this work from a Harvard-trained gastroenterologist into an Emory-trained student of heart disease and have been fortunate to participate in multiple speaking and publishing activities related to this transformation. Dr. Kushner has helped me through every stage of this transition and dissertation and his support and knowledge has been invaluable in the research and writing of it. I don't believe I could have completed this dissertation without his sage advice, criticism and generous support.

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I would also like to acknowledge all the individuals whom I interviewed for this dissertation, whose oral histories form such a large and rich part of the discussion. All were kind in their support and generous with their time.

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Chapter 1: Introduction: The Evolution of an Epidemic

> **As natural selection works solely by and for the good of each being, all corporeal and mental endowments will tend to progress towards perfection.[1]**
>
> **At least once every second, seventy times a minute, four thousand times or more an hour, one hundred thousand times a day, three or four million times a month, sleeping or waking, active or quiet, heedful or heedless, summer, winter, spring, and fall, our heart spins out its irrevocable time as it beats its muffled marches to the grave.[2]**

Defining the Disease

Writes physician-historian William B. Bean "Myocardial infarction and other aspects of coronary artery disease have a reasonably clear and well-known history. Our understanding is relatively recent."[3] This dissertation is a critical look at coronary heart disease (CHD) and its evolution as a disease and major cause of death over the course of the twentieth century. More pointedly it is an attempt to explain the reason or reasons for the abrupt decline in its mortality that is well documented to have begun in 1968 and continued to date. Not all cardiovascular disease (CVD) is CHD. It therefore becomes necessary to first define terms to be sure that what is included in this project is clear and internally consistent. CHD is the result of disease of the coronary arteries and is viewed as a result of coronary artery atherosclerotic disease (CAD).[4] But for the purposes of this project we will use the terms CHD and CAD interchangeably to mean the same thing. Today and for the majority of the last one hundred years CAD and its sequelae have accounted for the vast

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[1] Charles Darwin. *On the Origin of the Species.* London: John Murray (1859): 489.
[2] William B. Bean. "Masquerades of Myocardial Infarction." *Trans Am Clin Climatol Assoc.* 87 (1976): 128–137.
[3] Ibid.
[4] http://www.heart.org/HEARTORG/Conditions/More/MyHeartandStrokeNews/Coronary-Artery-Disease---Coronary-Heart-Disease_UCM_436416_Article.jsp

majority of cardiovascular disease and cardiovascular related deaths. In 2011, CAD accounted for 67% of the deaths identified as cardiovascular (CVD) in nature.[5] Some of the major distinctions between CAD and the rest of CVD can be made quite easily and lesions that are unrelated to the coronary arteries[6] can be excluded. These include diseases of the heart valves, pericardium, heart chambers, and surrounding vasculature supplying blood to and from the rest of the body. For the purposes of this work then I will be looking at diseases and lesions specifically and exclusively related to the coronary arteries. Atherosclerosis defines the underlying pathology and occlusion of the coronary arteries and its sequelae; myocardial ischemia and infarction, the disease of interest. The term coronary thrombosis, often used interchangeably with myocardial infarction and "heart attack," came into prominence in the early 20th century and was popularized by individuals like Samuel A. Levine and James Herrick. Thrombosis, both pathologically and clinically, is a major component of what is now considered CAD. By distinction, naturally occurring embolization, which occurs elsewhere in the vasculature of the human body, is not characteristically seen in the coronary arteries.

The disease is deeply rooted in the concept that it derives from the process of atherosclerosis and involves obstruction of arteries supplying the heart with blood. J. O. Leibowitz wrote a history of coronary heart disease, published in 1970, and explained therein that the term CHD "is meant to include the older notion of angina pectoris, as well as the more recent terms: coronary thrombosis and myocardial infarction."[7] This inclusion is modeled on the work of the astute and celebrated cardiologist Paul Dudley White who addressed the issue

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[5] A.M. Miniño, S. L. Murphy, J.Xu, K.D. Kochanek. Deaths: Final data for 2008. National Vital Statistics Reports; vol 59 no 10. Hyattsville, MD: National Center for Health Staistics. 2011.

[6] The arteries that supply blood, oxygen and nutrients to the heart itself.

[7] J. O. Leibowitz. *The History of Coronary Heart Disease.* Berkeley: University of California (1970): xv.

of nomenclature at some length in his much earlier work on the subject.[8] According to Leibowitz, inclusion as such "most nearly expresses the manifold effects of coronary arterial disease on the heart."[9]

The brief historiography of Coronary Artery Disease

Writing in 1992, Lawrence Deckelbaum of Yale University, noted that "Coronary artery disease has probably affected human beings throughout [all of] history, but it is only in the last century or so that it has emerged as a leading cause of death."[10] A chronic disease whose clinical elucidation and establishment as such recently celebrated 100 years of clear acknowledgment, there is little doubt on pathological grounds that the disease was present in antiquity. [11] In terms of its clinical manifestations, CAD identity emerged slowly over the course of time as symptoms and pathology eventually would became melded into one disease; "the syndrome of anginal pain…recognized as a well-defined entity in the second half of the eighteenth century, and that of myocardial infarction early in the twentieth,"[12] eventually became one.

A pathological finding for much of modern history, that was seen not infrequently on post-mortem examination, but rarely recognized in "individual living cases," until they "were described in 1910 and 1912…'coronary disease' and 'coronary thrombosis' were not diagnoses that any clinical doctor made in the first 10 years of the twentieth century and most not for the first 20 years. Thrombosis and coronary narrowing and myocardial degeneration were known to

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[8] Paul D. White. *Heart Disease.* 4th edition. New York: Macmillan (1951): 517-518.
[9] J. O. Leibowitz. *The History of Coronary Heart Disease*: xv.
[10] Lawrence Deckelbaum. "Chapter 11: Heart Attacks and Coronary Artery Disease." In Barry L. Zaret, et al ed. *Yale University School of Medicine Heart Book.* New York: Morrow (1992): 133.
[11] J. O. Leibowitz. *The History of Coronary Heart Disease*: 125.
[12] Ibid: 1.

pathologists and angina pectoris was known to clinicians, but clinical and pathological correlation was missing."[13] One explanation, given by historian Leibowitz, is that "medical research at the end of the nineteenth century was absorbed by the great discoveries in other spheres such as surgery, bacteriology and roentgenology, while the medical profession was yet reluctant to accept a diagnosis known chiefly through dissections."[14] Confusion also resulted from the fact that multiple theories of predecessor diagnosis angina pectoris existed at the turn of the century. Another particular obstacle to linking clinical disease to known pathological evidence can be attributed to the great German pathologist Julius Friedrich Cohnheim working in the dawn of the twentieth century. His 1881 experiments, in which he ligated the coronary arteries caused considerable confusion in the medical community. Because he believed the coronary arteries were "end arteries" without anastomosis an immediate cessation of ventricular activity resulted from obstruction, ligature or otherwise, and such complete occlusion he believed resulted in immediate death. Given his reputation, these ideas, plausible at the time, but nonetheless completely wrong, resonated far and "were an obstacle linking the clinical observations and the pathological facts."[15]

In the preeminent American medical textbook of the time, *The Principles and Practice of Medicine* (5th edition), published in 1904, Sir William Osler made just three mentions of what today we know as coronary artery disease.[16] The diagnosis of coronary thrombosis and myocardial infarction appeared to elude Osler. Thomas East explains:

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[13] A. Stewart Truswell. *Cholesterol and Beyond: The Research on Diet and Coronary Heart Disease 1900-2000.* Heidelberg: Springer (2010): 1.
[14] J.O. Leibowitz. *The History of Coronary Heart Disease*: 141.
[15] Terrence East. *The Story of Heart Disease: The FitzPatrick Lectures for 1956 and 1957 given before The Royal College of Physicians of London.* London: William Dawson and Sons (1958): 115.
[16] Personal review of William Osler. *The Principles and Practice of Medicine*. 5th edition. New York: Appleton, 1904.

> The Lumleian Lectures given by Sir William Osler at this College [The Royal College of Physicians of London] in 1910 are an important milestone in our study of the development of our knowledge of the disease of the coronary circulation. They make wonderfully good reading. Everything he wrote had charm and brilliance. Here I think he reached as high a level as at any time. At the height of his powers, after forty years of experience, he had something to say worth hearing. The remarkable fact that must strike us at the present time is that he had reached the Fellowship of this College before he saw a case![17]

It would be twenty years before "the first papers on coronary thrombosis in British journals [only] appeared in 1925, reporting a few cases."[18] Three years later, in *The Lancet,* J. Parkinson and D.E. Bedford, reported their first cases of diagnosed coronary artery disease in London hospitals. As would occur with other aspects of the disease there were skeptics, including Sir Clifford Albutt, Professor at Cambridge University, who opposed the attribution of angina pectoris to a coronary artery origin. Many years later, in his 1968 Harvey Lecture, Bedford shed light on the early 20th century recognition and origins of coronary artery disease and what had by that time become a modern day epidemic. He wrote, "As a student I had never heard of coronary thrombosis and did not make my first clinical diagnosis until 1924 in a case admitted to the surgical ward at Middlesex Hospital as an acute abdomen, as often happened in those days. Working at the London Hospital with Parkinson in 1926, I watched the epidemic spreading round the neighborhood as local practitioners began to recognize coronary thrombosis, and by 1930 it had become a common and familiar illness."[19] As we will see the year of his lectureship (1968) would be fateful in related but very different terms.

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[17] Terrence East. *The Story of Heart Disease*: 117.
[18] A. Stewart Truswell. *Cholesterol and Beyond: The Research on Diet and Coronary Heart Disease 1900-2000:* 3.
[19] D.E. Bedford. "Harvey's third circulation. De Circulo Sanguinis in Corde." *Br Med J* ii (1968): 273-277.

An analysis of coronary artery disease over the course of the majority of the twentieth century (1900-1974) is more than just a historical exercise. It is an opportunity to look at the evolution of a disease that for the greater part of written history occupied only a small and rather elusive place, but when fully recognized and documented roared to an extremely prominent position in the health of the world's population. When we talk of last to first we often are making reference to sports teams and their rise to prominence as power houses of athleticism. With coronary artery disease the same metaphor can be applied in the evolution of a disease that would over the course of a century become the leading cause of death in the western world; arising it would appear from nowhere. But as it continued to lead the way in mortality for most of its recognized existence, quite precipitously and almost without any warning its lethality began to decline and for reasons that have, to this date, remained for the most part fairly elusive. This rapid development and progression of disease cannot help but to remind the medical historian of the Black Plague or in a more contemporary context of AIDS. But by all appearances, unlike both of these epidemics, coronary artery disease lacks a specific etiologic agent. For coronary artery disease there appear to be more elaborate and varied forces at play.

This project looks at CAD, tracing its rapid rise in eminence among deadly chronic diseases, the historical seeds for its epidemic, and most importantly explanations for its eventual, unpredicted and extraordinary decline in mortality. Theoretical as well as practical, narrow as well as global, explanations exist for both its rise and fall and this dissertation will look at all. According to Thomas McKeown, "there have been few attempts to assess the contribution of medical and other influences to mortality as a whole, or the relation of mortality

to the growth of population."[20] This dissertation in the main attempts to answer a number of related questions including is CHD a new disease, where did it come from and when and why did it suddenly begin to change in terms of its natural history and lethality? Answers to these questions should help in better defining the disease and perhaps finding important factors that will aid interested individuals in combating its ill effects. But before one can fully understand the reasons for decline in its mortality one must understand and appreciate the nature of its origins and the evolution of the disease from obscurity to full blown epidemic.

Although early evidence of atherosclerosis exists, Leibowitz notes that "investigators interested in the historical aspects have not been unanimous as to how long coronary artery disease had been in existence." Early observations were often "overlooked, since they did not easily fit into the existing systems of medicine. This further delayed the recognition and acceptance of the condition as a clinical syndrome."[21] Although he believes that the historical record does document the early existence of the disease clinically, through many of the "signs and symptoms" described, there are a number of historians and physicians who do not agree with his assessment. L. Michaels, a Canadian physician-historian, writing in the British Heart Journal in 1966, made the following observation of clinical medicine in the 18th century:

> …clinical description, as exemplified by gout and migraine, was of high order. That a symptom like angina pectoris could have gone unobserved seems particularly unlikely in view of its dramatic features, fully recognized at the time the disease was first described. The remarkable absence of systematic descriptions before 1768 therefore raises the distinct possibility that angina pectoris first made its appearance to any appreciable extent in the second half of the eighteenth century and had hardly existed previously.

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[20] Thomas McKeown. "A Sociological Approach to the History of Medicine." In Gordon McLachlan and Thomas McKeown, editors. *Medical History and Medical Care.* London: Oxford (1971): 7.
[21] J.O. Leibowitz. *The History of Coronary Heart Disease:* 172.

In putting angina pectoris and coronary artery thrombosis into a historical context Michaels continues:

> There are almost no clearly recognizable descriptions of angina pectoris before that of Heberden in 1768. A possible explanation is that angina pectoris first made its appearance at about that time rather than having been prevalent but unrecognized previously. During the next one and a half centuries angina pectoris appeared to have remained extremely rare. Before 1912 coronary thrombosis remained virtually unrecognized as a clinical entity and the possibility must be considered that it had been almost non-existent rather than prevalent but unrecognized. [22]

But for others like William B. Bean, of the University of Texas, such a view would appear to be extremely reductionist. Writing an intriguing and perceptive piece on clinical masquerades of coronary disease he believes that "heart attacks must have occurred ever since there first were people to have heart attacks."[23] His point, which may very well be the most plausible, based on the evidence that atherosclerotic lesions in the coronaries date to antiquity[24], is that the disease probably did exist but may have been disguised and not recognized to be of coronary origin. At odds with the opinion of Michaels and like-minded clinician historians, for Bean the disease was felt to be clearly present for a long period of time, based on modern knowledge of coronary artery disease manifestations, but was masquerading, and probably not recognized for lack of adequate tools and procedures; an issue that would in large part be resolved in the early 20th century with the advent of the electrocardiogram. This historical explanation speaks to the belief that many cases of the disease, perhaps the majority,

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[22] L. Michaels. "Aetiology of coronary artery disease: An historical approach." *Br Heart J* 28 (1966): 259, 263.
[23] W. B. Bean. "Clinical masquerades of acute myocardial infarction." *J Iowa St. Med Soc.* 52 (1962): 781-83.
[24] A.T. Sandison, "Degenerative Vascular Disease." In Don Brothwell and A. T. Sandison, editors. *Diseases in Antiquity: A Survey of the Diseases, Injuries and Surgery of Early Populations.* Springfield: Charles C. Thomas (1967): 474-475.

were probably "obscured by atypical and inadequately understood factors" until much later when they could be more easily sorted from other clinical entities and diagnosed for what they truly were.[25]

Harvard cardiologist and avid physician historian Howard B. Sprague (1895-1970) spent his entire professional career at the Massachusetts General Hospital (MGH) taking care of patients with heart disease. Medical students and physicians alike have long been acquainted with the stethoscope, Sprague-Rappaport, which bears his name. His close association at MGH with Dr. Paul Dudley White began in 1924. Sprague was of the belief that coronary artery disease had a rather long historical record. Like White, he believed that one's environment impacted the development of coronary disease, being one of the first clinicians to view risk as an etiologic factor in the development of the disease. In his 1966 article on the impact of environmental factors on coronary artery disease development he stated his view in support of the more protracted history of coronary artery disease remarking quite emphatically that "certainly the disease did not suddenly leap into existence about 1920, fully armed for destruction like Athena from the brow of Zeus." Rather, he believed that the literature, medical and otherwise, documented the existence of the disease for at least two hundred years. For Sprague, the incidence of the disease was also evolving, as those at risk were changing.[26] Bean concurs, writing "Heart attack, myocardial infarction, occurred in the older people in every society that became well enough organized to permit a man or woman to last beyond the stage of physical utility as a warrior, hunter, planter or harvester."[27] In this respect, Sprague believed

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[25] J.O. Leibowitz. *The History of Coronary Heart Disease:* 174.
[26] Howard B. Sprague. "Environment in relation to coronary artery disease." *Arch Enviro Heal* 13 (1966): 4-12.
[27] William B. Bean. "Masquerades of Myocardial Infarction." 129.

that other challenging causes of death, especially tuberculosis, other infections and infant mortality, deeply affected what was seen of coronary artery disease in earlier periods.[28]

Sprague, and probably Bean too, appeared to be emulating, almost predicting, the somewhat later theory of Abdel R. Omran, not yet articulated in the literature, that there existed an epidemiological transition of disease, with incidence and mortality of a disease reflecting competition with other diseases in existence at the time. Although it would be a few years before the latter would publish his theory, Sprague, writing in the mid-1960s, expressed the belief that "failure to die early of other diseases, and the delay in recognition by the medical profession of the clinical pattern of acute coronary occlusion and myocardial infarction prior to about 1920," explains the increase in incidence of the disease over the first part of the twentieth century.[29]

Although in retrospect symptomatology can now be unmistakably linked to pathology, for most of written history a diagnostic dichotomy existed in trying to link symptoms to disease and long before there was coronary artery thrombosis there was angina pectoris. Historically crucial, William Heberden's description of angina pectoris, as outlined in his address to the Royal College of Physicians in London in 1768 is as salient and accurate today as it was then. Writes Heberden:

> … there is a disorder of the breast marked with strong and peculiar symptoms, considerable for the kind of danger belonging to it, and not extremely rare, which deserves to be mentioned more at length. The seat of it, and the sense of strangling, and anxiety with which it is attended, may make it not improperly be called *angina pectoris*.
>
> They who are afflicted with it, are seized while they are walking, (more especially if it be up hill, and soon after eating), with a painful and most disagreeable sensation in the breast, which seems as if it would extinguish life, if it were to increase or to

[28] Howard B. Sprague. "Environment in relation to coronary artery disease." 4-12.
[29] Ibid.

> continue; but the moment they stand still, all this uneasiness vanishes.[30]

Not to preempt the priority of Heberden, but to reiterate the notion that angina pectoris, clearly established as a leading manifestation of coronary disease, in the twentieth century, existed for far longer, Paul Dudley White declared, "angina pectoris although not clearly defined until…1768 [and the work of Heberden]…must be 'as old as the hills.'" White notes that clear accounts of angina and sudden death were documented in the "times of Hippocrates, Galen and Pliny the Elder."[31] But, according to Leibowitz, "the belated recognition of infarction of the myocardium especially, has puzzled most historians."[32]

Historian Bean believes, "The reason for the long delay in recognizing the distinction between angina pectoris and myocardial infarction or coronary thrombosis lies in the hands of pathologists and authorities like Sir Clifford Allbutt, who thought that all 'heart' pain came from the aorta. Everyone assumed that a clot in a coronary artery was fatal, promptly fatal."[33] Because a diagnosis of angina pectoris was not universally fatal it was not associated, until the early 20th century, with disease of the coronaries. When it became clear that coronary artery thrombosis was not "coroner's thrombosis," when the left anterior descending coronary artery was no longer considered "the artery of sudden death," angina pectoris became the leading symptom and clinical evidence that CHD was present in a patient.

In summarizing the debated length of existence of CHD and for that matter other diseases, Bean writes, "a clinical disease may not have been recognized, though widespread for

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[30] Park W. Willis III. "Diagnosing Angina Pectoris." In Oglesby Paul. Ed. *Angina Pectoris.* New York: Malcolm (1974): 19.
[31] Paul Dudley White. "Angina Pectoris: Historical Background." In Oglesby Paul. Ed. *Angina Pectoris.* New York: Medcom (1974): 1.
[32] J.O. Leibowitz. *The History of Coronary Heart Disease*: 1
[33] William B. Bean. "Masquerades of Myocardial Infarction." 129.

a long time. It emerges from its subterranean caverns when some perceptive person recognizes and describes its signs, symptoms, lesions and malfunctions."[34] It would take the work of two Russian clinicians and James Herrick in the second decade of the 20th century to show this to be the case for CHD.

Emergence of a Chronic Disease Entity

Conceptualization and elucidation of the nature, pathology and physiology of the entity of angina pectoris and ultimately coronary artery disease did not occur until the process of atherosclerosis itself was better recognized and understood. This ensued in the early 19th century and can be attributed to the work of two individuals, Antonio Scarpa and J.G.C.F.M. Lobstein. Scarpa's *Sull Aneurisma,* published in 1804, and based on dissection, gave the first evidence for the pathological lesion of atherosclerosis. It was Lobstein, who some 30 years after Scapa's description, coined the term "atherosclerosis," giving credit to his predecessor as well as amplifying the findings of Scarpa.[35] His work was followed shortly thereafter by the work of pathologist Rudolf Virchow, considered the "father of modern pathology," who began to publish his findings in 1846, and although he did not display a significant interest in coronary artery disease per se, "his concept of thrombosis gave the start to further developments in [the] field of cardiac pathology."[36]

By the mid-nineteenth century a number of researchers looking specifically at coronary circulation appeared on the scene, including German Julius Cohnheim, who studied the effects of ligation of the coronary arteries. But in terms of true pathology it was Swedish pathologist G.W.J. Düben in 1859 and German Carl Weigert, in 1880, who first described both the gross and microscopic findings of myocardial infarction. Not long thereafter, in 1884, fellow German E.

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[34] Ibid.
[35] Ibid. 7.
[36] Ibid, 8.

Leyden came the closest to the first clinical description of it. Unfortunately, in not distinguishing it fully from the rest of his body of work on the heart he "failed to give a final touch to the diagnosis of myocardial infarction."[37]

In the evolution of CHD being recognized as a chronic disease, the 19th century was notable for research in cardiac pathology that "was instrumental in producing a gradual shift of interest from the coronary arteries [themselves] to the myocardium" and "in this changed atmosphere many of the facets of myocardial infarction were [first] detected."[38] Paul Dudley White wrote, years later, that "although the clinical symptoms and signs of coronary thrombosis with or without myocardial infarction were described in individual cases through the 19th century and early in the 20th, especially by pathologists interested in cardiovascular disease, a full description of the total syndrome, with years of survival in some cases, was [only] first presented in the famous paper by James Herrick, entitled 'Clinical Features of Sudden Obstruction of the Coronary Arteries,' published in 1912 in the *Journal of the American Medical Association."*[39]

In 1896, pathologist, internist and medical pioneer George Dock, a student of William Osler, and then Professor of Medicine at the University of Michigan, wrote a short book entitled *Notes on the Coronary Arteries,* in which he described three out of four cases of myocardial infarction that he had recognized during the lifetime of each and not just on post-mortem alone.[40] Russian clinicians, W.P. Obrastzow and N.D. Straschesko, of Kiev subsequently published a clinical description of coronary artery disease in 1910. One year earlier they had

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[37] Ibid, 10.
[38] Ibid, 10.
[39] Paul Dudley White. "Angina Pectoris: Historical Background." In Oglesby Paul. Ed. *Angina Pectoris:* 6.
[40] George Dock. *Notes on the Coronary Arteries.* Ann Arbor: Inland Press, 1896.

presented their findings on the diagnosis of coronary thrombosis at the first Russian Congress of Internal Medicine, held in Moscow in December 1909. A number of cases of coronary artery thrombosis were described, some with post-mortem results and some without. In two the diagnosis was made while the patients were still alive, the first of which being seen in 1899. It was stressed by Obrastzow and Straschesko that the acute episodes of the disease were precipitated in most cases "by physical exertion or emotional upset." They broke down their cases into three groups. The first, which they labeled "status anginosus" manifested "an almost continuous retrosternal pain." The second, called "status dyspnoeticus," manifested "severe and prolonged difficult respiration," which they viewed as an anginal equivalent. The third group termed "status gastralgicus" had pain localized to the upper portion of the abdomen, rather than the chest, often leading clinicians to suspect an acute abdomen rather than the correct diagnosis of coronary disease. It was their paper in 1910 and that of Herrick's two years later that are regarded as "classics" in the clinical cardiology literature, as they endeavored "to establish the diagnosis [of CHD] based on bedside observations, often confirmed by autopsies, but primarily aiming at clinical recognition during the patient's life."[41]

Although strictly speaking it was the Russian physicians who first described many of the clinical manifestations of CHD it is American James Herrick whose work is significantly better known. In his landmark paper, "Clinical features of sudden obstruction of the coronary arteries," he described two cases, one who lived for fifty hours and whose autopsy revealed red clot in the "calcareous coronary arteries" and a "yellow-red softening of the myocardium with acute pericarditis."[42] Symptoms included pain, shock, and evidence of pulmonary edema clinically. It was ostensibly the first time that a unification of patient symptoms, pathology and clinical

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[41] J.O. Leibowitz. *The History of Coronary Heart Disease*: 148-149

[42] James B. Herrick. "Clinical Features of Sudden Obstruction of the Coronary Arteries." *JAMA* 59 (1912):2015.

course was clearly articulated in the United States and the reaction initially was, to say the least, quite mixed. In sharp contradiction to the earlier teaching of William Osler, Herrick explained that the initial "accident was not necessarily fatal." But more importantly his paper "which discusses all clinical aspects of the disease and its history, brought the matter to general notice" in 1912. [43] It clarified and improved the definition of coronary artery disease's varied clinical course and for the first time marked it as a disease with a clearly chronic component.

But the real question in this historical project that looks at changing outcomes of a chronic disease is not when clinically apparent coronary artery disease was first described but, in a manner of speaking, did the first description follow closely the early discovery of the disease itself. This is a critically important question when considering a change in the understanding of the longitudinal nature and outcome course of the disease. According to White, perhaps the most preeminent cardiologist of his time and long considered the "father of preventive cardiology," as well as the founder in 1924 of the American Heart Association, coronary artery disease was "a rare disease until the 20th century." He makes the point "that until after the first two or three decades of the 20th century, coronary heart disease, as indicated by either the symptom 'angina pectoris' or the symptoms and signs (most importantly electrocardiographic) of coronary thrombosis with or without myocardial infarction, was rare or uncommon, not just missed by ignorance." For evidence he points out that both Austin Flint in his textbook of medicine published in 1866 and William Osler, in his earlier 1892 edition of his textbook, describe it as rare. With a sense of clarity and possibly clandestine purpose, he ties the onset of the epidemic of coronary artery disease, which eventually permeated and engulfed all industrial nations, to the increasingly widespread use of the automobile (circa 1920s).[44]

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[43] Terrence East. *The Story of Heart Disease: The Fitzpatrick Lectures for 1956 and 1957 given before the Royal College of Physicians of London*: 118-119.
[44] Paul Dudley White. "Angina Pectoris: Historical Background." In Oglesby Paul. Ed.

The belief that industrialization and changes in the means of transport and its effect may have impacted coronary artery disease was reiterated in the *New England Journal of Medicine* at the time of White's death in 1973. Franz Ingelfinger, then editor of the journal, alluded to the beliefs of White when he wrote "practically everyone knows that Dr. Paul Dudley White rode a bicycle and preached exercise."[45] It was indeed White who, early in the twentieth century, ahead of most of his contemporaries, "did much to boost the popularity of exercise – and the economic fortunes of the bicycle industry –by espousing the health benefits of physical activity in his lectures and writings."[46] Based on knowledge of the work of White it seems quite clear, if only in hindsight, that White was making a connection between the automobile, a consequent decline in physical activity, and CHD.

Thus, by the onset of the twentieth century the diagnosis of angina pectoris as a distinct clinical entity appeared to no longer be either comprehensive or correct. It was Obrastzow and Straschesko in 1910 and Herrick, in the United States, in 1912 who deserve equal credit "for having initiated the definitive understanding of cardiac infarction as a clinically recognizable morbid entity, which was later acknowledged to be a very common condition and of paramount statistical importance." It was largely their work that moved the clinical condition from one of angina pectoris to "thrombosis and obstruction of the coronaries." The connection between symptomatology and pathology was also greatly aided by "the advent of electrocardiographic studies" which made diagnosis of coronary disease and particularly myocardial infarction significantly easier.[47] More will be said about this shortly.

Angina Pectoris: 9.

[45] F. J. Ingelfinger. "Paul Dudley White, 1886-1973." *NEJM* 289 (1973): 1251.

[46] Gregory D. Curfman. "The Health Benefits of Exercise – A Critical Reappraisal." *NEJM* 328 (1993): 574-576.

[47] J.O. Leibowitz. *The History of Coronary Heart Disease*: 11-13.

W. Bruce Fye, cardiologist and medical historian at the Mayo Clinic, believes that "many factors contributed to the nearly 140-year delay between the first published descriptions of angina and acute myocardial infarction [coronary thrombosis]." According to Fye, the factors that "contributed to the delay in the recognition of acute myocardial infarction as a distinct entity until the twentieth century" include: "(i) the belief that sudden coronary occlusion was invariably fatal; (ii) the invariable relationship between symptoms and pathological findings in ischemic heart disease; (iii) the dependence on auscultation as an indicator of cardiac disease; (iv) the failure to examine the coronary arteries and myocardium routinely at autopsy; (v) the slow incorporation of new pathological and physiological knowledge into clinical practice; (vi) the preoccupation of physicians and medical scientists with the new field of bacteriology; (vii) the lack of any diagnostic tests to identify coronary artery obstruction or its consequences during life; and (viii) satisfaction with the standard classification scheme, which lumped what came to be called acute myocardial infarction with angina pectoris."[48]

This dissertation looks at the natural history of coronary artery disease over an historical period of time. In order to answer the question of why there was a decline in mortality in an epidemic disease one needs to firmly establish a time course in which the disease became epidemic. It should be clear so far that symptomatology and pathology did not alone aid in the diagnosis of coronary artery disease. As already mentioned a lack of diagnostic studies severely hampered early clinicians in diagnosing coronary artery disease. This however would not be for

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[48] W. Bruce Fye. "Acute Myocardial Infarction: A Historical Summary." In Bernard J. Gersh and Shahbudin H. Rahimtoola. *Acute Myocardial Infarction.* Second Edition. New York: Chapman and Hall (1997): 1-2.

long and in Richard Franck's early use of the phrase "necessity is the mother of invention" a technology would soon come along to aid in this respect. [49]

The advent of the electrocardiogram (ECG) added significantly to the ability of clinicians to diagnose coronary thrombosis and myocardial injury. In 1903, Dutch physiologist Willem Einthoven "published his invention of the accurate and practicable string galvanometer." This machine, which followed his prior invention of the "capillary electrometer" would revolutionize the practice of medicine and particularly the clinical and diagnostic practice of cardiology. Initially, its use was focused on disorders of rhythm. Its utilization in the diagnosis of angina pectoris and coronary thrombosis took several years to evolve. It did come in 1918, just six years after James Herrick's first publication, in which he demonstrated that coronary thrombosis was not uniformly acute and fatal but had a chronic component.[50] Herrick's initial report, as already alluded to, was met with very little response or enthusiasm by the medical community. It was not until 1919 and his second publication on the subject, which included electrocardiographic tracings, that the medical world sat up and took greater interest.[51] Herrick would lament years later, in his autobiography, the reluctance of his colleagues to recognize the true nature and natural history of coronary thrombosis. He wrote:

> The paper when read in 1912 before the Association of American Physicians aroused no interest. It fell like a dud. Firmly convinced that I was right, I doggedly kept at the subject, doing what I called "missionary work." I hammered away at the topic…When, however, in 1918 before the Association…I read my paper on "Coronary Thrombosis," in which were included reports of two more cases with autopsies…coronary thrombosis came into its own, to become later a household word translated by the layman

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[49] Richard Franck was believed to have made use of this proverb in 1694 in his book *Northern Memoirs* although some have credited Plato with the first use of the expression.
[50] J.O. Leibowitz. *The History of Coronary Heart Disease*: 157-158
[51] Ibid. 150.

into "heart attack."[52]

"From a consideration of the clinical histories of numerous cases in which there had been careful autopsy control, from animal experiments and from anatomic study" [alone], Herrick believed, "that there is no inherent reason why the stoppage of a large branch of a coronary artery, or even of a main trunk, must of necessity cause sudden death. Rather may it be concluded that while sudden death often does occur, yet at times, it is postponed for several hours or even days, and in some instances a complete, i.e. functionally complete, recovery ensues."[53] The use of the ECG no doubt accelerated acceptance of Herrick's observations. It was only with the work of Herrick that the disease became recognized as one with both an acute phase (sudden death) and one with a more indolent and protracted course. It was with this affirmation of the disease's natural history that investigators and researchers could begin to track incidence, mortality and case fatality in a manner consistent with a disease that was not acutely and universally fatal.

In this manner Herrick almost single handedly helped to transform a relatively recently described clinical event, felt by most to be lethal, into a chronic disease. In the words of Bean, Herrick was the "perceptive person" who helped the disease emerge from "its subterranean caverns" by recognizing and describing its "signs, symptoms, lesions, and malfunctions."[54]

While others of his time associated death with coronary disease; "Herrick's motive was rather different, tending to stress the fact that the disease is not immediately fatal."[55] It would

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[52] James Bryan Herrick. *Memories of Eighty Years.* Chicago: University of Chicago (1949): 196.
[53] James B. Herrick. "An intimate account of my early experience with coronary thrombosis." *AHJ* 27 (1944): 9.
[54] William B. Bean. "Masquerades of Myocardial Infarction." 129.
[55] J.O. Leibowitz. *The History of Coronary Heart Disease*: 152.

be the remainder of the twentieth century that would see this newly evolved variably fatal affliction blossom into a full blown chronic disease of epidemic proportions. It is neither novel nor surprising that such events would take shape in this manner. As historian Leibowitz explains:

> It is often the case that important insight emerges more organically once planted in the fertile soil of history. Discoveries do not make their appearance abruptly, and they stand out even more prominently when seen against the background of past endeavor.[56]

The electrocardiogram and other techniques and procedures to follow brought greater acumen and precision to the diagnosis of coronary artery disease. Writes Leibowitz:

> It is even probable that the awareness of the condition and sureness in the diagnosis of coronary diseases increased in proportion to the availability of tools and methods. This explains why the condition became more often identifiable. Thus diagnosis was brought within the range of the average physician, and not left exclusively in the hands of a select group of especially interested investigators.[57]

Bertram Pitt at the University of Michigan notes however that even with the work of Herrick and the availability of the ECG "the diagnosis of AMI (acute myocardial infarction) was made only infrequently until 1929, when Levine reported on 145 patients with AMI and awakened interest in this entity."[58] The impact of social and occupational influences, as already alluded to, has historically been considered responsible for the emergence of coronary artery disease in the period under discussion. Well-educated, high socioeconomic status males over the age of 50 were often implicated in this regard. A paper in the *British Heart Journal* in 1949,

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[56] Ibid, 149.
[57] Ibid, 160.
[58] Bertram Pitt. "Acute Myocardial Infarction: Historical Perspectives." In Jeffrey L. Anderson, ed. *Acute Myocardial Infarction: New Management Strategies.* Rockville: Aspen (1987): 2.

by J.A. Ryle and W.T. Russell, although perhaps not truly representative of the general population, documented certain occupations as high risk for coronary artery disease.[59] It was William Osler, in his Lumleian lectures that alluded to angina pectoris as "morbus medicorum" because of the apparent high incidence of the disease in physicians.

As cardiac epidemiologist Henry Blackburn and others have documented, the mortality of coronary artery disease showed a progressive upward climb though the early period following Herrick's initial work and into the 1960s, punctuated only by dips in case fatality during the two world wars and the depression.[60] Mortality from the end of World War II until the late 1960s climbed steeply but then in 1968 something rather acute and unexpected happened and there was an inflection point in the case fatality rates, followed by a slow but progressive decline in mortality of this epidemic disease. The decline was not immediately recognized, but within 10 years it was clear that coronary artery disease, although still remaining the greatest threat to human life in the industrialized world, was on the decline in terms of its mortality and it has continued to fall in this respect ever since. A federally funded *Conference on the Decline in Coronary Heart Disease Mortality*, often referred to as just "the Decline Conference," chaired by Sidney Blumenthal, gathered the leading experts, clinicians, researchers and epidemiologists of the time, in Bethesda in 1978, in an attempt to discern the reason for the yet unexplained drop in mortality. Their findings were published in May 1979 with little additional light or added insight shed on the topic or its explanation.[61]

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[59] J.A. Ryle and W.T. Russell. "Natural history of coronary artery disease." *Br Heart J.* 11 (1949): 370-89.
[60] Website of Professor Henry Blackburn. http://www.epi.umn.edu/cvdepi/
[61] Richard J. Havlik, and Manning Feinleib, editors. *Proceedings of the Conference on the Decline in Coronary Heart Disease Mortality.* U.S. Department of Health, Education, and Welfare. Public Health Service. National Institutes of Health. NIH Publication No. 79-1610. May 1979.

Explanations for the decline in mortality, beginning in 1968, have been extensively speculated upon ever since but never clearly elucidated. It is the goal of this PhD dissertation to investigate and explain what to date has remained largely unexplained: why a disease whose natural history became clear only 50 years earlier, rose to prominence in terms of the lives it took, during that short time period, saw its mortality begin to sharply decline in 1968. A number of considerations for this decline seem clear. Can the decline be attributed to improvements in care and treatment, did prevention play a major role or could it be a combination of factors? Finally, can the decline be explained by factors clearly outside of the field of heart disease itself, a result of modernity, social and cultural factors, an "invisible hand" of sorts that impacted other diseases as well and worked to universally improve overall disease mortality?

Jeremy Greene and David Jones have written on the decline in coronary artery disease mortality from 1974 to 2010. Their work, using a combination of epidemiological studies and extensive disease modeling, shows that a combination of care, innovation and prevention account for the continued decline in coronary disease mortality after 1974.[62] But for the time period leading up to the initial decline in 1968 the data and conclusions remain unclear. In this project I will depart from traditional approaches of using epidemiological data alone to discern the reasons and explanation for the decline in mortality that began in 1968. The approach used in this study will be more historical in nature using a combination of oral histories, archival data, primarily institutional, epidemiology and secondary sources concerning health, morality and their determinants to discern the most salient features that account for the early decline in coronary artery disease mortality.

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[62] David S. Jones and Jeremy A. Greene. "Analysis and Commentary: The Contributions of Prevention and Treatment To The Decline in Cardiovascular Mortality: Lessons From A Forty-Year Debate." *Health Affairs* 31 (2012): 2250-2258.

A thorough historical reconstruction of events of the twentieth century in terms of health and illness in general and heart disease more specifically will be necessary to help determine all factors impacting a change and specifically a decline in mortality. In the end we will hopefully be able to pinpoint exactly what transpired over the time period and how CHD mortality was impacted. Known and presumed etiologic factors will be looked at because a thorough exploration of all of these can hopefully help determine their impact and how they may have been modified to effect mortality in this important way.

Methodology

Although the decline in coronary artery disease mortality is not unique to any one country and it appeared to occur widely if not sporadically in other industrial nations worldwide at about the same time, this study will focus on an examination of the decline in the United States only. Occasional reference will be made to the experience in other countries, but only as comparison and in relation to what occurred in the United States. Although the study of coronary artery disease is one distinguished by international investigation, including the landmark Seven Countries Study by Ancel Keys and colleagues, a number of reasons exist for limiting the scope of this study. These include the ability to draw on the National Center for Health Statistics and on the "Decline Conference" for data, both of which are unique to this country's experience. Additionally, since a major part of the research involves oral histories, interviewing individuals with first-hand experience and expertise during the period, the expense involved in travel beyond the United States to collect these would have been prohibitive. It would also require additional and international IRB approvals. Finally, tackling the diversity and disparity of experience in this country, including the impact of important changes in the way care was paid for, should be an adequate challenge without venturing into other parts of the world where these concerns and matters are often quite different. But, in a sense since medical

information and the implementation of medical practice has, for the period under study, been global in terms of similarly industrialized nations, what occurred in the United States during the time period, in relation to CHD, should be applicable to other westernized countries.

Initial evidence for the decline in coronary artery disease mortality will be presented in terms of statistical evidence and trends that existed in the United States at the time the decline was noted and in the period of time before the decline began. The use of NHANES[63] data in this respect will be particularly helpful. Other researchers, including Greene and Jones, have identified a dichotomy that exists in terms of factors that influence mortality of this disease. This is best identified as an ongoing debate between the forces of disease prevention and the management of risk, on the one hand, and disease management and treatment on the other. Since these have been identified as the two major forces that exist to explain a decline in mortality, it will be these two that will be primarily examined in great depth in this study. Other issues, including socioeconomic factors, improvements in public health, general changes in health care policy, third party reimbursement, cultural issues, education and non-disease specific issues will be addressed as well as they arise in the historical context.

Oral histories from those intimately and critically involved in the care of individuals with coronary disease, experts in the field, and others (epidemiologists and scientists) who have first-hand knowledge of the disease during the period under consideration will be utilized to better delineate the issues and multitude of factors that existed, were in play, and had the potential to impact changes in mortality. The range of experts used in this respect will be wide, diverse and as broad as possible, and will in some ways parallel the experts that participated in the Decline Conference of 1978. Some may in fact overlap. The panel of experts will derive from those

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[63] National Health and Nutrition Examination Survey. http://www.cdc.gov/nchs/nhanes.htm

known to still be living and those suggested by advisers and others knowledgeable in the field. IRB waiver has been obtained for the purpose of soliciting oral histories. Participants will be purposely selected and not randomly so to obtain the most authoritative opinions available from known involved individuals at the time.

Archival data will be used to substantiate practices and policies in effect at and surrounding the period of the decline. This will include pertinent textbooks, journals, memoirs and other writings that bear directly on the period under consideration and the disease, as it was known at the time. Hospital archives and records, as available, will also be used to evaluate prevailing practices and facilities of care that existed at the time.

Finally, epidemiological studies, an examination of healthcare policy over the time period, and a variety of models will be looked at and reported in terms of their ability to inform the data and substantiate claims made through other means. In the debate between prevention and treatment, Jones and Greene point out "much can be learned by studying the history of the intersection of cardiovascular epidemiology and health policy." In addition, they write "Modeling has now become a popular tool in cardiovascular epidemiology, applied both to explain past declines and to predict future possibilities."[64] Unfortunately, in this respect few models appear to be useful in explaining the changes in mortality for coronary artery disease before 1970.

The Validity of Oral History

[64] David S. Jones and Jeremy A. Greene. "Analysis and Commentary: The Contributions of Prevention and Treatment To The Decline in Cardiovascular Mortality: Lessons From A Forty-Year Debate." 2250-2258.

The assertion has been made that all too often "history is the verdict 'of those who weren't there on those who were.'"[65] Writer and philosopher George Santayana, best known for his aphorisms, reiterated, writing "History is a pack of lies about events that never happened told by people who weren't there."[66] The use of oral history as a method in helping to determine and better define actual events that occurred in the past is well documented. Ken Howarth writes oral history "should be seen as a vital tool in collection research about almost any object or document. It is perhaps a process of re-evaluation and re-education. Oral history in one of its many guises should be considered as an essential part of the recording process and included in any forward plan. It is fundamental in assessing and understanding the use, social context and cultural worth of objects and documents. Oral History should be an accepted part of any formal acquisition process and/or collecting policy."[67]

In this study, oral history is not the sole source of data or research but it acts as one of the major primary source components in the project. There is good documented justification for its use in this context. The utility and "the strength of oral history lies in the fact that it complements written, printed and visual sources and can often clearly call into question those other sources. It can be, and often is, a fundamental method of acquiring information that cannot be obtained in any other way." What is often the concern in the use of oral history is the question "over the reliability of memory." But as Howarth notes, "despite its inadequacies…its track record in terms of accuracy is as good as the printed word and is usually far, far better. At least you can ask your informant questions: typefaces do not tend to answer back."[68] According

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[65] Donald A. Ritchie. *Doing Oral History: A Practical Guide* (Second Edition). New York: Oxford (2203): 27.
[66] Dan Mayer. *Essential Evidence-Based Medicine.* Second Edition. Cambridge: University Press (2010): 1.
[67] Ken Howarth. *Oral History: A Handbook.* Gloucestershire: Sutton (1998): viii.
[68] Ibid. viii.

to Donald A. Ritchie, historian of the United States Senate, "Oral History is as reliable or unreliable as other research sources. No single piece of data of any sort should be trusted completely, and all sources need to be tested against other evidence."[69]

It might strike ardent healthcare investigators, researchers and number crunchers as strange and rather unscientific to use this methodology in the context of health care investigation and research. But according to Howarth, the use of "oral history in health care may seem at first glance very unlikely, but advocates of oral history have proved beyond doubt the usefulness of the technique." In weaving the historical record "oral history complements official records" and often provides a more complete and substantiated record of events and actions that have impacted medical history over time than other sources.[70]

One major goal in the use of oral history, in a subjective research project such as this, has to be validation of the oral evidence. Authentication can be divided into two parts namely "the degree to which any individual interview yields reliable information on the historical experience, and the degree to which that individual experience is typical of its time and place." As Trevor Lummis suggests a "major concern is to suggest ways in which simple aggregation can be used to assess validity, for as the data in oral history archives lacks the random quality required for formal statistical validity, some acceptable method of generalizing from a number of interviews has to be developed." He continues "the main concern for oral history is the degree to which accurate recall of the past is possible."[71] In this project, multiple oral histories will be obtained to develop a consensus of opinions among individuals considered to be experts

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[69] Donald A. Ritchie. *Doing Oral History: A Practical Guide* (Second Edition): 26.
[70] Ken Howarth. *Oral History: A Handbook*: 78-79.
[71] Trevor Lummis. "Structure and validity in oral evidence." In Robert Perks and Alistair Thomson, editors. *The oral history reader*. London: Routledge (1998): 273.

in the field.[72] Fortunate to this dissertation project and its time frame is the fact that "it is known that when memory fails it is the most recent memories which go first, while early memories remain clear or are even enhanced."[73] The information sought by oral history here will be, for the most part, at least 50 years old.

What is particularly important in terms of the use of oral history here is that the data otherwise is scant and to a large extent unrevealing. According to Howarth, in this circumstance "oral history is a rich source of information for the researcher, particularly in areas where written or manuscript evidence is sparse. Most curators record oral history because they recognize that the oral source is likely to be the main one available about a particular subject, and that is reason enough."[74] Studies to date, on this topic, that have not made use of oral history and relied solely on statistics and archival information alone have been largely unrevealing.[75]

The Role of Medicine and Biology

This dissertation encompasses both theoretical considerations and also data obtained in the field. It both embraces and challenges medical science and achievements made over the time period of consideration, 1900-1974, and attempts to bring into view the overarching concern at the time for improving health. But a purely biomedical approach to the question of health, disease and specifically changes in mortality over time is destined to be drastically incomplete in nature and flawed.

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[72] Each interview was graded on a scale of 1-5 by the interviewer, at the time of the interview, based on their deemed accuracy. This information is available upon request.
[73] Ibid.
[74] Ken Howarth. *Oral History: A Handbook*: 175.
[75] Richard J. Havlik, and Manning Feinleib, editors. *Proceedings of the Conference on the Decline in Coronary Heart Disease Mortality.*

Claude Bernard believed that medicine was concerned with what he termed the "internal environment."[76] The state of health then "involves the maintenance of constant, or nearly constant, conditions in the internal environment – conditions that enable cells and organs to function properly." The disease state on the other hand is manifested by "deviations from these 'normal' conditions." Evolutionary biologists appreciate the concern of medicine for its attention to the internal state of the body but "are more interested in studying the interactions of organisms with their external environments." Because medicine and evolutionary biology historically have dealt with different biological issues, their approaches to the study of human health and disease have diverged and as a result they have evolved as very separate and unrelated disciplines. Robert Perlman however believes that the two "different perspectives are complementary." And in a study of this nature, I believe there is much to be learned and gained by a combined approach. By integrating the two into what has been termed "evolutionary medicine" one has a better chance of understanding health and disease. According to Perlman, "understanding evolutionary processes helps to explain our evolved vulnerabilities or susceptibilities to disease and our current burden of disease."[77]

The view of theorists, including Thomas McKeown and evolutionary biologists like Perlman, will be explored in great length throughout the dissertation and particularly in chapter 3. For McKeown, the role of medicine looms both large and small in terms of the health of the population. His book, *The Role of Medicine: Dream, Mirage or Nemesis* has two aims that have influenced the evolution and permeated the research and writing of this dissertation, namely, "to examine the validity of a concept which is rarely stated explicitly but on which medical

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[76] Claude Bernard. *An introduction to the study of experimental medicine.* New York: Dover (1957): 64.
[77] Robert L. Perlman. "Evolution and Medicine." *Perspec in Bio and Med.* 56 (2013): 178-179.

activities largely rest, namely that human health depends essentially on a mechanistic approach based on understanding of the structure and function of the body and of the disease processes that affect it; and to consider the significance of the conclusions for medicine, particularly in relation to health services, medical education, and medical research."[78]

Although interesting in and of itself the examination of a historical phenomenon in medicine bears its greatest importance and contribution in how it can be applied to other present and future considerations. In doing so the significance of the work becomes amplified and the findings that much more important to human health and the population at large. According to Perlman, "since disease has served as an important selection factor in evolution, knowledge of the present patterns of disease gives insights into our evolutionary history."[79] The lessons of this dissertation will have their greatest impact on the way they can be projected and applied to other diseases and also how they inform us about the evolution of disease and the impact on mortality in general.

Organization of the dissertation and chapter outline

This dissertation consists of 6 chapters. The approach has been to define the disease and the goals of the study in this the first chapter or introduction.

Chapter two (**The Decline**) looks at documenting and substantiating the validity of the decline in the mortality of coronary artery disease, bringing to light the evidence for the decline and the myriad of factors that might have played a role. It looks specifically at archival and statistical information for the decline and will introduce related areas that may have played a role. In this chapter the statistical information and evidence for the decline in mortality as it existed at the time of the decline in 1968 is presented. It draws largely on data known at the

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[78] Thomas McKeown. *The Role of Medicine: Dream, Mirage or Nemesis.* Princeton: Princeton University Press (1979): 3.
[79] Robert L. Perlman. "Evolution and Medicine."179.

time, including information from the National Center for Health Statistics, NHANES and the Decline Conference. As a point of departure, it is the section that defines what was known at the time in terms of statistical as well as epidemiological evidence.

Chapter three (**Determinants of Health, Disease and Mortality**) looks at the determinants of disease and mortality, both generally and specifically in terms of their impact on coronary artery disease, exploring the theories and evidence for what impacts disease development and what factors may have influenced and affected the decline in disease mortality in this respect. The work of Thomas McKeown is discussed at great length, including his thesis on the factors that caused a near universal decline in disease mortality during the 20th century. His work on both infectious disease mortality and non-infectious chronic diseases is looked at critically to see what can be learned and applied to the evolution of the coronary artery disease epidemic and its decline in mortality that began in 1968. Because there is evidence that coronary disease mortality might have been impacted by an earlier cataclysmic event, that changed the group at risk and in this way may have caused the rising epidemic of coronary artery disease to occur and ultimately for its mortality to decline, this will also be explored. Largely theoretical the event involves the 1918 Influenza epidemic and related infections. Chapter three further examines factors and policy in play at the time that are external to the disease itself but may have influenced mortality by some other means. Finally, the chapter looks at the role that both genetics and more importantly perhaps epigenetics might have played in the evolution of chronic diseases including coronary artery disease.

Chapter four (**The Role of Prevention: Myth of Hygieia**) draws its inspiration from the ancient myth of Hygieia, goddess of health, sanitation and hygiene, and looks specifically at prevention and risk mitigation in improving the mortality of coronary artery disease and what role this might have played in the period leading up to the decline in 1968. Risk factors do

change over time, especially when new information and data comes to light through investigation and research, so this chapter addresses risk factors as they were known in the first half of the twentieth century, leading up to the late 1960s. Many areas of risk prevention are explored and this chapter draws on medical textual information, popular literature addressing risk and prevention, and oral histories of experts in investigating and documenting the impact of prevention and risk reduction on the mortality of coronary artery disease. It brings into view the role of risk reduction in medical care as well as its impact on disease and mortality. Chapter four presents the evidence for prevention and risk factor containment on the decline in coronary mortality and exactly what impact it might have played. It also outlines other factors and issues at play during and before the period in which mortality declined, to better understand the plausibility of risk reduction as an important element in the explanation of the initial decline of coronary artery disease mortality.

Chapter five (**The Role of Treatment: Myth of Asclepius**), the longest chapter in the dissertation, also draws from classical tradition, that of the myth of Asclepius, the God of Medicine, discussing the role of treatment and care in the decline of coronary artery disease mortality in the 1960s. Important milestones, inventions, implementation and changes in the care of patients through to the late 1960s are looked at in depth. Factors including the use of the cardiac chair, anticoagulants, cardiopulmonary resuscitation, emergency medical care, the coronary care unit and the changing roles of medical personnel during the period are examined in depth. It explores the standards of practice that prevailed at the time as well as when those standards were put into place and their impact. It looks at the state of medicine in terms of care and treatment that existed leading up to the decline in mortality and factors and changes in both that might have seriously impacted disease mortality. Issues related to changes in reimbursement and the payment of care (specifically Medicare and Medicaid) are addressed in

this chapter. It is the chapter that draws heaviest on oral history as quite a number of those interviewed were actively practicing the specialty of clinical cardiology in the 1950s and 60s.

Chapter six (**Conclusion: What can and cannot be said**) brings all the evidence together, comparing the arguments for prevention, and treatment as well as considerations related to neither and provides a synthesis and cogent argument for what most likely played a role in the initial decline of coronary artery disease mortality and what most probably did not. This chapter presents conclusions arrived at in this project as well as the conclusions of others looking at the same question. Finally, it attempts to apply the lessons learned from this historical project to other issues of health, illness and disease elsewhere.

Chapter 2: The Decline

> **The spectacular decrease in the mortality caused by infections during the past century bears testimony to the effectiveness of the measures aimed at eradication of microbes. In reality, however, the role of these measures may not have been so great as commonly believed.[1]**
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> **"…misinterpretation of the major influences, particularly personal medical care, on past and future improvements in health has led to misuse of resources and distortion of the role of medicine."[2]**

The Twentieth Century, as we have already seen, is remarkable for great strides in the quality of healthcare, broad sweeping improvements in life expectancy and near universal reductions in both the morbidity and mortality of all manner of disease. With fairly substantial documentation of a genuine decline in the mortality of coronary artery disease in the 1960s, the consensus of data and opinion pinpointing its inception to 1968, one is left with the task of further verifying a disease specific decline and discerning the true reason for it. Four and a half decades after the decline began, we are probably no closer to knowing the exact cause than we were when it was first noted or ten years later when a national conference of experts, the Conference on the Decline in Coronary Heart Disease Mortality, was convened in Bethesda, Maryland to address this very issue. In addition to their failure to reach a consensus, a number of well-constructed epidemiological studies also failed to help clarify precisely why a modern day chronic disease epidemic like coronary artery disease with an escalating morbidity and mortality through the 1950s would suddenly see its rate of death decline rather precipitously.

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[1] Rene Dubos. *Mirage of Health: Utopias, Progress, and Biological Change.* New York: Harper (1959): 63.
[2] Thomas McKeown. *The Role of Medicine: Dream, Mirage or Nemesis?* Princeton: Princeton University (1979): xiii.

The initial evidence for a decline in the devastating epidemic of coronary artery disease came in 1964 in the form of a California state public health report that noted a decline in cardiovascular disease mortality. The thrust of the paper was the recent changes and decline in CVR (cardiovascular-renal) disease mortality. According to the report, the greatest decline in mortality in this rather broad category of diseases occurred in those with hypertensive cardiovascular disease. Although there was significant age-sex-race variability, for all groups there was also a decrease in mortality "attributed to arteriosclerotic heart disease, including diseases of the coronary arteries," during the period from 1950 to 1960.[3] For unclear reasons, perhaps that the California report was published in a somewhat obscure, narrowly read journal, it received little attention.[4]

Even as a decrease in the mortality of coronary artery disease was occurring it was still the conviction of most that the epidemic was accelerating and more individuals young and old were succumbing. In a "Special Communication" in *JAMA* in 1974, Weldon Walker decried the popular belief among both medical and governmental leaders that the mortality of coronary artery disease was continuing to rise. He wrote, "The vital statistics of the United States tell a different story! The only meaningful rate is the age-adjusted death rate, which peaked in 1963 and has declined since. To continue to disregard this fact would seem to be 'too unreasonable.'"

The data for this startling proclamation came from the National Center for Health Statistics and included adjustments made for changes in ICD classification, a topic we will

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[3] N.O. Borhani and H.H. Hechter. "Recent changes in CVR disease mortality in California." *Pub Heal Rep 79 (1964): 147-60.*

[4] David S. Jones and Jeremy A. Greene. "The Contributions Of Prevention And Treatment To The Decline In Cardiovascular Mortality: Lessons From A Forty-Year Debate." *Health Aff* 31 (2012): 2251.

address shortly. It clearly indicated that there was a decline in age-adjusted death rates in each decade of life from 35 to 85 years of age and that the only increase appeared in the age group over 85. This last age segment, by its very nature, was open ended and Walker believed that an increase here may be a reflection only of the fact that people were living longer and the average age at death had risen. The dichotomy between this finding and popular belief at the time may have reflected the failure to differentiate between age-adjusted and crude death rates. Crude death rates for coronary artery disease had increased, probably reflecting "population aging;" a shift in the age composition of the population. As people live longer crude death rates from diseases like coronary artery disease should be expected to rise even though each individual age group per se is seeing a decline in mortality.[5] This was indeed what was occurring. Walker, in his editorial, made reference to the "Surgeon General's Report" on smoking which came out in 1964 and the establishment of a "vigorous educational program against risk factors by the American Heart Association" as possible explanations for the decline, calling for a redoubling of efforts in this respect to further reduce atherosclerosis.[6] The effort was noble but as an explanation for the decline probably fell quite short in its credence. In the same issue of *JAMA*, in an editorial entitled "Signs of Spring?" the editor tempers the enthusiasm of Walker, writing:

> Of course, we all would like to believe that the improved mortality statistics are not some subtle artifact of numbers and really reflect increasing public awareness about coronary risk factors. However, there is no apparent evidence that western man is moving toward a more spartan life style (unless it is the occasional chap who runs out of gas on the highway); there are no indicators to suggest a

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[5] The crude death rate, the total number of deaths per year per 1,000 people. If people are living longer one would expect that more would die of a specific chronic disease that impacts preferentially the elderly so the crude death rate for the population would be expected to rise even though true mortality from the disease was decreasing.

[6] Weldon J. Walker. "Coronary Mortality: What Is Going On?" *JAMA* 227 (1974): 1045-1046.

> decrease in cigarette smoking or a decline in caloric or saturated fat intake. Certainly, there is no immediate evidence that the jogging (or other daily "routine exercise") population is expanding.[7]

Nonetheless, in the 1960s statistical data saw an initial rather subtle plateauing of mortality that by 1968, at the latest, showed a definite inflection point of decline. It was evident by 1975 that "between 1968 and 1973 coronary heart disease (CHD) mortality in the United States decreased for 4 out of 5 consecutive years" and although "the decrease in the mortality rate for CHD [had] been small" it appeared real.[8]

According to medical historians David Jones and Jeremy Greene, writing about contributions to the decline occurring after 1974, "depending on how epidemiologists parsed mortality data, coronary heart disease reached its peak in either 1963 or 1968."[9] The pattern of decline has persisted and although coronary disease continues to be the leading cause of death in the United States[10] as well as the rest of the western industrialized world[11] it appears that on some level this rather enormous health burden is diminishing at least in the number of individuals it takes as victims.

To date there has been enormous speculation about why the decline in mortality from coronary artery disease began in 1968. Treatment of coronary disease, like most chronic

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[7] R.H. Moser. Editorial: "Signs of Spring? *JAMA* 227 (1974): 1049.
[8] Tavia Gordon and Thomas Thom. "The Recent Decrease in CHD Mortality." *Prev Med* 4 (1975): 115-125.
[9] David S. Jones and Jeremy A. Greene. "The Contributions of Prevention and Treatment To The Decline In Cardiovascular Mortality: Lessons From A Forty-Year Debate." 2251.
[10] As of 1989 "the toll from heart disease nearly equaled the combined death rate from cancer, accidents, pneumonia, influenza, and all other causes….it was estimated that in 1992, nearly 1.5 million Americans would sustain a heart attack; of these, about a half a million would probably die." Bernard Lown. *Practicing the Art While Mastering the Science.* Winston-Salem: Harbinger (1995): 20.
[11] Jean-Claude Tardif. "Coronary artery disease in 2010." *Eur Heart J Suppl* 12 (2010): C2-C10.

illnesses of the time, was accelerating and expanding, with multiple new interventions coming into play during the period. At the same time, a greater interest and awareness of the need for prevention was evolving. Not unlike most diseases throughout history, with coronary artery disease "new understandings of its causes made prevention campaigns both possible and essential."[12] And then beyond the disease itself, there was an overall improvement in health in general that some attribute to better public health, making the argument that coronary artery disease mortality declined because disease outcomes in general improved. This possibility also suggested "a more general positive health force operating in the United States, such as higher income or better access to medical care." [13]

The fact that a decline in mortality occurred is a historical certainty with only varied speculation for its explanation. One might ask if the explanation is really even important. Does it warrant the effort needed to try to sort out the contributing factors? More than a historical endeavor or mere rhetorical exercise, it is an important question to ask for a number of reasons. If one can discern the true explanation, ending for once years of speculation, one potentially has the ability to direct efforts, both financially and in terms of labor, to further improvements in that area for this particular disease as well as other chronic diseases. The dichotomy of prevention versus treatment of disease are both important healthcare and public health concerns. Both impact the course and outcomes of disease. With limited manpower and increasingly limited resources, including funding, available to direct efforts fully in both

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[12] David S. Jones. *Broken Hearts: The Tangled History of Cardiac Care.* Baltimore: Johns Hopkins Press (2013): 8.

[13] Richard J. Havlik, and Manning Feinleib, Eds. *Proceedings of the Conference on the Decline in Coronary Heart Disease Mortality.* National Heart, Lung, and Blood Institute. NIH Publication No. 79-1610. Bethesda: National Institutes of Health (1979): xxiii.

directions, it appears crucially important to be able to know where best to make future investment.

In this respect, warns epidemiologist Michael Stern, it is "important to guard against polarizing opinion between preventative and curative medicine." But recognizing that both approaches are very costly, he believes that there is an urgent need for information about the relative contribution of each if "intelligent decisions about the allocation of scarce resources" are to be made in the future. In his words, it is the only way "to make optimum use of available resources for controlling the coronary heart disease epidemic."[14] Noting the many "expensive innovations" during the period, Lee Goldman and E. Francis Cook from the Brigham and Women's Hospital, state that "in an era when the ultimately finite nature of medical resources is becoming apparent, it is important to examine which of these many innovations may have had the most substantial effect on ischemic heart disease mortality." They continue, the exercise "may also serve as a guide for determining what types of expenditures have been most beneficial and are most likely to have future rewards."[15] Furthermore, believe Harvard economists David M. Cutler and Ellen Meara, "Disentangling the role of [the] different factors in reduced mortality is a difficult task but one that is increasingly important in light of the vast fiscal consequences of an aging society."[16]

By necessity this is an historical project. Medicine and epidemiology alone have failed to fully explain the decline and the most plausible way to arrive at an explanation is by using the

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[14] Michael P. Stern. "The Recent Decline in Ischemic Heart Disease Mortality." *Ann Int Med* 91 (1979): 639.
[15] Lee Goldman and E. Francis Cook. "The Decline in Ischemic Heart Disease Mortality Rates: An Analysis of the Comparative Effects of Medical Interventions and Changes in Lifestyle." *Ann Int Med* 101 (1984): 825-836.
[16] David M. Cutler and Ellen Meara. "Changes in the Age Distribution of Mortality over the Twentieth Century" in David A. Wise, ed. *Perspective on the Economics of Aging.* Chicago: University of Chicago Press (2004): 364.

multitude of tools and resources available to the historian. In this respect and every other this study is one employing classical historical means and techniques. They include archival research, statistical data research and an extraction of valuable information through the means of oral histories. But before looking specifically at prevention efforts historically and treatment for coronary artery disease during the period preceding the decline in mortality it is critical to look at all the evidence and documentation for the decline and specifically to look at what is already known epidemiologically. That is the essence of this particular chapter.

Establishment of the NHLBI and the Decline Conference

In 1948, Congress passed the National Heart Act establishing what many older physicians and authorities still refer to as the "Heart Institute," now the National Heart, Lung and Blood Institute (NHLBI), a constituent institute of the National Institutes of Health. It was then and remains today a major center for research and training, counting numerous luminaries in the field as alumni. Thirty years after its initial establishment the Institute recognized that the mortality of coronary disease had taken a new direction and convened in its Bethesda backyard *The Conference on the Decline in Coronary Artery Disease Mortality,* dubbed by most in the field simply the "decline conference" for short. It brought together 84 experts in the fields of cardiology, cardiac surgery, epidemiology, economics, sociology, laboratory science, statistics, anesthesiology and animal science. The conference was held over two days in October, 1978. Its mission was to sort out the reasons for the "major decrease in coronary heart disease mortality" that began in the 1960s and that had continued in this country during the ensuing decade. The NHLBI was looking for answers in part to direct future research efforts, no doubt concentrating efforts where definitive improvements were already evident and future gains were likely to be made. According to the conference chroniclers, Richard J. Havlik and Manning Feinleib, "although the organizers would have liked to produce a definitive conclusion, it became obvious

quite early that the conference would serve only as a beginning of a longer process of insightful study of a very complicated problem."[17]

There were three primary objectives outlined for the conference:

(1) to consider whether the greater than 20% decline in coronary heart disease mortality since 1968 is real
(2) to discuss possible causes, and
(3) to recommend further studies to elucidate the causes.[18]

The conference reached three major conclusions as follows:

(1) the decrease in coronary heart disease mortality is real and not a result of artifacts or changes in death certificate coding,
(2) both primary prevention through changes in risk factors and fundamental and clinical research leading to better medical care probably have contributed to but do not fully explain the decline, and
(3) a precise quantification of the causes requires further studies, especially those designed to document whether the frequency of nonfatal coronary events is changing.[19]

A point of clarity, utilizing the epidemiological independent variables of incidence and severity, did emerge in the conference report that would prove valuable in framing the contributions of both prevention and treatment. That is

> If the total number of heart attacks is decreasing or the severity of clinical disease is lessening, this would favor risk reduction as the probable cause of the decline. If the total coronary heart disease incidence is unchanged, it would support the conclusion that fundamental and clinical research leading to modern medical treatment is the probable cause of the decline.[20]

For a further analysis of this hypothesis, it would probably be best to turn to the most convincing and pervasive evidence on trends in the incidence and course of CHD over the period

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[17] Richard J. Havlik, and Manning Feinleib, Eds. *Proceedings of the Conference on the Decline in Coronary Heart Disease Mortality.* National Heart, Lung, and Blood Institute. NIH Publication No. 79-1610. Bethesda: National Institutes of Health: iii.
[18] Ibid, xxiii.
[19] Ibid, xxiii.
[20] Ibid, xxiii.

in question. The Framingham Heart Study provides such evidence and in so doing a direction in which to begin an analysis of relative contributions to the decline. But before turning here I would like to first discuss information and data presented at the Decline Conference held in 1978.

Documenting the Decline in CHD mortality

Infectious disease mortality declined quickly in the first half of the 20th century and by 1960 death due to infectious disease was extremely low. Between 1900 and 1960 the cumulative decline in infectious disease mortality was a staggering 92%. Cardiovascular diseases were the leading cause of mortality in this country in 1960, constituting 59% of all deaths. At the time, cancer by comparison was the cause of 15% of total deaths and death due to infection only 5%. Between 1955 and 1965 reductions in mortality on the whole appeared to slow and overall mortality flattened. By 1965, cardiovascular disease mortality as a whole began to rapidly decline, through the end of the twentieth century, at a rate of approximately 2% per year. Because the elderly are predisposed to cardiovascular disease, the majority of the mortality gains were in this group. According to Cutler and Meara, "cardiovascular disease is so prominent among the elderly that the decline in cardiovascular disease mortality explains essentially all of the overall reduction in mortality for elderly since 1965." Furthermore, "for the population as a whole, 98 percent of mortality reductions between 1960 and 1990 were a result of reduced cardiovascular disease mortality."[21] Of interest, death rates for ischemic heart disease during the decade 1960-70 increased in Britain by 16 percent for men and 14 percent for women, indicating no waning in the CHD epidemic or its mortality across the ocean. A slight

[21] David M. Cutler and Ellen Meara. "Changes in the Age Distribution of Mortality over the Twentieth Century": 354.

reduction in these increases, but certainly no decline, was noted when correction for the "change in age structure of the population over the decade" was made.[22]

According to the publication that came out of the Decline Conference, entitled *Proceedings of the Conference on the Decline in Coronary Heart Disease Mortality* (PCDCHDM), the decline in mortality from the disease initially appears to have not been demographically uniform and in all probability there was evidence for it in the mid-1960's or even sooner in various parts of the country, particularly among white women.[23] Evidence from a variety of sources points out that "while decline in stroke mortality began as early as 1915, the decline in coronary mortality has varied in the time of onset and magnitude between sexes, across geographic regions, and, to a lesser extent, between age groups." Additionally, "there was more regional variation in the onset time for women than for men with the decline occurring between 1958 and 1975 for white women and between 1968 and 1975 for white men."[24] Nevertheless, it was clear that by 1968 the reduction in mortality was seen across gender and racial lines and in all groups. Although not all were equally effected there was evidence of decreasing mortality from coronary artery disease in the United States by the mid-60s. Women, on a national level, experienced a larger decline than men and perhaps surprising, of all the ethnic, racial and gender groups, the overall rate of initial decline was highest among African-American women.[25] Robert Levy, past director of NHLBI, a few years later, agreeing with the findings of the

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[22] Thomas McKeown and C. R. Lowe. *An Introduction to Social Medicine.* Second Edition. Oxford: Blackwell (1974): 59-60.
[23] Regional decline appeared to occur first in the western U.S. and spread thereafter to the East with areas of Appalachia being among the last to decline in CHD mortality.
[24] Pamela A. Sytkowski, et al. "Sex and Time Trends in Cardiovascular Disease Incidence and Mortality: the Framingham Heart Study, 1950-1989." *Am J Epi* 143 (1996): 338-350.
[25] Ibid, 338.

conference, notes that the data "suggests that a decline in CHD mortality began first in the nonwhite and the female in the early 1960s (about 1963)" and according to his data it was 1967 before Caucasian males experienced the same decline. In terms of geography the decline was also not uniformly distributed nationally with the decline beginning in the far west and continuing to be the highest there with much slower rates of decline in Appalachia, notably West Virginia and Kentucky.[26]

The decline was also sustained and continued in the period between 1968 and the time of the Decline Conference (1978) such that "if the death rates operating in 1968 were still in effect in 1977, when the population of the country was larger and older, theoretically there would have been 191,500 additional deaths in 1977 in the United States" than there actually were. Mortality reduction that was documented across the board in 1968 was a reality when tested against statistical data ten years later. What is particularly noteworthy is that at a time when mortality from coronary disease was already in decline in the United States, except for a handful of countries, this was not the case worldwide. The experience showed, with the exception of Australia, Belgium and Canada and "perhaps England, Finland, Israel and Japan," that mortality from coronary disease elsewhere was either unchanged or increasing.[27] In Iceland, where coronary artery disease is the most common cause of death, the mortality from ischemic heart disease continued to rise during the period. From 1951 to 1985, coronary artery

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[26] Robert I. Levy. "Declining Mortality in Coronary Heart Disease." *Atherioscler Thromb Vasc Biol* 1 (1981): 314-315.

[27] Richard J. Havlik, and Manning Feinleib, Eds. *Proceedings of the Conference on the Decline in Coronary Heart Disease Mortality*. National Heart, Lung, and Blood Institute. NIH Publication No. 79-1610. Bethesda: National Institutes of Health: xxiii.

disease mortality for men in Iceland rose in every age group and by 1985 the mortality had not yet peaked.[28]

In the United States several remarkable findings were noted in the time period between 1968 and 1978 when the issue of declining mortality was being clarified. Data as we know it today on frequency of cases of myocardial infarction not resulting in death were rather scanty and difficult to quantify. The number of patients being discharged from hospitals with the diagnosis of coronary artery disease or myocardial infarction did not significantly change over the course of 10 years but the number of patients dying in the hospital with the diagnosis of CHD had decreased.[29] Although it has been suggested that the diagnostic codes used by hospitals had changed this does not appear to be a major factor in capturing the number with the disease. The admissions practice, however, did change, during the period, with more patients entering the hospital with the diagnosis of CHD for treatment and interventions. But any belief in the power of hospitalization or medical care in this area must be tempered, according to the report of the Decline conference, with the knowledge that "70% of coronary heart disease deaths occur out of the hospital." The data on community based emergency medical services (EMS) is limited and generally although there was some evidence for its utilization in urban areas, rural areas enjoyed very little of this benefit. [30]

The Decline Conference invoked the possibility of improvement in hypertension, a reduction in smoking, and improved dietary habits as contributing to the decline in mortality, but such interventions could not be shown to be of significance based on logistic and temporal

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[28] Vilhjalmur Rafnsson. "Mortality from ischemic heart disease in Iceland, 1951-1985." *Ann Epi* 1 (1991): 493-503.
[29] Suggestive of better in-patient treatment
[30] Richard J. Havlik, and Manning Feinleib, Eds. *Proceedings of the Conference on the Decline in Coronary Heart Disease Mortality*. xxiii-xxiv

relationship considerations. Although they may have contributed incrementally, their contribution, based on statistical data alone, would have been extremely small. Write Havelik and Feinleib, "Besides the problem of a proper temporal relationship, a major assumption necessary with such a calculation is that the risk is reduced immediately or almost so to the level expected with a lower level of the risk factor." There is little evidence to support such an assumption at the time.[31]

A striking finding in this discussion of falling mortality is that cardiovascular mortality in general began to decline in 1948, the same year that the National Heart Institute began to operate, but that coronary artery disease itself did not begin to participate statistically in improved mortality for another 20 years.[32] In fact, through the 1950s, while other diseases of the heart were seeing an improvement in this respect, coronary artery disease mortality was actually still on the rise. A plateau became evident in the early 1960s and generalized decline was first clearly and uniformly manifested in 1968. When coronary artery disease began to participate in the decline it contributed heavily proportionally to the overall decline in cardiovascular mortality. In this respect, after 1968, "the absolute decline in cardiovascular deaths," was "led primarily by the striking decline in stroke and heart attack death rates."[33]

Levy was director of the NHLBI from 1975 to 1981. It was during his tenure that the Institute expanded to include blood diseases and it was under his direction that the Decline Conference was organized. By way of introduction to the conference, he wrote in the publication of its findings:

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[31] Ibid, xxvi.

[32] This initial decline in overall cardiovascular mortality may be attributable to the much earlier decline in stroke mortality, which as already alluded to earlier in this chapter is classified as "cardiovascular disease."

[33] Richard J. Havlik, and Manning Feinleib, Eds. *Proceedings of the Conference on the Decline in Coronary Heart Disease Mortality*. , 1.

> Since 1968, the decline in coronary heart disease death rates has occurred in both men and women; has occurred in every age range, and has occurred in our minority and majority populations. Any explanations which are put forth to explain the decline in mortality must be cognizant of the fact that the decline has been seen in our entire population.[34]

What made the conference so significant and important in terms of heart disease and healthcare was the stated and implied impact that the findings would have on the future direction of cardiovascular research and prevention, and specifically in terms of the direction the NHLBI itself might take in the future. Levy explained:

> We are here to examine the trend, its validity, its uniqueness, its causation…perspectives will be broadened by what we hear at this conference. The National Heart, Lung, and Blood Institute's direction, vis-á-vis cardiovascular disease prevention, may be affected greatly by what is said during this conference.[35]

The question of causation addressed at the conference came down basically to a consideration of prevention versus treatment and care versus possible artifact. Asked Sidney Blumenthal, the conference chairman, if the decline in mortality is not artifactual, how much is due to improvements in care and how much to "alteration in risk factors." Are the contributions equal, or is most of the decline due to one or the other? There was also the realization and concern among participants, echoed by Blumenthal, that the contributions of both care and prevention to the decline in mortality might be minimal and that the origins of the cause for the decline might be neither and so remain unclear.[36] Levy, writing years after the conference, noted that "the decline has been temporally related to risk factor awareness and modification" as well as

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[34] Ibid, 1.
[35] Ibid, 1.
[36] Ibid, 3.

improvements in care concluding that "both primary prevention through lifestyle changes and improved treatment regimens have played a role in the decline."[37]

The Decline Conference broke down into four sessions: The first examined trends in the morbidity and mortality of coronary heart disease. The second changes in patient care. The third was devoted to the evaluation of risk and its impact on mortality and the final was "devoted to considering and developing strategies for quantifying and studying changes in mortality due to coronary heart disease." Wrote Blumenthal "We may not be able to arrive at a definitive answer regarding the cause of the decline in mortality but we do anticipate constructive recommendations for future action."[38]

The Framingham Heart Study: Incidence of disease

The Decline Conference in many respects grew out of an appreciation that there were a number of factors in play in defining both the etiology of heart disease in general and coronary artery disease specifically. It was the Framingham study, after 1948 when it was initiated and the original cohort assembled, which in large part came to define the face of coronary artery disease, its contributing factors and the historical course of the disease thereafter. Epidemiological in nature, it is a perpetual work in progress that continues to give valuable information about CHD even today and it is a project that we will keep coming back to in addressing issues related to CHD and myocardial infarction throughout the course of this dissertation.

Eugene Braunwald, preeminent cardiologist and former Chairman of Medicine at the Brigham and Women's Hospital, called Framingham "one of the cornerstones of cardiac

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[37] Robert I. Levy. "Declining Mortality in Coronary Heart Disease." *Atherioscler Thromb Vasc Biol* 1 (1981): 312-325.
[38] Richard J. Havlik, and Manning Feinleib, Eds. *Proceedings of the Conference on the Decline in Coronary Heart Disease Mortality*: 3.

epidemiology" and "one of the first major efforts dedicated to the study of the epidemiology of chronic disease."[39] Framingham not only gives us vital data and statistics about the importance and impact of risk on coronary disease, it also helps clarify the incidence, prevalence and mortality of the disease over time. The variations that existed in the early decline in coronary artery disease mortality may also help to identify causal factors at play, be they prevention of risk factors isolated to certain groups or medical treatment. In this respect "The Framingham Heart Study offers a unique opportunity to study the interplay of secular trends in biologic, behavioral, and environmental factors within a free-living, stable population."[40]

An important paper from Framingham was published in the *American Journal of Epidemiology* in 1996. It reported on cardiovascular disease incidence and mortality of study participants between 1950 and 1989. From it we are able to glean the most reliable existing information on incidence of coronary artery disease during the period under consideration. In both male and female cohorts between 1950 and 1970 there was no significant change in incidence of myocardial infarction. In the male cohorts of this period there was also no significant difference in the incidence of coronary artery disease in general and the diagnoses of sudden death, non-sudden death, angina pectoris and coronary insufficiency in particular.[41]

Although the numbers are relatively small, the fact that incidence appeared to remain fairly stable despite an established decline in mortality of CHD would argue, by the writing of Havlik and Feinleib, that the etiology of the decline would favor improvement in treatment of the disease rather than risk factor reduction and improvements in prevention. Improvements in

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[39] Eugene Braunwald. "Cardiovascular Medicine at the Turn of the Millennium: Triumphs, Concerns, and Opportunities." *NEJM* 337 (1997): 1360-1369.
[40] Pamela A. Sytkowski, et al. "Sex and Time Trends in Cardiovascular Disease Incidence and Mortality: the Framingham Heart Study, 1950-1989." 338.
[41] Ibid,338-350.

prevention of the disease would no doubt, over the 20 year period studied, lead to a fall in incidence of all aspects of disease related to atherosclerotic heart disease.

Artifact Challenge: Change in the International Classification of Disease (ICD) and Death Certificate Reporting

It was not until 1929, almost two decades after Herrick's initial description, that the international classification of causes of death was revised into a version similar to its present form. An emphasis on etiology and the start of a departure from strict anatomical classification began with the agreement of the fourth revision committee to transfer more disease categories to an etiologic basis as greater knowledge was accumulated about etiology of diseases. It was the first revision that dealt more comprehensively with causes of death, not morbity, and as a result the true magnitude of the mortality from coronary artery disease became better appreciated only after 1929.[42] Most graphic displays of CHD death rates only commence in the late 1920s for this very reason. Further revisions would follow at roughly ten year intervals. "Unfortunately," according to Gordon and Thom of the Biometrics Research Branch at NHLI, "there was a considerable break in comparability with the revision that came into use in 1939 but from 1939 to 1967 [one] can trace trends for this disease without major problems arising from the decennial revision of the international lists."[43]

The crude death rate of CHD increased 49.5% between the years 1940 and 1960. Some of this has been attributed "to an increase in the number of physicians trained to recognize the disease." Also autopsies during this period showed that many who succumbed to sudden death did so because of documented CHD leading to a tendency during the period of accelerating

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[42] Iwao M. Moriyama, Ruth M. Loy and Alastair H.T. Robb-Smith. *History of the Statistical Classification of Diseases and Causes of Death*. Centers for Disease Control and Prevention. National Center for Health Statistics (2011): 16. and Tavia Gordon and Thomas Thom. "The Recent Decrease in CHD Mortality." 116.

[43] Tavia Gordon and Thomas Thom. "The Recent Decrease in CHD Mortality." 116.

death rates to attribute unattended deaths and those without adequate diagnostic evaluation to CHD as the cause of death on death certificates.[44] Some of this increase in crude death rate no doubt can be attributed to improved control of infectious diseases leading to greater longevity of the population and as a consequence to a population more vulnerable to CHD. But despite these factors the rise in mortality from the disease itself appears quite real as evidenced by both the crude and age adjusted death rates for the disease. Between 1940 and 1960 "the age-adjusted CHD death rate for white men rose 25.7%." During the same period it rose 48.2% for men of color and 34.4% for non-white women. There was no change in the age-adjusted rate for white women during the period. When World War II broke out 21% of all deaths in this country were attributed to CHD. Twenty years later, in 1960, the percentage had risen to 31.9% and with adjustment for comparability the number of deaths due to CHD had more than doubled from 272,000 in 1940 to a staggering 546,000 in 1960. The twenty year documented rise in both crude and age-adjusted death rates for CHD peaked in 1963. In retrospect it appeared that the age-adjusted rate for white men between 1960 and 1967 had changed very little and the same rates for nonwhite men and women had plateaued by 1962. For all intents and purposes, in retrospect, "by 1967 reported CHD mortality had generally stabilized in this country."[45]

When the decline in coronary artery disease mortality was first noted it was believed by many that the improvement and trend was perhaps not real. The way diseases are categorized and classified over the course of the years in question (1950 to 1968) had changed three times.

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[44] Although the diagnosis of CHD, under these circumstances, is a presumptive one, autopsy proven study by David M. Spain, et al (*JAMA* 174 (1960): 384-388), showed accuracy of 90% for a diagnosis of CHD when "duration of the witnessed fatal episode was less than one hour.")

[45] Tavia Gordon and Thomas Thom. "The Recent Decrease in CHD Mortality." 116-117.

The International Classification of Diseases, Adapted (ICDA), a World Health Organization (WHO) endeavor and publication, is revised regularly to reflect advancement and changes in medical knowledge. The classification itself is often expanded or narrowed depending on the progress of medical knowledge. In the 6th and 7th revisions coronary artery disease was listed under ICDA No. 420 and labeled "atherosclerotic heart disease including coronary disease." It was commonly however referred to only as "coronary heart disease." In 1968, the WHO began using the new 8th edition of ICDA and the labeling changed altogether. The new rubric was "ischemic heart disease," accompanied by new category numbers (ICDA Nos. 410-413).[46] According to Gordon and Thom, "the new classification represented a substantial and, in our judgment, irreparable break with previous classifications. In particular, a sizeable proportion of deaths previously assigned to hypertensive heart disease was shifted into ischemic heart disease, almost all of it to the category Chronic Ischemic Heart Disease (ICDA 412)." They believe that although it may be possible to separate out some of the deaths it is not possible to completely do so and therefore recommend examining post 1967 death trends separately from those trends that occurred earlier.[47]

When Gordon and Thom looked at mortality trends from 1968 to 1972 sorting by age, color and sex they discovered something rather remarkable; "that in every specific group there [had] been a decrease in CHD mortality and that the percent decrease varied relatively little from one group to another." This was in marked distinction to earlier experience "where trends by race and sex differed radically." They also discovered that the crude death rates understated the decrease in CHD mortality. Between 1968 and 1972, the crude death rate declined 2.9% while the adjusted declined by 7.3% (varying from 6.2% for white men to 11.7% for non-white

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[46] Richard J. Havlik, and Manning Feinleib, Eds. *Proceedings of the Conference on the Decline in Coronary Heart Disease Mortality*: 11.
[47] Tavia Gordon and Thomas Thom. "The Recent Decrease in CHD Mortality." 117.

women). Furthermore, "age-adjusted death rates declined faster than crude rates." They also discovered that the decreases recorded in this period were not restricted to CHD with declines at least as large for other cardiovascular diseases, as well as non-cardiovascular causes of death. During this period, the only exceptions to the downward trend in death rates were seen in cancer, accidental death, death due to violence and cirrhosis of the liver. In these the death rates either remained constant or went up. Between 1968 and 1972, the United States was experiencing "a steady decline in the all-causes death rate, the age-adjusted total death rate declining year by year, until by 1972 it was 5.6% lower than it had been in 1968."[48]

Always a concern when mortality statistics decline is the possibility that diseases previously classified on death certificates as such are being shifted to other causes. Writes Michael Stern, "A major cause of spurious mortality trends is a shift in assignment of cause of death from one mortality category to another." He asks the question: "Is it possible that in recent years deaths formerly assigned to ischemic heart disease are now being assigned to other causes?"[49] If this were the case, Stern argues, then most likely coronary artery disease as a cause of death would find its way into other cardiovascular diseases in terms of reporting. This would appear unlikely in the present scenario because at the same time of the decline in coronary artery disease mortality, as pointed out by Gordon and Thom, all cardiovascular diseases had a decline in age-adjusted mortality, as did each major subcategory of cardiovascular disease, including cerebrovascular disease, hypertensive heart disease and even rheumatic heart disease. All in all these subcategories, showing declines, accounted for 90% of cardiovascular diseases and for the remaining 10% mortality was essentially flat. For this reason, "the absence of a rise in any of the nonischemic heart disease causes of cardiovascular

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[48] Tavia Gordon and Thomas Thom. "The Recent Decrease in CHD Mortality." 117-120.

[49] Michael P. Stern. "The Recent Decline in Ischemic Heart Disease Mortality." 630.

death precludes the possibility that any significant number of ischemic heart disease deaths could have been shifted into these other categories of mortality." Furthermore, during the period almost all categories of non-heart disease related deaths declined as well, with the exception of malignancy, which rose slightly during the period. So unless the cause of death previously ascribed to coronary artery disease was shifted to a malignancy as cause, points out Stern, "it does not appear that the decline in ischemic heart disease mortality can be explained by shifts in assignment of cause of death" on death certificates.[50] And although there have been a variety of reports ascribing to the increased use of heart attack as a cause of death when the exact etiology is unclear and assumed to be myocardial,[51] this would only increase the mortality statistics for ischemic heart disease and not decrease them.

In addition, arguing against specious mortality data is the fact that the decline was seen in both males and females, in all age groups, with the possible exception of the very elderly, and in all the major racial and ethnic groups in this country. Some have also argued that the decline can be directly attributable to the fact that there has been no major epidemic of influenza in this country since the decline began. Stern believes as do others (see discussion of influenza in chapter 3) that it is likely we will see a rise in CHD mortality with the next influenza epidemic, but it is quite unlikely that the resultant rise would wipe out the gains that have been made in the mortality of coronary artery disease over the past four plus decades.[52]

It is curious that the decline in CHD mortality began the same year as a major change in the cause of death classification. Although Gordon and Thom believe that a small contribution

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[50] Ibid, 630.
[51] "may overestimate the frequency of coronary heart disease by 7.9% to 24.3%." Donald M. Lloyd-Jones, et al. "Accuracy of Death Certificates for Coding Coronary Heart Disease as the Cause of Death." *Ann Int Med* 129 (1998): 1020-1026.
[52] Michael P. Stern. "The Recent Decline in Ischemic Heart Disease Mortality." 631.

to the decline in mortality is attributable to the change in classification that occurred with the 8th ICD edition in 1968, there are too many other factors in play to believe that the decline of CHD mortality at the time was not real. These include, they point out, the decrease in mortality of CHD in 4 out of 5 consecutive years, which had not occurred in the past and, as pointed out also by Stern, that all cardiovascular disease mortality had declined, many to even greater extent, in the same period, making major shifts in cause of death reporting away from CHD most unlikely.[53]

Two Decades of Achievements

Serious changes in the care of patients with coronary artery disease began to occur in the 1950s. Prior to this time, care was rather rudimentary and consisted in large part of watching people die. A number of thoughtful investigators and the ramping up of efforts to professionalize the care of patients with heart disease began in the 1950s. One of these early pioneers was Samuel A. Levine, cardiologist at the Peter Bent Brigham Hospital (PBBH), and another was Bernard Lown, his student. The achievements are well documented in Lown's short book *Practicing the Art while Mastering the Science.* These early milestones combined clinical acumen with technological advancement and included: Invention of the DC defibrillator, invention of the cardioverter, the establishment of coronary care units for close observation in the critical post infarct period of patients with coronary thrombosis, introduction and use of lidocaine to treat arrhythmias, demonstration that certain rhythm disturbances identify those at risk for sudden death and clarification of the role of psychologic stress in perpetuating life endangering rhythm disturbances of the heart.[54]

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[53] Tavia Gordon and Thomas Thom. "The Recent Decrease in CHD Mortality." 120.
[54] Bernard Lown. *Practicing the Art While Mastering the Science: A Cardiologist Reflects on Healing.* Winston-Salem: Harbinger (1995): 25.

At the same time Framingham was pointing out evidence that risk reduction and disease prevention were important in curbing the epidemic of ischemic heart disease. Early findings from this study that morbidity and mortality could be reduced with judicious reduction of factors that contributed to ischemic heart disease were beginning to emerge. The question here lies in terms of broad implementation of risk reducing measures. Epidemiologists and investigators alike long knew the effect of cholesterol and hypertension on atherosclerosis. They likewise long suspected that among the ill effects of tobacco use, cardiovascular disease was to be included. But was this information translated to the public and more importantly to the physicians who could implement appropriate measures in this regard in a timely manner? Timely enough to have impacted early gains in mortality? Or was it too little too late to be considered a serious contender for improving the early mortality of coronary artery disease?

Chapters 4 and 5 of this dissertation address the important contributions, or lack of such, made by both prevention and treatment on the early decline in mortality of coronary artery disease. They explore the discoveries made and implementation of each in impacting mortality and the relative contribution that can be assigned to each one, if any. But before doing so we need to explore determinants of health, disease and mortality in more general terms. We first need to ask the question of whether other factors, outside the disease itself, played a significant role in changes that contributed to the decline in mortality. This is the basis and essence of chapter 3; Determinants of Health, Disease and Mortality.

Chapter 3: Determinants of Health, Disease and Mortality

> **The development of civilization has brought about drastic changes in the conditions of life of the human organism[1]**
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> **As scientists discover or reveal new information about the natural world, the discoveries must be correlated with one another in innovative theories. Each theory is then intensely and rigidly tested by subsequent observations, which provide either additional proof and acceptance or error and rejection. This is how truth is revealed.[2]**

General Considerations

Before one can hope to explain the history of a particular disease – whether over time, by all parameters of health, it has improved or worsened - one has to begin by considering the determinants of disease in general and of that disease in particular. It would be very difficult to understand, let alone explain, why the mortality of a disease changed so abruptly without first understanding how it came to exist in the first place and what factors played a role in that evolution. In some diseases the determinants are clear and relatively easy to explain. For example, one cannot get tuberculosis without the tubercle bacillus or AIDS without the virus that causes AIDS. But why do people develop cancer, hypertension, diabetes and still others coronary artery disease? In the history of time, we have come far in discerning factors that impact the development of disease. We know that individuals who smoke have a much greater chance of developing lung cancer, people who drink cirrhosis and destruction of the liver, and those who eat high fat diets a greater chance of developing atherosclerosis. But not all who smoke, even heavily, will develop lung cancer. And not all who drink heavily develop liver disease. For this and numerous other reasons it is important to establish the determinants of a disease and how they might change over time in terms of morbidity and mortality. This is particularly true when dealing with the history of a disease like coronary artery disease where

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[1] Stephen Boyden. "Cultural Adaptation to Biological Maladjustment." In S.V. Boyden, ed. *The Impact of Civilisation on the Biology of Man*. Toronto: University of Toronto Press (1970): 206.
[2] Jimmy Carter. *Our Endangered Values: America's Moral Crisis.* New York: Simon and Schuster (2005): 49.

development of the disease is dependent on a constellation of environmental elements, on demographics, and factors that predispose individuals to it.

Coronary artery disease is very much a clinical disease of the twentieth century. Although there is little doubt that it did exist in some form or another much earlier, dating by a number of accounts all the way back to antiquity, it emerged as a major healthcare issue and epidemic only in the twentieth century. Is this just an expected manifestation of the epidemiologic transition of disease[3] or does it represent something greater and much more complicated? What Thomas McKeown called "diseases of affluence," heart disease and diabetes among others, "seem to be due to 'mismatches' between our current environment and the genetic endowment we inherited from our evolutionary ancestors."[4]

One could argue convincingly that a decline in infant mortality and a prolongation of life, coupled with elimination of other more immediate and often fatal diseases, infectious predominantly, allowed for great awareness and consideration of a disease that could only be seen in a group predisposed to the disease. Biological anthropologist Frances Barnes notes that evidence exists in early hunter-gatherer groups that both cancer and coronary thrombosis were rare but admits "that the relatively young age at death introduces problems in evaluating the significance of this evidence."[5]

In this respect one would expect that improvements in infant mortality and an ever improving and increasing life span would have just the opposite effect on the distribution of

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[3] "the determinants and consequences of changing disease patterns that have accompanied modernization in most western countries" from Abdel R. Omran. "The Epidemiologic Transition: A Theory of the Epidemiology of Population Change." *Mil Mem Fund Quart* 49 (1971): 511.
[4] Robert L. Perlman. "Evolutionary Biology: A Basic Science for Medicine in the 21st Century." *Perspect in Bio and Med* 54(2011): 80.
[5] Frances Barnes. "The Biology of Pre-Neolithic Man." In S. V. Boyden, ed. *The Impact of Civilisation on the Biology of Man.* Toronto: University of Toronto Press (1970): 12.

disease and disease specific mortality. If people are surviving childhood and adolescent illnesses and living longer, then you would expect a greater burden of chronic degenerative disease and consequently a greater segment of the population dying of those diseases. In the words of S. Bryan Furnass, Director of the Australian National University Health Service, "in technologically developed nations which enjoy a high standard of material comfort the survival of increasing numbers of persons into middle life as a result of improved standards of nutrition, hygiene, and obstetric care has had the effect of increasing the proportion of deaths which are attributable to the so-called degenerative diseases." In this assessment he was referring specifically to cancer and diseases of the heart and lungs.[6]

Biologist Stephen Boyden theorizes that species adaptation occurs through a process of "biological maladjustment." According to Boyden, "the capacity to adapt to changing conditions is an essential property of living matter, and the fate of species in evolution and of individual organisms in their lifetimes is determined largely by the degree of effectiveness of their adaptive processes." The mechanisms by which adaption occurs, according to Boyden, fall into three categories: (1) "evolutionary adaptation." By definition, evolutionary adaptation "consists of the modification of the genetic constitution of populations through natural selection so that they become better fitted, in the Darwinian sense, to the prevailing conditions of life." Enduring changes in the environment of a given species will introduce a set of new selection pressures such that the species will either (genetically) adapt to the new conditions or will become extinct. (2) "innate or genetically-coded adaptation." He defines this form as "all those inbuilt responses which occur spontaneously in the individual animal in the face of

[6] S. Bryan Furnass. "Changes in Non-Infectious Diseases Associated with the Process of Civilisation." In S.V. Boyden, ed. *The Impact of Civilisation on the Biology of Man*. Toronto: University of Toronto Press (1970): 84.

environmental change and which render the organism better able to cope in the new conditions."[7] Robert Perlman calls the process "gene-culture coevolution." Analogous to "host-parasite coevolution" it is "the extent that people with specific genotypes preferentially reject or adopt specific cultural practices." An example of this is seen with the "coevolution of dairying and lactase persistence." In this example, "the domestication of cattle and the development of dairying led to the availability of fresh milk as a potential energy source, which in turn led to selection of individuals who could utilize the lactose in milk as a nutrient after the weaning period." In this respect "diseases such as diabetes and hypertension may well result from a culturally-driven changing human environment, in which the availability of food has increased and the need for physical labor to produce food has decreased."[8] In terms of the present discussion, the onset of the industrial revolution may have introduced environmental circumstances that, on a genetic or on an epigenetic basis, required the human species to adapt. Resistance to industrially generated pollutants may be an example of this type of adaptation.

The final category of adaptation (3) is thought to occur through learning and conditioning. It is dependent on the previous experience of the individual and on the learning process. It is unique to primates and "achieves its greatest significance in Homo sapiens." Within this category is included "cultural adaptation," which is highly dependent "on the capacity of human society to accumulate knowledge gathered by its members and to pass this knowledge on to other individuals and to subsequent generations." Given the recent pace of environmental change and the short history of coronary artery disease it Is more than likely that any impact of adaptation on the disease derives from this category rather than genetic although

[7] Stephen Boyden. "Cultural Adaptation to Biological Maladjustment." 190-193.
[8] Robert L. Perlman. "Why disease persists: an evolutionary nosology." *Med, Health Care and Phil.* 8 (2005): 348.

this far from precludes the contribution of epigenetics to the development and course of coronary artery disease.[9]

In the past the processes involved in cultural adaptation received very little serious consideration by either scientists, natural and social, or even scholars of the humanities. But as Boyden explains:

> The fact that neither evolutionary adaptation nor adaptation genetically-coded responses can possibly explain the survival and multiplication of the human species in the new conditions helps us to appreciate the supreme importance for civilized man of the third category of adaptive mechanisms-those which depend on learning and in particular on cultural processes.[10]

In the short term, therefore, it is cultural adaptation that plays a significant role in shaping disease and illness. The nature of disease and a society's ability to modulate its impact is in large part dictated by the ability to adapt to that disease over time. It is education that plays a significant role in cultural adaptation. In this respect, "when new knowledge is acquired which throws light on the causation of a disorder and indicates suitable curative or preventive measures, the relevant information must be transmitted from specialist scientific circles to other interested parties, be they doctors, administrators, or plain citizens." [11] A hallmark of the 20th century was a general acknowledgement by governments in industrial nations to disseminate information about nutrition.[12] This by enlarge occurred early in the century, accompanying wide sweeping changes in sanitation and hygiene, and the notion of proper nutrition was in many ways married to the other improvements. Much later, governments also recognized the need to

[9] Stephen Boyden. "Cultural Adaptation to Biological Maladjustment." 190-193.
[10] Ibid, 193.
[11] Ibid, 201.
[12] C. Ware, K. M. Panikkar, and J.M. Romein. "History of Mankind." *UNESCO* 6(1966): 457-8.

educate the public about the health hazards of smoking.[13] The Surgeon General's report was released in this country in 1964 but full impact of this form of education was not felt for quite a few years. The importance of education in terms of cultural adaption cannot be underestimated but it needs to be tempered in terms of its effect on health by the adverse propaganda of commercial interests advocating for habits that are less healthy and as a result for biological maladjustment.[14]

The epidemic of coronary artery disease is often tied to industrialization for a variety of reasons. As a process of civilization, this period of time resulted in a state of "biological maladjustment," represented by physiological changes including increased stress, smoking, economic concerns and changes in diet, not least of which the incorporation of substantial quantities of "refined carbohydrates" into the diets of industrialized man, and the reduction of physical activity, made such by the introduction of mechanized transportation.[15] This state of biological maladjustment more than likely, according to the theory, resulted in undesirable consequences including symptoms and manifestations of coronary thrombosis, recognized only once the new conditions prevailed.

Cultural activities in the form of remedial actions helped to result in a curtailment of the undesirable effects. In terms of coronary disease, the development of subspecialty care and the expansion of the field of cardiology would be considered a cultural adaptation to a biological maladjustment.[16] Another would be the early contribution of Paul Dudley White. White was particularly interested in the decline of physical activity during the early 20th century leading up to an expansion to epidemic proportions of coronary artery disease. His advocacy for exercise is

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[13] Stephen Boyden. "Cultural Adaptation to Biological Maladjustment." 201.
[14] Ibid, 202.
[15] Also a decrease in exposure to microbes
[16] Ibid, 194.

believed to have added greatly to the sale of bicycles in Boston; with the automobile as a form of "biological maladjustment," having contributed to the disease. Evidence of his contribution to the notion that exercise is important in terms of adaptation to an increasingly compromising milieu is seen in White's hometown of Boston, where the bicycle path around the Massachusetts General Hospital bears his name.[17] On this point and in the broader context, Boyden would agree with White. He notes that

> …on the level of the individual, it is worth drawing attention to what is one of the most significant of the biological consequences of civilization – the fact that 'doing what comes naturally' is no longer equivalent to 'healthy living.' Under the new conditions the individual must exercise a considerable degree of self-discipline in order to avoid ill-health. This is well illustrated by the situation which has developed with regard to physical work. Cultural developments over the centuries, and especially in the last few years, have tended steadily to decrease the amount of physical work performed each day by the average city dweller. While the evidence that this change gives rise to biological maladjustment is not absolutely conclusive, it is nevertheless very suggestive, and anecdotal evidence strongly supports the view that some regular physical exercise is necessary for optimal health in most people…Palaeolithic man did not have this problem, for he got his physical exercise without any act of self-discipline when his hunger drive finally overcame his natural lethargy.[18]

According to Boyden, the result of modernization was the introduction of a variety of biological maladjustments becoming manifest in the population as a result of changes in the biological circumstances of the organism.[19] One would conjecture that with the meteoric rise in the incidence of coronary disease in the early 20th century that it indeed might represent such a biologic maladjustment at the population level. Boyden believes that such disorders, the result of biological maladjustment, "often become the targets of adaptive processes set in motion by the community." Following this reasoning, one would postulate that there is a "natural

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[17] Paul Dudley White. "Angina Pectoris: Historical Background." In Oglesby Paul, ed. *Angina Pectoris.* New York: Medcom (1974): 9.
[18] Stephen Boyden. "Cultural Adaptation to Biological Maladjustment." 202-203.
[19] Ibid, 203.

selection" that takes place "among the different kinds of biological disorders that arise in society as a consequence of the changing conditions of life." Both drastic and milder forms of maladjustment exist in the population triggering different responses, according to Boyden. Those "which interfere drastically with the business of living or which threaten early death to a fairly high proportion of the community will be the most likely to engender an effective cultural adaptive response, and these will tend to be eliminated early." The ones that represent milder maladjustments with more gradual onset, often not recognized as disorders, are more likely to persist in society for longer periods of time. As civilization proceeds, the mild, insidious, chronic forms will persist and the more severe and drastic, life threatening should be eliminated naturally over time.[20]

Successive industrial revolutions have over the course of time resulted in profound changes in the environment and conditions of life. Human biology, as a result, has gone through drastic and numerous changes since the Neolithic revolution first began over 300 generations ago, many of which, perhaps the majority, having been introduced in the last dozen centuries. Included in the changes, besides the level of physical work, were changes in the degree of sexual stimulation, the wearing of garments for purposes other than warmth, changes in food consumption and sleeping patterns, responding to the changing demands of an industrial society and changes in the exposure to other species, including infections and other animals, and changes in the contacts with members of the same species. [21]

To understand determinants of health and disease and to ultimately unravel the mystery of changes in mortality one must no doubt reconcile the "distinct disciplines" of evolutionary biology and medicine because they have developed with very different concerns.

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[20] Ibid, 203-204.
[21] Ibid, 205.

The former "is concerned with ultimate causes of biological phenomena, causes that have operated during the phylogenetic history of a species; these are the causes that have led to the variety and diversity in the natural world. In contrast, medicine focuses on proximate causes of disease, causes that operate during the lifetime of an individual, because these are the causal pathways in which medicine can intervene." According to Perlman, "an evolutionary nosology, a nosology of ultimate causes, complements the traditional medical classification of disease."[22]

The Thomas McKeown Thesis

I will now turn to a consideration of the determinants of coronary artery disease, laying the ground work for a careful look at the epidemic of the disease that occurred in the twentieth century leading up to the beginning of the decline in its mortality by the late 1960s, in the hope that it might shed light on what may have in fact impacted that decline. One of the most important contributions to understanding the impact of culture and contemporary events on health and disease was made by the English physician and historian Thomas McKeown. Over the course of 30 years (1950s to 1980s), he "put forth the view that the growth in population in the industrialized world from the late 1700s to the present was due not to life-saving advancements in the field of medicine or public health, but instead to improvements in overall standards of living, especially diet and nutritional status, resulting from better economic conditions." Even though "McKeown's thesis," as it became known, is now considered flawed in both its foundation and conclusions, the question at the heart of his work, namely, "What are the most important determinants of a society's patterns of morbidity and mortality" and where efforts should be focused in terms of health strategies, "remain as relevant today as when they were first proposed."[23] A study that looks at improvement in mortality of a disease in

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[22] Robert L. Perlman. "Why disease persists: an evolutionary nosology." 348.
[23] James Colgrove. "The McKeown Thesis: A Historical Controversy and Its Enduring Influence." *Am J Pub Hlth.* 92 (2002): 725.

particular, as this one does, is lacking if it does not explore theories of disease progression and evolution more generally based. But before we can answer the question of what was the cause of an improvement in coronary artery disease mortality we need to return to the question of what caused the disease to reach epidemic proportions in the first place. Could coronary artery disease only emerge as a significant health issue after other diseases which prevented individuals from reaching an age where coronary disease becomes manifest began to decline? Are we looking at more of a demographic transition than an epidemiologic one? McKeown, as demographic historian, perhaps better than any other individual, can help us answer these questions.

McKeown has attempted to lay out what he believes is a classification of "conditions" that will help in clarifying the determinants of disease in general and diseases like coronary artery disease specifically. He divides diseases and disabilities broadly into two groups with further division into four classes. The first group he labels "Conditions determined at fertilization" and the second "Conditions which occur only in an appropriate environment." He then subdivides the first between "Genetic diseases" and "Other diseases determined at fertilization" and the second between "Diseases in which the environmental influences are prenatal" and "Diseases in which the environmental influences are post-natal."[24]

Using McKeown as a template to deciphering where the 20th century malady coronary artery disease sits one would labor little in eliminating the first classification in each group. Although family history appears to be important statistically as a risk factor for coronary artery disease, the ailment itself has never been proven to have a genetic basis.[25] Many authorities

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[24] Thomas McKeown. *The Role of Medicine: Dream, Mirage or Nemesis.* Princeton: Princeton University Press (1979): 24-25.

[25] Familial Hypercholesterolemia and Mendelian disorders of metabolism exist but a more general Mendelian association with CHD has not been found.

believe that the importance of family history stems more from shared environmental exposures than from DNA. Bill Roberts, editor-in-chief of the American Journal of Cardiology, commented that family history of coronary artery disease, in his mind, is the result of "the whole family sitting around the breakfast table eating bacon and eggs" and not from a gene that specifically codes for the disease.[26] Others agree with this observation. Its rather precipitous appearance over the past century also makes a genetic etiology most unlikely.[27] Not likely to be genetic it is also probably not, except perhaps in rare instance, the result of prenatal influences, although the latter might be harder to prove.[28] It may be one whose seeds are planted at the time of fertilization, "not simply inherited, but are attributable to multiple genes which are nevertheless highly specific," resulting in diseases that are "associated with the genetically programmed wearing-out of organs at the end of life." Whether this can be proven or demonstrated convincingly is hard to say but it is clear that post-natal influences play a huge role in disease development and manifestation in coronary artery disease. This latter group is "usually described as multifactorial," a mixed bag of contributions, which translated means "that their aetiology is complex and their genetic basis obscure." [29] It is McKeown's belief also that "in principle all the diseases in the fourth class [post-natal environmental influences] could be prevented by appropriate environmental modifications;" in practice "control of infections is often relatively simple, whereas control of non-communicable diseases may be difficult or impossible."[30]

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[26] Interview with Dr. William C. Roberts, Baylor Heart Institute, November 16, 2012.
[27] Notwithstanding an epigenetic explanation may inure and appears more plausible in the evolution of the disease than a clearly genetic one.
[28] The existence of risk factors in the mother, hypertension, smoking, high cholesterol intake, diabetes, etc. could theoretically impact the development of atherosclerosis early in the fetus, as well as low birth weight ("The Barker Hypothesis") which is now widely accepted.
[29] Thomas McKeown. *The Role of Medicine: Dream, Mirage or Nemesis*: 25.
[30] Ibid, 25.

There is clear-cut evidence that the past three centuries have resulted in a significant improvement in health in the western world. Up until that point historically a considerable percentage of the population succumbed during the first few years of life. Although infant mortality continues to be a problem in the developing world, "in technologically advanced countries today, more than 95 per cent survive to adult life."[31] In considering the decline in mortality of coronary artery disease one needs to examine determinants that might impact that decline both specifically and generally. It is the contention of McKeown and others that, irrespective of advancements in specific disease entities, a decline in mortality can be explained or at least aided by a general change in the population and the achievements gained in seemingly unrelated areas. This, in part, may help to explain not only the decline of coronary artery disease mortality but also its rise in incidence during the first half of the twentieth century.

Abdel Omran and others have signaled this shift as the "epidemiologic transition" of disease where diseases come to light and significance because others have either disappeared or become insignificant threats to health.[32] But beyond this exchange, it is often possible to explain declines by understanding the general health of a population and the reasons for the change in health statistics more generally. What may appear as background noise or mere artifact can contribute to shifts in health and mortality that have seemingly very little to do with the disease itself. It was McKeown's belief that "the rise in population [decline in mortality] was due less to human agency in the form of health-enhancing measures than to largely invisible economic forces that changed broad social conditions."[33] For McKeown health and disease was

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[31] Ibid, 29.
[32] Abdel R. Omran. "The Epidemiologic Transition: A Theory of the Epidemiology of Population Change." *Mil Mem Fund Quart* 49 (1971): 509-538.
[33] James Colgrove. "The McKeown Thesis: A Historical Controversy and Its Enduring Influence." 725.

more related to a demographic transition than to anything man had done or could do. He wrote in 1962, that "the rise of population was due primarily to the decline of mortality and the most important reason for the decline was an improvement in economic and social conditions" rather than any specific improvements in treatment.[34] Although he primarily targeted infectious diseases in his statement and in his body of work, a belief in such should be applicable to all diseases and his work makes reference to inclusion of chronic degenerative diseases as well.

Based on statistics from England and Wales, where the causes of death were first registered in 1838, ahead of accurate recording of such in almost all other countries, besides Sweden, the overall death rate for both sexes and for all causes, declined steadily between the time of first registry and 1971. The majority of reduction occurred between 1901 and 1971 and roughly 73% of that reduction can be attributable to control of infections. Conditions, including CHD, not considered the result of infection, enjoyed a 25.6% reduction in mortality during the same period. Prior to 1901, it appears "reasonable to conclude that the Registrar-General's [England and Wales] statistics provide no convincing evidence of a reduction of deaths from non-infective causes between 1848-54 and 1901" and estimates to the contrary may be due to certification and classification errors.[35] Believing this to be the case one would agree that an epidemiological transition did occur in the diseases of the 19th century and those of the 20th century, giving rise to diseases of non-infectious origins once those of infectious were controlled. One would also argue that the reduction in infectious disease mortality appeared to predate the first use of antibiotics[36] and established treatment making the argument that other forces were at work in the reduction of mortality besides medical therapy.

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[34] Thomas McKeown and RG Record. "Reasons for the decline of mortality in England and Wales during the nineteenth century." *Popul Stud.* 16 (1962): 94-122.
[35] Thomas McKeown. *The Role of Medicine: Dream, Mirage or Nemesis*: 43.
[36] Alexander Fleming discovered Penicillin in 1928 but first clinical use did not occur until the 1940s.

It is clear, without debate or argument, that the greatest contribution to an improvement in disease determinants in the past two centuries was related to a decline in the mortality of infectious diseases. Since the end of the seventeenth century, the fall in disease mortality overall was due largely to fewer deaths from infectious diseases and their agents. Beginning in the 20th century, 1901 up until 1976, fully a quarter of the decline in disease mortality can be attributed to non-infectious diseases.[37] Given the fact that it appears, in terms of chronology, that antibiotics and disease specific treatments played a less significant role in the decline in the mortality of infectious diseases than most would have thought may help in explaining the same trend that occurred later for non-infectious diseases and for this reason is worth reviewing. McKeown provides us with a basis for the analysis of the decline in mortality from infectious diseases in a classification that brings into play four significant factors, namely the "interaction between organism and host…Immunization and therapy…modes of spread…and the nutrition of the host."[38] These, I would argue, provide a mode of examination for any disease, infectious or otherwise.

Interaction between organism and host in terms of a non-infectious illness could be translated into an interaction between causative agent and host. In this respect, in terms of coronary artery disease, one would be looking at atherosclerosis and specifically the impact and interaction of lipids with the development of the lesion. As Bill Roberts and Jeremiah Stamler both pointed out to me, atherosclerosis is the cause of coronary disease.[39] Although for years the "cholesterol hypothesis" was debated, its basis for the development of atherosclerosis is

[37] Ibid, 45.
[38] Ibid, 46.
[39] Interviews with Dr. William Roberts and Dr. Jeremiah Stamler in 2012. See Appendix 2 for details.

now universally accepted.[40] Going further, Roberts stated to me unequivocally that "the cause of atherosclerosis is an elevated cholesterol." Stamler points out "If the serum cholesterol is low and the dietary lipids are low you can have hypertension, you can have cigarette smoking until the cows come home. You'll have other kinds of disease but not atherosclerotic disease and not atherosclerotic coronary disease." He continued "the sine qua-non for atherosclerotic coronary disease is a disturbance of lipid metabolism and for its mass occurrence that's a diet induced population-wide event."[41]

In terms of immunization and treatment, there is currently no immunization for coronary artery disease, although there may be some programs and efforts working to this effect in the research pipeline. Certainly though therapies exist and have existed that may have modified the illness. Modes of spread in terms of coronary artery disease may or may not exist. There is some thought that certain organisms may inhabit the coronary arteries and lead to disease but this has not been proven. Additionally, researchers in Brazil believe there is a connection between the 1918 influenza epidemic and coronary artery disease.[42] We will address this particular matter later in this chapter.

Finally, the fourth factor in determining disease manifestation is the nutrition of the host. Here little doubt exists as to the role of diet in chronic disease modification but it is a complicated consideration and will be discussed later in this dissertation when issues related to prevention are fully considered (see chapter 4).

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[40] Daniel Steinberg. *The Cholesterol Wars*: *The Skeptics versus the Preponderance of Evidence.* San Diego: Academic Press (2007).
[41] Interview with Dr. Jeremiah Stamler, Riverside Drive Apartment, New York, NY November 30, 2012.
[42] Maria Inês Azambuja and Bruce B. Duncan. "Influenza and Coronary Heart Disease." *Cad Saúde Púb, Rio de Janeiro* 18 (mai-jun 2002): 557-577.

For McKeown decline in mortality of disease "was due substantially to a change in the character of the diseases, essentially independent of both medical intervention and identifiable environmental (including nutritional) improvements."[43] McKeown's *The Modern Rise of Population* published in 1976, was "an accessible summary of over two decades of painstaking empirical work, applying the insights of current medical and epidemiological knowledge to a historical analysis of Britain's detailed national series of death records." The work was in many ways revolutionary and iconoclastic, "overturning a long-standing general orthodoxy regarding the importance of medical science and the medical profession in bringing about the decline in mortality which accompanied industrialization in Britain." His contention was "that those advances in the science of medicine which form the basis of today's conventional clinical and hospital teaching and practice, in particular the immuno- and chemo-therapies, played only a very minor role in accounting for the historic decline in mortality levels." What McKeown was saying was that many noteworthy diseases in Britain had declined or disappeared well ahead of significant medical interventions designed or put into place for those specific diseases. His findings gave credence to the fact "that the forward march of modern 'scientific medicine' cannot be given the credit for the historical fall in mortality" that was being documented. For McKeown, epidemiological data showed that rather than medical intervention and scientific advancement in treatment and prevention, mortality decline could in great part be accounted for by improvement in the "standard of living" and most significantly and importantly improvement in diet. It was his belief that decline in mortality in England and Wales could "be

[43] Thomas McKeown. *The Role of Medicine: Dream, Mirage or Nemesis*: 46.

primarily accounted for by the benevolent 'invisible hand' of gradually rising living standards, particularly in the form of increases in per capita nutritional consumption."[44]

For those who embraced the reductiveness of McKeown's argument it became mantra "that all medicine, the medical profession and, in fact, organized human agency in general had remarkably little to do with the historical decline of mortality in Britain until the inter-war period at the earliest." McKeown generally recognized the public health movement, improvements in hygiene and sanitation, as positive, but concluded that their influence was merely secondary and of a reinforcing nature. For him "public health measures came along relatively late in the day, when the momentum of declining mortality was already established." He calculated that sanitary measures at most could account for reducing mortality by 25% but that the rise in nutrition was responsible for probably twice that amount.[45] Cardiologist and Nobel Peace prize recipient, Bernard Lown, who I spoke to in November 2013, from our conversation, would tend to agree with McKeown that decline in mortality had less to do with medical intervention and prevention than with an overall general global improvement in underlying conditions impacting disease and its mortality.[46]

The critics of McKeown found two basic flaws in his thesis; namely, his contention that population growth was due to declining mortality rather than an increase in the birth rate and "that active human intervention in the form of medical and public health measures had little to do with the fall in death rate." There were other criticisms as well which included methodological issues and a strong ideological bias which distorted data and resulted in failure

[44] Simon Szreter. "The Importance of Social Intervention in Britain's Mortality Decline c. 1850-1914: A reinterpretation of the role of public health." *Soc Hist Med* 1(1988): 1- 2.
[45] Ibid.
[46] Interview with Dr. Bernard Lown, Chestnut Hill, Massachusetts, November 4, 2013.

to consider other significant work in the area. [47] But one point made by McKeown did resonate with many of his colleagues and critics, finding agreement even among modern day health practitioners, and that was "that the increasing emphasis in the second half of the 20th century on high-technology, curative medical efforts was a misguided division of resources away from more environmentally focused health programs."[48]

Although numerous scholars take issue with the McKeown thesis, the strongest and most strident critique came from Cambridge professor of History and Public Policy Simon Szreter. Utilizing the same epidemiological data he formulated "a revisionist account which directs attention to the leading role played by the public health movement and its locally administered preventive health measures in combating the urban congestion created by industrialization." In opposition to McKeown, who argued that it was improving nutrition that was at the heart of the fall historically in Britain's mortality, Szreter using the quantitative evidence of McKeown argued "that the public health movement working through local government, rather than nutritional improvements through rising living standards, should be seen as the true moving force behind the decline of mortality in this period."[49] Economists David Cutler and Grant Miller at Harvard offer another perspective, making a convincing argument that it was clean water technologies that reduced mortality in major cities during the early twentieth century. They found that, during the period of roughly 1900 – 1940, "clean water was responsible for nearly half the total mortality reduction in major cities, three quarters of the infant mortality reduction, and nearly two thirds of the child mortality reduction."[50]

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[47] James Colgrove. "The McKeown Thesis: A Historical Controversy and Its Enduring Influence." 727.
[48] Ibid, 726.
[49] Simon Szreter. "The Importance of Social Intervention in Britain's Mortality Decline c. 1850-1914: A reinterpretation of the role of public health." 1-2
[50] David Cutler and Grant Miller. "The Role of Public Health and Improvements in Health Advances: The Twentieth-Century United States. *Demography* 42 (2005): 1-22.

Allan Mitchell analyzes McKeown's argument in terms of the decline in mortality of tuberculosis in late Nineteenth-century France and makes note that in the "larger debate…between the McKeownites and their critics, the jury is still out."[51] Fairchild and Oppenheimer agree, noting that "although McKeown's work suffers from distinct weaknesses so does that of his critics. These critics, who stress the role of human agency in the form of public health interventions, lack a body of valid quantitative data to support their position." [52]

Although harshly critical of the research of McKeown and associates, and believing that the conclusions reached were flawed, Szreter makes an important point, quite germane to this project and it is worth quoting here in its entirety, as it will no doubt impact claims made later in the dissertation in terms of prevention and treatment. It is here that Szreter and other critics appear to find consensus. Writes Szreter, Mckeown's

> work achieved something of a conceptual revolution in the disciplines of history and medicine, overturning a long-standing general orthodoxy regarding the importance of medical science and the medical profession in bringing about the decline in mortality which accompanied industrialization in Britain. It effectively demonstrated that those advances in the science of medicine which form the basis of today's conventional clinical and hospital teaching and practice, in particular the immuno- and chemo-therapies, played only a very minor role in accounting for the historic decline in mortality rates.

Szreter stresses that the achievement of Thomas McKeown "in deflating the historical claims of one particular section of the medical profession and its 'high tech' invasive and biomedical medicine, remains unaffected" by the criticism he has for his work. He agrees with the "negative finding that the forward march of modern 'scientific medicine' cannot be given the credit for the

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[51] Allan Mitchell. "An Inexact Science: The Statistics of Tuberculosis in Late Nineteenth-century France." *Soc Hist Med* 3 (1990): 403.
[52] Amy L. Fairchild and Gerald M. Oppenheimer. "Public Health Nihilism vs Pragmatism: History, Politics, and the Control of Tuberculosis." *Am J Pub Heal* 88 (1998): 1107.

historical fall in mortality" but sharply disagrees with McKeon's propounded "positive explanatory thesis." [53]

In his historical analysis of the "McKeown thesis" James Colgrove, Associate Professor at Columbia University, Mailman School of Public Health, finds very limited consensus about its validity among historians. In one narrow aspect he agrees with Szreter, "that curative medical measures played little role in mortality decline prior to the mid-20th century." But like Szreter and other critics he believes "that most of its other claims, such as the assessment of the relative contributions of birth rates and of public health and sanitation measures to population growth, were flawed." Colgrove points out that although there is wide consensus that McKeown's analysis of the reasons for improved mortality from disease in the U.K. was unsound and considerably distorted methodologically, leading to conclusions that cannot be fully accepted on the strength of the data he amassed, it is the belief of many scholars in the field that "his underlying ideas regarding the effects of poverty and economic well-being on health were essentially correct." What may bear even greater relevance to the question at hand, the notion that the mortality of coronary artery disease declined significantly, where every indication, especially that of a growing population of individuals at risk (after all life expectancy during the period in question increased significantly making the development of chronic disease in general and coronary disease more specifically greater in the population) would predict that it would increase, the fundamental question at the heart of McKeown's thesis has lost little relevance. That is: "are public health ends better served by narrow interventions focused at the level of the individual or the community, or by broad measures to redistribute the social,

[53] Simon Szreter. "The Importance of Social Intervention in Britain's Mortality Decline c. 1850-1914: A reinterpretation of the role of public health." 2.

political, and economic resources that exert such a profound influence on health status at the population level?" [54]

I would like to return to McKeown for one more fundamental point which, even though it has been highly debated and largely refuted by many, warrants mention. In his seminal work, *The Role of Medicine: Dream, Mirage, or Nemesis,* written in 1976, McKeown examines determinants of disease but focuses mainly on infectious diseases, although "non-infectious conditions" are addressed as an extension of his beliefs. The implication is that the decline of infections was not the result of either medical intervention or of measures including improved hygiene and nutrition, but rather because of a fundamental "modification of the relation between micro-organisms and their hosts." Referring vaguely to scientific evidence and opinion he states "some biologists have suggested that a change of this type was important, and even that it was the main reason for the decline of mortality and improvement in health." Following from this interpretation, McKeown would lead one to believe that "the trend of mortality from infectious diseases has been essentially independent of both medical measures and the vast economic and social developments of the past three centuries."[55] The implication led McKeown to the suggestion "that the decline of mortality was due substantially to a favorable change in the 'ever-varying state of the immunological constitution of the herd.'" McKeown based such a radical judgment on the work of Thomas Magill who documented the rather dramatic decline in mortality from both tuberculosis and diphtheria "uninfluenced by therapeutic measures." The declines in mortality of both began before effective treatment for TB became available and ahead of the "introduction of antitoxin" for diphtheria. Likewise, pneumonia mortality was on the decline before antibiotics were known and the course of scarlet fever appears to have been

[54] James Colgrove. "The McKeown Thesis: A Historical Controversy and Its Enduring Influence." 728.
[55] Thomas McKeown. *The Role of Medicine: Dream, Mirage or Nemesis*: 46-47.

independent of effective medical intervention. Writes Magill, "The physician or the medicine man of each age has attributed the control and cure of disease during his own particular era to the therapeutic procedure then in vogue. The possibility that infection is a biological phenomenon dealing chiefly, perhaps, with ecological relationships escaped the past, as it has escaped the present."[56]

Although McKeown unequivocally ties this concept of herd immunity to infection, one could extrapolate the concept to a basic constitutional change in the species that might impact the fate of all diseases in a similar way; that is by genetically or even epigenetically reducing future generations' susceptibility to the disease. He states this quite clearly as follows:

> The immunological constitution of a generation is influenced largely by the mortality experience of those which precede it. This was particularly true in past centuries, when the majority of liveborn people died from infectious diseases without reproducing. Under such conditions there was rigorous natural selection in respect of immunity to infection. The proposal that the decline of mortality resulted from a change in the immunological constitution of the population therefore implies that there was heavy mortality at an earlier period which led to the birth of individuals who were genetically less susceptible.

Implicit in this interpretation is the belief that the decline in infectious disease mortality was not due to improvements over the course of time, "but to an earlier deterioration of conditions which led to the high mortality which must have preceded it." [57]

McKeown's thesis addresses both infectious and non-infectious diseases but in the main draws its argument from what he perceives as immunological mechanisms impacting health and mortality. The determinant at the heart of his argument is a change in the capacity of the species to combat disease. Although he argues that changes in treatment and care may have in

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[56] Thomas P. Magill. "The Immunologist and the Evil Spirits." *J Immunol* 74 (1955): 1-8.
[57] Thomas McKeown. *The Role of Medicine: Dream, Mirage or Nemesis*: 48.

a small way impacted the lethality of certain illnesses it is not, according to McKeown and others who embrace this notion, if not his entire thesis, the main cause for improvements in health and a decline in mortality. Coronary Heart Disease (CHD) has traditionally been considered a chronic degenerative and non-infectious condition. Unfortunately, pursuing this notion of the nature of CHD alone does not help in and of itself to explain the trend in mortality that occurred in CHD during the latter half of the 20th century. The results of a number of experimental and clinical studies, carried out since the late 1970s, have "challenged the traditional notion of CHD as a degenerative condition, supporting instead an alternative view of CHD as an immune inflammatory disease."[58] Furthermore, there are individuals who believe that infection may indeed play a role in either the initiation or progression or both of CHD.[59] Although no causal relationship has yet been established, a species of the organism Chlamydia has been isolated from individuals with the disease.[60]

Thus a second paradigm has emerged in trying to explain the events that have transpired in the CHD epidemic over the course of the 20th century. The traditional approach which views CHD as a chronic degenerative disease attempts "to explain the CHD epidemic as secondary to time-trend variation in exposures to risk factors for development of disease." An explanation based on the notion that CHD represents an infectious or inflammatory condition at its origins, would support the work of McKeown with an explanation that is based not on risk factors or interventions but rather "based more on a variation in individual susceptibility to CHD over time."[61] It is unlikely however, based on rigorous substantiation of the cholesterol

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[58] Maria Inês Azambuja and Bruce B. Duncan. "Influenza and Coronary Heart Disease." 557-577.
[59] Ibid, 558.
[60] P. Saikku. "Serological Evidence of an Association of a novel Chlamydia, TWAR, with Chronic Coronary Heart Disease and Acute Myocardial Infarction. *Lancet* 332 (1988): 983-986.
[61] Maria Inês Azambuja and Bruce B. Duncan. "Influenza and Coronary Heart Disease." 558.

hypothesis, that a role for infection and inflammation, even if proven, will supplant, in any substantial way, the importance of cholesterol in the development of CHD.

The Influenza Theory

Tying the earlier presented notion that disease virulence is in some manner impacted by high mortality that proceeded it, investigators in Brazil have theorized that "a massive occurrence of an infectious disease could have led to the emergence of the CHD epidemic, even if other environmental exposures (e.g. high fat intake, smoking) had not changed over time, by modifying individuals' susceptibility to their effects." Historically, such an event did occur. The 1918 influenza epidemic which impacted the entire world preceded the ascent in CHD mortality.[62] The year of the influenza epidemic was the same year that James Herrick presented to the medical community his data for a second time on the chronic nature of CHD and soon the disease became epidemic. A coincidence? Possibly but the cataclysmic consequences of both epidemics may have more than the year of their recognition in common. The 1918 Influenza impacted 25 percent of the U.S. population and according to historian Alfred Crosby there were at least 500,000 deaths as a result of influenza and consequent pneumonia. Worldwide the mortality is believed to have reached at least 21 million and estimates run as high as 30 to 40 million.[63] Largely reflecting the work of immunologist T.P. Magill[64] and the theory of social historian Thomas McKeown, this group of researchers believes that the burden of this particular

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[62] Ibid, 558.

[63] A.W. Crosby. *America's Forgotten Pandemic: The Influenza of 1918.* New York: Cambridge University Press (1989).

[64] "It would seem to be a more logical conclusion that during recent years, quite regardless of our therapeutic efforts, a state of relative equilibrium has established itself between the microbes and the 'ever-varying state of the immunological constitution of the herd' – a relative equilibrium which will continue perhaps, just as long as it is not disturbed, unduly, by biological events." Presidential address to the American Association of Immunologists, 1954. Magill, TP. "The immunologist and the evil spirits." *J Immunol* 74 (1955): 1.

influenza infection on the United States dramatically impacted the population in a manner that made them more susceptible to CHD and can be used to explain the epidemiological pattern of CHD mortality in the 20th century.[65]

During the 1918 Influenza epidemic, a significant proportion of the consequent mortality was found in those in the second and third decades of life. According to Crosby, it was the consensus of the American Public Health Conference, held in December 1918, that those most likely to succumb to the disease were "those who had been in the best of physical condition and freest from previous disease."[66] It was likewise the belief of experts that "death was due not to direct viral damage but to the strength of the immune-inflammatory response to infection, greater in robust young (white, male) adults."[67] It is the hypothesis of investigators who believe in a relationship between the 1918 influenza epidemic and the CHD epidemic that would follow, that the survivors of the flu were "primed" in a very similar manner to the development of CHD in the future. Assuming the hypothesis to be correct, "the relative distribution of influenza-related deaths among individuals ages 15 to 49 in 1918-1919 (a proxy for the distribution of some particular kind of immune-inflammatory response to infection across the range of exposed birth cohorts) should predict the occurrence of CHD mortality in survivors from the corresponding birth cohorts (from about 1870 to 1915) in subsequent years."[68]

Of further interest, both the activity of Influenza and death rates from CHD seemed to vary across the United States in the period from 1918 to 1957. The explanation for this, if one believes in the relationship of the two, can be explained by further hypothesis "that the

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[65] Maria Inês Azambuja and Bruce B. Duncan. "Influenza and Coronary Heart Disease." 558.
[66] A.W. Crosby. *America's Forgotten Pandemic: The Influenza of 1918*: 216.
[67] Maria Inês Azambuja and Bruce B. Duncan. "Influenza and Coronary Heart Disease." 558.
[68] Ibid, 559.

reported geographic variation in time of onset of the decline in CHD death rates depended on the varying persistence of H1N1 viruses across the United States, and through their effect, on a lower level but continuing CHD "initiation" taking place in later birth cohorts."[69] Gordon and Thom in 1975 suggested that the decline in coronary artery disease mortality could in part be attributed to a continuous decline in influenza activity and the fact that pandemics of influenza after 1968 were largely absent.[70] Azambuja and Duncan, in this respect, believe that the "reduction in repeat exposure of H1N1 'primed' individuals to subsequent influenza infections might have been the determining factor in the change in disease-host relationship regarding CHD progression and death."[71]

Further evidence and clues for the impact of influenza infection on CHD can be found historically. An earlier publication by the same investigators in Brazil indicates that there may have been an earlier impact on the mortality of CHD in Britain during the last 30 years of the 18th century. Heberden first described, to the Royal College of Physicians in England in 1772, the anginal syndrome. This description, which at the time did not yet have an established cardiac or coronary origin for it, occurred in Britain after rather significant influenza activity with recorded epidemics in 1727, 1732, 1737 and 1760.[72] Additional clues exist to lend support to the idea that the influenza epidemic of 1918 might have impacted death from CHD. One such clinico-pathologic clue exists in the entity of sudden death.

In my interview with Bernard Lown, he pointed out that sudden cardiac death is very important in the overall mortality from CHD, something that was not known until he described

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[69] Ibid.
[70] Tavia Gordon and Thomas Thom. "The recent decrease in CHD mortality." *Preven Med* 4 (1975): 115-125.
[71] Maria Inês Azambuja and Bruce B. Duncan. "Influenza and Coronary Heart Disease." 563.
[72] M. I. Azambuja. "Rise and fall in ischemic heart disease mortality: It may have happened before." *Rev de Saude Pub* 29 (1995): 440-443.

"sudden arrhythmic death."[73] It was in any event a major hallmark of the CHD epidemic, especially in the early phase when mortality was climbing. According to McKinlay and associates acute arrhythmic deaths, which were usually sudden, unexpected and occurred outside of hospitals accounted for nearly two thirds of CHD deaths at the height of the CHD epidemic. During the decline in CHD mortality it was this component that fell most dramatically; more so than did mortality from acute myocardial infarction or longer term post myocardial infarction mortality.[74] Sudden death also played a significant role in the course of cardiovascular deaths during influenza epidemics.[75] Further correlation between sudden death, and influenza can be found in evidence that vaccination against influenza has been shown to be protective against sudden death.[76] The exact mechanism by which either CHD or influenza might result in sudden death is not known, although there is some evidence that obstruction of the artery or arteries which supply the conduction system of the heart may be involved.[77] Historical evidence reveals that "during the 1918 influenza pandemic, the most frequently observed circulatory disturbance was bradycardia." Although highly speculative, "infection and inflammation of arteries supplying the conduction system of the heart could explain both arrhythmias during the 1918 pandemic and sudden CHD deaths occurring during the decades of relatively high influenza activity."[78]

Other biological links between Influenza and CHD have been postulated but remain far from proven. Using the paradigm of "original antigenic sin" and drawing on examples including

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[73] Interview with Dr. Bernard Lown, Chestnut Hill, Massachusetts, November 4, 2013.
[74] J.B. McKinlay, M. McKinlay and R. Beaglehole. "A review of the evidence concerning the impact of medical measures on recent mortality and morbidity in the United States." *Int J of Heal Serv 19 (1989): 181-208.*
[75] R. Oseasohn, L. Adelson and M. Kaji "Clinicopathologic study of thirty-three fatal cases of Asian influenza." *NEJM* 260 (1959): 509-518.
[76] D.S. Siscovick, T.E. Raghunathan, et al. "Influenza vaccination and the risk of primary cardiac arrest." *Am J Epid* 152 (2000): 674-677.
[77] D. Velican, G. Serban-Piriu, et al. "Prevalence of thick intimas and of obstructive lesions in the vessels supplying the conduction system of the heart." *Medicine Interne* 27 (1989): 197-208.
[78] Maria Inês Azambuja and Bruce B. Duncan. "Influenza and Coronary Heart Disease." 563.

the reactivation of rheumatic heart disease following a reinfection by the causative agent group A beta-hemolytic strep, as well as multiple sclerosis exacerbations after infection with virus, Brazilian investigators have postulated that "immune responses elicited at each new encounter with an influenza virus could reactivate inflammatory pathways to CHD, originally established by a first encounter with a H1N1 influenza virus and some specific immune response to it."

Besides the model of reinfection and the reactivation of an inflammatory response possibly leading to acute coronary events another model for impact of influenza on coronary artery disease has also been postulated. This involves an interaction between the virus and lipid metabolism such that infection, or more likely the immunological response to it, somehow impacts lipids and an increase in coronary susceptibility to elevated levels of cholesterol.[79] Evidence exists for molecular mimicry in terms of certain strains of influenza viruses and their amino acid sequences that are involved in cell attachment of the hemagglutinin and amino acids of apolipoproein B which is involved in binding of LDL to its receptors. This process, upon reinfection of influenza virus, could result in LDL accumulation in the intima of coronary arteries.[80] If correct it could shed greater light on the mechanism for the impact of cholesterol on coronary disease, providing the link between infection and coronary artery disease mortality, and shedding important light on what Blackburn and Jacobs have termed the "diet-heart controversy."[81]

Whether one believes that the 1918 influenza or influenza more generally has had an impact on the mortality of coronary artery disease over the course of time, it is the belief of

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[79] Ibid, 563-564

[80] V.M. Pleskov, A.I. Bannikov and I.V. Zaitzev. "The receptor-mediated endocytosis of influenza viruses and low-density lipoproteins by tissue cells." *Voprosy Virusologii* 39 (1994): 121-125.

[81] Henry Blackburn and David Jacobs. "Sources of the diet-heart controversy: confusion over population versus individual correlations." *Circulation* 70 (1984): 775-780.

many that "current evidence demonstrates that the diet-heart paradigm, which gave support to most of the research and intervention policies related to CHD during the 20th century, cannot [alone] adequately explain all the features related to the CHD time trends." [82] Another factor appears to be needed to make this paradigm work.

Epigenetics: Its potential impact on the history of coronary artery disease

In McKeown's work we see arguments for evidence that a disease and its mortality could have been impacted by another cataclysmic event as just discussed in terms of the 1918 Influenza epidemic. We also see reference to the possible role that epigenetics might have played. In this section, I would like to address the theoretical role of epigenetics in the course of disease evolution, specifically coronary artery disease, and its potential impact for altering mortality.

The term epigenetics, which taken literally means "above genetics," was first coined by developmental biologist Conrad Waddington in 1939. He used the term to describe "the causal interactions between genes and their products, which bring the phenotype into being." Subsequent to the discovery of the structure of DNA by James Watson and Francis Crick in the 1950s, epigenetics was "defined as those heritable changes in gene expression that are not due to any alteration in DNA sequence."[83] As we have learned in the years since both the coining of the term epigenetics and the elucidation of the material that makes up the genome, it is quite clearly not just the DNA that determines phenotype. All cells of an organism contain the same DNA coded genetic material but nonetheless manifest both morphological and functional differences. It is clear that the field of genetics alone cannot explain all human variation and

[82] Maria Inês Azambuja and Bruce B. Duncan. "Influenza and Coronary Heart Disease." 564.
[83] Manuel Esteller. "An Introduction to Epigenetics." In Manuel Esteller, ed. *Epigenetics in Biology and Medicine*. Boca Raton: CRC Press (2009): 1.

disease. As an example, monozygotic twins, who possess the same DNA sequence, identical genomes, have different phenotypes and "degrees of sickness penetrance." Their health and illness profiles diverge as they age. Environmental influences are often invoked to explain the divergence. But epigenetics, it is believed, helps to perhaps better explain both.[84]

It is the field of epigenetics that "studies the additional layers of information on top of the bare genomic sequence that dramatically extend the information potential of the genetic code." In this way, it permits "the cells to respond to certain internal as well as external environmental cues and confer phenotypic plasticity." But as Brian Hall, points out "epigenetic or epigenetics does not mean nongenetic." Epigenetic control incorporates both genetic and environmental factors. It can take environmental signals, and with time and selection, make them into inheritable genetic factors. One can no longer speak of genetic versus epigenetic. Mathematician and theoretical biologist Rene Thom points out that "from the point of view of efficient causality, everything is also 'epigenetic', as even the local triggering of a gene's activity requires – in general – an extra-genomal factor."[85]

If we believe the work of evolutionary biologists and if we put stock into the notion that aspects of one's makeup can be transmitted or passed down across generations in a transgenerational manner then we must put stock into the idea that epigenetics plays a role in the transformative process of both inheritance and development. It pulls together the genome with the environment to develop the phenotype manifested by health and illness. The role of genetics in disease is a complicated matter. Sheffield and Stone writing in a 2011 review article in the *New England Journal of Medicine* about the genomics of the eye and specifically

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[84] Ibid.

[85] Bryan K. Hall. "A Brief History of the Term and Concept Epigenetics." In Benedikt Hallgrimsson and Brian K. Hall, ed. *Epigenetics: Linking Genotype and Phenotype in Development and Evolution*. Berkeley: University of California Press (2011): 11

uncovering the genetics of disease, in this respect ophthalmic disease, note that "a major challenge in using…emerging genetic information in the clinical domain is the gap that exists between the amount of information that is needed to convincingly demonstrate a pathogenic role of a given gene in a group of research subjects and the amount of information that is needed to reliably assert that a given genetic variation is responsible for a disease in an individual patient." The gap can perhaps be explained by mutation, genetic heterogeneity, "non-phenotype-altering variations" at many different genes, or epigenetics.[86]

The phenomena of epigenetics in disease became inevitable. The human genome, after being elucidated approximately 10 years ago, did not appear to give all the answers that scientists and researchers believed or hoped it would. Chief among these were an explanation of why identical twins emerged with differences in phenotype, specifically health and disease. Geneticists saw the need to look elsewhere and as a result epigenetics was invoked as an explanation. The discovery of epigenetics has clearly blurred and appropriately so, according to the authors, "the distinction between genotype and phenotype established over 100 years ago." It "falls broadly within the area of systems biology premised on the concept that system-level phenomena are essential as explanatory factors in biology." Because the complexity of biological systems prohibits the construction of a comprehensive deterministic framework, a conceptual framework like epigenetics is required to do so. For this reason, "epigenetic explanations arise whenever we create theoretical constructs to make sense of the complex relationships between genetic and phenotypic variation and evolution."[87] As Brian K. Hall notes,

[86] Val C. Sheffield, and Edwin M. Stone. "Genomics and the Eye." *NEJM* 364 (2011): 1932-1942.
[87] Benedikt Hallgrimsson and Brian K. Hall. *Epigenetics: Linking Genotype and Phenotype in Development and Evolution.* Berkeley: University of California (2011): 1-2

"Phenotypic variability results from intrinsic genetic effects, heritable epigenetic effects and non-genetic environmental effects, some of which act epigenetically."[88]

Epigenetics may play a role in the substantiation of claims made by Thomas McKeown in terms of classification relative to fertilization. Animal studies, in the vole, water flea, locust and lizard to name a few, have substantiated the role that epigenetics plays in fetal development. No longer can the genome alone be held responsible for the way DNA is expressed and the resulting characteristics in the offspring. The influence of the mother's experiences on the expression of the genome in the offspring is labeled "a predictive adaptive response or maternal effect." This effect has broad implications in humans and represents a significant paradigm shift in the way we view the role of genetics and inheritance in general. It brings an entirely new meaning to the designation of disease etiology and the pattern and course of inheritance. One can no longer fully count on inherited characteristics to follow a strict pattern established by Mendel and other classical geneticists. The role of genetics in health and disease takes on a much more Lamarckian character in the age of epigenetics.[89]

It is believed that early pregnancy, immediately after conception, may represent the most vulnerable period in terms of the impact of epigenetic mechanisms (markers) at play. It is this time period when many of the critically important genes are switched on and off and the earlier that one of the epigenetic mechanism like methylation takes hold the more critical the impact on the fetus. This may help to explain the effect of maternal smoking and alcohol use on the fetus; recognized for years as a problem, but for which the mechanism was largely unknown and poorly understood until recently.

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[88] Brian K. Hall. "A Brief History of the Term and Concept Epigenetics." 11.
[89] Sharon Moalem. *Survival of the Sickest: A Medical Maverick Discovers Why We Need Disease*. New York: Morrow (2007): 155-162.

Cancer was the first clinical frontier in which epigenetics appeared to play a role. It is today classified as "both a genetic and an epigenetic disease." The process of oncogenesis or literally cancer development in all likelihood "occurs as a result of sequential heritable events." It probably requires a number of different events occurring over many years. Since there are at least 300 different diseases classified as cancer, many of which act in very different ways, it is more than likely that the process of oncogenesis has many different pathways.[90] Simplistically, cancer is characterized as an abnormal growth of cells leading in most instances to uncontrolled proliferation. In the past, research in oncogenesis has concentrated its efforts on the identification of a number of genomic changes, including amplifications, translocations, deletions and mutations that were deemed critical to cancer development. What resulted from this work with the genome was the identification of involved oncogenes and tumor-suppressor genes. It was discovered subsequently that although genetics concerned itself with the inheritance of a certain gene sequence and of oncogenes, and genes for tumor suppression fit in well to the model, it did not address the "inheritance of information based on gene expression levels," the domain of epigenetics. Modifications such as DNA methylation and histone modification (epigenetic mechanisms) affected the expression of the gene and how it interacted with cells both normal and abnormal. Hypermethylation of regions of tumor-suppressor cells was shown early on to lead to cancer development. Specifically the hypermethylation of CpG segments of DNA were found to be associated with cancer in laboratory animals where these segments or "islands" were found to be unmethylated in normal tissues. The knowledge of these types of molecular changes associated with disease (in this case cancer, but generalizable

[90] Lee B. Riley and David W. Anderson. "Cancer Epigenetics." In Trygve Tollefsbol, ed. *Handbook of Epigenetics: The New Molecular and Medical Genetics*. Amsterdam: Elsevier (2011): 521-523.

to other chronic diseases) have the potential to lead to early risk determination for disease, early disease detection as well as monitoring of disease and prognosis.[91]

In terms of coronary artery disease, epigenetics can explain the etiology of the disease in populations with few discernible risk factors and perhaps explain as well the reason coronary artery disease presented itself epidemically only at the start of the twentieth century. It may in particular be the missing link in a unifying approach to incorporating risk with other factors of causation. The inheritable predisposition may not reach deep enough into the genome to explain a clear cut Mendelian pattern but may have rather been initiated or propagated by an epigenetic marker in one of the parents or even one of the grandparents.

By comparison to the work that has already been done in terms of cancer, the field and study of cardiovascular epigenetics is still in its infancy. But, nevertheless some understanding of the impact of epigenetics on atherosclerosis and coronary artery disease has been achieved. The interplay between epigenetics and heart disease however is potentially huge because of two factors considered important in the etiology of heart disease; that being, nutritional and environmental components. Both, as already noted, are considered important in a very complex etiologic picture especially with the documented importance that risk factor association plays in the worldwide incidence of coronary disease. The latter in particular is unlikely to be purely genomic and more than likely reflects "nongenetic mechanisms of gene expression" that are regulated by environmental and particularly nutritional factors. According to Gertrud Lund and Silvio Zaina, "In principle, epigenetics provides unique conceptual and experimental instruments to understand how…CVD risk factors act at the molecular level to

[91]Santiago Ropero and Manuel Esteller. "Epigenetics and Cancer: DNA Methylation." In Manuel Esteller, ed. *Epigenetics in Biology and Medicine.* Boca Raton: CRC Press (2009): 3-13.

change gene expression patterns." There exists already very strong evidence for an "epigenetic component in the etiology of atherosclerosis and CVD."[92]

It was P. E. Newman, in 1999, who was the first to propose an epigenetic basis for atherosclerosis arguing that deficiency of folate, vitamin B6 and vitamin B12 result in DNA hypomethylation and lead to atherosclerosis.[93] Four years later, in animal studies, it was dramatically demonstrated that supplementation with folate can control DNA methylation and gene expression even transgenerationally. Although, subsequent clinical studies of the effect of folate and B vitamin supplementation on atherosclerosis failed to give consistent results, the finding "that DNA hypomethylation is associated with the natural history of atherosclerosis has been confirmed experimentally by a number of studies." In advanced atherosclerotic lesions in both humans and a number of animal models, global DNA hypomethylation has been observed in vascular tissues as well as blood cells including mononuclear cells. Additionally, there are strong data supporting the notion that atherogenic lipids in individuals with hyperlipidemic profiles result in direct effects on the epigenome causing aberrant DNA methylation.[94] So risk factors for coronary disease, including hyperlipidemia, obesity, and smoking, may actually mediate their effect epigenetically resulting in aberrant and pathologic effects on the epigenome.

In a study conducted by British Geneticist, Marcus Pembrey and colleagues, men who smoked before puberty were discovered to have sons who by the age of nine were found to be significantly more obese than normal. The correlation was only noted in male offspring of

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[92] Gertrud Lund and Silvio Zaina. "Epigenetics and Cardiovascular Disease." In Manel Esteller, ed. *Epigenetics in Biology and Medicine*. Boca Raton: CRC Press (2009): 207-208.
[93] P.E. Newman. "Can reduced folic acid and vitamin B12 levels cause deficient DNA methylation producing mutations which initiate atherosclerosis? *Med. Hypotheses* 53 (1999): 421–424.
[94]Silvio Zaina, Marie Wickstrom Lindholm, and Gertrud Lund. "Nutrition and Aberrant DNA Methylation Patterns in Atherosclerosis: More than Just Hyperhomocysteinemia?" *J. Nutr.* 135 (2005): 5-8.

fathers with this particular habit. For this reason researchers believe that epigenetic effects from this environmental impact are passed on through the Y chromosome and in this manner transgenerational transmission of a risk factor for coronary disease appears to be implicated.[95] Findings of this nature may in some small way help explain the association of heart disease between fathers and their at risk sons and the age long notion that family history plays a role in the development of coronary artery disease.

More than likely epigenetics functions as a mediator of risk for coronary artery disease rather than an explanation for the disease itself. It is likely that environmental factors impact the epigenome in ways that increase the risk of developing atherosclerosis and consequent coronary artery disease. Epigenetic changes appear to be transgenerational in nature and may help to explain what has to date been considered unclear and that is the predisposition to CHD within the family structure, namely why the sons of fathers with the disease appear to be at increased risk for its development. It may also help explain the potential link between infection, influenza and the historical course over time of CHD and its mortality. Influenza's role, if there truly is one for CHD, more than likely would have been mediated epigenetically.

The knowledge of epigenetics has truly revolutionized the way we look at inheritance, biology, health and disease. No longer can one look only to the genome and an individual's DNA to give answers about heredity and why certain diseases develop the way they do. The connection between epigenetics and risk factors for coronary disease I believe will result in a further substantiation of the importance of risk in the development of heart disease. In an era when chronic diseases predominate, a multifactorial approach to illness needs to be considered

[95] Marcus E. Pembrey, Lars Olov Bygren, et al. "Sex-specific, male-line transgenerational responses in humans." *Eur J Hum Genet* 14 (2006): 159-166.

and invoked in order to understand and interpret illness. The notion of specific causation appears to fall by the wayside and factors that both directly and molecularly, on a biologic and on an epigenetic basis, impact health must be considered. To study chronic illness, and specifically cardiovascular disease without a knowledge of genetics would be shocking but without a basic epistemology of epigenetics, at the present time, "unthinkable." Considering the present state of knowledge, it is altogether likely that epigenetics plays a role in the epidemic of coronary artery disease that began in the early 20th century and also may provide an explanation for the precipitous decline in mortality that was seen in the late 1960s.

Evolution and Vulnerability to Disease

> **The theory of evolution by natural selection provides a framework for understanding why people get sick, the manifestations of disease, the effects of our interventions on the evolution of disease, and the relationships between population health and individual health.[96]**

Finally, we need to consider evolution and the vulnerability to disease as an explanation, if only theoretical, for the decline in coronary artery disease mortality. Robert Perlman and others have written extensively on the role of natural selection and the evolution of disease resistance. We have already touched on this issue in the earlier argument about the influence of the Influenza epidemic on coronary artery disease and its mortality. Diseases that result in premature death or reduced fertility will over time reduce prevalence by means of natural selection. But the majority of chronic diseases, including coronary artery disease, do not affect all members of the population nor are those affected impacted to the same degree. Variation in both resistance and response to disease exists throughout the population. A proportion of this

[96] Robert L. Perlman. "Evolutionary Biology: A Basic Science for Medicine in the 21st Century." *Perspec Bio and Med* 54 (2011): 86.

variation can be attributed to some form of heritable (genetic or epigenetic) difference in the population. Since coronary disease is known to impact a significant proportion of individuals who remain fertile, especially males, "individuals who survive and remain fertile in the face of a disease will on average produce and raise more children than will people who die from or become infertile as a result of the disease." In a disease of epidemic proportions like CHD that "spreads through a population, natural selection will increase the frequency of alleles that are associated with resistance to it" leading to a larger proportion of the population that is resistant and therefore an expected eventual decline in mortality from the disease.[97]

Whether the history of CHD is long enough to result in evolutionary change in the time period under consideration is certainly debatable. If we accept the notion that coronary artery disease is a disease whose history is relatively short, rather than one that has existed for a millennium or more, it may be hard to attach an evolutionary explanation to the decline in mortality that began in 1968. After all, natural selection on its own is a slow process and "even when selection is intense, allele frequencies in populations change only gradually over many generations." Environmental change in a given population is much more rapid than genetic change but not necessarily epigenetic modification.

It is rather more likely that evolutionary biology could explain the rather remarkable emergence of coronary artery disease in the 20th century than its sudden decline in mortality. Evolutionary change can come about by other mechanisms than natural selection. Perlman explains:

> New alleles can enter populations either by mutation or by gene flow from other populations of the same species. Once these alleles enter a population, their fate is determined by genetic drift (changes in allele frequency due to random sampling in the transmission of alleles from

[97] Robert L. Perlman. *Evolution and Medicine*. Oxford: Oxford University Press (2013): 11.

> one generation to the next) as well as by natural selection. These other evolutionary processes may counteract the effects of selection by introducing or increasing the frequency of alleles associated with susceptibility to disease.

However, given the importance of environment, "disease may result…from a mismatch between the environment in which we now live and the genes we have inherited from our evolutionary ancestors, genes that enabled these ancestors to survive and reproduce in the various environments in which they lived." Consider the example of the increase in prevalence of both obesity and hypertension. At one time the genetic material that might have enhanced the fitness of past generations may now make that population at greater risk for disease.[98]

When invoking theories of evolution in disease progression, it is hard not to think of Malthus' original contention that without regard to natural selection, survival and the ability to reproduce may in large part be constrained by the limits of environmental resources. In this respect, McKeown would agree that nutritional resources "have played a major role in [disease] evolution, and nutritional deficiencies are still important causes of disease and death," the improvements in which have resulted in an overall decline in disease mortality. Evolution provides an understanding for disease susceptibility and traditional biomedicine an understanding of both "etiology and pathogenesis." As Perlman notes, a combining of the "two perspectives on health and disease, the ultimate and the proximate causes of disease, will help us understand why we get sick as well as how we get sick, and will provide insights into interventions that might reduce the burden of disease."[99]

The Cholesterol Hypothesis and multifactorial risk

Despite all the theories and evidence presented so far in this chapter, regarding determinants of disease, multifactorial risk and the cholesterol hypothesis remain preeminent in

[98] Ibid, 11-12.
[99] Ibid, 12.

terms of the development of CHD. Much debate, over the past 60 years, has revolved around the validity of this hypothesis but substantial proof now exists for its role.[100] The "heart-diet/cholesterol hypothesis" has been extensively tested by randomized clinical trials and has been supported by evidence. Skeptics have largely disappeared over the course of time. Although the role of cholesterol has been mentioned in this chapter, a detailed discussion of the importance of cholesterol in the development of CHD will appear in chapter 4, where the role of risk and prevention are discussed.

Conclusion: Multiple determinants and theories abound

This discussion should make clear that multiple factors determine the nature and course of disease. Unlike infectious diseases where a specific etiology exists, as in tuberculosis, AIDS, malaria, and others, in diseases with no specific single identifiable etiology, where multiple factors determine the develop of the disease, as in coronary artery disease, the course and outcome of the disease can be quite variable. Like infectious diseases, however, the host appears to play a significant role in the morbidity and mortality of the disease and this is governed by the host and a multitude of factors impacting that host. From the evidence presented in this chapter there is ample reason to believe that the mortality of disease may indeed be impacted by factors totally outside the actual disease itself; factors that impact health in general, including socioeconomic status, improved hygiene, improved nutrition and improvements in other diseases that may have a shared morbidity and mortality. As suggested in this chapter by McKeown and others, the impact of medical therapy, and disease prevention, may play only a small role in the improving mortality of a disease, the greater impact being from a shared improvement in health and mortality overall. The remainder of this dissertation will

[100] Daniel Steinberg. *The Cholesterol Wars: The Skeptics vs. the Preponderance of Evidence.* San Diego: Academic Press, 2007.

look at the historical evidence for a decline in coronary artery disease mortality, and the forces at play impacting the disease, at the time. In it, I will attempt to discern what factors were and were not important and contributory to that decline.

Chapter 4: The Role of Prevention: Myth of Hygieia

> **For worshippers of Hygieia, health is the natural order of things, a positive attribute to which men are entitled if they govern their lives wisely. According to them, the most important function of medicine is to discover and teach the natural laws which will ensure a man a healthy mind in a healthy body.[1]**
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> **The Physician's function is fast becoming social and preventive, rather than individual and curative. Upon him society relies to ascertain, and through measures essentially educational to enforce, the conditions that prevent disease and make positively for physical and moral well-being. [2]**

Introduction

Did prevention influence the initial decline in coronary artery mortality? Many have claimed a role of some degree all along for prevention in reducing mortality. According to Michael Stern, who analyzed the decline between 1968 and 1976, "favorable changes in risk factors [during the period], while they appear to explain a portion of the decline in ischemic heart disease mortality, probably do not account for all of it."[3] Robert I. Levy, former director of NHLBI, argues that "it is not at all clear that primary prevention is the major cause of the decline."[4] The notion that prevention can impact both the morbidity of disease and mortality is an ancient one ascribed to by the worshippers of Hygieia. In diseases with clear cut etiologies the process of prevention is one that can often be accomplished relatively easily. One needs only to look at diseases like Rheumatic Heart Disease, Syphilis or Tuberculosis to see effective prevention at work in impacting mortality. But prevention is never a straight forward process when the etiology is either unclear or appears to be of a multifactorial nature. Coronary artery disease is indeed a disease of this kind where the risk factors are multiple and the exact cause

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[1] Rene Dubos. *Mirage of Health.* London: George Allen and Unwin (1960): 109.
[2] Abraham Flexner. *Medical education in the United States and Canada: A report to the Carnegie Foundation for the Advancement of Teaching.* Bulletin No. 4 Boston: D. B. Updyke, Merrymount Press (1910): 26
[3] Michael P. Stern. "The Recent Decline in Ischemic Heart Disease Mortality." *Ann Int Med* 91 (1979): 635.
[4] Robert I. Levy. "Declining mortality in coronary heart disease." *Arterioscler Throm Vasc Biol* 1 (1981): 323.

not entirely known. In this chapter, I will look at the major known risks for coronary artery disease and with the use of statistics, archives, epidemiology and oral history determine the impact that prevention could have possibly had on the decline in mortality in 1968. The scrutiny of causative factors for this disease began early, as already alluded to in previous chapters, even before a full description of the disease and its nature were known. I begin with historical considerations in the discovery of coronary artery disease risk.

Shortly after the end of World War I and not long after James Herrick's description of coronary thrombosis, Sir James Mackenzie, considered one of the great pioneers in cardiology, planned and embarked on a study of heart disease in the population of St. Andrews, Scotland. His work at the St. Andrews Institute of Clinical Research was published in 1926, one year after his own death from myocardial infarction.[5] His goal to carry on a long term longitudinal study of heart disease in a defined population was never completed. It would be almost 30 years before an attempt again was made. Because of the expense for such a study and the need for it to be carried out over an extended period of time it appeared beyond the capacity of an individual investigator to complete.

For this reason, in 1947, the United States Public Health Service, because of a "growing interest in chronic diseases," particularly ischemic heart disease, in conjunction with local and state health agencies, began plans for an epidemiologically based long term longitudinal study of coronary and cardiovascular diseases. Because so little was known of the epidemiology of atherosclerotic and hypertensive cardiovascular diseases and they seemed the most important

[5] Sir James Mackenzie. *The Basis of Vital Activity: Being a Review of Five Years Work at the St. Andrews Institute for Clinical Research.* London: Faber and Gwyer, 1926.

at the time to study, given their epidemic nature and disproportionate mortality, the focus of the study which would be located in the town of Framingham, Massachusetts was on them.[6]

By the middle of the 20th century, "modern cardiology allowed [for the] diagnosis of heart attack with survival and the ability to count cases." The notion that vulnerability existed in patients was considered by clinicians but there was really not good evidence about the traits of vulnerability. Paul Dudley White's first textbook on cardiology, published in 1941, only mentioned heart disease prevention in terms of rheumatic fever prophylaxis. By 1946, White "recognized coronary disease as epidemic and had the idea that characteristics of vulnerability would be most clearly expressed in the youngest who experienced a heart attack." His early case–control study of 100 survivors of myocardial infarction, under the age of 40, 97% of which were men, matched to controls, failed to show any differences in risk. But when he converted the study into a cohort study which went on for 25 years, he "produced a substantial volume that included the first multivariate analysis of risk factors, using discriminant function analysis."[7] So was the notion of prevention and risk factors for coronary artery disease born and with it emerged a new field of study, namely cardiovascular epidemiology.

Epidemiology today is taken for granted as a field of study enabling researchers to explore relationships, both in health and disease that cannot be observed by more direct means. Originating as a field of investigation in the mid-19th century with the work of Peter Ludwig Panum, who was commissioned to investigate a measles epidemic in the Faroe Islands, and John Snow, who used epidemiology to sort out a cholera outbreak in London about the same time, it had already been used with success in this country in sorting out nutritional deficiencies like

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[6] Thomas R. Dawber, Gilcin F. Meadors and Felix E. Moore, Jr. "Epidemiological Approaches to Heart Disease: The Framingham Study." *Am J Pub Heal* 41 (1951): 279-286.
[7] Henry Blackburn. "Address to the AHA Council on Epidemiology's 50th Anniversary." American Heart Association Meeting, San Francisco, California. March 19, 2014.

beriberi, pellagra and scurvy. Epidemiologic studies were also instrumental in defining rheumatic disease and the relationship of streptococcal infection to subsequent rheumatic activity, enabling control measures to be put into place that have helped in the management of the disease.[8]

With the expansion of scientific and medical research that followed World War II, initiated by President Roosevelt, and put into practice under Truman and Eisenhower,[9] funding for medical research followed and with it multiple studies to show the impact of risk factors on the course of coronary artery disease. The most comprehensive and well known of these was "The Framingham Study." Deemed the most successful epidemiological study of its kind, it continues to this date. It is from this study that much of what we know about the natural history of coronary artery disease, its risks and prevention, over time, have been documented. For this reason it becomes a natural departure point to talk about risk factors and the role of prevention in the decline of coronary artery disease mortality.

The Framingham Study

Shortly after plans for the study were drawn up, Thomas R. Dawber and his associates from the newly formed National Heart Institute presented their anticipated approach to Framingham at the 78th annual meeting of the American Public Health Association in 1950. They wrote:

> Of the epidemiology of hypertensive or atherosclerotic cardiovascular disease almost nothing is known, although these two account for the great bulk of deaths from cardiovascular disease. The scanty epidemiological knowledge of these diseases which does exist is based either on the study of mortality statistics, which in the investigation of long-term diseases are

[8] Thomas R. Dawber, Gilcin F. Meadors and Felix E. Moore, Jr. "Epidemiological Approaches to Heart Disease: The Framingham Study." 279.

[9] Vannevar Bush. American engineer and director of the US Office of Scientific Research and Development during World War II, under directive from FDR wrote the *Endless Frontier* in 1945 calling for a post war expansion of government support for science and the development of the National Science Foundation. It was the inspiration for government support of research in medicine.

> often not very revealing, or on clinical studies, which have the disadvantage from the epidemiologist's point of view of being based on the study of those who already have the disease. Clearly, what is required is the epidemiological study of these diseases based on populations of normal composition, including both the sick and the well as they are found in the community.[10]

Unlike in other epidemiologic studies where a single cause existed (infectious diseases for the most part which formed a major core of epidemiology to date), it was assumed that in the case of atherosclerotic disease there was no single cause and that the etiology and pathogenesis was the result of multiple factors and etiologies working in concert. It was also further acknowledged "that, for the most part, specific and unambiguous tests for precise diagnosis of the early stages of these diseases are lacking." Because of these two factors a methodology was constructed such that "a group of randomly selected persons in the ages where arteriosclerotic and hypertensive cardiovascular disease are known to develop is selected for study. Based on as complete a clinical examination as feasible, there are selected out of this initial group those persons who are free of definite signs of these diseases. These persons will be termed the normal, and they will be observed over a period of years until a sizeable number are found to have acquired the diseases. At that time a search is made for the factors which influenced the development of disease in the one group and not the other."[11]

The town of Framingham was chosen, for a number of reasons, for the site of the heart study. It was felt that a town of 25,000 to 50,000 could supply the number of needed individuals in the limited age group, approximately 6,000. In addition, it provided "the type of community approach required to secure full cooperation and coverage…that within-community variance is very much greater than between-community variance, and a wide range of type-situations influencing development of these diseases may be found in any community."

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[10] Thomas R. Dawber, Gilcin F. Meadors and Felix E. Moore, Jr. "Epidemiological Approaches to Heart Disease: The Framingham Study." 280

[11] Ibid.

Furthermore, the U.S. Public Health Service had the full cooperation of the Massachusetts State Health Commissioner for setting up the study in his state. And finally, Framingham had previously been the site for another community epidemiologic study on tuberculosis that had continued with success for six years. As a community in New England with a town meeting form of government, it was felt that Framingham also had a necessary sensitivity and sensibility to a "group approach to their problems," enhancing the public health nature of the endeavor. In addition, the program received the active support of the local medical community which insured greater compliance and cooperation with the project at hand. As a community, Framingham "accepted the program as its responsibility, and [recognized] that when people participate they make a real contribution to medical research." A medical advisory committee made up of 11 physicians from the Boston area who were experts in cardiology and also public health was formed. The committee for the most part determined which factors, in terms of etiology, would be looked at and what studies in terms of examination and laboratories would be performed. After securing medical and laboratory information on each individual included in the study the cohort of participants was divided into two groups. The first had definite signs of cardiovascular disease and the second had none. The latter termed "normal" was the focus of the study. It was anticipated that they would be followed with biennial examinations for up to 20 years to discern the development of heart disease and the factors that contributed to it. Initial examinations were scheduled for completion in 1952. In this way "the more truly epidemiological parts of the analysis [were] essentially retrospective and must wait the passage of time." Over time, it would then "be possible to study the differences, as of the time of the initial examination, between those who remained essentially normal, and those who subsequently became abnormal (or diseases)." It was anticipated that the impact of various factors on disease development should be made apparent in this retrospective view.

Furthermore, for the group that developed cardiovascular disease over the time period of the study, "the rate of progression of disease can be measured, and from the entire group there will be data which will yield estimates of incidence of atherosclerotic and hypertensive cardiovascular disease for a more representative population group than has hitherto been studied."[12]

Four years after the initiation of the study and the completion of initial examinations and follow-up examination the following information in terms of risk factors for atherosclerotic disease (ASHD) became clear: "(1) It is clear that HBP is significantly associated with the incidence of ASHD ($x^2=10.2$, $n=4$, $p=0.04$). (2) The data…support the hypothesis that obesity is related to risk of coronary attack ($x^2=12.8$, $n=3$, $p=0.005$). (3) There is an increased risk of ASHD in persons with elevated cholesterol levels ($x^2=16.2$, $n=2$, $p<0.001$)." (4) The three attributes listed above "make independent but varying contributions to risk, and the joint elevation of two or three is associated with a greatly increased risk." "(5) Very little evidence [exists] in these data to suggest a relationship of socioeconomic status with the appearance of ASHD. (6) These data do suggest that the association of ASHD with smoking is not as strong as that shown with elevated blood pressure, relative weight, and cholesterol." They concluded from this initial four year follow-up in the Framingham Study, published in 1957, that hypertension, overweight and hypercholesterolemia "are frequently present in advance of the development of definite ASHD." They each appear to have an association with the development of coronary artery disease and in "the group of individuals in which all three are coincidentally high show great increases of incidence of ASHD." In this small cohort that looked only at men 45-62 years of age, because

[12] Ibid, 281-286.

that was the only group with sufficient data in this early reporting, "neither smoking habits nor educational background were notably associated with the development of new ASHD."[13]

In 1961, the Framingham group, which now included William B. Kannel, presented their data to the 42nd Annual Session of the American College of Physicians. It represented the six-year follow-up experience of factors of risk in the development of coronary heart disease. Unlike the report at four years this one included both men and women in the age group under observation. They reported that "one hundred and eighty-six men and women aged 30 to 59 years on entry into the study developed coronary heart disease in the six years of observation, representing an over-all six years' incidence of 36.3 per thousand." The report confirmed "the well-recognized influence of hypertension and hypercholesterolemia on the development of coronary heart disease." Their experience documented "that these factors precede the development of overt CHD and are associated with increased risk of its development." The risk factor of hypertension in this study was "associated with a 2.6 fold increase in risk in men 40 to 59 years of age and six fold increase in women the same age." According to the results it represented a greater risk in women than in men. Conversely, the study demonstrated that an elevation in "serum cholesterol levels contributed only slightly to increased risk among women as compared with men." An elevation in serum cholesterol of 245 mg per 100 ml or greater "was associated with more than a threefold increase in risk among men aged 40 to 59 years." No mention of smoking or weight as risk factors were included in this report but a new association with left ventricular hypertrophy was made. The results of the six year follow-up

[13] Thomas R. Dawber, Felix E. Moore, and George V. Mann. "II. Coronary Heart Disease in the Framingham Study." *Am J Pub Heal* 47 (1957): 13-23.

experience demonstrated "that the electrocardiographic pattern of left ventricular hypertrophy [was] also associated with increased risk of developing CHD."[14]

Although epidemiological studies formed a core area for research into risk factor analysis and prevention, and continues to this date in helping to define this area, thanks to the then NIH director James Watt, it was not the only form of research into the potential role of prevention. Knowledge about the pathophysiology of the disease also emerged, through basic bench research which substantiated the importance of lipid metabolism in the development of atherosclerosis. So, by the early 1960s, the evidence that emerged from the first reports of the Framingham study, and other epidemiological studies, as well as research done in the laboratory helped to put into clear view risk factors associated with the development of coronary artery disease. As a result, individuals including Paul White, at Harvard, Ancel Keys, at the University of Minnesota, and Jeremiah Stamler at Northwestern began to clamor for programs of prevention for the benefit of public health. But was the knowledge generated through these studies, and its dissemination to the medical community and general public, at the time, enough to influence the early decline of coronary artery disease mortality? David Jones and Jeremy Greene have shown rather convincingly a role for prevention and risk factor mitigation in the mortality of the disease beginning in 1974.[15] The task here is to determine whether measures, recommendations and guidelines were in place early enough to make a significant impact on disease mortality by 1968. This chapter will examine that question, through statistical analysis of the data, a review of relevant literature, and the use of oral history from clinicians and social scientists working in the field at the time.

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[14] William B. Kannel, Thomas R. Dawber, et al. "Factors of Risk in the Development of Coronary Heart Disease – Six-Year Follow-up Experience." *Ann Int Med* 55 (1961): 33-50.

[15] David S. Jones and Jeremy A. Greene. "The Contributions of Prevention and Treatment to the Decline in Cardiovascular Mortality: Lessons From A Forty-Year Debate." *Health Affairs* 31 (2012): 2250-2258.

Defining the Risks

When a man dies, he does not just die of the disease he has; he dies of his whole life.[16]

There is no one alive and more involved, with more experience in the field of coronary artery disease risk factors and prevention, than Jeremiah Stamler. In 1963 he, together with Associated Press staff writer Alton Blakeslee wrote and published what became a widely popular trade book, entitled *Your Heart has 9 Lives.* Paul Dudley White applauded it as "the best book of its kind," praising the message of the authors that "it is the establishment of unhealthy habits of over nutrition, physical lethargy, and excessive cigarette smoking in the twenties that sets the stage for the prevalent and crippling or fatal atherosclerotic diseases of heart and brain."[17] The information was not new, still quite contested and debated by many in the medical community, but the message to the American public was novel and somewhat earth-shattering. A scientist had joined with a medical journalist to spread the word about unhealthy habits that impact the heart and mortality. Knowledge about cholesterol and atherosclerosis was known at that point for almost 60 years, but general acceptance and the practice of risk factor prevention was largely not followed until the notion that you could do something about the development of heart disease became generally known in the early 1960s with the publication of this book and others. The 1960s was a period of rapid enlightenment in terms of the relative risks of unhealthy behavior on the heart. Ancel Keys published ground breaking work on the impact of weight (specifically he looked at BMI: Body mass index) on heart disease but ultimately declared that obesity was "ugly but does not itself cause CHD."[18]

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[16] Attributed to Charles Pierre Peguy

[17] Paul Dudley White. "Introduction." In Alton Blakeslee and Jeremiah Stamler. *Your Heart Has 9 Lives.* New York: Prentice Hall (1963): xix-xx.

[18] "Diet and health." *Time Magazine* 77 (1961).

Blakeslee and Stamler in their book variously called the risk factors for coronary disease, "coronary conspirators" and the "deadly syndicate." The "chief suspects in this deadly syndicate," they declared, numbered nine and were well known; "no major newcomer has been uncovered in the last few years of intensive research."[19] What are these nine risk factors, what do we know about them and have they changed in the period under question? The "roll call" of risk factors to which they allude as causing myocardial infarction have indeed remained stable over time and include elevated serum cholesterol level, high blood pressure, overweight, diabetes, over-nutrition, little exercise or physical activity, excessive smoking, excessive stress and tension, and a hereditary predisposition. The extent to which they each contribute to risk varies and at this time it is worth reviewing the major risks for the evidence that exists concerning their contribution to the development of coronary artery disease.[20]

The early Framingham data, as has already been stated, identified hypertension and elevations in serum lipids as two of the major risk factors for the development of atherosclerotic heart disease. Although smoking was not specifically or officially identified in early Framingham reports (those prior to 1968) it is generally considered a major risk factor for a number of diseases including coronary artery disease. Writes Nemat O. Borhani, "hypertension is the most powerful of all coronary heart disease risk factors, especially in association with other risk factors such as cigarette smoking and elevated cholesterol. The interaction among those three risk factors, alone or in the presence of other abnormalities, greatly influences the force of mortality from coronary heart disease and from all causes."[21] My discussion of risk factors for coronary artery disease and the mitigation of those risks will therefore be largely limited to a

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[19] Alton Blakeslee and Jeremiah Stamler. *Your Heart Has 9 Lives*. New York: Pocket Books (1966): 3
[20] Ibid.
[21] Nemat O. Borhani. "Mortality Trend in Hypertension, United States, 1950-1976," In Richard J. Havlik and Manning Feinleib, ed. *Proceedings of the Conference on the Decline in Coronary Heart Disease Mortality.* Bethesda: NIH Publication (1979): 218.

discussion of the three major risks: hypertension, cholesterol and smoking. Although EKG evidence of left ventricular hypertrophy was identified by Framingham as a risk factor, it represents more of a "sign" than potentially manageable and mitigatable risk so I will not address it here. In terms of the other risks, I will touch only briefly upon the evidence that they may have also contributed to the epidemic of coronary heart disease and its mortality.

Hypertension

In terms of blood pressure, Blakeslee and Stamler considered a systolic of 120 or below to be significant in terms of protection from this risk factor, noting that "persons with a systolic pressure below 120 had one-*fourth* the rate of coronary disease expected for people of their age and sex." At the upper extreme they found that "those with a systolic pressure of 180 or higher developed *twice* the expected amount of coronary disease."[22] They note anecdotally, as well, the absolute mortality of hypertension alone:

> *The doctor removed the blood pressure cuff, knowing there was nothing more he could do except hope. His patient's galloping blood pressure had risen again within a month. Very likely he would die within a year. The time – 1949.*[23]

The passage is important because it points out that so little was available for controlling hypertension in the period of the 1940s and for approximately the ten years that would follow. Medical textbooks of the time discussed the care and treatment of hypertension but the absence of truly effective therapy resulted in suggestions that in hindsight could only be considered primitive. One textbook, published in 1941, advocated that "treatment in the beginning should be directed toward the establishment of a sane attitude of the patient toward his condition. An optimistic viewpoint should be presented." Treatment consisted of prevention "primarily in protection against or avoidance of those conditions which are conducive to or

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[22] Alton Blakeslee and Jeremiah Stamler. *Your Heart Has 9 Lives.* 54
[23] Ibid,141.

aggravate blood pressure rises." Included in this precaution were "nervous shocks, overactivity, especially high pressure business and competitive athletics, overindulgence in stimulants, overeating, and consequent overweight." "Moderation in all things" was advocated and "use of coffee, tobacco, and alcohol should be interdicted. " The author notes that when the elevation in blood pressure is continuous and persistent, rather than occurring in paroxysms, prophylactic measures must be prescribed, including "rest and relaxation…the best therapeutic measures" and the absolute abstention from "stimulants." Sedatives were advocated, in the form of chloral hydrate, together with early retirement in the evening as "restful sleep is desired" which should "accomplish relaxation of the vascular bed under most conditions." In terms of diet, "moderate restrictions" were advocated but "sharp restrictions of the protein intake and of salt are hardly justifiable." In addition as "normal intestinal function as possible should be established without the use of cathartics." Hot baths with temperatures up to 102 degrees Fahrenheit were advocated "whenever the patient feels under tension and before retiring at night." In terms of drugs, for the treatment of hypertension, beyond small doses of chloral hydrate or phenobarbital, little existed. Reference was made to the use of potassium iodide "for its mild vasodilating effect" and theophylline for the same reason. Stimulation of the thyroid with small doses of iodide or thyroid extract was also mentioned but noted to bring on nervousness and therefore not felt to be of tremendous therapeutic benefit for patients with hypertension. All other potential drug therapies were felt to be fraught with severe side effects. Surgery was a consideration for treatment of severe hypertension at the time. Early in the 20th century "heroic surgical procedures" including "removal of the sympathetic nervous control of vessels, such as laminectomy and resection of the anterior spinal motor nerve roots from the

sixth thoracic to the second lumbar on both sides, [had] been done and attended with some success" and "resection of the splanchnic nerves has been advocated by some surgeons."[24]

Another textbook at the time advocated the use of denial, writing the following as its recommendation for dealing with patients who have elevation of their blood pressure:

> Many patients with hypertension have no complaints as long as they are unaware of the condition. As soon as they learn about their high blood pressure they become the prey of numerous troubles. It is therefore unwise to speak of the high pressure to the patients, particularly if their habits of life are reasonable and do not require essential modification. If the patient already knows about his condition, it is advisable to minimize the significance of hypertension. The patient should not be allowed to focus his interest on his blood pressure, and everything should be avoided that might draw attention to it.

In terms of drug therapy, this author and respected cardiologist noted that "the various drugs which are praised as cures for high blood pressure either have no effect or cause but a temporary lowering of the arterial pressure." He did agree that "of all the drugs used in hypertension, *chloral hydrate* generally proves the most beneficial" in addition to a few other sedatives. He mentioned the use of potassium thiocyanate as one that "has been repeatedly advocated to reduce the blood pressure" or at least help with some of the symptoms of hypertension but noted the need for periodic blood testing with its use and the possibility of side effects and "serious toxic effects" should the dose or level become too high. He did not encourage the previous practice of phlebotomy as a treatment for hypertension and felt that surgical therapy was often short lived, of limited benefit long term and "still in an experimental stage."[25]

The great Samuel A. Levine, early 20th century cardiologist-in-chief of the PBBH and professor at Harvard Medical School, in his book, *Clinical Heart Disease,* published in 1945 had

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[24] George R. Herrmann. *Synopsis of Diseases of the Heart and Arteries.* St. Louis: Mosby (1941): 163-166.
[25] William Dressler. *Clinical Cardiology.* New York: Paul B. Hoeber (1942): 464-468.

very little to say about the care and treatment of hypertension, noting instead that "the prognosis in hypertension in general is variable." He made no mention of drug therapy stating instead that "many patients live for ten to twenty years or more with a constantly elevated blood pressure. Once either angina pectoris or congestive heart failure develops the outlook changes. But even then some carry on for years." He believed it was difficult to predict the impact or course of hypertension on the heart and that it was too early to tell if surgical treatment was advantageous, although he recognized that the operation of Smithwick (dorso-lubar sympathectomy) "appears to have certain advantages and [at the time had] gained some support."[26]

The first truly effective anti-hypertensive medications for essential hypertension came into existence in the period between 1953 and 1962. Norman Kaplan's 4th edition of *Clinical Hypertension* outlines the progress made in the development and utilization of anti-hypertensive medications. The first pharmacologic therapy for hypertension was thiocyanate which was introduced in 1903 and in use from 1925 to 1945. It was initially studied pharmacologically by Claude Bernard in 1857 but it was the German Wolfgang Pauli who was the first to use it as an antihypertensive in medical practice. As an anti-hypertensive thiocyanate had the ability to reduce systolic blood pressure by 60 mm and diastolic by 40 mm and was also effective for headaches. Its use was also felt to produce a general feeling of well-being. But its toxic effects became evident by the 1920s. In 1929 "the Council on Pharmacy and Chemistry of the American Medical Association refused to accept the elixir and tablets of Potassium Thiocyanate for inclusion in the 'New and Non-official Remedies,' because of their toxic qualities." In a study of 74 patients treated with thiocyanate, mostly for essential hypertension, thirteen showed toxic symptoms, six developed a toxic psychosis and two died.

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[26] Samuel A. Levine. *Clinical Heart Disease.* Philadelphia: Saunders (1945):135-136.

The drug also resulted in three cases of motor aphasia in this study. Numerous other case studies reported toxic and fatal complications from the use of this drug.[27] By 1945 its use in the treatment of essential hypertension and other maladies was discontinued. Surgical sympathectomy was first introduced in 1925 and was used during the period 1935-1960. According to Kaplan, "the basic problem with sympathectomies was that it relieved the hypertension but you could not stand up."[28] Vertrum alkaloids and ganglionic blocking drugs were introduced in the 1940s but by the early 50s, the use of both had been discontinued. In 1949, hydralazine and Rauwolfia were both introduced and they have remained in use since 1953. In the late 1950s and 60s a number of better tolerated medications for the treatment of hypertension came into use as well, including thiazide diuretics, spironolactone, guanethidine and alpha-methyldopa. According to Kaplan, "by the mid-60s we had combination of those … and the most popular medication was called serapas which was reserpine, hydralazine and hydrochlorthiazide."[29]

Harrison's 5th edition of *Principles of Internal Medicine,* published in 1966, documents that skepticism still existed at the time for the need for treating hypertension with medication, but notes evidence of "well-documented cases in which the use of depressor drugs has aborted or reversed progressive changes of malignant hypertension." According to the textbook, guanethidine, put into use in 1960, represented "a significant advance in therapy." It worked by blocking "the peripheral release of catecholamines from the postganglionic sympathetic nerve fibers," but unfortunately "left unopposed parasympathetic action," with predictable side effects. Other agents at the time worked in the same manner but guanethidine appeared to be

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[27] Warren F. Gorman, Emanuel Messinger and Morris Herman. "Toxicity of Thiocyanates used in treatment of Hypertension." *Ann Int Med* 30 (1949): 1054-1059.
[28] Interview of Dr. Norman Kaplan in office at University of Texas, Southwestern, Dallas, Texas, November 16, 2012.
[29] Norman M. Kaplan. *Clinical Hypertension.* 4th edition. Baltimore: Williams and Wilkins (1986): 186.

superior because of its rather "gradual and prolonged effect." It was however not without other significant side effects, among which was "impairment of ejaculation." Impotence, according to Harrison's, was also a result of the use of a number of other antihypertensives available at the time.[30] These and other side effects of pharmacologic treatment limited the use and acceptance of anti-hypertensive medications in the 1960s. But according to Blakeslee and Stamler, the early decades of treatment and management of hypertension saw some early and important progress with "deaths of middle-aged American men and women due to high blood pressure [declining] 44 per cent."[31] As they indicate however most hypertension is asymptomatic and the figures quoted reflect only those who came to light because of their hypertension. Mild essential hypertension often went unnoticed and if detected mostly untreated.

In my interview with Kaplan, he noted that the first real data, according to NHANES,[32] for hypertension came in about 1972 and it showed "that only 12% of patients with hypertension were considered to be adequately controlled." It was the "first of the NHANES data" on hypertension, according to Kaplan, "and when you look at what we have done in the ensuing years it is now 47%. We still are not identifying and treating the majority of people with hypertension…but for the sake of being under some kind of treatment and thereby presumably lowering risk we are now at 80%." But, in terms of "adequate control, usually defined as 140/90, the number is still 47%." So right now "80% are treated and 47% controlled."[33]

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[30] T.R. Harrison, et. al, ed. *Principles of Internal Medicine.* 5th Edition. New York: McGraw-Hill (1966):712-715

[31] Alton Blakeslee and Jeremiah Stamler. *Your Heart Has 9 Lives.* 141

[32] NHANES stands for the National Health and Nutrition Examination Survey – a program of epidemiological studies designed to assess the health and nutritional status of adults and children in the United States. It began in the early 1960s and has been conducted since as a series of surveys focusing on different population groups and health topics.

[33] Interview of Dr. Norman Kaplan in office at University of Texas, Southwestern, Dallas, Texas, November 16, 2012.

Kaplan returned from his training and work at the NIH to his hometown of Dallas and the University of Texas, Southwestern in 1961, committed to working on hypertension. A trained and board certified endocrinologist he largely gave up interest in all other aspects of endocrinology to devote all his time and effort to working on furthering medical knowledge of hypertension and to the treatment of patients with high blood pressure. In assessing the status and importance of the treatment and care of hypertension in 1961 he noted that "there was a general apathy." Although by that time, "from the work of Framingham" hypertension was listed "as one of the 7 or so number of risk factors" for heart disease, people didn't seem too interested or concerned about it except in the extremes of malignant hypertension. According to Kaplan, "part of it was because we didn't have easy medications. Guanethadine was terrible. Aldomet was a very popular medication. You know methyldopa but it was also difficult. It caused a lot of side effects so even though we then began to see medications that would work by oral administration and without major side effects it really didn't grow that quickly." He indicated that back in the 1960s there was very little control of essential hypertension. According to NHANES by '76 to '80 it was a mere 10%, less than what Kaplan had thought in terms of control of hypertension.[34]

Kaplan, who is now working on the 11th edition of his book, *Clinical Hypertension,* in its 6th edition, published in 1994, writes "at least partly as a result of the improved control of hypertension, there has been a steady decrease in the mortality rate of coronary heart disease and an even greater decrease in that of stroke in the U.S. since 1968." But he continues "the explanation for the reduced mortality rate of cardiovascular disease in the U.S. remains uncertain." According to Kaplan "stroke is more closely related to hypertension than is coronary heart disease, and the fall in mortality due to stroke would logically be attributable to improved

[34] Information obtained at interview with Dr. Kaplan while he reviewed NHANES data with me

control of hypertension." But the evidence does not bear this out. Looking at an "analysis of vital statistics for the entire U.S. population" writes Kaplan, "shows no correlation between the decline in mortality due to stroke and improved antihypertensive therapy. Moreover, morbidity and mortality from stroke remain considerably higher in treated hypertensives than in normotensive subjects." Thus, he concludes "we have to look elsewhere to explain much of the improvement in coronary and cerebrovascular mortality rates which have occurred since 1968." Furthermore, he writes, in the 6th edition, "the evidence that drug therapy [for hypertension] protects against stroke and heart failure seem strong, although doubts remain about the benefits of therapy for prevention of coronary disease."[35]

Kaplan's writing is supplemented by his oral history, in terms of the impact that the treatment and control of hypertension had on the decline in coronary artery disease mortality, particularly in the 1960s. I asked him specifically what the state of the field of hypertension was when he returned to Dallas from his year at the NIH to practice clinical medicine in 1961. He responded with "we did very little outpatient…we had no community programs…we had no nurse practitioners dealing with them (patients)." He also noted in passing, the nature of hypertension and its lack of symptoms, that as "an asymptomatic problem you have people come here and you say you know your blood pressure is elevated, you've got to take medication and they will take them for the time of the first prescription but they don't feel any better and when we had the drugs back then which made them feel worse it was tough to keep people on medication. So it was really a reflection of what was available in the way of medication. And also what I think you were saying increasing recognition that hypertension was a major risk factor." I asked him specifically if "back in the 60s was hypertension touted as a risk factor?" Kaplan responded "it didn't seem at the time to be something that was motivating us to go out

[35] Norman M. Kaplan. *Clinical Hypertension.* 6th edition. Baltimore: Williams and Wilkins (1994): 19-20.

and try to identify and treat more and more. We just didn't seem to have that impetus" at the time. According to Kaplan, that really didn't start until the mid-1970s, when pharmaceutical companies got involved. The pharmaceuticals "began to advertise for the treatment of hypertension. It wasn't done immediately. It took a while."[36]

It was Ed Fries, "the father of the trials on hypertension" who got it started. He was the one who "did really the first controlled trial of the treatment of hypertension which was published in '64." Fries did studies that no longer would be considered ethical to do today, between treatment and controls with no treatment or placebo. It was after these initial studies [Kaplan reading from his book] that "the decision to treat became justifiable and the enthusiasm for the use of treatment for patients with relatively mild hypertension began in the late 70s." He concluded by stating to me that "so really as far as having an impact it probably was not a major effect by the time we began to see the fall [in mortality]" in 1968, but "I feel certain that it began to play an additional role as more and more people were treated." Additionally, he related to me in my interview with him, that back in the 1950s and 1960s cardiology did not pay much attention to hypertension, or at least that was his impression. According to Kaplan, cardiologists "dealt with the consequences, but they were really not interested in the treatment of the mild patients, the uncomplicated patients." He believes that the risks were known in the 1960s "but we did not seem to apply them as we should have and to the general population." [37]

One of the first multi-author textbooks of cardiology was *The Heart* edited by Emory cardiologists J. Willis Hurst and R. Bruce Logue. The first edition of the book was published in 1966. In it, a full section of the book, with multiple chapters, was dedicated to the topic of hypertension. In terms of the definition of hypertension at the time, it notes "no full agreement

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[36] Interview of Dr. Norman Kaplan in office at University of Texas, Southwestern, Dallas, Texas, November 16, 2012.
[37] Ibid.

among physicians as to what constitutes normal as contrasted to elevated blood pressure." Rather there was general agreement "that hypertension is present when blood pressure rises above 150 mmHg systolic and 100 diastolic. Based on the work of Framingham, first published in 1961, it did claim that hypertension was a risk for the development of coronary artery disease but found "little general agreement as to when treatment for hypertension should be instituted." In terms of the impact of treatment and control of hypertension on mortality, at the time, the following observation was made:

> Although mortality has been reduced by therapy in severe hypertensive states, insufficient time has elapsed to judge the effectiveness of new drugs in the milder forms of hypertension, either upon the prevention of vascular disease or upon ultimate mortality…Because of these considerations, some clinicians will not treat mere "figures" during the long asymptomatic phase of benign hypertension, since they regard the value of such therapy as unproved, annoying because of side effects, injurious because of toxic reactions, and expensive because repetitive observations are needed.[38]

In speaking with Norman Kaplan it became quite apparent that it was not until considerably after the initial decline in coronary artery disease mortality that a concern for essential hypertension as a risk factor for the disease became manifest. Prior to 1980 hypertension was a disease, according to Kaplan, of primary interest and treatment to the nephrologists. It was "the nephrology group that took care of the bad [hypertensives]…the cardiologists at that time they did not seem to me to be interested." Kaplan continued, "Obviously and I think this is true, they looked at the heart failure and the myocardial infarctions, and the cardiomyopathies, but they didn't really go after it as far as primary prevention. That was not part of their game." In fact, according to Kaplan, both cardiologist Charles Friedberg on this side of the Atlantic and Sir George Pickering in Great Britain, back in the 1950s advocated not treating hypertension. Pickering also "loved salt and he said I will not

[38] J. Willis Hurst and R. Bruce Logue, ed. *The Heart.* New York: McGraw-Hill (1966): 788-789.

tell people to cut back on salt. I remember him at a dinner and he took the salt shaker and he was very English showing everyone and he poured salt on his food." Anecdotal but "nonetheless it sort of demonstrates the fact that we were not really going out after the general population as far as prevention." Leaning back in his chair, Kaplan summarizes and reiterates "at the time going back to the '60s, hypertension wasn't that much on the screen as far as an important element in causing cardiovascular disease and I think as we've talked treatments were generally not very easy and there was very little impetus from the pharmaceutical companies." The push for control of hypertension, according to Kaplan, was driven in large degree by pharma to sell their products but this did not come about until the 1970s with the first renin inhibitors and the 1980s "with more beta blockers and more ace inhibitors and then later even more."[39]

I had the opportunity also to speak with W. Dallas Hall, a nephrologist at Emory, who completed his training in the mid to late 1960s and for many years was director of the Division of Hypertension at Emory University. He corroborated much of what Norman Kaplan had told me, especially the lack of concern in the 1960s and early 1970s for hypertension as a risk factor for coronary artery disease. J. Willis Hurst, then chairman of medicine set up the division of hypertension with Hall as physician and then director but his interest in hypertension was "only on the side" according to Hall; "he was much more interested in heart disease." The end result of hypertension was "strokes and heart failure" according to Hall not ischemic heart disease and the concern for primary prevention did not occur until much later, again when the pharmaceuticals made the push in the late 1970s and 1980s. It was then that "the medicines got better and there was more emphasis on hypertension." As a "matter of fact," Hall recalled,

[39] Interview of Dr. Norman Kaplan in office at University of Texas, Southwestern, Dallas, Texas, November 16, 2012.

"there was a period of time when diastolic hypertension was considered necessary." Elevations in systolic blood pressure alone were usually ignored. According to Hall, "the real breakthrough in treatment did not come until the 1970s" and perhaps even later. Everything before that time was directed to severe and malignant hypertension and very little treatment to the outpatient with hypertension.[40]

It appears that much of the advances in treatment of high blood pressure and hypertension awareness were not in place early enough to have impacted coronary artery disease mortality by 1968. A double blind, placebo controlled study by Wolff and Lindeman, published in 1966, substantiated the evidence for "treatment of severe and malignant forms of hypertension" but failed to show that treatment with drugs available at the time, had any value "in less severe forms of hypertension which are still uncomplicated or where complications result primarily from progressing atherosclerosis." Specifically, the study showed "little difference in the incidence of atherosclerotic complications such as myocardial infarction and cerebral vascular accident" between patients treated with combination reserpine, thiazide diuretic and guanethidine and controls.[41] The Veterans Administration carried out two studies in the 1960s looking at patients with elevated diastolic pressures to see the impact of treatment with anti-hypertensive medications. The first of the two, the results of which were published in *JAMA* in 1967, looked at patients with diastolic blood pressures of 115 to 129 mm Hg and showed a clear cut treatment effect in reducing blood pressure. The second, also published in *JAMA* in 1970, and more relevant to the cardiovascular impact of hypertension, looked at patients with diastolic blood pressures of 90 to 129 mm Hg over an approximately three year period. These were randomized double blind, placebo controlled, prospective studies. Dr. Ed

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[40] Interview with W. Dallas Hall, MD, at his home in Atlanta, GA, November 23, 2012.
[41] Frederick W. Wolff and Robert D. Lindman. "Effects of Treatment in Hypertension: Results of a Controlled Study." *J Chron Dis* 19 (1966): 227-240.

Fries, referred to earlier by Dr. Norman Kaplan, led the collaborative group study. The treatment group, like the one in the Wolff and Lindeman study, received a combination of reserpine, hydralazine and hydrochlorthiazide. Results were similar to the Wolf and Lindeman study showing more dramatic and immediate results in the patients with higher levels of hypertension but failing to show clear benefit in terms of cardiovascular disease in those with more moderate and mild hypertension.[42] According to Borhani one of the questions that failed to be answered by these and other studies at the time was "Would the incidence of myocardial infarction and death from coronary heart disease in the community be significantly reduced by judicious treatment of hypertension?"[43]

Finally, it appears that "hypertension awareness" was slow to develop and it was not until the 1970s that there was a significant improvement in education and public as well as professional cognizance of the issue. Almost 50% of patients with hypertension in 1960 were unaware of their status. This degree of lack of awareness was reduced to half by 1974.[44] This statistic further substantiates the claim of Kaplan that a general "apathy" and lack of impetus for the treatment of hypertension existed prior to the early decline in coronary artery disease mortality, making it most unlikely that the treatment of hypertension as a risk factor for coronary artery disease had any impact on its mortality whatsoever.

It was probably not until the early 1980's, that hypertension as a risk factor for coronary artery disease became firmly imbedded in medical practice and manageable. An improvement in treatment, through improved pharmaceuticals, as well as a recognition of the importance of weight control and salt intake made such a transition to an emphasis on prevention not only

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[42] Veterans Administration Cooperative Study Group on Antihypertensive Agents: Results in patients with diastolic blood pressures averaging 90-114 mm Hg *JAMA* 213 (1970): 1143-1152
[43] Nemat O. Borhani. "Mortality Trend in Hypertension, United States, 1950-1976,"225-226.
[44] Ibid, 224.

important but also practical. Norman Kaplan teamed up with Jeremiah Stamler in co-editing a book entitled *Prevention of Coronary Heart Disease: Practical Management of the Risk Factors* that was published in 1983. The chapter on hypertension confirms much of the primary data on chronology collected in this section, beginning with its statement that "of all the known risk factors for cardiovascular disease (CVD), hypertension deservedly has received the greatest attention over the past 15 years."[45] Its timing, in this respect, speaks to the fact that hypertension treatment and control and its impact on CHD mortality can only be substantiated after the decline had already begun.

Hypercholesterolemia

> **…the importance of hypercholesterolemia in human atherosclerosis should have been appreciated decades earlier than it was.[46]**

The case for a role of hypercholesterolemia in the pathogenesis of atherosclerosis is neither ancient nor new; its roots distinctly Russian. Roughly one hundred years ago, in the year following Herrick's initial description of coronary thrombosis, a young pathologist, working at the Imperial Military Medical Academy in St. Petersburg, Russia "first demonstrated the role of cholesterol in the development of atherosclerosis. His classic experiments in 1913 paved the way to our current understanding of the role of cholesterol in cardiovascular disease." It is often cited as one of the greatest medical discoveries of the 20th century.[47] But this initial work and "subsequent epidemiologic studies triggered a passionate debate as to whether cholesterol is the root cause of human atherosclerosis, the disease process that underlies heart attack and

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[45] Norman M. Kaplan and Jeremiah Stamler. *Prevention of Coronary Heart Disease: Practical Management of the Risk Factors.* Philadelphia: Sanders (1983): 61

[46] Daniel Steinberg. *The Cholesterol Wars: The Skeptics vs. the Preponderance of Evidence.* San Diego: Academic Press (2007): xv.

[47] Igor E. Konstantinov, Nicolai Mejevoi, and Nikolai M. Anichkov. "Nikolai N. Anichkov and His Theory of Atherosclerosis." *Tex Heart Instit J* 33(2006): 417.

strokes."[48] The process was termed the "lipid hypothesis" and simply stated it is the proposition that elevation in serum cholesterol level, "hypercholesterolemia," is the major etiologic factor in the process of atherosclerosis and coronary heart disease. But the hypothesis does not propose that hypercholesterolemia is the only causative factor in the process. And other factors, some of which have already been mentioned, are also relevant in the pathogenesis. But what the lipid "hypothesis does propose is that hypercholesterolemia is what might be called a determining factor" and by this we mean that "it is sufficiently dominant that correcting it will significantly reduce the burden of disease and its clinical consequences even if hypercholesterolemia is the sole variable manipulated."[49]

Many knowledgeable and interested parties, including cardiologist William Roberts, commented to me that without cholesterol you cannot have atherosclerosis, even if you have all the other risk factors present. When I interviewed Roberts in his Dallas, Texas office he made the following observation: "multi-causes of atherosclerosis has been pushed into every medical student since 1950…so that as a consequence in my opinion the real cause of atherosclerosis has been diffused. And people think that smoking is just as bad as cholesterol, and maybe it is, because smoking causes all kind of trouble but in my view the cause of atherosclerosis is an elevated cholesterol." Without it, despite having all the other risks for the disease, Roberts believes, you cannot have atherosclerosis.[50] So in this respect it is "sufficiently dominant." Jeremiah Stamler, noted national and international authority on atherosclerosis, agreed strongly with Roberts' statement. He told me:

> If you have high blood pressure you can get various vascular lesions

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[48] Michael S. Brown and Joseph L. Goldstein. "Forward." In Daniel Steinberg. *The Cholesterol Wars: The Skeptics vs. the Preponderance of Evidence*. San Diego: Academic Press (2007): xi.
[49] Daniel Steinberg. The Cholesterol Wars: The Skeptics vs. the Preponderance of Evidence. San Diego: Academic Press (2007): 1.
[50] Interview with William C. Roberts, MD at his office at the Baylor Heart Institute in Dallas, November 16, 2012.

> but you never get atherosclerosis. If the serum cholesterol is low and the dietary lipids are low you can have hypertension, you can have cigarette smoking until the cows come home. You'll have other kinds of disease but not atherosclerotic disease and not atherosclerotic coronary disease. The sine quo non for atherosclerotic coronary disease is a disturbance of lipid metabolism and for its mass occurrence that's a diet induced population-wide event. A very important generalization. It is sort of like, oh yea risk factors are equal but some are more equal than others. The pivotal one is cholesterol.[51]

Unfortunately, in the period through the 1960s, although the Framingham study did establish a clear association between elevated levels of serum cholesterol and coronary disease it did not establish causality and for many, physicians and patients alike, that was a real bone of contention and grounds for skepticism.

The role of cholesterol in atherosclerosis and coronary artery disease and the management of arteriosclerosis were discussed briefly in Harrison's fifth edition (1966) of the *Principles of Internal Medicine* by William Dock, one of the 20th century's most luminary physicians and cardiologists. His comments draw attention to what became known as the "diet-heart" hypothesis. Dock writes, "In the past two decades it has become evident that diets rich in saturated fats (beef, butter, coconut oil) cause an elevation in plasma lipids, including phospholipids, triglycerides, and cholesterol…Human populations shifted from diets rich in saturated fats to those low in these items, show a fall in rate of postoperative thromboembolism and in myocardial infarction."[52] Despite the existence of evidence that Americans were consuming less in the way of saturated fats beginning in the post-World War II period[53] holes in the explanation were also documented by Dock as follows: "Although diet and

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[51] Interview with Jeremiah Stamler, MD at his home on Riverside Drive in New York, November 30, 2012.
[52] William Dock. "Atherosclerosis and other forms of Arteriosclerosis." In T.R. Harrison, et al. ed. *Principles of Internal Medicine.* 5th edition. New York: McGraw-Hill (1966): 699
[53] Martha L. Slattery and D. Elizabeth Randall. "Trends in coronary heart disease mortality and food consumption in the United States between 1909 and 1980." *Am J Clin Nutr* (1988): 1060-7.

elevated levels of cholesterol and triglyceride are of established importance both in atherogenesis and thrombogenesis, many remarkable deviations from a simple diet→plasma lipid→vascular disease pattern remain unexplained."[54] This was certainly true in animal studies. Additionally the experience of President Eisenhower was still fresh in the public's mind at the time.

Despite meticulous attention to diet, Dwight Eisenhower, after his myocardial infarction in 1955, was unable to reduce his plasma lipids to a non-atherogenic point, with persistent elevations in serum cholesterol, and continued repeated injury to his coronary arteries and heart.[55] Termed the "Eisenhower Paradox," Daniel Steinberg is quick to point out by way of explanation that the lipid "hypothesis relates to blood lipids, not dietary lipids, as the putative directly causative factor. Although diet, especially dietary lipid, is an important determinant of blood lipid levels, many other factors play important roles. Moreover, there is a great deal of variability in the response of individuals to dietary manipulations."[56] Nevertheless, the fact that Ike, with the best of medical care (Paul Dudley White was his cardiologist) could not impact his serum cholesterol level with all manner of dietary treatment did not help promotion of the lipid hypothesis at the time.

Such was the case also in the observational study entitled Multiple Risk Factor Intervention Trial (MRFIT). That study, the results of which were published in 1982, had subjects follow a modified diet that was designed to lower serum cholesterol levels. In addition, subjects were advised to stop smoking and exercise. The study showed no significant decrease in coronary artery disease, challenging in many circles the validity of the lipid hypothesis. What

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[54] William Dock. "Atherosclerosis and other forms of Arteriosclerosis." 699
[55] Gary Taubes. *Good Calories, Bad Calories: Challenging the Conventional Wisdom on Diet, Weight Control, and Disease.* New York: Knopf (2007): 3-5.
[56] Daniel Steinberg. *The Cholesterol Wars: The Skeptics vs. the Preponderance of Evidence*: 1.

the nay sayers failed to take into consideration in panning the role of serum cholesterol as a risk factor for CHD was that, despite a low cholesterol diet in subjects, the blood level of cholesterol in the subjects and controls was only different by 2%, a difference too small to be expected to reveal a significant result.[57]

The American Heart Association and the AMA began in 1961 recommending that patients with coronary artery disease or at risk for it, reduce their intake of saturated fat and reduce their total fat intake and cholesterol consumption. Despite Framingham, already in the history books for documenting an association of coronary artery disease with cholesterol, "those recommendations were seriously questioned at the time."[58] Harrison's textbook five years later recommended that "conservative management" should be "to persuade patients to accept a sane diet and way of life, with minimal use of tobacco, alcohol, dairy fat, eggs, and stall-fed beef or pork, and minimal use of drugs." Drug treatment was only recommended "when cholesterol levels remain over 200 mg per 100 ml on such a regimen, 2 to 6 Gm of nicotinic acid daily, chlorophenoxyisobutyrate, 3 Gm per day, dextrothyroxin, 2 to 8 mg, or USP thyroid extract, 60 to 180 mg daily, may prove effective."[59] Hurst and Logue's textbook *The Heart,* published in 1966, has this to say about diet, fat and coronary disease:

> The relationship of the diet to the development of coronary atherosclerosis has been studied extensively during the last 20 years. Most investigators claim that the high fat content of the diet is detrimental, while some believe that the high carbohydrate content of the diet is the culprit. Although much work has been done in the field, the absolute scientific proof that coronary disease may be prevented or altered by modifying the diet is still lacking…If the evidence were clear that an extremely low-fat diet would routinely prevent coronary atherosclerosis, then the present authors would obviously recommend its use.[60]

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[57] Multiple Risk Factor Intervention Trial Research Group. "Multiple risk factor intervention trial. Risk factor changes and mortality results." *JAMA* 248 (1982): 1465-1477.
[58] Daniel Steinberg. *The Cholesterol Wars: The Skeptics vs. the Preponderance of Evidence*: 38.
[59] William Dock. "Atherosclerosis and other forms of Arteriosclerosis." 701.
[60] J. Willis Hurst and R. Bruce Logue. *The Heart.* 713

Hurst and Logue, who themselves wrote the chapter in their edited textbook, instead recommend a diet less stringent in lipid control called *The Prudent Diet,* stating that such a diet is "far more acceptable to the patient." In terms of this more reasonable diet they make the following observations and recommendations:

> …this diet is recommended for patients with angina pectoris and myocardial infarction. Asymptomatic patients who are coronary-prone especially those with a strong family history of coronary disease, may also be motivated to try such a diet. The emotional reaction of an occasional patient to a stringent change in diet may temper its use. While most observers claim that serum cholesterol can be lowered by this diet, excessive emphasis on the exact level of cholesterol from time to time is not justified and, indeed may create additional emotional problems. The diet is not indicated in elderly patients with coronary atherosclerosis. Such patients eat poorly, their dietary habits are not easy to break, and the benefit of the diet in such a setting is very questionable…It must be realized by all concerned that absolute proof of benefit is not yet available.[61]

When I spoke to Dr. Jeremiah Stamler he told me the cholesterol story was not new in 1961. Individuals like William Dock and himself had been preaching the risk of cholesterol and lipids on the coronaries for years but it made general public and greater medical awareness only in 1961 when the Page Committee of the American Heart Association published its report and recommendations in *Circulation* in 1961.[62] According to Stamler, "there were many papers and many of us kept writing not just scientific papers but also if you will policy papers – the implications of the developing science for public policy. But it was this one. The key organizations were getting on record, the American Heart Association and then eventually the Federal government…the Heart association was nervous…felt it had to do something like this." Stamler was on the Paige Committee, chaired by Irvine H. Page of Cleveland, and vividly recalls that "we proposed recognize and make public the issue of risk factors particularly through safe

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[61] Ibid, 714.
[62] Irvine H. Page, et. al. "Dietary Fat and Its Relation to Heart Attacks and Strokes." *Circ* 23 (1961): 133-136.

life style steps without medication. In those days there was no medication or virtually no medication. The first really useful mass medication was the statins" available not until the 1980s. Everything else that was available in terms of medicine for lowering cholesterol was difficult to use, according to Stamler. So it was generally not used.[63]

One of the major roots of contention about the role of lipids as a risk factor for coronary artery disease evolved over an almost ten year period beginning in 1953. In that year Ancel Keys wrote two articles that began a fire storm of controversy and probably set the importance of the "lipid hypothesis" as a risk factor back several decades. In his article entitled "Atherosclerosis: A Problem in Newer Public Health," Keys wrote that an elevation in serum cholesterol is the putative agent for atherosclerosis because it exists in the plaque. Notes Keys "It is a fact that a major characteristic of the atherosclerotic artery is the presence of abnormal amounts of cholesterol in that artery. The atherosclerotic plaque consists of 40 to 70 per cent cholesterol. It is extremely probable that most or all of this cholesterol is derived from the blood."[64] The second more seminal article based on his seven country study entitled "Prediction and Possible Prevention of Coronary Disease," went even further in advocating for the "diet-heart" hypothesis and fueling the storm further. In it he writes "The changes in mortality in countries forced to alter their diets during the late World War cannot be ignored. These changes conform to the concept that the proportion of fat in the diet is closely related to the development of arteriosclerotic heart disease."[65] To many at the time this seemed an over-simplification. E.H. "Pete" Ahrens, Jr. working at Rockefeller University in the 1950s and "considered by many investigators to be the single best scientist in the field of lipid metabolism"[66] and the father of

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[63] Interview with Jeremiah Stamler, MD at his home on Riverside Drive in New York, New York, November 30, 2012.
[64] Ancel Keys. "Atherosclerosis: A Problem in Newer Public Health." *Atherosclerosis* 1 (1953): 122.
[65] Ancel Keys. "Prediction and Possible Prevention of Coronary Disease." *Am J Pub Heal* 43 (1953): 1405.
[66] Gary Taubes. *Good Calories, Bad Calories.* New York: Knopf (2007): 157.

the prestigious *Journal of Lipid Research*[67] warned against attributing etiology of atherosclerosis entirely to fat in the diet. His research indicated that rather than a high fat diet it might be a high carbohydrate diet that led to atherosclerosis. Four years after Keys' seminal article Ahrens was "warning about the dangers of oversimplifying the diet-heart science: maybe fat and cholesterol caused heart disease, or maybe it was the carbohydrates and triglycerides." Ahrens wrote at the time, "We know of no solid evidence on this point and until the question is further explored we question the wisdom of prescribing low-fat diets for the general population."[68] Ahrens remained unconvinced on this point for nearly 30 years, penning an article in the *Lancet* in 1985 entitled "The diet-heart question in 1985: has it really been settled?"[69]

Ahrens was not alone in his view, further complicating the situation and hampering a public health effort at prevention begun by Ancel Keys. Margaret Albink, a physician and promising clinical researcher at Yale, measured triglyceride and cholesterol levels in patients with heart disease as well as normals in the late 1950s. She and her collaborators published two papers. The first in 1959, concluded with the suggestion "that an error in the metabolism of triglycerides is the lipid abnormality operative in coronary artery disease." Everything else, including cholesterol, they concluded had a secondary role. They wrote: "It may be that other findings commonly reported in this disease, such as increased cholesterol, increased low-density lipoproteins rich in triglycerides, and prolonged and intensified alimentary lipemia, are secondary to decreased efficiency of triglyceride utilization with resulting accumulation of triglycerides in plasma."[70] The second paper appeared in the *American Journal of Medicine* in 1961, reinforcing the results of the first and playing down the importance of cholesterol to

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[67] Jules Hirsch. "A Tribute to Pete Ahrens." *J Lip Res* 42 (2001): 891-893.
[68] Gary Taubes. *Good Calories, Bad Calories*: 158.
[69] E. H. Ahrens. "The diet-heart question in 1985 – has it really been settled?" *Lancet* 1 (1985): 1085-1087.
[70] Margaret J. Albrink and Evelyn B. Man. "Serum Triglycerides in Coronary Artery Disease." *AMA Arch Int Med* 103 (1959): 7.

coronary artery disease. It began with the statement "Upon closer scrutiny, abnormal concentrations of serum cholesterol and various lipoproteins have not proved to be universally present in patients with disease of the coronary arteries."[71] Their conclusion was that high cholesterol levels were less common in patients with coronary artery disease than elevations in triglycerides.

At about the same time that the Page Committee report came out in 1961 and the American Heart Association publicly supported the work of Keys' and his hypothesis, Ahrens and Albrink presented their research at the American Association of Physicians meeting. They "both reported that elevated triglycerides were associated with an increased risk of heart disease, and that low-fat, high-carbohydrate diets raised triglycerides."[72] The *New York Times* on May 4, 1961 ran an article entitled "NEW VIEWS GIVEN ON FATS IN DIET; Foods Rich in Starches and Sugars Appear to Raise Level of Triglycerides FINDINGS ARE SURPRISE Rockefeller Institute Report Challenges Belief That Fat Is Major Factor." The article began with the statement that "A diet rich in carbohydrates (sugars and starches) and low in fats tends to raise the level of fats in the blood."[73] What emerged was the belief that it was dietary carbohydrates and not fats in the diet that was at the core of the "diet-heart" hypothesis and that the public needed to modify their diets in this way, rather than lowering the fat content, to prevent coronary artery disease. The result was chaotic in terms of policy, public health and what patients were to do in terms of prevention. It would be more than 20 years before clear and simple recommendations would be forthcoming in the mitigation of this risk factor.

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[71] Margaret J. Albrink, J. Wister Meigs and Evelyn B. Man. "Serum Lipids, Hypertension and Coronary Artery Disease." *Am J Med* 31 (1961): 4.
[72] Gary Taubes. *Good Calories, Bad Calories*: 159.
[73] John A. Osmundsen. "NEW VIEWS GIVEN ON FATS IN DIET; Foods Rich in Starches and Sugars Appear to Raise Level of Triglycerides FINDINGS ARE SURPRISE Rockefeller Institute Report Challenges Belief That Fat Is Major Factor. *NYTimes,* May 4, 1961:39.

The controversy over the "lipid hypothesis" and the role of cholesterol in the blood and diet continued well past the initial decline in coronary artery disease mortality that began in 1968. Even by 1983, Gotto and Wittels writing on the role of diet and primary prevention of coronary disease stated that "although the relationship between level of serum cholesterol and incidence of CHD has been established in epidemiological studies, the importance of diet in the development of coronary artery disease has been a matter of controversy. Several trials have addressed the question of whether consuming a diet low in dietary cholesterol and saturated fats protects against CHD. In the various trials conducted, there is suggestive evidence of protection by such a fat-modified diet, but there has not been a definitive study."[74] This lack of evidence, the high level of skepticism that existed through at least the 1970s, coupled with the information that effective drug therapy for elevated serum cholesterol did not exist until the statins were introduced in the 1980s, makes a strong argument against the proposition that prevention by risk factor mitigation for cholesterol had any impact whatsoever on the decline in coronary artery disease mortality that began in 1968.

Smoking and Tobacco use

> **I can't think of one good reason why anyone should smoke but whether it really does anything for ischemic heart disease or coronary artery disease I am not sure about that.[75]**

When I first began this project, I spoke with one of the cardiac epidemiologists at the Rollins School of Public Health at Emory University to discern his thoughts and understanding for the decline in coronary artery disease mortality that began in 1968. In a direct, unequivocal and

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[74] Antonio M. Gotto and Ellison H. Wittels. "Diet, Serum Cholesterol, Lipoproteins, and Coronary Artery Disease." In Norman M. Kaplan and Jeremiah Stamler, ed. *Prevention of Coronary Heart Disease: Practical Management of the Risk Factors.* Philadelphia: Saunders (1983): 44.

[75] Richard Conti, MD, chief of cardiology emeritus, University of Florida, during an interview in his office, August 14, 2012.

matter of fact way he responded to me that it was the result of the Surgeon General's report of 1964, condemning smoking as a health hazard, and a rapid decline in smoking by the general population as a consequent result. In this section, I will discuss the evidence for this statement and show by a review of statistics, textual information and the results of interviews with medical experts why this statement is very far from the truth.

The impact of tobacco and smoking on the lungs was already well known by the 1960s and it was this particular effect, in terms of lung cancer and emphysema that influenced the surgeon general's report. But decidedly little was known or proven about the effect of smoking on other organ systems at the time. Harrison's 5th edition of *Principles of Internal Medicine,* published in 1966, has a total of 8 pages, out of more than 1800 which mention smoking effects and only very briefly. In terms of the digestive system it mentions only a delay in ulcer healing because of smoking. For angina pectoris, only the statement that "tobacco should be prohibited when it clearly induces pain, premature beats, or pronounced increase in heart rate or blood pressure." Equally little is said about tobacco's impact on atherosclerosis, only that "tobacco, which acts much like epinephrine, accelerates atherosclerosis, but part of the higher death rate from coronary disease among smokers may be due to the fact that tense, competitive persons seek sedation from smoking."[76] More recently, it is believed that the impact of cigarette smoking on the heart is mediated through tobacco's effect on platelet function; with "platelet activation by cigarette smoking" resulting in "thrombosis formation" leading to myocardial infarction.[77]

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[76] T.R. Harrison, et al. ed. *Principles of Internal Medicine.* 5th edition. New York: McGraw-Hill (1966): 981, 833, 700.

[77] Teruo Inoue. "Cigarette Smoking as a Risk Factor of Coronary Artery Disease and its Effects on Platelet Function." *Tob Induc Dis* 2 (2004): 27-33.

The third edition of Paul Wood's *Diseases of the Heart and Circulation,* published in 1968, noted that although some authorities had exonerated smoking's impact on the heart "statistical studies have shown that ischemic heart disease is about one and a half times more common in cigarette smokers than non-smokers." In terms of angina, it recommends that "Cigarette smoking should be limited to 10 to 15 per day, or given up altogether if it is found to precipitate attacks." Cigars and pipe smoking, according to the text, "seem relatively innocuous."[78] *The Heart* edited by Hurst and Logue (1966) dedicated considerably more length in number of pages to its discussion of "The Effects of Tobacco on the Cardiovascular System" but little more substantive information. In all individuals, experienced smokers and non-smokers, the physiologic effects of smoking include "significant increases in heart rate, in systolic, diastolic, and pulse pressures, in cardiac output, and in stroke volume…There is an increase in coronary blood flow after smoking that parallels rises in systemic blood pressure and in left ventricular output…No electrocardiographic changes are associated with smoking which cannot be explained by the increase in heart rate." It points out several studies that document a considerable "excess of cardiovascular deaths in heavy cigarette smokers…the consumption of 20 or more cigarettes daily is associated with at least a three times greater hazard of myocardial infarction than is found in nonsmokers or in cigar or pipe smokers." They point out however that there is no difference in the incidence of angina pectoris between smokers and non-smokers. Most interesting and provocative in the book's evaluation of the impact of cigarette smoking on the heart is its "observation that the risk of myocardial infarction in the ex-cigarette smoker reverts to that of the nonsmoker or cigar or pipe smoker, suggesting that the effects of cigarette smoke are acute rather than chronic."[79] This was an observation made by Dr. Eugene

[78] Paul Wood. *Diseases of the Heart and Circulation.* Philadelphia: Lippincott (1968): 810, 820, 828
[79] J. Willis Hurst and R. Bruce Logue. *The Heart.* 1120-1123.

Braunwald as well, which I will address shortly.[80] In terms of blood pressure, note Hurst and Logue, "epidemiologic findings are that heavy cigarette smokers tend to have lower blood pressure readings than nonsmokers." Although the information, at the time, on the effects of cigarette smoking specifically on the coronary arteries appears sketchy and incomplete the section on the effects of tobacco on the cardiovascular system concludes with the following statement: There is a

> …threefold greater hazard of myocardial infarction in men who smoke 20 or more cigarettes daily. It is difficult to escape the conclusion that abstention from cigarettes may improve longevity, particularly since the same morbidity data indicate that former cigarette smokers experience little if any greater risk than nonsmokers or pipe or cigar smokers.[81]

Returning to the Framingham study, what do we know about the impact of cigarette smoking on coronary heart disease? William Kannel wrote an editorial in the *Annals of Internal Medicine* in 1964, the same year as the Surgeon General's Report on Smoking and Health, entitled "Cigarette Smoking and Coronary Heart Disease," in which he addressed the controversy surrounding tobacco as a risk factor for the disease. He pointed out the association of cigarette smoking "with an excess mortality from a number of diseases." According to Kannel, with the exception of lung cancer this excess mortality could be attributed to no specific cause but rather to, what he termed, "a more general nonspecific lethal effect." In this respect, cigarette smoking, unlike cholesterol, appears to have a "contributory" rather than a primary role in causing heart disease. He provided evidence for the claim made by Hurst and Logue in their book and Braunwald in his interview, that unlike tobacco's effect on the lung, long term studies both in Framingham and Albany, New York confirm "that the effects of cigarette

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[80] Interview with Dr. Eugene Braunwald in his office on Longwood Avenue, Boston, Massachusetts, October 18, 2012.

[81] J. Willis Hurst and R. Bruce Logue. *The Heart. 1120-1123.*

smoking on coronary heart disease morbidity and mortality are not cumulative and persist only as long as the exposure continues." This lack of cumulative effect plus the fact that coronary artery disease was the leading factor in excess deaths among male smokers, he believed, should be an indication of the considerable risk that smoking has on disease mortality. In Framingham, that excess risk was also "shown to be independent of almost every identified factor of risk in coronary heart disease." According to the early results of the Framingham study, "for any given level of blood pressure, serum cholesterol, vital capacity, or relative weight, the incidence of disease observed among cigarette smokers exceed that of nonsmokers by twofold." He ended his editorial with a number of significant data observations as follows:

> Although CHD is far from rare in nonsmokers, almost without exception prospective studies, with remarkable consistency of findings, have shown that cigarette smokers develop more coronary heart disease and die from the disease at a greater rate than do noncigarette smokers. The magnitude of the excess risk increases with the number of cigarettes smoked each day. Heavy smokers have about a threefold excess risk. Very significantly, those who gave up smoking have been uniformly shown to have a lower risk than those who continue to smoke. Ex-smokers appeared to rapidly revert to the nonsmokers' relatively low risk of coronary heart disease.

Kannel pointed out that there appeared to be no evidence, by autopsy studies or otherwise, that smoking had any effect on coronary artery anatomy or the development of atherosclerosis. This in part explaining the reversal of risk when smokers give up the habit.[82]

In 1983 the Surgeon General issued a follow-up report looking specifically at health consequences of smoking on cardiovascular disease. With it was established what some termed "conventional wisdom" on the relationship of smoking to coronary heart disease. Six years later, an article by Carl C. Seltzer from Harvard appeared in the *Journal of Clinical Epidemiology*

[82] W. B. Kannel. "Cigarette Smoking and Coronary Heart Disease." *Ann Int Med* 60 (1964) 1103-1106.

questioning the newly established wisdom. According to Seltzer the Surgeon General was seriously overstating the case based on data from Framingham. His key points were as follows:

> For men, univariate-association between cigarette smoking and CHD is reported as strong by the Surgeon General, but is weak in the Framingham data . The Surgeon General notes a fourfold greater CHD incidence in "heavy" smokers over nonsmokers, but the Framingham data report relative risk ratios less than two . For multivariable analyses (involving confounding factors) the Surgeon General states that the independent effect of cigarette smoking on CHD is independent and strong, but the Framingham data, on the other hand, do not support this contention.
> With respect to women, the Surgeon General asserts that cigarette smoking has a definite association and an independent effect on CHD, but the Framingham data find no association or independent effect.
> For both men and women, the Framingham data do not agree with the Surgeon General's conclusion that the risk of developing CHD increases with the total duration of smoking .[83]

The differences may appear subtle and insignificant in the scheme of things but it stirred controversy and a questioning of the degree to which smoking represented "significant" risk for coronary artery disease and specifically its impact on mortality. Its assertion was "that the Framingham Heart Study [did] not support the conclusion that cigarette smoking is a major risk factor for CHD."[84] A follow-up report from Framingham in 1993 entitled "The Health Risks of Smoking. The Framingham Study: 34 Years of Follow-up," although not exclusively focused on tobacco and coronary artery disease, appeared to be largely a response to Seltzer's article. It updated previous reports from the study and found "an association between cigarette smoking and CHD in men 45 to 64 years." Consistent with earlier reports from Framingham it failed to show an "association between smoking and CHD in women" and had no explanation for it. They noted that "a potential explanation for the lack of association [in women] may lie in the analysis

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[83] Carl C. Seltzer. "Framingham Study and 'Established Wisdom' About Cigarette Smoking and Coronary Heart Disease." *J Clin Epidemiol* 42 (1989): 743-750.
[84]Karen M. Freund, et al. "The Health Risks of Smoking - The Framingham Study: 34 Years of Follow-up." *Ann Epidemiol* 3 (1993): 417.

that excluded angina pectoris from the definition of CHD."[85] The article however did little otherwise to debunk the arguments of Seltzer and squelch those skeptical of the effect of smoking on coronary artery disease and its mortality.

Even if we accept cigarette smoking as an established risk factor for coronary artery disease and for contributing to its mortality over the 20th century we need to ask whether there is significant evidence that the public mitigated this risk by reducing tobacco use and specifically the smoking of cigarettes? Looking at statistics for the consumption of tobacco during the period leading up to the decline is one way to do it. The other is by sampling the opinion of those involved in health care and specifically heart disease during the period.

Beginning with consumption, there are data and good statistics available, from the Department of Agriculture, that look at both the consumption and production of cigarettes in the United States starting at the turn of the 20th century. There are also data from the National Center for Health Statistics (NCHS) that "quantify the possible influence of changes in prevalence of smoking on age-specific ischemic heart disease (IHD) mortality."[86] Unfortunately this latter information is available only from 1965, the first year it was collected.

Although the use of tobacco products in North America preceded Columbus and chewing tobacco, snuff, pipes and cigars were heavily used in the 18th and 19th centuries, cigarette smoking has been largely a 20th century pastime. The consumption of the various types of tobacco over a 115 year period is illustrated in Figure 1 in the appendix. Figure 2 shows cigarette production and per capita consumption from 1900 to 1995. Both were produced by the Department of Agriculture in 1996. Smoking prevalence varies greatly across multiple

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[85]Ibid, 417-424.

[86] Joel C. Kleinman, Jacob J. Feldman and Mary A. Monk. "Trends in Smoking and Ischemic Heart Disease Mortality." In Richard J. Havlik and Manning Feinleib, ed. *Proceedings of the Conference on the Decline in Coronary Heart Disease Mortality.* Bethesda: NIH Publication (1979): 195.

demographic categories. Generally the prevalence of smoking among males is considerably higher than females. Beyond sex, prevalence appears also to be related to age, race and educational level. The consumption of tobacco and smoking behavior over the course of the 20th century was "influenced by events and trends in the larger social environment within which smoking occurs as well as by the addictive properties of cigarettes acting within the psychologic and physiologic structure of the individual." Advertising over the course of the 20th century played a huge role in the sale of cigarettes and its expanded use. The first papers on the health risks of smoking appeared only in the mid-1950s. They surfaced in the scientific as well as the lay press. The tobacco companies responded by introducing cigarettes with filters and also ones that were low in tar and nicotine, trying to diffuse the issue and confuse the public into thinking that published health hazards were being combated by these measures. It seemed to work, because if you look at both Figures 1 and 2, a small dip in consumption in the mid '50s was followed by a greater surge in consumption that continued until the early 60s when it plateaued. Significant decline in consumption did not take place until the "non-smokers rights movement" began in 1977 and the 'Great American Smoke-out' the following year."[87]

From 1937 until 2007, a span of seventy years, the Economic Research Service of the Department of Agriculture published quarterly reports on the outlook of tobacco including information on production, consumption, prices, stocks, imports, exports and the trade of tobacco products. These reports were called *The Tobacco Situation* (TS) and they give a very precise history and accounting of the prevalence of cigarette smoking and tobacco consumption over that period of time. In 1954 consumption of cigarettes in this country appeared to dip for the first time in its history after unprecedented gains in consumption throughout the century.

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[87] David M. Burns, et al. "Cigarette Smoking Behavior in the United States." In *Smoking and Tobacco Control Monographs/Monograph #8: Changes in Cigarette Related Disease Risks and Their Implications for Prevention and Control.* Bethesda: NCI (1996): 13-18.

In retrospect, the seeds for this dip could be seen in the 1953 *TS* report, where at the end of the year, they saw annual consumption reach 387 billion cigarettes, "only about 1 percent above 1952, the smallest rate of gain since the war except from 1948 to 1949." It was postulated that this might have been due to the introduction of extra length or "king size" cigarettes which contained more tobacco and as a result those who preferred them were smoking fewer numbers of cigarettes.[88] In 1954 consumption was down to 374 billion, 13 billion less than in 1953 and 20 billion less than the peak in 1952. But king size cigarettes (with 17% more tobacco) and king size with filters made considerable gains. Of added importance is that it was the very first year that the *TS* report made mention of health concerns. It noted that "The publicity relating to cigarette smoking and health in the past year and a half has been a factor that adversely affected cigarette consumption. Another factor of some importance is the change in the age structure of the population in recent years." Despite a growing U.S. population from 1947 to 1952, those in the age bracket of greatest consumption, between 20 and 44, failed to grow in size whereas those over 45 years of age, a group that typically smokes less (rates of consumption decrease as smokers age) grew more. Also there was a decline in the size of the age group between 15 and 19 over the period 1947-1952 further impacting consumption or thought to do so. But if 1954 was a cause for celebration for early advocates of the ills of cigarette smoking, it was short lived because by 1955 consumption was again up by 3.9% to 383 billion and there was no further mention of health issues in the report. Per capita and total consumption continued to increase each year thereafter straight to 1962. 1957 would equal the total and per capital consumption peak reached in 1952 (approximately 408 billion) and continue to climb straight up for at least the next 5 years. In 1959, "cigarette consumption and

[88]Bureau of Agricultural Economics. *The Tobacco Situation.* Washington DC: USDA TS-66 (1953): 6-7.

output set new record highs" with further increases predicted likely in 1960. Americans were consuming 96% of domestic production with only 4% going abroad.[89]

The December 1962 *TS* report was startling for two reasons. In that year "cigarette consumption and output set new record highs for the sixth consecutive year," but the annual rate of growth appeared to be slowing somewhat. It went on to explain that "the considerable publicity in newspapers and magazines concerning cigarette smoking and health may have been a factor in retarding the rate of increase in cigarette consumption." The 1962 report predicted some carry-over of this effect into 1963. The report furthermore contained a paragraph concerning federal activity related to the publicity, as follows:

> The Surgeon General of the Public Health Service of the Department of Health, Education and Welfare in late October appointed 10 scientists to an Advisory Committee on Smoking and Health. This committee will review and study the nature and magnitude of the possible health hazard of tobacco smoking. The committee members held their first meeting on November 9-10. They agreed to begin an extensive review of the scientific literature and basic studies on all aspects of the use of tobacco and smoking habits, as well as possible contributing factors such as air pollution, industrial exposure, radiation and alcohol.[90]

But if the report in December 1962 seem to imply a reversal in consumption of cigarettes, the report one year later showed no evidence of such. It reported that "in 1963, for the seventh consecutive year, cigarette consumption and output reached new highs" and predicted continued growth in the number of smokers through 1964. In terms of the advisory committee it made only a very short mention, stating that it was "not now possible to judge how the impending smoking-health report" would impact cigarette and tobacco consumption.[91]

The *TS* report of December 1964 began with "Cigarette output and consumption were lower in 1964 than in 1963 in contrast with the steady uptrend during 1955-63. In the early

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[89] Bureau of Agricultural Economics. *The Tobacco Situation.* Washington DC: USDA TS-90 (1959): 6.
[90] Bureau of Agricultural Economics. *The Tobacco Situation.* Washington DC: USDA TS-102 (1962): 5-7.
[91] Bureau of Agricultural Economics. *The Tobacco Situation.* Washington DC: USDA TS-106 (1963): 5-6.

months of 1964, the Surgeon General's report on the hazards of smoking was released. Following the release "cigarette smoking showed considerable decline." But the end of the year *TS* reports that the drop was again short lived and "towards the end of 1964, cigarette consumption by U.S. smokers was close to the level of a year earlier." The impact of the report appeared to be just "a sharp short-term drop."[92] *TS* report 114, released in December 1965, confirmed the short term nature of the drop; "cigarette output and consumption in 1965 [reaching] new highs after" the dip in 1964. It predicted that the consumption of cigarettes would "continue to gain gradually as the population in the smoking-age brackets" increased. It announced that the warning about the hazards of smoking would be attached to all "cigarettes manufactured and packaged in the United States (or imported) for distribution in this country, or to its armed forces located outside of the United States" beginning January 1, 1966.[93]

Despite the warnings that appeared on cigarettes beginning on the first day of 1966, "cigarette consumption and output in 1966 were above any previous year." Although consumption dipped to 511 billion in 1964, the year the Surgeon General's report was published, 1965 consumption was up to 529 billion and U.S. smokers in 1966 consumed an estimated 542 billion cigarettes. The increase in consumption in 1966 by U.S. smokers was in part the result of more individuals of smoking age, "higher levels of consumer income, and heavier shipments to overseas armed forces" (Vietnam).[94] The year 1966 also showed an increase in per capita consumption that followed through in the following year. The year 1967 saw "new highs" in cigarette consumption, both total and per-capita. There was an 11 billion cigarette consumption increase between 1966 and 1967.[95] Americans if they read the warnings

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[92] Bureau of Agricultural Economics. *The Tobacco Situation*. Washington DC: USDA TS-110 (1964): 3, 7-8.
[93] Bureau of Agricultural Economics. *The Tobacco Situation*. Washington DC: USDA TS-114 (1965): 3, 6-7.
[94] Bureau of Agricultural Economics. *The Tobacco Situation*. Washington DC: USDA TS-118 (1966): 5.
[95] Bureau of Agricultural Economics. *The Tobacco Situation*. Washington DC: USDA TS-122 (1967): 5.

either didn't heed them or didn't believe them. Finally, in the first year of mortality decline from coronary artery disease, cigarette consumption held steady, with no decrease in either total consumption or per capita consumption. 1968 was remarkable as the year that "the U.S. Circuit Court of Appeals for the District of Columbia Circuit upheld a ruling of the Federal Communications Commission requiring radio and television stations which carry cigarette advertising to devote a significant amount of broadcast time to presenting information against cigarette smoking."[96]

One last point should be made about smoking and the decline in CHD mortality. In 1957, the NCHS began the National Health Interview Survey (NHIS) to monitor the health of U.S. households. Since then it has been "an ongoing survey of 40,000 households that constitute a representative sample of the U.S. population." In 1965, the survey began asking questions about smoking habits. Kleinman and associates compared the survey data obtained in this first year to that obtained in 1976 to gauge the impact of changing habits in smoking on mortality from ischemic heart disease at the very time that mortality appeared to first be declining. They looked at middle aged males and females, both white and black, 35 to 64 years of age. A number of important findings were noted. In males who were considered light to moderate smokers, less than 25 cigarettes per day, there was a decrease in the number of smokers between 1965 and 1976. But for males who were considered heavy smokers, 25 or more cigarettes per day, there was no change in number of smokers over the entire age range for that 9 year period of time. For women, who were mild to moderate smokers, less than 15 cigarettes per day, only white women 35 to 44 showed a decline in number of smokers. For the rest the numbers either stayed the same or increased. For heavy women smokers, greater than 15 cigarettes per day, the proportion of women in this group increased across the board for the

[96] Bureau of Agricultural Economics. *The Tobacco Situation*. Washington DC: USDA TS-126 (1968): 5.

same period. Over this time period it appeared that smoking was also being underreported. The conclusion of the data was that "Smoking could not account for the decline in IHD mortality among women, since women's smoking levels have actually increased" and also among males who smoked heavily "as the proportion of heavy smokers has remained constant between 1965 and 1976."[97]

In summary, the data clearly show, that for the U.S. population, consumption, both total and per-capita, did not decrease during the period leading up to the initial decline in coronary artery disease mortality making the argument that the Surgeon General's first report on the ill effects of smoking on health in 1964 and a decline in this country's most prevalent "unhealthy" habit an unlikely explanation for the initial decline in CHD mortality or even a contribution to that decline. With the epidemiological evidence and statistical data weighing heavily against cigarette smoking abatement as a cause of the initial decline in mortality, I turn to one more source of evidence, primary in nature, and that is the testimony of medical experts at the time.

When I spoke to doctors, nationwide, be they researchers, scientists, epidemiologists, or clinicians it became quite clear that although risk factors for coronary artery disease were spoken of and often touted there was little effort at prevention prior to 1970s. Early reports from Framingham and Minnesota, etc. did not translate into any significant action that would have an impact on the general public or for that matter on those reading the reports. When I asked Atlanta cardiologist Barry Silverman about risk factors in general he noted just that; "risk factors became a very important national goal in the 70s…from Framingham that is when blood pressure began to be aggressively treated." According to Dr. Silverman there was "no" real role for risk factors prior to 1970. When I asked him about smoking in particular his response was

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[97] Joel C. Kleinman, Jacob J. Feldman and Mary A. Monk. "Trends in Smoking and Ischemic Heart Disease Mortality." In Richard J. Havlik and Manning Feinleib, ed. *Proceedings of the Conference on the Decline in Coronary Heart Disease Mortality.* Bethesda: NIH Publication (1979): 195-199.

short and pointed; "doctors were smoking."[98] His response would not be different in substance from almost everyone else I interviewed. Richard Conti is skeptical about the role of smoking as a risk factor for CHD. He told me that he vividly recalled going to medical meetings in the 1960s, "where the damn smoke filled the rooms. Full of smoke." "Luther Terry," he told me "set the tone and pace in the mid-60s." He was the first to get "a lot of doctors to stop smoking and when that happened a lot of people said I stopped why don't you stop."[99] Dr. Jack Hyland, former chief of cardiology, at Baylor in Dallas, told me that the success rate in getting people to stop smoking in the 1960s was "not as good as it should have been." He elaborated, "I don't know any good statistics on it. I can tell you I can remember I smoked, every doctor I know smoked. Mason Sones[100] smoked during a coronary angiogram and blew smoke in a patient's face. He had a sprung Kelly clamp that he put on a sterile towel, he put on a cap and no mask and gloves and he had this sprung Kelly clamp with a cigarette burning and he would puff on the cigarette between shots." His nurse would hold the Kelly clamp with cigarette burning to his mouth so he could smoke. Hyland told me that he did not quit smoking himself until 1979 and it was because "Bernie Lown was down here [Dallas, Texas] giving a talk and I had to take him somewhere in my car and there were ashes in the tray and he almost didn't want to get in the car and ride with me. He reamed me out." In terms of the time period he told me "back in the 60s I started to see in every medical meeting the cloud of smoke was so great you could hardly see the slides. Everybody smoked back then. Everybody was smoking – the doctors, the accountants, the lawyers were smoking. Women were smoking. Everyone was smoking. It was

[98] Interview with Dr. Barry Silverman, in his office at Piedmont Hospital, Atlanta, Georgia, July 23, 2012.
[99] Interview with Dr. Richard Conti, in his office at the University of Florida, Gainesville, Florida, August 14, 2012.
[100] F. Mason Sones was a pediatric cardiologist, at the Cleveland Clinic, largely recognized as the pioneer of modern day coronary angiography and instrumental in the field of interventional cardiology. He trained numerous practicing cardiologists in angiography. He died of lung cancer at age 66

just unbelievable."[101] Jeremiah Stamler corroborated Hyland's observation, when I spoke to him, reminding me that "a majority of doctors were smokers not too long ago. A majority of physicians," he stated, "not just the general population."[102] Arthur Sasahara, former Chief of Medicine at the West Roxbury VA Hospital in Boston and Professor of Medicine at Harvard Medical School confirmed that there was little interest in stopping smoking for any reason especially coronary disease. "Veterans smoke a lot," he told me but even his role models in medical school, the chairman of pathology at Case Western Reserve would smoke during his lectures in the 1950s and despite the Surgeon General's report in 1964, smoking continued well into the next decade without much abatement.[103]

Eugene Braunwald added one additional insight into the relationship of tobacco use and CHD. He told me when we met in his office that the effect of smoking on the heart, unlike its effect on the lungs, is short lived and after a period of abstinence from smoking the coronary arteries in particular bear no witness to previous transgression.[104] Data from the Surgeon General and Framingham study, although somewhat different in content, appear to corroborate Braunwald's statement. According to the paper of Carl Seltzer on "established wisdom"

> The Surgeon General…states that the rate of CHD is gradually reduced in ex-smokers, eventually reaching a level between those of continuing smokers and nonsmokers, and sometimes (after many years) falling to the level of nonsmokers. The Framingham ex-smoker data, on the other hand, show immediate, prompt, reductions to CHD rates below the level of never smokers...[105]

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[101] Interview with Dr. Jack Hyland, in his office at Baylor Heart Institute, Dallas, Texas, November 16, 2012.
[102] Interview with Dr. Jeremiah Stamler, at his home Riverside Drive, New York, New York, November 30, 2012.
[103] Interview with Dr. Arthur Sasahara, in his office at Brigham and Women's Hospital, Boston, Massachusetts, October 18, 2012.
[104] Interview with Dr. Eugene Braunwald in his office on Longwood Avenue, Boston, Massachusetts, October 18, 2012.
[105] Carl C. Seltzer. "Framingham Study and 'Established Wisdom' About Cigarette Smoking and Coronary Heart Disease." 743-750.

But although an interesting fact and an observation that can be used in promoting tobacco cessation among smokers, it does not change the issue that reduction in smoking or the consumption of tobacco was the reason for a decline in CHD mortality. The data individually and in their entirety just do not support that supposition.

Other Risk Factors

According to Blakeslee and Stamler, writing in the 1960s, additional risk factors exist for coronary artery disease, including being overweight, having diabetes, over-nutrition, lack of physical exercise or physical activity, stress and heredity.[106] Unlike cholesterol, smoking and hypertension these risk factors have been much harder to study and changes over time, in terms of their mitigation, are unlikely to have moved in a positive direction in terms of impacting mortality. The Framingham Risk Score which is used to predict coronary artery events was first developed in 1998 and only takes into account the three risk factors already discussed, namely hypertension, cholesterol, both total and HDL levels, and smoking. None of the others are considered in this predictor of developing coronary artery disease over either a 10 or 30 year period.[107]

Greenland and colleagues, from three major institutions interested in risk prevention (Northwestern University, University of Minnesota and Boston University) published a paper which looked at major risk factors, in three prospective cohort studies, as antecedents of both fatal and non-fatal coronary events. In addition to the three risks of the risk score they also included diabetes as a major risk factor impacting coronary artery disease.[108]

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[106] Alton Blakeslee and Jeremiah Stamler. *Your Heart Has 9 Lives.* New York: Prentice Hall, 1963.
[107] Peter W. F. Wilson, et al. "Prediction of Coronary Heart Disease Using Risk Factor Categories." *Circ* 97 (1998): 1837-1847.
[108] Philip Greenland, Maria Deloria Knoll, Jeremiah Stamler, James D. Neaton, Alan R. Dyer, Daniel B. Garside, Peter W. Wilson. "Major Risk Factors as Antecedents of Fatal and Nonfatal Coronary Heart Disease Events." *JAMA* 290 (2003): 891-897.

The association of diabetes and coronary artery disease and atherosclerosis has been well documented in the literature. Causation however has been very difficult to prove. Jarrett at Guys Hospital, London believes that "it is more likely that diabetes develops in individuals who already possess characteristics which increase the risk of CHD in addition to the risk of developing diabetes." In other words the two diseases possess common risk factors that increase the incidence of both diseases, thereby increasing the chance that an individual will develop both, but not implicating one as a cause of the other. In contradiction to the paper of Greenland, et al he believes that "the prospective studies which have examined the predictive effect of the major known risk factors have failed to establish them as the explanation for the extra risk in diabetes." The argument that diabetes confers extra risk is also "weakened by the equally increased risk demonstrated in groups of people with impaired glucose tolerance, amongst whom there is a higher frequency of existing CHD, higher than average blood pressure levels, possibly also of cholesterol levels and an increased risk of episodes of CHD, of developing diabetes, or both." Rather than diabetes representing an antecedent risk factor for coronary artery disease "It is more likely that atherosclerosis and diabetes share a number of antecedents, the balance between them determining the clinical outcome."[109]

Although Paul Dudley White proclaimed the benefits of exercise and physical activity, beginning in the late 1920s,[110] it is unlikely that either had any significant impact whatsoever on CHD prior to 1968. Jack Hyland remembers an internist, in Dallas, named Ken Cooper who in approximately 1966 started advertising, before any doctors would advertise, advocating exercise. "Jogging," he proclaimed, "was going to cure your diabetes, your hypertension,

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[109] R. J. Jarrett. "Type 2 (non-insulin-dependent) diabetes mellitus and coronary heart disease – chick, egg or neither?" *Diabetologia* 26 (1984): 99-102.

[110] René Favaloro. "A Revival of Paul Dudley White: An Overview of Present Medical Practice and of Our Society." *Circ* 99 (1999): 1526.

everything you had to prevent coronary artery disease." He began a movement and an interest developed in Dallas in risk factors and particularly the role of exercise. But this was only starting to take shape in the late 1960s. According to Hyland, it was really "cardiac rehab" that got the whole idea of exercise for both primary and secondary coronary artery disease prevention started and this was not until the 1970s. He recalled the year it started at Baylor as 1976, because Hyland "hired the guy in '76" who began their cardiac rehabilitation program. But even at that time there was only a gradual acceptance of the concept.[111] Peter Wilson, now at Emory University, was Director of Laboratories for Framingham from 1983 to 2003. He concurred with the comments of Hyland and told me that an emphasis on physical fitness did not begin until Jim Fixx and others took up the cause of running and physical fitness in the 1970s. Fixx's two books, *The Long Distance Runner* and *The Complete Book of Running* were not published until 1977. It was not until then and later, according to Wilson, that the idea of fitness was fully implemented as a means of reducing risk for coronary disease, both primarily and secondarily.[112]

Two final points should be mentioned in terms of other risks for CHD, and these are obesity and heredity. When I spoke to Spencer King, President of the Heart and Vascular Institute at Saint Joseph's Hospital in Atlanta and former Professor of Cardiology at Emory, he told me that the patients now and back in the 1950s and 60s are different in many ways and one is in terms of weight. His remark that "back then all my patients weighed 150 pounds"[113] speaks to the obesity epidemic that only accelerated in the second half of the twentieth century. This is borne out by data and statistics. Corroborating King's remark quite closely is a CDC report

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[111] Interview with Dr. John Hyland, in his office at Baylor University Heart Institute, Dallas, Texas, November 16, 2012.

[112] Interview with Dr. Peter Wilson, in his office at Emory University, Atlanta, Georgia, September 24, 2012.

[113] Implication that patients were thin. Interview with Dr. Spencer King, in his office at St. Joseph Hospital, DATE

published in 2004 that showed that the average weight for men aged 20-74 years rose from 166.3 pounds in 1960 to 191 pounds in 2002, while the average weight for women the same age increased from 140.2 pounds in 1960 to 164.3 pounds in 2002. BMI also increased, for both groups, during that period from 25 to 28.[114] Furthermore, when Gregg and colleagues at the Centers for Disease and Prevention, looked at 40-year trends in CVD risk factors by BMI (1960-2000) in U.S. adults 20-74 years of age, they discovered a considerable decline of CVD risk factors, except for diabetes, in all BMI groups, even those at the highest level (BMI>30), leading them to believe that there was no clear cut association of obesity or BMI with cardiovascular risk, at least over the period studied.[115]

In terms of heredity, which has been addressed earlier in Chapter 2, there is no known or documented pattern of inheritance of CHD. Framingham found that parental history functioned as an independent risk factor for coronary artery disease. Not included in their risk prediction tool for coronary artery disease they noted:

> Family history of CAD, defined as parental death by CAD, was found to be a significant independent predictor of CAD in a logistic regression model controlling for standard risk factors and length of follow-up among the 5209 participants in the Framingham Study. Persons with a positive parental history have a 29% increased risk of CAD, and the strength of the association between parental history and CAD is similar to that found for other standard risk factors such as systolic blood pressure, cholesterol level, and cigarette smoking…no significant interaction was found between any of the risk factors and parental history of CAD.

Importantly there was no way to control for family history beyond controlling for the other major risk factors. In this respect Framingham added the following:

> CAD among persons who are predicted to be at low risk by standard risk factors may have a substantial genetic component and that the risk

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[114] Cynthia L. Ogden, et al. "Mean Body Weight, Height, and Body Mass Index, United States 1960-2002." *Advance Data From Vital and Health Statistics.* Hyattsville: US Department of Health and Human Services 347 (2004): 1-20.

[115] Edward W. Gregg, et al. "Secular Trends in Cardiovascular Disease Risk Factors According to Body Mass Index in US Adults." *JAMA* 293 (2005): 1868-1874.

> associated with parental history may not be reduced by modification of these factors. Nevertheless, among persons with a positive family history, those with a favorable risk profile are at substantially less risk for CAD than those with an unfavorable risk profile.[116]

Bill Roberts at Baylor, told me that it was his experience that "if you ask a group of doctors: what is the most important risk factor? They will say family history. Family History? Most families eat the same food. They get the same diseases." He told me his father, who died of coronary heart disease would have felt cheated if his mother didn't serve "two eggs, couple sausage, bacon for breakfast every day and buttered toast."[117] In this respect, improving family history, at least in part and to the extent that it can be mitigated or controlled, amounts to controlling for other concomitant risk factors, especially cholesterol, and it is unlikely that it alone could have played any role in changing mortality in the 1960s.

Summary:

Although it is clear that prevention and controlling for risk factors is critical in reducing both morbidity and mortality of disease, especially coronary artery disease, there is no evidence, based on the foregoing analysis, that risk reduction or prevention of the major risk factors played any significant role in the initial decline of coronary artery disease mortality that began in 1968. With better education, better medications and a greater realization of the importance of risk factors in causing disease, prevention would eventually play an important role in reducing coronary artery mortality. But for the purposes of this dissertation it cannot be implicated in such a role before 1968.

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[116] Richard H. Myers, et al. "Parental history is an independent risk factor for coronary artery disease: The Framingham Study." *Am Heart J* 120 (1990): 963-969.

[117] Interview with Dr. William C. Roberts, in his office at Baylor Heart Institute, Dallas, Texas, November 16, 2012.

Chapter 5: The Role of Treatment: Myth of Asclepius

> **The followers of Asclepius believe that the chief role of the physician is to treat disease, to restore health by correcting any imperfections caused by the accidents of birth or life.[1]**
>
> **The main duty of a doctor, who is engaged in general practice, is to combat ill health. To attempt this with a prospect of success he must understand what constitutes ill health, recognize the phenomena of ill health, and know how these phenomena have been produced.[2]**

As Thomas Huxley wrote, "Nature and disease may be compared to two men fighting, the doctor to a blind man with a club, who strikes into the mêlée, sometimes hitting the disease, and sometimes hitting nature."[3] His statement would suggest that medical interventions can variably be beneficial and harmful. This is true for both infectious and chronic diseases. In terms of coronary artery disease, Samuel A. Levine wrote "There is hardly any other condition in the general field of heart disease in which it is more difficult to appraise the value of specific measures of therapy than in the treatment of acute coronary thrombosis."[4] Early interventions in coronary artery disease consisted of putting both the patient and his disease at rest. If a heart attack was viewed as a stress on the heart, an overtaxing of sorts that caused the circulation to become compromised and thus result in damage to the muscle, allowing the heart to relax and rest would make sense in terms of healing and improvement. Prior to the work of Levine and his protégé Bernard Lown, as well as others, the primary and really only treatment for myocardial infarction was morphine for pain and prolonged bed rest. The latter however probably proved to be more detrimental than useful, and mortality continued to climb as most individuals with coronary disease were told to cut back on physical exertion both early in their

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[1] Rene Dubos. *Mirage of Health*. London: George Allen and Unwin (1960): 109.
[2] Sir James Mackenzie. *The Basis of Vital Activity.* London: Faber and Gwyer (1926): 23.
[3] Thomas H. Huxley. "The connection of the biological sciences with medicine." *Science and Education.* New York: D. Appleton (1881): 355.
[4] Samuel A. Levine. *Clinical Heart Disease.* Third Edition. Philadelphia: Saunders (1945): 119.

disease and over time. Time would show that early ambulation, early intervention and careful scrutiny for complications would be much more important in the care and treatment of patients. But did these changes and interventions help to drive down the mortality of coronary artery disease beginning in 1968? That is the subject of this chapter and using a combination of medical literature on treatment and practices of care at the time, oral histories from clinicians practicing at the time, hospital reports and statistics as well as an assortment of other data, I will explore the question of whether treatment and care leading up to the early decline can be implicated as the etiology for the precipitous initial decline of coronary artery disease mortality.

In January 2012 Elizabeth Nabel and Eugene Braunwald wrote a featured 200th Anniversary article in the *New England Journal of Medicine*. Entitled "A Tale of Coronary Artery Disease and Myocardial Infarction," it traced the history of coronary artery disease beginning with Heberden's description of angina in 1772 through to the present. One of its main features was to correlate the mortality of the disease with the scientific advances made over time in the field of cardiology (see Appendix I, Figure 3).[5] One can see that the number of scientific advancements prior to 1968 are few in number, largely dwarfed by all the achievements realized later. We will address these scientific and therapeutic achievements shortly but first it is important to trace the care and treatment of a disease whose chronicity demanded treatment when it first became such in 1912.

Bed rest and the development of "Chair" treatment

James Herrick in his initial description of the clinical features of coronary artery obstruction advocated total bed rest as treatment.[6] In the following decade, in an early series of

[5] Elizabeth G. Nabel and Eugene Braunwald. "A Tale of Coronary Artery Disease and Myocardial Infarction." *NEJM* 366 (2012): 54-63.
[6] James B. Herrick. "Clinical Features of Sudden Obstruction of the Coronary Arteries." *JAMA* 59 (1912): 2015-2020.

nineteen patients with documented myocardial infarction, at the PBBH, J.T. Wearn recommended that patients who had sustained a myocardial infarction be treated with "absolute rest, and every effort…made to spare the patient any bodily exertion."[7] British physicians Parkinson and Bedford, in 1928, reiterated the claim for bed rest stating that "complete physical rest is…essential in treatment" and that "all preparations for a serious and lengthy illness should be made." They wrote that "absolute rest in bed for not less than a month is imperative to allow healing of the infarct and to reduce the risk of embolism." "Convalescence," after cardiac infarction, according to Parkinson and Bedford, "will…be prolonged and the return to ordinary life postponed as long as possible."[8] A year later Samuel A. Levine wrote of coronary thrombosis "Our ideas of treatment, although partially based on experience, which in all practice may be fallacious, but particularly so in this connection, will need to rest in a measure on a theoretical basis, having in mind the pathological physiology of the underlying process and the gross anatomical changes that are being considered."[9]

For more than three decades after Herrick's initial article no one questioned the wisdom of prolonged bed rest, and for almost 40 years it was the mainstay of treatment for individuals with a myocardial infarction. According to Bernard Lown, "medical insistence on rigorous bed rest was based on a sacrosanct therapeutic principle, the need to rest a diseased body part, be it a fractured limb or a tuberculous lung. Unlike a broken bone, which could be immobilized in a cast, or a lung lobe, which could be collapsed by inflating a chest cavity with air, the heart could not so readily be rested." It was troubling to Lown, he later wrote, that doctors [found] ways to

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[7] J. T. Wearn. "Thrombosis of the coronary arteries, with infarction of the heart." *Am J Med Sci* 165 (1923): 268.

[8] John Parkinson and Evan Bedford. "Cardiac infarction and coronary thrombosis." *Lancet* 211 (1928): 10-11.

[9] Samuel A. Levine. *Coronary Thrombosis: Its Various Clinical Features* (Medicine Monographs Volume XVI) Baltimore: Williams and Wilkins (1929): 94.

"rationalize treatments that [were] not only without merit but draconian punishments to boot." Nevertheless, "bed rest was traditionally equated with heart rest" and few questioned it although "no one had studied the issue."[10]

As early as 1944 Levine decried the rationality of bed rest for patients with coronary disease.[11] He was the first individual to "cast doubt on the validity of this concept." Levine felt that strict bed-rest twenty four hours a day made neither "theoretical" nor "practical" sense.[12] At his hospital, the PBBH in Boston, "35 percent of heart attack patients admitted to the Brigham died."[13] In his 1951 article in the *American Heart Journal* he advocated for "a contrary method of cardiac care, i.e., to keep the patient in an appropriate chair with the feet down for as much of the day as is comfortable." And so the concept of the "cardiac chair," often dubbed the "Levine chair" was born. The argument is that to keep a person at strict and complete bed rest only leads to greater complications, more morbidity and more mortality. Levine makes the point that in putting the heart to rest one must consider the activity of both the right and the left ventricles. In a normal heart, work is decreased when at rest but this is not true in a heart that is diseased and although bed rest might help one side of the heart it inevitably will hurt the other. If there has been significant damage to the myocardium, felt Levine, bed rest can easily tip the individual into acute congestive heart failure. Bed rest also increases the risk of a pulmonary embolus occurring. Levine believed that "the reason that such harmful effects do not more often result disastrously and that they have generally been overlooked is that medical treatment instituted simultaneously with strict bed rest in most cases undoes the harm

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[10] Bernard Lown. *The Lost Art of Healing.* New York: Ballantine (1999): 177, 183.
[11] Samuel A. Levine. "Some Harmful Effects of Recumbency in the Treatment of Heart Disease." *JAMA* 126 (1944):80-84.
[12] Samuel A. Levine. "The Myth of Strict Bed Rest in the Treatment of Heart Disease." *Am Heart J* 42 (1951): 406-413.
[13]Bernard Lown. *The Lost Art of Healing.* 178.

produced." Such treatment includes the use of digitalis, diuretics and low salt diet. However, "when medical therapy is inadequate" wrote Levine, "we see the patient's condition grow worse rapidly, with even a fatal outcome." But before the advent of mercurial diuretics, putting a patient with a myocardial infarction and a propensity to failure at bed rest might have resulted in the mobilization of fluid from the peripheries where it was sitting and doing little harm to accumulate in the chest where it led to labored breathing and "threatened the life of the patient." Levine stated with a sense of absolute certainty "that in some instances putting such patients to bed rest caused a fatal outcome that otherwise would not have occurred."[14]

But according to Levine the benefits of the "chair" and sitting up approach extended well beyond pulmonary complications of acute myocardial infarction and heart failure. He writes:

> I have seen instances in which the mental state and distressing hiccup apart from breathlessness quickly improved after placing the patient in a chair. It is reasonable to assume that if a change in posture can produce such beneficial effects once these severe symptoms develop, the same complications might have been prevented if the patient had been kept in the proper position throughout the illness. This general type of reasoning has gradually led us to treat acute coronary thrombosis by keeping the patient in a chair. The purpose is still to rest the heart as much as possible and to prevent pulmonary congestion and other complications that might result from recumbency.[15]

At the time of this article's writing it was the practice of Levine and colleagues at the PBBH to keep patients "with an acute coronary thrombosis in a chair, beginning as early in the illness as possible." Levine noted also that patients had an increased sense of well-being in the chair and the "striking psychic advantages" were evident early. He adds:

> There is something ominous and foreboding in the mind of the average patient when told to stay absolutely quiet in bed for a month or so. He quickly develops great fear that something terrible is going on or that he might suddenly die if he makes the slightest effort or movement. The

[14] Samuel A. Levine. "The Myth of Strict Bed Rest in the Treatment of Heart Disease." 406-413.
[15] Ibid, 410.

> difference in the psychological state of the patient is readily seen in those who had had a previous attack and were treated by the strict bed rest regime. They immediately remark how much happier and less fearsome they were on the chair method of treatment. Nowadays, when the importance of the alarm reaction is being stressed, this factor in treatment gains greater reality.[16]

As already alluded to by Levine above, the chair did not replace other treatments that patients who would otherwise have been at bed rest received and all these treatments were continued, including nasal oxygen administration and anticoagulants. Only in cases where "significant shock" was present was the chair not used.[17]

In Levine's first paper, seventy patients had been treated with the chair for myocardial infarction and only seven had died. This represents a mortality of about 10%. Although the data were not controlled for and Levine felt that comparisons with known mortality figures, for this reason, were difficult to make, on the surface it represented an improvement in the mortality of coronary thrombosis patients. He writes, "in recent years at the Peter Bent Brigham Hospital where most of these cases have been treated, the expected mortality of acute coronary thrombosis under Dicumarol and strict bed rest treatment has been 15 per cent, which is greater than in the group treated in a chair." Also he continues "The development of acute pulmonary edema or dyspnea not already present or the aggravation of such states was extremely rare after chair treatment was begun." In terms of the impact on caregivers involved, he notes "The entire experience has left nothing but a favorable and optimistic impression on the physician and nurses in attendance."[18]

Levine together with Bernard Lown, his associate, student, protégé and in every way his successor in care of patients with coronary artery disease at the PBBH in Boston, wrote 3 follow-

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[16] Ibid, 411.
[17] Ibid, 410-411
[18] Ibid, 412.

up articles on the utility and improved mortality of "armchair" treatment in myocardial infarction. In the first of these articles, published in 1951, they describe "preliminary" results of using the chair in early treatment of coronary thrombosis in 65 patients. The diagnosis in each patient was established on both clinical and electrocardiographic grounds. Of this group of patients 50 were admitted to the medical service at the PBBH. They excluded patients with either mild symptoms or where there was any doubt of the diagnosis of myocardial infarction. The severity of their disease was attested to by the high rate of heart failure and arrhythmias. The majority of patients were gotten out of bed within the first two days of their coronary thrombosis. The mortality in this group was 10.8%. There were a small number of complications that occurred in this group but none could be directly attributed to the use of the "chair" in treatment. According to the authors "one of the most spectacular features in the 'chair' treated coronaries" was an "enhanced sense of well-being." Their description of the impact of bed rest on the patient's psychological state is profound and worth quoting:

> When a patient is placed at complete bed rest after an acute coronary thrombosis profound psychologic changes follow. The individual who was active and well a few hours before is now made to feel as though death was hovering close by. This impression is reinforced by the physician's insistence on complete bed rest and the prohibition of even minimal movements. The patient is thus abruptly subjected to the mercies of fortuitous forces over which he has no mastery. What is even more provocative of anxiety is that he is left without any gauge to assess the presence, extent and speed of progress…In contrast to this the patient in a chair can never view himself as hopelessly ill. What is most important, however, is that the gradually increasing time out of bed provides him with the clearest index of improvement. He is made to feel as an aware and active participant in the healing process. This awareness is more potent in allaying fear and dissipating anxiety than any of the physician's words of encouragement.

Levine and Lown noted in their several articles on the subject that having a method of control by alternating patients who received the "chair" treatment with those who did not "was not feasible" and so really precluded a statistical evaluation of mortality figures between chair and

recumbency. They did however offer as the only basis for comparison a group of 138 patients with acute coronaries treated with bed rest and anticoagulants at the PBBH in the period just prior to their chair study. In this group the mortality was 13.8% compared to the 9% in those who received "chair" treatment and anticoagulants. Although they admitted that the small series and lack of true controls prevented attaching much significance to the difference in mortality it did argue against the belief that sitting patients up out of bed increased mortality after an acute myocardial infarction.[19]

In 1952 they published in *JAMA* an expansion of their initial study of 65 patients; now with 81 patients, 57 of which were admitted to the PBBH and the other 24 were either admitted to other area hospitals or treated at home. The group was again characterized as "selected" with a "high frequency of paroxysmal arrhythmias." In terms of their coronary disease the condition of the group was noted to be "not mild" as "attested by the fact that nearly half the patients had pulmonary edema and a fifth of all the patients were rapidly digitalized after entering the hospital." Despite the severity of disease "the majority of patients were out of bed during the first two days." The protocol was as follows:

> They were helped out of bed and placed into a comfortable mobile chair, with care taken so that no pressure was exerted on the popliteal spaces. They remained in a chair until they experienced fatigue. Our goal was to have these patients out of bed as much of the day as was possible without discomfort to them. This was achieved in some who were in the chair most of the day from the beginning of their illness. For the majority, however, this usually meant that they were out of bed about one to two hours during the first day with increasing time intervals thereafter, so that by the end of the first week they spent the larger portion of the day in a chair.

[19] Samuel A. Levine and Bernard Lown. "The 'Chair' Treatment of Acute Coronary Thrombosis." *Trans of the Assoc Amer Phys* 64 (1951): 316-327.

In addition to being up in a chair, patients fed themselves and used bedside commodes or the toilet. Previously they were fed by nurses and forced to use bed pans. Otherwise they all received what was considered routine cardiac care. The mortality for this group was 9.9%. All but two patients were up in a chair the first week, the other two on days 8 and 9, and the majority (86%) within the first three days. In ten patients who were termed "critically or terminally ill," with one or more complications, their "recovery appeared to coincide directly with their being placed in the chair." Importantly, there were no complications that could be directly attributable to the use of the armchair and whereas the overall mortality of the group was 9.9%, in those who were both in the armchair and received anticoagulants (72 patients) the mortality was only 8.3%.[20]

According to Lown, "witnessing even one patient in a chair rapidly won converts…and the [original] study gained momentum." A follow-up of the study of 81 patients was published in 1954. The patients initially "were placed in a chair for half an hour; by the end of the first week of hospitalization," and "they remained seated [there] throughout most of the day."[21] The primary purpose of the study was to evaluate long term effects of armchair treatment. After the earlier article by Levine and Lown some critics argued that even though the short term course of patients with myocardial infarction appeared to improve with getting acute patients out of bed and upright early, the long range results may not be so good. The chief argument by skeptics was "that keeping patients sedentary in a chair during the acute phase of myocardial infarction may increase the possibility of localized weakening of infarcted tissue." The article looked therefore to see if there was an increased incidence of development of ventricular aneurysms over time with armchair treatment. Using the most reliable evidence for ventricular

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[20] Samuel A. Levine and Bernard Lown. "'Armchair' Treatment of Acute Coronary Thrombosis." *JAMA* 148 (1952): 1365-1369.
[21] Bernard Lown. *The Lost Art of Healing.*179-180.

aneurysm available at the time, "roentgenologic and fluoroscopic examination," revealed no cases of development of this defect in any of the patients treated with the chair over time. Investigators suspected that the development of such a long range complication may have actually been decreased in the patients who were cared for with early armchair intervention. The study concluded that there was no evidence that the work of the heart had been increased with use of the chair and that the data, in terms of diminution of blood pressure and constancy of both pulse and respirations, actually suggested that the work of the heart may have been lessened by the use of this treatment. Both the short term and long term results of early chair treatment appeared to validate the superiority of this method of treatment over the traditional strict and prolonged bed rest regimen which never had any scientific validation whatsoever.[22]

The use of what would be termed the "Levine chair" or often the "Brigham chair" spread fairly rapidly. Some physicians and family of patients, according to Levine, "refused to accept the suggestion that the patient should be put in a chair. The principle of strict bed rest in the treatment of coronary thrombosis [had] been so engrained in the minds of the lay public and the medical profession that it [was] difficult to make such a drastic change."[23] According to Lown, it "was yet another of the numerous examples of medical tradition derailing healthy skepticism and impeding commonsense approaches."[24] But Levine had a far reaching influence in Boston and well beyond. He had trained numerous leaders in the field that were beginning to take their places in cardiology at newly established and existing institutions. Levine and the PBBH were also not the only ones advocating for a demise of bed rest as treatment for acute myocardial infarction. C. Warren Irvin and Alexander M. Burgess, Jr., from Rhode Island, penned

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[22] Avard M. Mitchell, James B. Dealy, Bernard Lown and Samuel A. Levine. "Further Observations on the Armchair Treatment of Acute Myocardial Infarction." *JAMA* 155 (1954): 810-814.
[23] Samuel A. Levine. "The Myth of Strict Bed Rest in the Treatment of Heart Disease." 412.
[24] Bernard Lown. *The Lost Art of Healing.* 177.

an article in the *New England Journal of Medicine* in 1950 entitled "The Abuse of Bed Rest in the Treatment of Myocardial Infarction." They pointed out that there was no statistical evidence that bed rest or a marked restriction of activity over a prolonged time period had any advantage in either the short term or long term treatment of myocardial infarction. It was their "considered opinion that routine prolonged bed rest in myocardial infarction is not only unnecessary but also potentially harmful to the mental and physical well-being of the patients."[25] Additional literature and also primary data collected from speaking with clinicians, active during the period, bears witness to the fact that the chair and the approach of not putting patients at strict bed rest and for prolonged periods of time did spread with considerable speed.

Julian R. Beckwith and his colleagues in Virginia published a study in the *Annals of Internal Medicine* in 1954 where they did a controlled study comparing traditional bed rest to chair treatment in the management of myocardial infarction. The study consisted of alternative treatment in 80 consecutive patients admitted to the hospital who had survived their myocardial infarction by 24 hours or more. The diagnosis, like in Levine and Lown's studies was made on the basis of clinical and EKG grounds. In the head to head study the mortality of what they termed the "up patients," those treated with the chair, was 7.7%. The mortality of the "down patients," those at prolonged bed rest was 14.7%. Although again the series was small, chair treatment appeared entirely safe in the acute period and was accompanied by significantly lower mortality in the immediate post infarction period.[26]

When I spoke with Jack Hyland, the past chief of cardiology at Baylor Medical Center in Dallas, Texas, he told me that the care of coronary artery disease patients in the 50s and 60s

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[25] C. Warren Irvin, Jr. and Alexander M. Burgess, Jr. "The Abuse of Bed Rest in the Treatment of Myocardial Infarction." *NEJM* 243 (1950): 486-489.
[26] Julian R. Beckwith, et al. "The Management of Myocardial Infarction with Particular Reference to the Chair Treatment." *Ann Int Med* 41 (1954): 1189-1195.

was “boring” and that physicians did not want to take care of these patients because there was literally little that could be done for them except bed rest. He states that in his initial training at the PBBH and early on in Dallas, if a patient had a coronary “it was 6 weeks of bed rest. They weren’t allowed to feed themselves. The nurse fed them. It was totally different [back then]. They didn’t have exercise programs, or rehab programs or anything like that. They all got their nitroglycerin. Sometimes digitalis if they had any kinds of arrhythmias. I don’t recall that we put them on much of a diet in those days.” The chair was being used in Boston but took more time to catch on in Texas according to Hyland. In terms of anticoagulants alluded to by Levine, Hyland told me “they came in and out of favor.” When at bed rest and later in the chair, “there were times when we anticoagulated absolutely everybody. There were times when we didn’t do it and it depended on swing back and forth as to whether we had coronary spasm or not.”[27]

Tom Ryan, former chief of cardiology at Boston University, and a close friend and contemporary of Herbert Levine, Samuel Levine’s son, told me “it was Sam Levine that developed the cardiac chair and that was well before the cardiac care unit” which came into existence in the early 1960s. “It was Sam Levine,” explained Ryan, “who thought that being up in the chair was better than being in bed.” He continued, it was New York Hospital cardiologist “Tom Killip [who] took this up in his captive group of coronary patients. In addition to monitoring and looking at pre-arrhythmias and the ones that would go into v. fib he got them to sit up in a chair and then he had them walk around the bed and he got more into physical exertion being good for them.” According to Ryan this was all before 1961-62.[28]

Peter Gazes, the first formally trained cardiologist in the state of South Carolina, told me that as he was leaving training in Philadelphia in the late 1940s there was impetus emanating

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[27] Interview with Dr. Jack Hyland, Baylor University Medical Center, Dallas, Texas, November 16, 2012.
[28] Interview with Dr. Tom Ryan, Boston University Medical Center, Boston, Massachusetts, October 18, 2012.

from Boston to get patients up to a chair early and when he arrived in Charleston, South Carolina in the early 1950s patients were literally strapped to the bed after an infarction and he instructed nurses at the hospital to take the straps off and let the patients sit up. In addition when a patient called him to report what seemed like an AMI he instructed them to come to the hospital in a car sitting up rather than in an ambulance lying flat on a stretcher, supporting his belief that sitting up was not harmful to their heart.[29]

But it was Bernard Lown, who founded and opened the coronary care unit (CCU) at the PBBH that told me he thought the "chair" was critical in the early decline of coronary artery disease mortality. When I asked him if he thought, like others that it was the CCU that was instrumental in the initial decline of mortality, he said "No. I was there." He continued "you know what caused the decline in coronary mortality? *The Chair,"* he exclaimed! I had heard from other physicians that it had been called the "Levine chair," but when I referred to it as that Lown became a bit incensed rebuffing me with "you call it the Levine chair but you know the first paper I wrote." Lown then proceeded to give me his opinion of the chair and why mortality declined in the 1960s. He stated:

> It is very complicated. Levine thought that if you sit a person up gravity will pull fluid from the lungs to the legs where it suddenly bears no consequence rather than in the lungs and he based it on the fact that he was called for consultation to see a patient in Washington and the patient was in pulmonary congestion and was miserable and Levine did not know what to offer so Levine said why don't you sit him up? The moment they sat him up he could breath. So that must have happened in the '30s. Levine would say people are better out of bed. But he never did anything! When I came along in 1950 I said to Dr. Levine: Dr. Levine you talk a lot why don't you do it? He said I am too old Bernie. It is too big a project. The establishment will be too opposed. The establishment was opposed because doctors earned a good living out of it. Patient was in bed for 3 to 6 weeks you [the doctor] could come by and charge [the patient each day for a visit]. And I watched that and I was outraged. I was outraged by the mortality. The mortality at the Brigham when I came along at that time in 1950 was about 35%. That's it! That is what we saw. From acute

[29] Interview with Dr. Peter C. Gazes, at his home in Charleston, South Carolina, May 8, 2014.

> myocardial infarction and sudden death…So Levine says you do it. So I walk into the ward and I say 'get this patient out of bed' – it was a Levine patient. They say 'screw you Lown.' So I couldn't get him. So Levine of course had a lot of authority. He says 'please get this patient out of bed and Dr. Lown will supervise.' Next day I come in the whole house staff line up and when I walk in they say 'sieg heil.' They say you are going to be tried at Nuremberg, because this was shortly after Nuremberg in 1950. Yes but I persisted and we did 80…after the first 10 patients it was imminent. The house staff was wonderful. They saw that the patients were getting better and getting out of the hospital faster.[30]

Lown believes that getting them up, in sitting position, also helped with their general well-being, decreasing anxiety and depression with less bowel problems. There was less constipation and impaction, according to Lown, when the patients were able to sit up. He told me that Levine believed it was all fluid but in the words of Lown "that was non-sense."[31] Levine and Lown subsequently submitted a co-authored paper on the benefits of the chair in reducing mortality from myocardial infarction.

Levine and Lown worked together to promote chair treatment in the 1950s; however, as already alluded to in my face to face discussion with the latter, they differed sharply in terms of their explanations for why the chair improved the outcomes and mortality of those who had sustained a myocardial infarction. This is documented in the literature. Lown, in a rare criticism of his mentor, writes, "Levine eschewed psychiatric explanations, ascribing the benefits to mechanical factors. He resorted to the same line of reasoning that rationalized bed rest, but reversed the argument. In essence, he said, an upright posture reduced the heart's workload. In the prone position, gravity pooled blood into dependent parts of the body; with a decreased volume to pump, the heart worked less." To Lown, this "explanation made no sense. How could a patient's sitting up for thirty to sixty minutes out of twenty-four hours have such an extraordinary, long-lasting beneficial effect, especially as the heart rate and blood pressure were

[30] Interview with Dr. Bernard Lown at his home in Newton, Massachusetts, November 4, 2013.
[31] Ibid.

raised by sitting up?" Lown's "observation of many patients with myocardial infarction treated both with strict bed rest and the more liberal chair regimen suggested a different explanation, one that had more to do with psychological than physical factors." He explains his reasoning, in his book, as follows:

> To be well one minute and seriously ill the next is a major psychological shock. To be told that the discomfort came from a heart attack carried the dire connotation of disability and death. The ominous implication was reinforced by the physician's insistence on complete bed rest, proscribing all activity, even to prohibiting movement in bed. The patient was left to the mercy of forces over which he or she had no control. Adding to the anxiety was the absence of a way to assess the extent or speed of recovery…Lying in bed for twenty-four hours, in addition to being uncomfortable and unnatural, sapped physical strength and undermined the psychological resolve to recover. By the third week in bed, depression was the rule, and many patients lost interest in surviving. By contrast, patients managed in a chair did not consider themselves hopelessly ill. After all, in our culture the act of dying takes place in bed, so there was some sense of safety being out of it. The progressive increase in time allowed out of bed provided a gauge for judging progress. The patient was made an informed and active participant in the healing process. The empowerment, I came to believe, was the critical factor, far more potent in allaying fear and dissipating anxiety than any reassuring words from the medical staff.[32]

Lown concluded with "I think the chair treatment reduced mortality substantially because it shortened hospitalization, it got people out of bed. The mortality … you know what the mortality was? A large part of the mortality was from thromboembolism. Why do you think anticoagulants were introduced? Why did they introduce it? Because of the high mortality of acute coronary thrombosis from pulmonary embolus."[33] According to Lown, "In nearly 30 percent of bed-treated patients who died, pulmonary embolism was the cause of fatality. This dreaded complication, resulting from thrombophlebitis in leg veins, was not observed in any of

[32] Bernard Lown. *The Lost Art of Healing.*180-181.
[33] Interview with Dr. Bernard Lown at his home in Chestnut Hill, Massachusetts, November 4, 2013.

the eighty-one patients who were treated in a chair."[34] When I asked Lown if the chair impact was just at the Brigham, he responded "no it caught on in one year. Nationwide." He told me that the use of anticoagulation may have added incrementally to the effects of sitting patients with myocardial infarction (MI) up but was not that big a factor in mortality, the main impact being from the chair.[35]

Although there is ample evidence that the chair was being implemented in major centers from Boston, Massachusetts to Dallas, Texas, for one reason or another, not all doctors were comfortable with getting patients up and off bed rest early. A small study of physician practices by Martin Duke in Manchester, Connecticut attests to the reluctance of some doctors in a community setting to depart readily from old habits. Duke first analyzed all "previous" recommendations for bed rest from 1937 to 1969 and could find no consistent pattern. The fourth edition of Harrison's textbook *Principles of Internal Medicine*[36] published in 1962, reflecting standards of practice since the previous edition in 1958, alluded only briefly to the use of chair treatment stating "When the condition of the patient permits, often after a few days, he may be allowed to sit up in a chair, use a bedside commode, or even walk a few steps to an adjoining toilet."[37]

Despite the fact that by the 1960s few were recommending bed rest for any longer than 2 weeks, and Levine and Lown were at the lowest end with two days maximum, there was still no consistent standard for bed rest in the literature through 1970. Duke's study, published in

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[34] Bernard Lown. *The Lost Art of Healing*.181.
[35] Interview with Dr. Bernard Lown at his home in Chestnut Hill, Massachusetts, November 4, 2013.
[36] This book is viewed by many as the leading text in internal medicine and "what is arguably the most recognized book in all of medicine…Harrison's remains synonymous not just with internal medicine but with medicine in general." Preeti N. Malani. "Harrison's Principles of Internal Medicine." *JAMA* 308 (2012): 1813-1814.
[37] William H. Resnick and T.R. Harrison. "Ischemic Heart Disease (Angina Pectoris and Myocardial Infarction." In T.E. Harrison, et al. editors *Principles of Internal Medicine.* 4th edition. New York: McGraw-Hill (1962): 1456

1971, in the *American Heart Journal,* examined the practices of physicians or groups of physicians carrying for patients who were hospitalized for acute myocardial infarction. It was carried out from 1965 to 1968. In all 249 patients were studied, 26 of which had a second infarction during the period. The mean hospitalization for the 275 infarctions was 24.6 days and the mean number of days at bed rest was 10.5 days, varying from 7.4 to 15.2 days. Differences observed between different physicians were significant but there was no recognizable variation in the patient population to account for this difference. There was additionally no correlation between the length of bed rest and the length of hospitalization. Furthermore, no specific characteristics could be discerned between the physicians who kept their patients at bed rest longer from those that favored less bed rest, not in terms of physician age, length of practice or training. He found that many patients "are still subjected to a traditional period of prolonged bed rest, the disadvantages of which are either not considered or are viewed as more acceptable." He concluded that "The benefits of early chair and ambulatory treatment in avoiding thromboembolism, in preventing 'cardiovascular deconditioning,' and in relieving anxiety, together with the absence of complications …would appear to outweigh concerns of the physician that for the most part seem unfounded." It was further reasoned from this community study "that many patients still appear to be kept in bed and probably in the hospital for excessive and arbitrary periods of time that are not dictated by known facts about the course of this disease."[38]

Chair treatment was implemented early at the Veterans Hospital in West Roxbury, Massachusetts, according to its former Chief of Medicine Arthur Sasahara. He however attributes this to the fact that the hospital was affiliated with the PBBH and "was staffed by

[38] Martin Duke. "Bed rest in acute myocardial infarction: A study of physician practices." *Am H J* 82 (1971):486-491.

Brigham physicians and Brigham house staff." He believes that there was some reluctance on the part of physicians elsewhere to implement use of the chair because "clinical trials did not access very many patients….for example, the 81 patients in the Levine-Lown study……one could say, I'm not going to change my practice of bed rest….that study didn't have very many patients and the results could have been influenced by chance."[39] But as Roman DeSanctis of MGH confided in me many studies back then were small and by today's standards would never be looked at, let alone published.[40]

Unfortunately, the studies on the use of chair treatment and improvement in mortality were small and scanty and evidence for extensive use of the chair varies widely. There was a clear call from a number of centers referenced above for more investigation into the benefits of chair treatment to patients with acute myocardial infarction. Irvin and Burgess wrote, "It is to be hoped that the treatment of myocardial infarction may one day rest on the results of purposeful clinical study, rather than mere reasoned opinion."[41] It is probably safe to say that in the large academic centers curtailing bed rest and getting patients up to a chair was implemented not long after the pioneering work of Levine and Lown in the early 1950s. We certainly have early evidence in the literature and primary supporting data from interviews of individuals practicing at the time, but how extensive it was is unclear given the lack of published studies comparing bed rest to "armchair treatment." According to Richard Conti, the former chief of cardiology at the University of Florida, "The transition from bed rest to early ambulation

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[39] Email communication from Dr. Arthur Sasahara, May 4, 2014.

[40] Interview with Dr. Roman DeSanctis in his office at the Massachusetts General Hospital, October 19, 2012. He stated "I remember in the late 1960s early 1970s Dolph Hunter and I and a couple other people put together a study of the two week versus three week therapy of MI and we had 138 patients. They wouldn't even look at this study now and it was in the New England Journal of Medicine" back then. "A study like this they would laugh at you now."

[41] C. Warren Irvin, Jr. and Alexander M. Burgess, Jr. "The Abuse of Bed Rest in the Treatment of Myocardial Infarction." 488

was not done overnight, but it was accepted as standard practice gradually by cardiologists."[42] Dr. Jack Edwards, a cardiologist in practice in Dallas, Texas during the period recalled vividly that the practice of sitting up in the chair began, after his father had a myocardial infarction and died in 1950. He recollects that the use of the chair at Baylor Hospital began in the mid-50s. According to Edwards, "Dallas doctors followed the literature in terms of practice."[43]

Tom Ryan, started in the practice of cardiology in Boston in 1960. He writes "by then we were rather routinely putting MI patients out of bed and in a bedside chair on day 2 if uncomplicated."[44] Roman DeSanctis noted that when he "arrived at the MGH as an intern in 1955, the early chair treatment was used in uncomplicated MI's."[45] Robert Copeland who trained under DeSanctis in cardiology at the MGH in the 1960s began practice in 1967 in LaGrange, Georgia, a small city 70 miles south of Atlanta, where at the time Emory trained internist William Fackler was the "heart specialist." According to Copeland, upon his arrival in Georgia, "all acute MI patients and some others who had elevated LDH but normal SGOTs were treated with four weeks of bed rest." But shortly after arriving in LaGrange he had the local hospital order one of the "Brigham chairs" and started using it, "getting patients up [in the chair] and walking."[46]

In the 15 interviews of cardiologists I conducted that either trained or practiced or both during the period of time from 1950- 1970, by far the majority used Charles K. Friedberg's *Diseases of the Heart* as their primary textbook for cardiology. A single authored book which had only three editions, the last in 1966, "*Diseases of the Heart*," according to Dr. Nanette Wenger, "translated into half a dozen languages, was often referred to as the 'bible of

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[42] Email communication from Dr. Richard Conti, April 16, 2014.
[43] Telephone conversation with Dr. Jack Edwards, April 16, 2014.
[44] Email communication from Dr. Thomas J. Ryan, April 16, 2014.
[45] Email communication from Dr. Roman W. DeSanctis, April 17, 2014.
[46] Email communication from Dr. Robert Copeland, April 20, 2014.

cardiology.'"[47] In 1972, David H. Spodick, while reviewing another cardiology book, wrote "For cardiology, Friedberg's conspicuous success in maintaining uniform excellence while covering the entire field provides the stratospheric standard against which other single-authored texts continue to be judged."[48] In that same year Friedberg died tragically in an automobile accident. At the time he was working on the 4th edition of his textbook, which was never completed. The second edition of Friedberg's *Diseases of the Heart* published in 1956 is very helpful in realizing and evaluating armchair treatment in acute myocardial infarction in the early 1950s. Friedberg neither embraces it nor condemns it. He draws attention to it as an emerging therapy and the fact that its proponents claim great benefit for the treatment. He writes:

> It has been recommended that patients with acute myocardial infarction be treated continuously in a chair during waking hours, except in the presence of shock or extreme debility. Improvements of morale, relief of orthopnea and avoidance of pulmonary embolism are some of the claimed advantages. A diminution in cardiac output and in the work of the heart in the sitting position is another listed benefit of chair treatment.

Friedberg then points out that the dichotomy is based on what he calls "confusion" rather than physiologic fact. The first in terms of failure, he points out a confusion between "recumbency and rest" noting that the "problem of recumbency or upright position is not really directly related to the treatment of acute myocardial infarction. It is a problem in the management of left-sided heart failure with orthopnea or cardiac asthma…This has nothing to do with the problem of bed rest versus chair rest in acute myocardial infarction, per se." He continues, in terms of "the claim that chair rest may prevent pulmonary embolism is also based on confusion – between chair treatment and early ambulation." Early ambulation may reduce embolic phenomenon but "there should be no pretense that chair treatment means early ambulation." He concludes that "it is apparent that there is much to be learned or proved before we invoke

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[47] N.K. Wenger. "Profiles in Cardiology: Charles K. Friedberg." *Clin Card* 9 (1986): 356-359.
[48] David H. Spodick. "Clinical Cardiology." *JAMA* 221 (1972): 306.

physiologic arguments to support our prejudices for either bed rest or chair treatment. Repeated references to the 'dangers,' 'abuse' and 'myth' of bed rest have served to call attention to the need for reexamination of the basis for a long standing axiom." But according to Friedberg "it would be unfortunate if these discussions distracted us from grappling with the more important factors in mortality from acute myocardial infarction. Bed rest, especially when intelligently carried out, modified and individualized, is not a significant factor in this mortality; neither is chair treatment the cure."[49]

Friedberg's third and last edition of *Diseases of the Heart,* published in 1966, represented a greatly enlarged and expanded textbook. Incorporating new discoveries and changes in the standard of care, it stretched to over 1700 pages from its previous 1120 pages in the second edition published ten years earlier. Part IV on "Diseases of the Coronary Arteries and Coronary Heart Disease" was now 290 pages in length where it had been 176 in the earlier edition. Again, there is a section entitled "Armchair Treatment" which is virtually unchanged from the earlier edition. Like the second edition, there is no specific endorsement or condemnation of chair treatment only the statement "Sitting in a chair, for limited periods, for patients who can profit from such change in position, as part of an elastic, individualized program of bed rest is certainly permissible or desirable; sitting in a chair throughout the day, as a rigid, prescribed form of therapy, is not recommended."[50] He clearly addresses the issue, recognizes it as perhaps an improved alternative over strict and rigid bed rest, but again conveys the belief that other factors probably play a greater role in terms of mortality from myocardial infarction.

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[49] Charles K. Friedberg. *Disease of the Heart.* 2nd Edition. Philadelphia: W.B. Saunders (1956): 568.
[50] Charles K. Friedberg. *Disease of the Heart.* 3rd Edition. Philadelphia: Saunders (1966): 893-894.

J. Willis Hurst and R. Bruce Logue, both at Emory University, in the first edition of their textbook *The Heart,* published in 1966, wrote about rest in the management of myocardial infarction, clearly following the lead of Levine and Lown. Unlike some of their contemporaries they did not advocate bed rest but rather wrote that "the patient should be allowed to assume the position in which he is most comfortable, including the upright position. Motion in bed is not restricted." They advocated the use of a bedside commode when the patient was hemodynamically stable and free of chest pain and also believed that male patients should be allowed to urinate standing up at the bedside. Citing the papers of Levine and Lown from the early 1950s in their text they wrote "the patient may usually be helped to a large, comfortable chair by the side of the bed for ½ hr. or longer three to four times daily beginning on the second or third day" after their infarction.[51]

It would appear that chair treatment and removal from bed rest had additional early advocates in the South. Peter Gazes in Charleston, as already alluded to, was one of these advocates and Nanette Wenger at Grady Memorial Hospital (GMH) was another. A medical student at Harvard in the 1950s Wenger had first-hand exposure to the chair which she described as a "lounge chair, what we would think of as a recliner today" and it was being used extensively at the PBBH. Across the street at the Beth Israel Hospital (BIH), where she rotated with Herrman Blumgart, they had the "cardiac bed" in which "the patients were at strict bed rest, they couldn't even turn by themselves to have their bed linen changed." Wenger termed the chair "revolutionary" but not universally accepted. In her subsequent training at Mount Sinai Hospital (MSH) in New York she told her mentors and teachers that the chair was what they were doing at the Brigham but patients at MSH were for the most part at bed rest for six to

[51] R. Bruce Logue and J. Willis Hurst. "Management of Coronary Atherosclerosis and its Complications." In J. Willis Hurst and R. Bruce Logue, editors. *The Heart.* New York: McGraw-Hill (1966): 718.

eight weeks; the reasoning based on pathology and autopsy studies in those who died of myocardial infarction and the belief that it took that long for the area of infarction to heal.[52]

When Wenger arrived at GMH in Atlanta in 1958-59 Emory had no chair but she received her first federal research grant in the early '60s from Social and Rehabilitative Services (SRS) to study early ambulation after myocardial infarction. According to Wenger, "Grady had the first early ambulation program [beginning in 1962] in the world." It began as a 14 step program with a progressive step each day and patients were discharged home by day 18. What enabled Grady to do it was the early establishment there of a CCU[53] and the ability to monitor patients closely as ambulation progressed. In her words, "We basically walked the patient around the bed the first couple of days when they were still attached to the hard wire monitor and it was a combined program with physical medicine and rehab and cardiology." Much of the impetus for early ambulation, she told me, came from the space program which was looking at the time at "deconditioning" effects of weightlessness in space. Strict bed rest, according to Wenger, represented "partial weightlessness." It was felt that early ambulation prevented the process of deconditioning that occurred in MI patients with prolonged bed rest consequently leading to high rates of morbidity and mortality. Wenger attempted to study early ambulation versus bed rest in a randomized controlled study but it was impossible to complete she told me, because those randomized to bed rest in the CCU would see what those randomized to early ambulation were doing and they "imitated it." Although Wenger did not strictly use the cardiac chair per se, when she arrived in Atlanta, the concept of getting patients out of bed was put in full swing at GMH by the early 1960s.[54]

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[52] Telephone communication with Dr. Nanette Wenger, May 29, 2014.
[53] Grady Memorial Hospital established a CCU in the early 1960s shortly after Wenger arrived there from New York.
[54] Telephone communication with Dr. Nanette Wenger, May 29, 2014.

From what we know of later studies on early mobilization after myocardial infarction there is little doubt that getting individuals out of bed improved overall morbidity of the disease, mortality from complications and a generalized sense of well-being in all who suffered from the disease with little in the way of negative impact.[55] Besides reducing mortality, Lown "noticed many other salutary changes" in those treated with the chair. He writes,

> Within a day after admission, they no longer looked sick or wan. Their pain readily responded to small doses of morphine. Though their condition remained serious, their outlook was upbeat, and they were inpatient to resume normal living. Patients in chairs promptly began to harangue the staff to let them walk and to press for an early discharge.[56]

Although the time course from the initial description of chair treatment by Levine to the onset of decline in mortality is perfect in terms of a potential and significant effect (almost 20 years), and there is ample evidence for its use, there is just not enough statistical data substantiating the impact of the chair on early mortality to say that it was definitely the factor that singly caused the national decline in mortality to begin in 1968. Where it was used it seems to have impacted mortality in a significant way. It is quite likely that, coupled with other changes and early innovations in treatment at the time, it helped contribute in a significant way to the national decline in mortality. Desmond Julian who is identified by all as the originator of the concept of the coronary care unit credits his interest in coronary disease to his father who "sustained a nonfatal infarction in 1954" and the experience of being a Samuel Levine Fellow of Cardiology at the PBBH from 1957 to 1958, coming under the influence of Levine and "the armchair treatment of myocardial infarction" all prior to his formulation that would incorporate his experiences into a new way of caring for patients with acute myocardial infarction.[57]

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[55] Harold Herkner, et al. "Short versus prolonged bed rest after uncomplicated acute myocardial infarction: A systematic review and meta-analysis." *J Clin Epi* 56 (2003): 775-781.
[56] Bernard Lown. *The Lost Art of Healing.* 181
[57] Desmond G. Julian. "The evolution of the coronary care unit." *Cardiovasc Res* 51 (2001): 621.

The Development of the Coronary Care Unit

Next in the timeline of significant medical and scientific advancements in coronary artery disease was the development of selective coronary angiography. Mason Sones, one of the pioneers of the field, performed the first selective coronary arteriogram at the Cleveland Clinic on October 30, 1958.[58] According to Thomas J. Ryan this milestone "introduced a new era in cardiovascular medicine that was to revolutionize our understanding and management of the cardiac patient for the remainder of the twentieth century." It allowed for better documentation of the origin of symptoms of angina pectoris and for a better understanding of the natural history of the disease.[59] The impact of coronary angiography however, on the mortality from coronary artery disease, prior to the development of successful coronary artery bypass graft (CABG) surgery by Rene Favaloro in 1969, was probably nil. In fact, the mortality of the procedure in the late 1950s and 1960s (generally 2% to 4% for patients with single-vessel disease, 7% to 8% for 2-vessel disease, and 12% for 3-vessel disease),[60] fairly excessive by modern standards, probably contributed in a very small way to the overall mortality of coronary artery disease during the period. The impact of the procedure on improvement in mortality would not be realized until the 1970s and beyond, as it became a diagnostic tool for multiple therapeutic interventions.[61]

Following closely on the development of coronary angiography came the realization that patients with myocardial infarctions needed better care and observation during the initial period of their heart attack. Surgical intensive care units for care of post-operative patients had

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[58] Tsung O. Cheng. Correspondence. "First Selective Coronary Arteriogram." *Circ* 107 (2003): e42.
[59] Thomas J. Ryan. "The Coronary Angiogram and Its Seminal Contributions to Cardiovascular Medicine Over Five Decades." *Circ* 106 (2002): 752.
[60] Ibid. 753.
[61] S. Yusuf, et al. "Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomized trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration." *Lancet* 344 (1994): 563-570.

already begun to spring up around the country starting in 1927,[62] and by late 1953 and early 1954 intensive care units began appearing in a number of diverse locations from North Carolina to Connecticut to New York and Illinois. These "ICUs admitted patients from outside the hospital and from other units in the hospital in addition to those from the operating rooms." Although new in concept, they had the appearance of traditional wards partitioned by glass walls and "not surprisingly, they were usually crowded, makeshift areas."[63] With these already in place and according to some physicians used for a variety of patients, including those with heart disease,[64] the concept of intensive care for an individual with a life threatening event, like a myocardial infarction, was not novel. Prior to the development of coronary care units (CCU) "patients with acute myocardial infarction – if fortunate enough to survive until they reached a hospital – were placed in beds located throughout the hospital and far enough away from nurses' stations that their rest would not be disturbed. Patients were commonly found dead in their beds, presumably from a fatal tachyarrhythmia."[65]

The need for an entity like the CCU was probably first circulated and suggested by Samuel Levine in his 1929 book on coronary thrombosis. In it he wrote of "the abruptness of the onset of symptoms, the rapidity of the progress of the disease, and the suddenness of the complications that may arise."[66] He made special note of the risk of arrhythmias and heart block in patients post infarction, pointing out the immediate need for the use of drugs like quinidine

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[62] Dr. Walter Dandy established a separate, defined site for postoperative patients—the first in the US—at the Johns Hopkins Hospital in 1927.

[63] Julie Fairman and Joan E. Lynaugh. *Critical Care Nursing: A History.* Philadelphia: UPenn Press (1998): 12-13.

[64] Dr. Eugene Braunwald told me when I interviewed him that ICUs, not necessarily CCUs, were in place earlier than Julian's original description and cared for heart disease patients even though they were not formal CCUs.

[65] Elizabeth G. Nabel and Eugene Braunwald. "A Tale of Coronary Artery Disease and Myocardial Infarction." 56.

[66] Samuel A. Levine. *Coronary thrombosis: Its various clinical features.* Baltimore: Williams and Wilkins (1929): 94.

and adrenaline respectively in these patients. Levine pens, "There is one unusual complication of coronary thrombosis, which although rare is quite important because if unrecognized or improperly treated may in itself prove fatal, whereas under proper medication recovery can take place. This is the inception of ventricular tachycardia… [and]…when [it] develops the proper treatment is quinidine."[67] It was also the first known suggestion for having nurses monitor heart rate and rhythm to discern the onset and development of fatal arrhythmias.[68],[69]

By 1950 treatment of acute myocardial infarction included administration of intravenous fluids, oxygen administration, the use of subcutaneous atropine and papaverine, sublingual nitroglycerin in the form of glyceryl trinitrate for chest pain and the use of anticoagulants to prevent complications including pulmonary embolus. According to Eugene Braunwald the first half of the 20th century was remarkable for "establishing diagnostic criteria" for myocardial infarction and for "elucidating the natural history of the condition." But in terms of treatment that period was of little benefit to the patient with myocardial infarction except for the relief of chest pain.[70]

We have already discussed the development and implementation of chair treatment in the 1950s. The next great achievement in patient directed coronary care came in the dawn of American Camelot but not first in this country. The year was 1961 and in a paper presented in Britain, Desmond Julian, senior medical registrar at the Royal Infirmary in Edinburgh, proposed that patients with acute myocardial infarction be admitted to "special Intensive-Care Units." His article in Lancet in 1961 caught the immediate attention of the entire medical world. He

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[67] Ibid, 98-99.
[68] Ibid.
[69]Ibid, 101. "It would be helpful if the nurse were trained to use a stethoscope, as they are in some hospitals, and follow carefully the rate and rhythm of the apex beat. In this way important changes in the heart mechanism should be detected sooner and more quickly treated."
[70] Eugene Braunwald. "Evolution of the Management of Acute Myocardial Infarction: a 20th Century Saga." *Lancet* 352 (1998): 1772.

outlined the needs and requirements for the proper care of patients with myocardial infarction as follows:

> First, all medical, nursing, and auxiliary staff should be trained in the techniques of closed-chest cardiac massage and mouth-to-mouth breathing. Secondly, patients known to be at risk from ventricular fibrillation or asystole could have their cardiac rhythm constantly monitored. This means that all wards admitting patients with acute myocardial infarction should have a system capable of sounding an alarm at the onset of an important rhythm change and of recording the rhythm automatically on an E.C.G. In most cases, probably, an arrhythmia is present for at least 30 seconds (often for some minutes) before loss of consciousness: if it were diagnosed immediately the chances of resuscitation would be improved and the dangers of brain damage minimized. Such monitoring is particularly necessary during the first 48 hours after infarction, but cardiac arrest may occur at any time in the first 2 weeks. The provision of appropriate apparatus would not be prohibitively expensive if these patients were admitted to special intensive-care units. Such units should be staffed by suitably experienced people throughout the 24 hours, since it is unreasonable to expect good results when the care of the patients is entrusted to inexperienced residents who have many other responsibilities.[71]

According to Braunwald, "the world was ready for a concept of the CCU." Julian was the first but the idea was being "talked about in other places."[72] Within months CCUs were opened in this country, at Bethany Hospital in Kansas City by Hughes Day[73] and at Presbyterian in Philadelphia by Lawrence E. Meltzer.[74] Braunwald told me "it spread over the world like wildfire…actually over the United States." He thought it was much slower in Europe.[75] The

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[71] Desmond G. Julian. "Treatment of cardiac arrest in acute myocardial ischemia and infarction." *Lancet* 278 (1961): 843.

[72] Interview with Eugene Braunwald at his office on Longwood Avenue, Boston, Massachusetts, October 18, 2012.

[73] A community hospital. Hughes W. Day. "An Intensive Coronary Care Area." *Dis Chest* 44(1963): 423-427.

[74] An inter-city hospital, affiliated with the University of Pennsylvania, in 1965. Arlene W. Keeling. *Nursing and the Privilege of Prescription, 1893-2000.* Columbus: Ohio State University Press (2007): 112-113.

[75] Interview with Eugene Braunwald at his office on Longwood Avenue, Boston, MA, October 18, 2012. Desmond Julian agrees stating "The concept of coronary care had been quickly adopted in the United States, but much more slowly in Europe." See Desmond G. Julian. "The evolution of the coronary care unit." *Cardiovas Res* 51 (2001): 623.

origins of the CCU were very much tied to the new concept of closed chest resuscitation and the ability to terminate ventricular fibrillation by electrocardioversion. Paul Zoll and his colleagues at the Beth Israel Hospital (BIH) in Boston first reported "the successful termination of ventricular fibrillation in 4 patients by countershock applied externally across the closed chest." It demonstrated that by applying a current to the chest, ventricular fibrillation (VF) could be terminated safely and effectively.[76] Zoll used alternating current (AC) defibrillation in his study. Unfortunately, both in the lab and in the hospital, a significant number of animals and patients receiving AC defibrillation, although terminating their VF, ultimately died. As a result, Bernard Lown and colleagues at Harvard Public Health researched and introduced direct current (DC) electroshock which had a much lower risk of morbidity and mortality. One of the problems with AC countershock was that ventricular fibrillation reoccurred as a complication with a frequency ten times greater than when DC current was used. [77] Studies by the Lown group further determined that although both AC and DC injured tissue when shock was delivered, DC was associated with significantly less damage, potentially explaining the lower risk of complications. As a result, the use of AC fell out of favor in the early 1960s and DC for both defibrillation and cardioversion became and is currently the standard for cardioversion of malignant arrhythmias and for use in resuscitation after cardiac arrest.[78]

Julian viewed closed-chest cardiac massage as "an outstanding advance" in the care of patients with heart disease.[79] Braunwald added "the whole concept of closed chest resuscitation came out of Johns Hopkins and it was what the CCU was about."[80] W. B.

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[76] Paul M. Zoll, et al. "Termination of Ventricular Fibrillation in Man by Externally Applied Electric Countershock." *NEJM* 254 (1956): 727-732.
[77] Bernard Lown, et al. "Comparison of Alternating Current with Direct Current Electroshock Across the Closed Chest." *Am J Cardio* 10 (1962): 223-233.
[78] Regis A. DeSilva, et al. "Cardioversion and defibrillation." *Am Hear J* 100 (1980): 881-895.
[79] Desmond G. Julian. "Treatment of cardiac arrest in acute myocardial ischemia and infarction." 843.
[80] Interview with Eugene Braunwald at his office on Longwood Avenue, Boston, MA, October 18, 2012.

Kouwenhoven, a lecturer in Surgery at Hopkins, together with his resident and surgical assistant, wrote the first paper on closed-chest cardiac massage which appeared in *JAMA* in 1960. Prior to their pioneering work cardiac resuscitation after a cardiac arrest or after ventricular tachycardia required surgery with an open thoracotomy and then direct message of the heart. The procedure was fraught with complications and limited by the fact that it had to be done in a hospital or emergency room by a surgeon skilled in opening the chest cavity. Its success rate was also limited. With closed-chest massage, "Immediate resuscitative measures [could] be initiated to give not only mouth-to-nose artificial respiration but also adequate cardiac massage without thoracotomy." In their study 20 patients with cardiac arrest or ventricular fibrillation were treated with the new technique with "an over-all permanent survival rate of 70%." More importantly a technique had now been discovered that could be done anywhere and by anyone. As they make note "all that is needed are two hands."[81] According to Julian, "Kouwenhoven, et al at Johns Hopkins showed the effectiveness of combining mouth-to-mouth breathing, sternal compression and closed chest electrical defibrillation in restoring normal cardiac function in victims of ventricular fibrillation" and "it was this advance that triggered the interest in intensive care for myocardial infarction."[82] Thomas Ryan added, that when "closed chest cardiac massage was making the headlines… [we had] a sense of bravado when undertaking newer concepts" including getting patients out of bed early.[83] Although closed chest massage was not confined to the CCU it was intimately connected to it in a number of ways. By the 1960s, if a patient had an arrest and survived by resuscitation they were immediately moved to and cared for in the newly constructed CCUs. In addition, closed chest massage shared with the CCU the developing notion

[81] W. B. Kouwenhoven, James R. Jude and G. Guy Knickerbocker. "Closed-Chest Cardiac Massage." *JAMA* 173 (1960): 1064-1067.
[82] Desmond G. Julian. "The evolution of the coronary care unit." *Cardiovas Res* 51 (2001): 621.
[83] Email communication from Dr. Thomas J. Ryan, April 16, 2014.

that others, besides physicians, could preserve life "until the doctor arrives."[84] It is on this tenant that the CCU derives much of its power in reducing mortality of patients after a myocardial infarction. Both represented a significant change in course from traditional professional (doctor-nurse) concepts and relationships concerning the care of patients.

Eugene Braunwald and W. Bruce Fye both write extensively about the CCU. Braunwald has called it "the single most important advance in the treatment of AMI." It came about, according to Braunwald, because of "four separate developments," some already alluded to, as follows:

- The appreciation of the importance of arrhythmias as the principle cause of early death in AMI
- The ability to monitor the ECG continuously with cathode-ray oscilloscope
- The development of closed-chest cardiac resuscitation
- The delegation of the treatment of life-threatening arrhythmias, particularly ventricular fibrillation, to trained nurses in the absence of physicians.[85]

By 1966, writes Braunwald, "CCU treatment of AMI became the standard of care worldwide." Early mortality was cut in half, "from about 30% to 15%," in the CCU primarily because of the ability to detect and control fatal arrhythmias in this new setting. With the reduction in death due to arrhythmias, "pump failure secondary to extensive myocardial damage [remained and] emerged as the principal cause of death in these patients." But improvement in this latter complication of infarction would not occur until after 1970 and the development of the Swan-Ganz catheter which enabled the precise monitoring and treatment of ventricular function in the CCU. [86]

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[84] P.G.F. Nixon. "The Arterial Pulse in Successful Closed-Chest Cardiac Massage." *Lancet* 278 (1961): 845-846.
[85] Eugene Braunwald. "Evolution of the management of acute myocardial infarction: a 20th century saga." 1771-74.
[86] Ibid, 1772.

In his book, *American Cardiology,* Fye traces the development of the CCU as he details the emergence, in the same period, of greater medical specialization in cardiology. He describes the CCU as "a new heart care paradigm that united high-risk heart patients, technology, and specialized staff – nurses and doctors – in a specific hospital environment." Perhaps unlike chair treatment, where unwarranted tradition and skepticism may have stalled innovation, the concept of a specialized area for patients with AMI "spread quickly because it saved lives in a very visible and dramatic way." When the coronary care unit concept was proposed, its proponents "did not want to wait for scientific studies to prove its efficacy."[87] The pattern of care for patients with myocardial infarction, according to Fye however "had begun to change even before the advent of the coronary care unit" with "a significant increase in the number of chemistry tests, x-rays, and electrocardiograms" being performed between 1939 and 1969.[88]

To most caring for critically ill patients in an intensive care monitored setting seemed almost intuitive. In 1965, in an article entitled "The Coronary Care Area: A Tiger by the Tail," President of the American College of Cardiology Eliot Corday began his "President's Page" with the statement that "Possibly 100,000 patients with hearts that are too good to die can be saved each year with proper surveillance and treatment in acute coronary care units." He called the early survival results in the CCU "gratifying" and predicted in short course that all patients with evidence of infarction will be admitted there "as a matter of routine." He recommended, as a matter of course, that "extensive remodeling be avoided [by hospitals]" and "existing wards…be used without reconstruction…at least until the operating group can obtain some practical

[87] W. Bruce Fye. *American Cardiology: The History of a Specialty and Its College.* Baltimore: Johns Hopkins (1996): 250-251.
[88] Ibid, 254.

experience and measure the exact requirements of the hospital and community."[89] It was also probably intended to expedite the implementation of this new way of care.

Corday outlined the organization of a CCU in his article emphasizing the new roles and responsibilities of the nursing staff. He wrote "The most important part of the coronary care center is the staff, trained not only in routine nursing care but also in electrocardiography and the principles of resuscitation." It is in the latter that the CCU created a whole new role for nurses, as "on site" first responders. The CCU was established and predicated on the "general agreement that when cardiac arrest occurs, the nursing staff should [be able to act without hesitation or delay and] apply closed chest cardiac resuscitation, and either mouth-to-mouth breathing or pulmotor breathing until the medical staff arrives." With the knowledge of "electrocardiography, she [the nurse] should be authorized to apply an external pacemaker as soon as a standstill occurs, and in many hospitals the nursing staff is also permitted to apply electroshock when ventricular fibrillation supervenes."[90]

The implementation of the coronary care unit into hospitals in the 1960s, beyond how it changed the role of nurses, also ushered in several additional important elements that improved the care of coronary artery disease patients. An expanded job market created the need for additional cardiologists. According to Fye "by 1965 the American Board of Internal Medicine (ABIM) had certified only 803 cardiologists and the ACC (American College of Cardiology) had just 2,818 members."[91] Killip and Kimball, three years later published an article evaluating "the coronary care unit in concept and practice." They wrote "As currently organized the CCU is

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[89] Massachusetts General Hospital followed this recommendation with its first CCU of 4 beds in a large converted patient room on Bullfinch 3 and soon after the construction of a 6 bed unit with individual rooms in Phillips House.

[90] Eliot Corday. "President's Page. The Coronary Care Area: A Tiger by the Tail." *Am J Cardiol* 16 (1965): 466-468.

[91] W. Bruce Fye. *American Cardiology: The History of a Specialty and Its College.* 254

designed to provide the services of two specialists in the management of myocardial infarction. The physician-cardiologist and the trained cardiac nurse combine their talents to provide continuous experience and critical evaluation of results."[92] Based on this requirement Fye projected the need for over 2,000 cardiologist directors if every hospital in the U.S. with more than 100 beds opened a CCU. The number of CCUs in this country grew from none in 1960 to 2,300 in 1972.[93]

Suddenly the specialty of cardiology exploded and more individuals training in internal medicine were going on to become heart specialists. In the 1960s, due to the establishment of the coronary care unit and the need for specialists to run and staff them, but also in large part due to the recent introduction of selective coronary angiography being done by the same individuals, the care of coronary patients was no longer in the realm of the general internist, as it had been for the most part since the time of Herrick, but was moving firmly and quickly to the domain of those physicians specially trained in cardiology.

Jack Hyland told me that when the CCU was established at Baylor in Dallas, admission to the CCU "required that the patient not only have an internist involved but also had to have a cardiologist; so not just the unit [alone was important] but the fact that a cardiologist was also caring for the patient which was not generally required when a coronary patient or acute MI went to the ward and not generally true before CCUs came into existence." He thought when this rule was instituted that there would be outrage among the internists at his hospital, but that was not the case and the addition of a cardiologist to the care of all those in the CCU was viewed as "useful and probably did help a lot." Hyland also credited the requirement and institution of "standardized orders" for all those admitted to the CCU as critical to the care of

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[92] Thomas Killip and John T. Kimball. "A Survey of the Coronary Care Unit: Concept and Results." *Prog Cardiovas Dis* 11 (1968): 45-52.
[93] W. Bruce Fye. *American Cardiology: The History of a Specialty and Its College*. 254

those in the CCU. It eliminated calls in the middle of the night to weary physicians and allowed for nurses and others involved to care for patients in the CCU in a uniform, efficient and highly disciplined way. It really "raised the bar for the care of these patients substantially."[94]

As Fye explains, "although the advent of the coronary care unit transformed the care of heart attack patients and stimulated the job market for cardiologists, the nearly simultaneous expansion of indications for cardiac catheterization and angiography had an even greater impact on the specialty."[95] Cardiac catheterization was first performed by German physician Werner Forssman on himself in 1929. Using a urinary catheter and inserting it into his left antecubital vein he advanced it under fluoroscopic guidance into the right side of his heart, documenting his accomplishment with radiographs which can be seen in his original German publication.[96] The Nobel Prize winning achievement[97] helped advance an understanding of cardiac physiology but did not look at either the anatomy or function of the coronary arteries.

It was not until almost thirty years after Forssman's rather unconventional work, in 1958, that Mason Sones, a pediatric cardiologist at the Cleveland Clinic, discovered quite by accident that contrast media could be safely injected into the coronary arteries. He presented his findings at both the Heart meeting and American College of Cardiology meeting in 1959 but according to Fye "although Sones's oral presentations stimulated some interest in coronary angiography, few persons attempted it until 1962, when he published a brief paper on his

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[94] Interview with Dr. Jack Hyland, in his office, Baylor University Medical Center, Dallas, Texas, November 16, 2012.
[95] W. Bruce Fye. *American Cardiology: The History of a Specialty and Its College*. 255-256.
[96] Werner Forssman. "Die Sondierung des Rechten Herzens." *Klin Wochenshrift* 8 (1929): 2085-2087.
[97] Forssman shared in the 1956 Nobel Prize with Andre Frederic Cournand and Dickinson W. Richards, physicians at Columbia and Bellevue Hospital, who used the technique of cardiac catheterization to study heart failure, shock and congenital diseases of the heart.

selective technique in the American Heart Association's (AHA) widely circulated educational leaflet *Modern Concepts of Cardiovascular Disease*."[98]

Sones described the procedure and its utility as "a safe and dependable method for demonstrating the physical characteristics of the human coronary artery tree, which could be applied in any phase of the natural history of coronary artery disease, was needed to supplement available diagnostic methods." He believed its great utility at the time was to study patients "in whom the diagnosis of coronary artery disease is suspected, but ill-defined, or questioned because of atypical clinical features" but forecasted its eventual use for selecting patients that might benefit from surgical intervention aimed at "improving myocardial perfusion." In his initial study of 1,020 patients, the complication rate was exceedingly small and mortality rate 0.29 percent.[99] Although there were others working on catherization of the coronaries at the time, Sones is universally credited with perfecting selective coronary angiography (discovered initially quite serendipitously after accidental injection of dye into the coronaries) and after 1962 he was besieged by otherwise trained cardiologists seeking to learn his technique. Charles Hatcher told me that at the time a contingency of Emory cardiologists already on staff traveled in the dead of winter to the Cleveland Clinic to see Sones at work.[100] Others corroborated this in their travels to Cleveland and descriptions of Sones at work; his ever present lit cigarette held by a Kelly clamp always at his side in the catherization laboratory.[101]

Coronary angiography had a profound impact on the specialty of cardiology and its training. According to Fye it "changed the practice – and the profession – of cardiology, as the

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[98] W. Bruce Fye. *American Cardiology: The History of a Specialty and Its College*. 175
[99] F. Mason Sones and Earl K. Shirey. "Cine Coronary Arteriography." *Mod Conc of Cardiovasc Dis* 31 (1962): 735-738.
[100] Interview with Dr. Charles Hatcher in his home in Atlanta, Georgia January 31, 2013.
[101] Interviews with Dr. Thomas Ryan, Dr. Jack Hyland and Dr. Spencer King

electrocardiograph had half a century earlier."[102] It was the start of a transition from a specialty that was rather non-invasive to one that would become, over the next half century, very procedure oriented. This, with the economic stimulus to physicians that accompanied it, and the need for cardiologists to staff coronary care units emerging at the same time helped to increase the number of cardiologists in this country and the level of care delivered to patients with coronary artery disease. By the 1960s these "innovations in patient care were placing coronary artery disease at the center of cardiology research and practice."[103]

Thus, there is ample evidence, from the literature and from personal interviews that the CCU had an almost immediate impact on coronary artery disease mortality and that the expansion of cardiology as a specialty, in terms of the number of practitioners entering the field, after the events described above, may have contributed in terms of better and more specialized care for patients with disease of the coronary arteries. Coronary angiography, on the other hand, as already mentioned, could have had no impact on mortality until effective treatment for the findings was discovered. This did not occur until 1968 when Rene Favaloro, a surgical colleague of Sones at the Cleveland Clinic, reported on the surgical care of 15 patients with segmental coronary artery occlusion of the right dominant coronary artery using a saphenous vein autograph to bypass the occluded segment (CABG).[104] It was met with initial skepticism and much scrutiny because earlier attempts to treat coronary occlusion with surgery had been largely unsuccessful. But "despite these concerns, CABG quickly gained supporters because patients and doctors thought it worked."[105] It however had no impact on the early decline of

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[102] W. Bruce Fye. *American Cardiology: The History of a Specialty and Its College.* 256
[103] Ibid, 175.
[104] René Favaloro. "Saphenous Vein Autograft Replacement of Severe Segmental Coronary Artery Occlusion." *Ann Thor Surg* 5 (1968): 334-339.
[105] W. Bruce Fye. *American Cardiology: The History of a Specialty and Its College.* 259

mortality in this disease largely because that decline had already begun by the time Favaloro published his first paper on CABG treatment.

In 1967 a study of the management of acute coronary occlusion in the State of North Carolina was published substantiating the benefit of intensive care for patients with acute myocardial infarction. It was compiled from individual case abstracts prepared from clinical records by medical record personnel and reflect on the mortality of coronary artery disease in 44 hospitals across the state of North Carolina. It compared hospitals with coronary care units (5 hospitals), those with only intensive care units (6 hospitals) and all other hospitals with neither (33 hospitals). In hospitals with coronary care units the overall death rate of "coronary patients" was 25% (range 20-29%), in those with only intensive care units the death rate overall was 27% (range 14-42%) and in all the other hospitals where coronary patients were cared for outside of either type unit the death rate was significantly higher at 31% (range 14-80%). Across all the hospitals the death rate was highest in the first two days of hospitalization with 53% of deaths recorded in that time period.[106]

In addition to the work of Braunwald and others, Killip and Kimball probably provide the greatest support for the role of the CCU in reducing short term the mortality of coronary artery disease. Writing in 1968, seven years after coronary care units first came into existence and the year death from coronary artery disease began to decline, they note that "The mortality rates for patients with acute myocardial infarction cared for in a CCU *appear* to be lower than those described for patients treated in regular care facilities." Citing a number of authors who have compared the mortality rates prior to "opening of a CCU" to those after "have claimed an average reduction of mortality by about one-third." Furthermore, in terms of lag time for

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[106] Professional Activity Study. "Acute Coronary Occlusion: Its Management in North Carolina." *The Record.* Ann Arbor: Commission on Professional and Hospital Activities 5 (20 December 1967 and 9 February 1968).

improving mortality "It is commonly observed that mortality rates are lower after the CCU has been in operation for some months. This improvement reflects increasing experience and training of physicians and nurses." According to Killip and Kimball, although "no critical prospective study comparing the effects of CCU care and regular care in the same institution is available" a head to head randomized controlled study of CCU care versus "regular care" would "probably be impossible." In such a study, "freedom from bias in the allocation of patients [would be] highly unlikely since patients with pre-existing arrhythmias would preferentially move into the CCU" and not elsewhere. By 1968 it was evident that "The mere establishment of a CCU improves recognition and treatment of arrhythmias including cardiac arrest, thus upgrading medical care throughout the institution." So in this regard, "a critical, objective, unbiased evaluation of the CCU based on random allocation of patients to two types of care facilities within a single institution will never be feasible."[107] Killip and Kimball concluded that short of a prospective randomized controlled trial it is "abundantly clear…that the coronary care unit, by concentrating trained personnel and appropriate equipment in a specific area of the hospital, improves the efficiency and effectiveness of treatment in acute myocardial infarctions."[108]

Multiple forces came together in the CCU; advanced technology and new techniques of resuscitation, new medications that could be administered for lethal arrhythmias, and an expanding and highly skilled core of physicians. But as nurse historian Arlene Keeling writes, "The key to the entire coronary care project was, by necessity, the nurses' advanced training in the highly specialized area of coronary care" and their ability to act on it without hesitation

[107] The issue is an ethical one analogous to doing a placebo controlled trial on patients knowing that doing so subjects the control group to no treatment rather than already known effective treatment.
[108] Thomas Killip and John T. Kimball. "A Survey of the Coronary Care Unit: Concept and Results." 45-52.

when necessary to save patient lives.[109] The soundness of this paradigm shift and concept has endured. Writes Fye on the 50th anniversary of the coronary care unit concept, "The CCU-inspired empowerment of nurses represented a critical first step in the evolution of team-based care that is such a conspicuous part of current-day cardiology practice."[110]

A great feminist movement

> **Women's dominance in nursing nearly equals our monopoly on motherhood: nursing has always been a woman's job.[111]**
>
> **Nurses who had been "ordered to care" now stepped over the nursing practice domain line into the realm of scientific medicine and "cured" the patient's arrhythmias—in dramatic lifesaving moments.[112]**

The 1960s saw not only huge changes in the practice of cardiology with the development of selective coronary angiography and the coronary care unit but also the direct involvement for the first time by the government in healthcare. The federal government's "broad interventionist programs in civil rights, poverty and social welfare" during the period fit perfectly into an agenda of needed sweeping changes in healthcare. It began with President Kennedy's address to Congress in February 1963 in which he enumerated a long list of healthcare priorities, including improvements in nursing which came directly out of a report by the surgeon general in that same month. On September 24, 1963, two months before his assassination, Kennedy signed the *Health Professions Educational Assistance Act,* which addressed an urgent need for new training facilities and educational opportunities not only for

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[109] Arlene W. Keeling. *Nursing and the Privilege of Prescription, 1893-2000.* Columbus: Ohio State University Press (2007): 114.
[110] W. Bruce Fye. "Resuscitating a *Circulation* Abstract to Celebrate the 50th Anniversary of the Coronary Care Unit Concept." *Circ* 124 (2011): 1886-1893.
[111] Barbara Melosh. *"'The Physician's Hand' Work Culture and Conflict in American Nursing."* Philadelphia: Temple (1982): 3.
[112] Arlene W. Keeling. "Blurring the Boundaries Between Medicine and Nursing: Coronary Care Nursing, circa the 1960s." *Nurs Hist Rev* 12 (2004): 139-164.

physicians and dentists, but also for nurses and other healthcare professionals. With Kennedy's death, Lyndon Johnson, took up the call for needed improvements in healthcare including nursing. In February 1964, he stated "the rapid development of medical science places heavy demands on the time and skill of the physician. Nurses must perform many functions that were once done only by doctors." Part of his goal was to increase the role of nurses in the direct management of care.[113] On September 4, 1964 Johnson signed into law the *Nurse Training Act of 1964* stating that "Nurses today are essential members of our Nation's health team. The health needs of a growing population cannot be met without their help."[114]

In the nineteenth century, the majority of nursing care was carried out in the "home as part of women's domestic duties." Florence Nightingale wrote in her manual of 1860, *Notes on Nursing,* that "every woman is a nurse." Imbedded initially in the "sphere of women's domestic work" nursing gradually separated as medical care became more complex and primarily associated with paid labor in hospitals. But the image of nursing as distinctly a woman's service continued well into the 20th century. With the development of increasingly modern technology and advances in hospital care no longer would anyone proclaim, one hundred years after Nightingale, "that every woman is a nurse." But the fact remained that the "cultural ideology of woman's place" still informed a medical division of labor with "nearly every nurse…a woman."[115]

With the actions of the federal government and the words of individuals like Eliot Corday and others a new movement was under foot in cardiology as well as elsewhere in medicine. Eugene Braunwald called it "a great feminist movement." Corday alluded to it when

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[113] Joan E. Lynaugh. "Nursing the Great Society: The Impact of the Nurse Training Act of 1964." *Nursing History Review* 16 (2008): 13-28.
[114] Lyndon B. Johnson. "Remarks Upon Signing the Nurse Training Act of 1964." *The American Presidency Project.* Septmeber 4, 1964.
[115] Barbara Melosh. *"'The Physician's Hand' Work Culture and Conflict in American Nursing."* 3.

he addressed the nurse as "she." According to W. Bruce Fye, "The widespread implementation of the CCU model in the mid-1960s triggered a major shift in the traditional relationship between doctors and nurses."[116] Prior to the 1960s and the development of CCUs, "the relationship between nurses and physicians and the division of the work of patient care was always negotiated against a backdrop of social, economic, political, and gender constraints that limited nurses' authority in patient care decisions."[117] According to Braunwald, before the CCU, nurses, "women 99% of the time," had to call doctors, "a man 99% of the time," when they needed to defibrillate a patient and then often wait 20 minutes or more for the doctor to arrive. With the CCU "this broke this apart and nurses began to defibrillate patients" before the doctor arrived.[118] Writes Barbara Melosh in *The Physician's Hand,* "nurses have never been content to define their work solely in relation to doctors. Both in professional associations and on the job, nurses have sought to claim and defend their own sphere of legitimate authority."[119] According to Lawrence E. Meltzer, director of the coronary care unit at Presbyterian-University of Pennsylvania Medical Center in Philadelphia and his colleagues, "intensive coronary care is primarily, and above all, a system of specialized nursing care and that its success is predicated almost wholly on the ability of nurses to assume a new and demanding role."[120] The new setting "invited physicians, albeit influenced by geography and situations at hand, to discard traditional assumptions gained through professional socialization and education about the expertise and abilities of nurses."[121]

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[116] W. Bruce Fye. "Resuscitating a *Circulation* Abstract to Celebrate the 50th Anniversary of the Coronary Care Unit Concept." 1891.
[117] Julie Fairman and Joan E. Lynaugh. *Critical Care Nursing: A History:* 70.
[118] Interview with Eugene Braunwald at his office on Longwood Avenue, Boston, Massachusetts, October 18, 2012.
[119] Barbara Melosh. *"'The Physician's Hand' Work Culture and Conflict in American Nursing."* 7.
[120] Lawrence E. Meltzer, Rose Pinneo and J. Roderick Kitchell. *Intensive Coronary Care: A Manuel for Nurses.* Philadelphia: The Charles Press (1970): Preface.
[121] Julie Fairman and Joan E. Lynaugh. *Critical Care Nursing: A History*: 77.

A four bed coronary care unit, the "Levine Cardiac Center," opened in February 1965 at the PBBH. Dr. Lown was the director of the unit and Bette Jane Bonneville was its head nurse. Writing in 1967 Bonneville notes "The nurse today is assuming a new role, with a number of new challenges and responsibilities. Especially in the care of coronary patients, her function has become drastically altered. From observing precautions under a physician's direction, from charting temperatures and the like, she has become a key element of a complex team whose orientation is toward guaranteeing the survival of the patient. According to many authorities, whether or not the patient survives depends, in the final analysis, on the training and proficiency of the nurse." The coronary care unit was predicated on empowering nurses with a new role in patient care, a set of "responsibilities which previously [had] been exclusively within the domain of physicians." Included in the majority of CCUs were standardized orders and the institution of a "pre-arranged program of antiarrhythmic therapy." Nurses were taught to react to rhythm disturbances of all types, including ventricular premature beats as well as bradycardia with the ability to administer drugs or cardioversion in a pre-set manner. The CCU nurse became "a sentinel whose job it is to interpret the patient's record as it appears on the oscilloscope" and respond with appropriate action.[122] Traditional nursing responsibilities continued as well, but in the CCU, "nurses expanded their role to include curing as well as caring."[123] In the environment of the CCU nurses had to act in the best interests of patient care and survival. Explains Melosh:

> The pace and character of intensive care left no room for the old formulas of nursing deference. No critical care nurse would call a doctor to report meekly, 'Mr. Brown's pulse appears to have ceased.' She would yell for emergency equipment, pound the patient's chest, inflate his lungs, initiate closed-chest cardiac massage, perhaps even begin to administer the drugs used in resuscitation. In turn, doctors recognized and depended on the skills and judgment of

[122] Bette Jane Bonneville. "Patient Monitoring – A Nurse's View." *JAAMI* January/February 1967: 24-27.
[123] Arlene W. Keeling. "Blurring the Boundaries Between Medicine and Nursing: Coronary Care Nursing, circa the 1960s." 156.

these nurses.[124]

Jack Hyland told me that initially his plan was to send a group of four nurses to Kansas City, where Hughes Day had already established one of the first CCUs in this country, to train nurses for the new CCU at Baylor, but the cost was too high and the administrator cancelled the trip. Instead, he was told by administration that he was going to train the nurses himself to work in the CCU at Baylor. According to Hyland, "all of a sudden I was faced with having to teach nurses and mainly EKG." The task was initially daunting but the movement broke down along lines of age. He continued, "It was amazing to give these courses and the young gals they would sit in the front row and get everything right. The old gals would sit in the back and never could get it. The old supervisors. So we picked out the best and they became CCU nurses. And that was about all they learned to start with. They learned some nursing things for sure. From my point of view to read arrhythmias and look at the monitor and stuff like that. That was quite a step. When we got to do defibrillation I use to have to come down the central expressway 80 miles an hour at night just to shock somebody because I was the only one trained on the defibrillator in those days. I quickly saw that was not going to work and I didn't like it so I trained the nurses" to do defibrillation on their own, when indicated. According to Hyland, the nursing board of the hospital at first objected to empowering nurses to critically observe patients and give them the responsibility to respond in therapeutic ways with medicines and technology that were previously reserved exclusively and legally for physicians. But the younger nurses embraced the new challenges and responsibilities and once "they learned how you couldn't keep them from it." In fact he told me, with time, nurses in the CCU became better at reading and interpreting EKGs and rhythm disturbances than internists.[125] This observation was

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[124] Barbara Melosh. *"'The Physician's Hand' Work Culture and Conflict in American Nursing."* 190.
[125] Interview with Dr. Jack Hyland at Baylor University Medical Center, Dallas, Texas, November 16, 2012.

also noted over time at Presbyterian Hospital in Philadelphia where "even when a resident or intern [physician] was present, the nurse might have to take the lead in treating the patient because some of the CCU nurses soon knew more than the house staff about the interpretation of cardiac arrhythmias and the necessary treatments."[126]

According to Fairman and Lynaugh, in their book on critical care nursing, "Traditional socialization patterns were more easily breached when physicians realized the advantages and had both the courage and the opportunity to work with nurses in a less authoritative and self-conscious manner." The CCU "served as a testing ground on which a more collaborative structure was explored and found to be beneficial"[127] and in this respect ushered in a new standard in care for both physicians and nurses. In most early CCUs an "unusually close camaraderie developed between nurses and physicians" in large part because of the small areas involved and a "shared sense of adventure in the new setting." One nurse noted "we [nurses and physicians] were all in this together…we all learned from each other."[128] As new boundaries in patient care were negotiated, the role of the nurse in the CCU evolved to become a full and near equal partner in administering care at critically needed times in the best interests of the patient. In actuality they had to evolve in this manner for "a continued monopoly on decision-making by physicians in intensive care units [CCU] would have been out of step with the realities of patient care and potentially dangerous to patients."[129] Writes Meltzer, et al. "In accepting this challenge and demonstrating remarkable competence as the key members of the coronary care team, nurses have been instrumental in saving the lives of thousands of patients with acute myocardial infarction; in doing so, they have broadly expanded the horizons of clinical nursing

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[126] Arlene W. Keeling. "Blurring the Boundaries Between Medicine and Nursing: Coronary Care Nursing, circa the 1960s." 157.
[127] Julie Fairman and Joan E. Lynaugh. *Critical Care Nursing: A History*: 78.
[128] Ibid. 85
[129] Ibid. 90.

and have earned the sincere respect of their physician and nurse colleagues and the gratitude of their patients."[130] According to historian Arlene W. Keeling, nurses in the coronary care units "experienced a new level of autonomy and gained a new level of respect. If the physicians did not like the nurses' new role, they either did not express their feelings or perhaps only discussed them in private with colleagues."[131]

Boundaries on general medical floors also changed with time, but they did so much slower, in part because the care for these patients was less critical and urgent, and in part because negotiations in this setting were held hostage "by the effects of educational socialization, economic forces, and control issues."[132]

The evolution of nurses from traditional roles of "caring" to greater roles of "curing" was by no means confined to the CCU alone and during the same time period, the decade of the sixties, the early nurse practitioner movement emerged empowering nurses with greater roles in the care of patients that had traditionally been the domain predominantly of male physicians. According to nursing historians, Julie Fairman and Patricia D'Antonio, "the 'baby boom', the ferment of the civil rights and feminist movements, changes in medical practice patterns, and the opening up of new opportunities for nursing practice and education all supported the emergence of the nurse practitioner movement as negotiated trades between physicians and nurses that met the needs and expectations of both groups in different ways. Physicians traded a piece of their traditional power base, clinical thinking, to nurses for the opportunity to focus on the more important, satisfying, and less boring aspects of medical practice."[133] In this

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[130] Lawrence E. Meltzer, Rose Pinneo and J. Roderick Kitchell. *Intensive Coronary Care: A Manuel for Nurses.* Preface.
[131] Arlene W. Keeling. "Blurring the Boundaries Between Medicine and Nursing: Coronary Care Nursing, circa the 1960s." 159.
[132] Julie Fairman and Joan E. Lynaugh. *Critical Care Nursing: A History*: 90.
[133] Julie Fairman and Patricia D'Antonio. "Virtual power: gendering the nurse – technology relationship." *Nurs Inquiry* 6 (1999): 178-186.

context, the evolution of the nurse practitioner in the 1960s represented "a grassroots paradigmatic shift" in the way women were perceived in the business of healthcare. New relationships, rules and "deviations from the authoritarian norms of the traditional healthcare hierarchy"[134] were forged in this period, paralleling the early development of the CCU that would forever change the role of nurses and women in medicine.

Role of Emergency Medical Services (EMS)

> **In terms of emergency medical systems (EMSs), World War II may have been the first venue where a functioning system of triage, transport, and acute attention to casualties resulted in improved outcomes, and Korean War EMS took this to a new level…but the dissemination of the principles of EMS to the civilian world was very slow.[135]**

Because approximately 70% of deaths from coronary artery disease occur outside of the hospital, the role of emergency medical services (EMS) is important to consider when addressing a decline in mortality.[136] I alluded to this in chapter 2 but will go into the impact of EMS on the survival of patients in greater detail here. EMS has been defined as "an organized system designed to transport sick or injured patients to the hospital."[137] In perhaps its crudest sense it traces its earliest origins, at least in part, to the French revolution and the Italian campaign of 1794. At the time Baron Dominique Jean Larrey felt that leaving his soldiers wounded on the field of battle would lead to a significant increase in morbidity and mortality. He devised a system of rapidly evacuating those wounded on the battle field during combat using "flexible medical units which he named *ambulances volantes* ('flying ambulances')." In so doing he began

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[134] Ibid. 181.
[135] Brian J. Zink. *Anyone, Anything, Anytime: A History of Emergency Medicine.* Philadelphia: Mosby (2006): 7-8
[136] Richard J. Havlik, and Manning Feinleib, eds. *Proceedings of the Conference on the Decline in Coronary Heart Disease Mortality.* xxiii-xxiv
[137] Charles N. Pozner, Richard Zane, Stephen J. Nelson, Michael Levine. "International EMS Systems: The United States: past, present, and future." *Resus* 60 (2004): 239-244.

a system in which army medical personnel began treatment, as it was known at the time, on the battlefield and as the wounded were transported to the field hospital.[138]

In this country, EMS originates during the conflict between the states in which both the union and confederate armies tried to emulate the system initiated by Larrey. Initial success was hampered on both sides by multiple factors including lack of funds, government support and trained medical personnel. The Battle of Second Manassas (Bull Run) in 1862, where a considerable number of soldiers were wounded and left on the battlefield to die, led the Union to transfer the direction of medical care to General Jonathan Letterman, a military surgeon, who followed the lead established by the French in the revolution. Letterman, like Larrey "staffed and trained an ambulance corps of men to operate horse teams and wagons to pick up wounded soldiers from the field and bring them back to field dressing stations located next to the battlefield for initial treatment such as application of tourniquets and dressings. They could then be evacuated to nearby Field Hospitals for emergency surgery, and later to a larger hospital further away for any prolonged treatment."[139]

Over the course of history and through to the 20th century it was not unusual for the military to take the lead in terms of implementing emergency medical care, in large part due to the immense morbidity and mortality inflicted on the field of battle.[140] It was the success of Letterman during the Civil War, felt to have given the Union a distinct military advantage over their enemy[141] that led civilian society to appreciate the importance of emergency medical

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[138] Panagiotis N. Skandalaskis, et al. "To Afford the Wounded Speedy Assistance": Dominique Jean Larrey and Napolean." *World J Surg* 30 (2006): 1392-1399.
[139] Christopher R. Blagg. "Triage: Napolean to the present day." *J Nephrol* 17 (2004): 629-632.
[140] The Vietnam War saw great strides in carrying for those injured in the line of duty which eventually was replicated in civilian, non-combat, situations.
[141] There is a belief that Union superiority in medical care during the war may have been instrumental in defeating the Confederacy which did not do as well in terms of medical and emergency care. It is the premise of the book by Frank R. Freeman, *Gangrene and Glory: Medical Care During the American Civil War.* Madison, NJ: Fairleigh Dickinson University Press, 1998.

service. In the same year that the Civil War ended, Commercial Hospital in Cincinnati implemented the first civilian hospital based ambulance service. This was in short order followed by the implementation of the first municipal emergency medical service at Bellevue Hospital in New York. Despite these early individual efforts, the EMS situation progressed very slowly indeed, evidenced by the fact that throughout the first half of the 20th century, even as late as the 1960s, especially in rural areas of the country, hearses from funeral homes doubled as ambulances in transporting the ill to hospitals. It was not unusual for this to be seen in a number of parts of the country. Writes Carl J. Post, even in cases of trauma, "Funeral homes supplied the transportation from the accident site to the hospital in Illinois, Kentucky, New York, and elsewhere while nobody seemed to notice."[142] This was corroborated by Dr. Robert Copeland, the first fully trained cardiologist to establish practice in LaGrange, Georgia. When I spoke to him he told me that when he arrived in this small city in South Georgia to start practice in 1967 "the original ambulance service there was awful." According to Copeland "they were still picking them [patients] up in a hearse" to bring them to the hospital; "the EMS concept came along [in LaGrange] in the 70s."[143]

As already alluded to, military practice played an important role in the development of EMS. This was especially true in both World War I and II and later in the Korean War. Quite a few authorities and "writers have attributed the beginnings of all of EMS to lessons learned in the Korean War and confirmed by the Vietnam War."[144] According to Pozner and associates, advances made in "military EMS…were not replicated in the civilian setting until well into the 1950s when JD "Deke" Farrington and Sam Banks, two civilian physicians, established a first-aid

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[142] Carl J. Post. *Omaha Orange: A Popular History of EMS in America*. Second edition. Sudbury: Jones and Bartlett (2002): 3.
[143] Interview with Dr. Robert Copeland in his home in LaGrange, Georgia, April 18, 2013.
[144] Carl J. Post. *Omaha Orange: A Popular History of EMS in America.* Second edition. 2.

training program for the Chicago Fire Department." It went on to "become the prototype for the first basic emergency medical technician (EMT) training program in the U.S."[145]

All said however, the 1960s represented a period of rapid growth in EMS and one that was in part focused on heart disease patients in particular. According to Post, "in 1964, cardiac emergencies had as good a chance as trauma of being the principal emphasis within organized emergency care systems." In fact, although currently trauma is a significant part of EMS care and resources, it was not until the 1970s that it consumed the great bulk of EMS attention.[146] In terms of EMS care for patients having heart attacks, in Los Angeles, Miami and Seattle there emerged a model that was used by paramedics who had been trained in advanced life support (ALS) which included training in defibrillation, basic airway management and the administration of some lifesaving medications. The paradigm appears to have paralleled the new responsibilities that nurses were receiving in the CCU but, unlike nurses, these personnel were more rudimentarily trained in patient care. A second model was also emerging and this one was more specifically focused on caring for those who had sustained a myocardial infarction. The "heartmobile" as it was termed was staffed with not paramedics but with physicians and nurses and were similar to a model developed in Belfast, Northern Ireland termed the "Pantridge system" or "Pantridge and Geddes system" which amounted to a mobile intensive care unit (MICU) with a portable defibrillator.[147] It became popular in cities like Cincinnati and New York. But full implementation of this latter model did not come into existence in major cities until the

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[145] Charles N. Pozner, Richard Zane, Stephen J. Nelson, Michael Levine. "International EMS Systems: The United States: past, present, and future." 239-244.
[146] Carl J. Post. *Omaha Orange: A Popular History of EMS in America*. Second edition. 2.
[147] J.F. Pantridge, J.S. Geddes. "A mobile intensive care unit in the management of myocardial infarction." *Lancet* 2 (1967):271.

mid-1970s and until then in most cities, like New York, EMS only provided basic life support for medical emergencies.[148]

Authorities mark 1966 as the watershed year in which modern EMS as we know it began. In that year a paper entitled: "Accidental death and disability: the neglected disease of modern society" was published by the National Research Council of the National Academy of Sciences, enumerating a host of issues and inadequacies of pre-hospitalization and emergency care in this country and made 24 specific recommendations for improvement. It provided the stimulus for federal support of an organized system of emergency and trauma care and in no small measure led Congress to pass the Highway Safety Act of 1966 which had been proposed by then President Lyndon Johnson in his State of the Union address that year. The congressional act led to the development of a new executive agency as well, the Department of Transportation. This new branch was given the task of improving EMS in this country and standardizing emergency medical technician training.[149]

Of interest Medicare and Medicaid came into existence just prior to the start of modern EMS. Although it had an enormous impact on the delivery of healthcare to the elderly and poor, its initial impact on EMS was inconsistent and spotty. Writes Post:

> Medicare and Medicaid were created just before the dawn of an EMS era. Together Medicare and Medicaid would enable EMS to do a great deal, while at the same time prohibiting efforts by EMS to do what logically might appear to be both necessary and appropriate. A strong and solidly conceived health care finance system was created for people over a certain age. A flawed, inconsistent, and defeatist solution was doled out to the states in the hope that they would somehow pay for the needs of the sick or injured poor. Liberal states did pay, but conservative and poor ones didn't.[150]

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[148] Emil F. Pascarelli, and Irwin B. Katz. "Planning and Developing a Prehospital Mobile Intensive Care System in an Urban Setting." *AJPH* 68 (1978): 389-393.
[149] Charles N. Pozner, Richard Zane, Stephen J. Nelson, Michael Levine. "International EMS Systems: The United States: past, present, and future." 240.
[150] Carl J. Post. *Omaha Orange: A Popular History of EMS in America.* Second edition. 3.

Inadequacies and disorganization in EMS existed throughout the 1960s. According to Brian J. Zink, this was made quite apparent when Robert Kennedy, while campaigning for the Presidency, was shot in Los Angeles. He writes "The City of Los Angeles ambulance personnel operated out of a receiving hospital that did not have good emergency or trauma capacity. Kennedy was transported by an ambulance crew who passed by a qualified hospital on the way to the receiving hospital, 'There was nobody there to take care of them and then they had to go back.' Kennedy died of his wounds, and a grand jury investigated the emergency services response."[151] In small measure as a result of this unfortunate event and others the state of California passed and then Governor Ronald Reagan signed into law in 1970 "The Wedwoth Townsend Act" allowing non-physicians for the first time to provide a level of advanced care to patients under the supervision of an off-site, usually emergency department, physician. Three years later the federal government passed the EMS act of 1973 which was intended to "improve and coordinate EMS care throughout the country." But the act fell short in accomplishing its goal and EMS development after 1973 "progressed in a disorganized manner resulting in a heterogeneous mosaic of systems, some of which met the intended goals" of a well-coordinated system but "others fell short."[152]

None of the experts I spoke to for this project believed that EMS impacted mortality of coronary artery disease in any substantial way prior to 1970. This was largely because, as demonstrated in the literature, little was in place at the time that could have saved the lives of those that did not survive prior to getting to the hospital. Stern writes that "the 'wall-to-wall' coverage necessary" to have impacted the decline in mortality of CHD that occurred between

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[151] Brian J. Zink. *Anyone, Anything, Anytime: A History of Emergency Medicine.* 121.
[152] Charles N. Pozner, Richard Zane, Stephen J. Nelson, Michael Levine. "International EMS Systems: The United States: past, present, and future." 240.

1968 and 1976 "was not in place" during the period.[153] EMS and emergency departments were only beginning to come into their own in the 1960s. MICUs in the model of Pantridge and Geddes were not of significant number in this country until at least the mid-1970s. Furthermore, pioneers in the field of emergency medicine, like Lewis Goldfrank at Bellevue Hospital and Sheldon Jacobson, at Jacobi Hospital, did not begin to take up the cause of EMS until well into the 1970s and only after improvements in the emergency departments themselves were made.[154] According to Zink, "The large scale utilization of trained, experienced physicians in emergency care would not be realized until at least 30 years after the end of World War II."[155] Clearly much changed in emergency care between 1950 and 1990. But in reading the history of emergency medicine it is fairly safe to say that prior to 1970s and even well into the decade, if you survived a heart attack on the way to the hospital you probably did so despite EMS not because of it.

Standard of care – Review of Medical Textbooks

Now this is not a bad way to see what people were thinking.[156]

I turn now to a review of texts that were in publication in the mid-20th century and by all accounts help us understand the medical standard of care that existed in the time period. Samuel A. Levine's book on heart disease, entitled *Clinical Heart Disease* was one of the first textbooks devoted exclusively to the subspecialty of cardiology. Its first edition was published in 1936 and in the preface to that edition Levine wrote "the purpose of this book is to present in a simple form the important aspects of the diagnosis, prognosis and treatment of heart disease." It was meant to be a bedside companion to what he called the "intelligent physician." It was not

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[153] Michael P. Stern. "The Recent Decline in Ischemic Heart Disease Mortality." *Ann Int Med* 91 (1979): 637.

[154] Brian J. Zink. *Anyone, Anything, Anytime: A History of Emergency Medicine*: 229

[155] Ibid. 8

[156] Eugene Braunwald during interview in his office referring to the use of old textbooks of the period.

an attempt, according to the author, to cover every aspect of heart disease but the content of the book was based on the opinions "shared by present-day authorities on the subject."[157] The fifth edition of his textbook published in 1958 would be his last.[158] According to Dr. Peter Gazes and others, Levine's textbook was widely read in the 1940s and even 1950s but was eventually displaced when Friedberg's textbook, longer and more definitive, came into widespread use in the 1950s.[159] In the 5th edition, Levine spends considerable time discussing the misconception of bed rest for the heart that he had written about and published extensively on in the seven years that separated his fourth and fifth editions. He refers to the conundrum of "rest in Bed or in Chair" facing the treating physician as "a psychological quandary" explaining that "No one is blamed if a coronary patient dies in bed. But if he had been out of bed the physician is likely to be held responsible." According to Levine this is most likely the explanation for the resistance that some physicians might have had when the chair was first introduced as an innovation in care and a way to reduce mortality and complications. But this view writes Levine "sorely needs to be corrected so that cardiac patients may obtain the maximum physical and psychological advantages that are available at present" and in so doing he established a new standard of care for patients after a myocardial infarction. He advised to start chair treatment in the first day or second after the heart attack and notes that since arm chair treatment was introduced in the early part of the decade he has "observed a sharp decrease in immediate mortality from acute coronary thrombosis." He also wrote that although there is no investigation as to the long-range benefits of the chair there is no reason to believe, in his experience, that it would not be beneficial in terms of long term survival. The remainder of the chapter on treatment of patients with coronary disease focuses on traditional pre-CCU aspects of care including pain relief,

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[157] Samuel A. Levine. *Clinical Heart Disease.* Philadelphia: Saunders (1958): vii.
[158] Levine died in 1966.
[159] Interview with Dr. Peter A. Gazes at his home in Charleston, South Carolina, May 8, 2014.

oxygen and anticoagulation. What is striking in this textbook is the full endorsement and recommendation for arm chair treatment for patients with acute myocardial infarction and the repudiation of strict bed rest as effective and rational treatment.[160]

In the 5th edition of Harrison's textbook *Principles of Internal Medicine,* published in 1966, the section on Ischemic Heart Disease is divided into two sections; Angina Pectoris and Acute Myocardial Infarction. Distinguishing the two is made on the basis of whether the insufficiency of blood flow and oxygen to the heart muscle "is permanent, complete, and accompanied by necrosis of muscle fibers." If so then it is deemed infarction. If not and the deficiency is "temporary, relative, and without concomitant evidence of destruction" then one is dealing with angina pectoris which may, if left untreated go onto infarction in the future. More chronic conditions that may be due to long-standing ischemic disease are not addressed in Harrison's 5th edition under the heading of ischemic heart disease. In the 1960s these, as was the case earlier in this dissertation discussed (see chapter 2), are not included in the mortality statistics for coronary artery disease. The leading manifestation of chronic myocardial disease is pump failure or as it is more commonly termed "Congestive Heart Failure" (CHF). Harrison's sees CHF as "a frequent but much less specific complication of ischemic heart disease" that "may set in abruptly following myocardial infarction, or…may appear gradually over a period of months or years." When there is a history of chest pain or infarction then coronary disease is usually identified as the cause for the heart failure. But in the absence of pain and with no ECG changes indicating a history of infarction it was hard in the pre-catherization era to ascribe heart failure to ischemia. The diagnosis was often made in those days because no other cause was evident. Today it is much easier to discern the etiology of CHF but up through the writing of Harrison's 5th edition, in the mid-1960s, it was not. The book notes that "in the absence of clear

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[160] Samuel A. Levine. *Clinical Heart Disease*. Philadelphia: Saunders (1958): 153-163.

evidence of a critical diminution of coronary flow, either by the presence of infarctional scars or through a previous clinical history of angina or infarction, the relationship between coronary disease and…heart failure must be uncertain."[161] For this and other reasons the discussion of chronic sequelae of coronary artery disease has been excluded from this discussion in terms of mortality or treatment, the latter of which was largely confined at the time to the use of digitalis, salt restriction and diuretics.

In terms of the treatment of angina, pain relief was emphasized but physical activity in terms of exercise was, at the time, thought to be "not only harmless but likely to be positively beneficial." Harrison's believed that "exertion which does not cause [chest pain] should be encouraged." In terms of emotional stress the authors encourage a curtailment of anxiety and worry, especially of the heart.[162] Until widespread use of coronary angiography, bypass surgery, and more advanced therapeutics appeared in the late 1960s and 1970s, little else could or was done for patients with angina pectoris or what was termed pre-infarction angina.

The treatment of myocardial infarction, as outlined by Harrison's 5th edition, calls for "complete rest" during the first few hours after the infarction has occurred. Administration of oxygen was recommended as was the cautious administration of intravenous fluids and drugs. No mention is made of the Levine chair and none of the coronary care unit. The cautious use of anti-coagulants was advocated but the authors acknowledge and "recognize that no large, well-controlled series of cases has demonstrated beyond question that this recommendation is justified."[163] This represented somewhat of a departure from the previous 4th edition of Harrison's (1962), which stated that "despite the risk of anticoagulant therapy, such as the

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[161] William H. Resnik and T.R. Harrison. "Ischemic Heart Disease (Angina Pectoris and Myocardial Infarction)."T.R. Harrison, et al, editors. *Principles of Internal Medicine,* 5th edition. New York: McGraw-Hill (1966): 828-829

[162] Ibid, 832-835.

[163] Ibid, 839.

occurrence of bleeding, of increasing the gravity of cerebral and other embolisms, of promoting the development of hemopericardium, the benefits accruing from this form of therapy now appear definitely to outweigh the risks. Inasmuch as a serious thromboembolic episode may occur even in an individual who has sustained only a mild infarction, we believe that it is probably wise to administer anticoagulants to all persons."[164]

Both editions discuss and handle the treatment of anxiety in the same way, but except in general terms no specific recommendations are made in this regard in either except to say it must be recognized by the treating physician and not overlooked or made insignificant. They also both address a return to work and normality of routine with the same words saying that individuals who have sustained a mild attack usually return to work in 4 to 6 weeks and those with more serious or severe infarction "may require many weeks or months, or may never be able to return to work again, particularly when the occupation is one in which strenuous exertion is unavoidable."[165]

Again, clearly absent in the 5th edition of Harrison's are the movement of patients post infarction from bed to chair and also the use of the coronary care unit.[166] As pointed out to me in my interview with Eugene Braunwald textbooks are often written at least two years prior to the time they are published. In this case then we would be looking at standards more likely in effect in 1964, or perhaps a bit earlier, rather than 1966. Although this chronology may appear on the surface to be of minor significance it is actually critically important when considering the

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[164] William H. Resnick and T.R. Harrison. "Ischemic Heart Disease (Angina Pectoris and Myocardial Infarction)." In T.E. Harrison, et al. editors *Principles of Internal Medicine*. 4th edition: 1455,

[165]William H. Resnik and T.R. Harrison. "Ischemic Heart Disease (Angina Pectoris and Myocardial Infarction)."T.R. Harrison, et al, editors. *Principles of Internal Medicine*, 5th edition: 841. William H. Resnick and T.R. Harrison. "Ischemic Heart Disease (Angina Pectoris and Myocardial Infarction." In T.E. Harrison, et al. editors *Principles of Internal Medicine*. 4th edition: 1457.

[166] Although as pointed out in earlier section on armchair treatment there was a brief mention in Harrison's 4th edition textbook (1962) that condition permitting the patient could a few days post-infarction be allowed to sit up in a chair, use a bedside commode or even walk a few steps.

rapidly changing landscape in the care of coronary artery disease occurring during the 1960s. We need therefore turn to an examination of other textbooks of the time, ones specifically devoted to cardiology, including Hurst and Logue's *The Heart* published in 1966, and Friedberg's 3rd edition textbook, published in the same year, as well as the next edition of Harrison's textbook, the 6th edition, published in 1970 which, according to Braunwald, may more accurately reflect standards in place in the late 1960s.

The Heart begins in its preface with the statement "As long ago as 1955 it was obvious that the discipline of cardiology, the largest subspecialty of medicine, was growing so rapidly that to prepare a book authored by one or two average men would be a very difficult task." Editors Hurst and Logue therefore solicited "the help of many contributing authors" to produce the first multi-authored textbook in cardiology.[167] The fourth edition of *Diseases of the Heart* which Charles Friedberg was writing at the time of his tragic death was never completed although attempts by his publisher were made to get Braunwald to complete the book.[168] By the late 1960s with the expansion of information and knowledge about heart disease, a single authored textbook was neither tenable nor doable. *The Heart* was iconoclastic in many respects in terms of treatment for acute myocardial infarction. As already noted, it embraced Levine and Lown's notion that patients be moved to a chair at the side of the bed by the second or third day after injury. It dispelled the belief held by most that oxygen should be administered to patients, simply stating that "most patients with acute myocardial infarction do not require oxygen" and it should only be administered if there is accompanying "respiratory depression, shock, cyanosis,

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[167] R. Bruce Logue and J. Willis Hurst. "Management of Coronary Atherosclerosis and its Complications." In J. Willis Hurst and R. Bruce Logue, editors. *The Heart*.xi.

[168] Braunwald told me when I interviewed him that the year was 1972 and he had just arrived in Boston to assume the Chairmanship of Medicine at the PBBH and did not have the time to finish Friedberg but he told the publisher that if they waited 8 years they could have a "Braunwald." In 1980 the same publisher, Saunders, brought out the first edition of *Braunwald's Heart Disease*, a multi-authored textbook.

mild dyspnea, cough, and wheezing, and when the respiratory rate is increased." Otherwise, according to the authors, "it is of dubious value in relieving pain" or accelerating recovery from a heart attack. Anticoagulants were recommended for "all patients in whom the diagnosis of myocardial infarction is definite and when no contraindication to such therapy exists" but the authors confessed that "after an enormous amount of study the controversy regarding the value of anticoagulant therapy still rages." It was the first textbook to discuss "intensive-care cardiac units…for the care of patients with myocardial infarction" noting all the multiple advantages of such a unit already mentioned earlier in this chapter but cautioning the reader that as the CCU evolved to "not forget that no amount of equipment can substitute for the good judgment of the physician." Finally, the authors strongly advocated that all attempts be made to prevent and alleviate "anxiety, fear and anger" on the part of the patient, emphasizing early and total rehabilitation and the expectation instilled early of a return to work after an appropriate period of convalescence.[169]

As already alluded to under the discussion of armchair treatment, Charles K. Friedberg's three editions of *Disease of the Heart* were by far the most widely read cardiology textbooks during the period 1950 to 1970. Peter Gazes, himself the author of the textbook *Clinical Cardiology: A Bedside Approach* cited it as the single most important textbook he used during the period.[170] In both the second edition, published in 1956, and the third edition, published ten years later, Friedberg emphasizes the same four points in the treatment of myocardial infarction; "reduce the work of the heart until the infarcted area is healed, alleviate pain or other discomfort, overcome shock and cardiac failure if present, and cope with dangerous

[169] R. Bruce Logue and J. Willis Hurst. "Management of Coronary Atherosclerosis and its Complications." In J. Willis Hurst and R. Bruce Logue, editors. *The Heart*.711-719.
[170] Interview with Dr. Peter C. Gazes, at his home, Charleston, South Carolina, May 8, 2014.

cardiac arrhythmias or any complications that arise."[171] In the second edition there is no mention of coronary care units which would not be initially described for another five years. Instead, Friedberg makes the point that "Most patients with acute myocardial infarction can be treated satisfactorily at home." He recommends hospitalization under certain circumstances including "when the patient's home is at a considerable distance from his physician and the severity of the attack and its complications warrant frequent and prompt medical attention." In terms of nursing care, he writes that "Its purpose should be to help the patient avoid undesirable exertions, to protect him from the telephone and from visits by his business associates, friends and relatives, and to provide a cheerful atmosphere, as well as to administer mediations and other therapeutic measures."[172]

Treatment of myocardial infarction, still emphasizing the same four points, is vastly expanded and rewritten in the third edition. In terms of hospital versus home care, he has now modified his statement to "most patients with *uncomplicated or relatively mild* acute myocardial infarction can be treated satisfactorily at home." "However," he continues, "there is a constant danger of a serious arrhythmia or other complication which is less likely to be recognized and treated early and effectively at home than in a hospital," concluding that "in general, hospitalization is preferable."[173] Friedberg then goes onto praise all the benefits of the coronary care unit in reducing the mortality of coronary artery disease. He writes, "Since the most serious complications and the highest mortality in acute myocardial infarction occur in the first few days and especially in the first 24 hours, it has been recommended that patients with this disease, or at least those who appear most seriously ill, should be carefully observed in an intensive care unit during the period of greatest danger." According to the third edition, "any

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[171] Charles K. Friedberg. *Disease of the Heart.* 2nd edition. Philadelphia: Saunders (1956): 562.
[172] Ibid, 569.
[173] Charles K. Friedberg. *Diseases of the Heart.* 3rd edition. Philadelphia: Saunders (1966): 894.

substantial improvement in mortality from acute myocardial infarction depends on the reduction in deaths from the three major complications, cardiac arrhythmias, cardiogenic shock and heart failure" and the "management of shock and acute heart failure demands continuous observation by skillful personnel [and] control of the arrhythmias offers greater promise of diminishing the mortality rate." Of the three major complications of acute myocardial infarctions resulting in death, the book notes "about one third to one half…occur in the first 24 hours, about 70 per cent within the first 3 days and 80 to 85 per cent in the first week."[174]

As already noted, there is a clear departure in the third edition from treating most myocardial infarction in the acute period at home. Ventricular fibrillation resulting in cardiac arrest, writes Friedberg, "is a significant factor in the mortality from acute myocardial infarction in the first 2 weeks after onset but especially…in the first 72 hours."[175] Furthermore, there was no telling who would succumb to one of the fatal complications as they often came without warning. The move to early hospitalization and careful observation in an intensive care unit setting, with the mortality statistics in the acute period as noted, clearly played a role in rapidly reducing mortality of the disease. Furthermore, physicians were guided by this text and others to move from a provincial method of care in the home to a technological innovation, coronary care, which improved both morbidity and mortality of the disease.

Called "the greatest British cardiologist of his time,"[176] Paul Wood, a heavy smoker, died in 1962 at the age of 54, from a myocardial infarction, while working on the third edition of his textbook *Diseases of the Heart and Circulation.* The second edition of his book was published in 1956 in Great Britain but distributed widely in the United States. According to Silverman and Somerville, "Paul Wood, the leader of European cardiology during the mid-20th century, was

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[174] Ibid, 880-882.
[175] Ibid, 881.
[176] George Dune. "In memoriam: Paul Wood." *Helton Into* 4,1 (2012).

internationally admired for his bedside teaching, clinical investigations, and an important textbook on cardiology." He was "the gale force wind of British cardiology and the inspiration and role model for many students" leaving "a legacy of great accomplishments as the transition figure between the old and modern era of cardiology." The first edition of his book, published in 1950, "brought Wood worldwide recognition," as would the second.[177] The third edition was about one-third done, with notes in place for later chapters, when Wood died. Because of "unabated demand in the bookshops" for a revision and the fact that much was already in place for it, a number of Wood's colleagues "with the approval of his wife" completed the third edition which was published in Great Britain as well as the United States in 1968 (two years after Friedberg's third edition).[178]

It had twenty-four contributors headed by Walter Somerville and so represented, like Hurst and Logue's textbook *The Heart,* an early multi-authored textbook and the last of Paul Wood's contribution to the field.[179] It reflects much of what transpired during the decade of the 1960s given the wide expanse over which it was written. Somerville wrote the preface to the third edition. In it he states "Intensive coronary care has made some inroad into the hospital mortality of acute myocardial ischaemia, but the point of highest mortality in the patients who never reach hospital, is still virtually untouched." On the topics of "anticoagulants, cholesterol-lowering agents, low-fat diets and long-acting coronary vasodilators" Somerville writes they "have all failed to make any impact on long-term management." The concept of 'New coronaries for old,' a pipe-dream at the time of the previous editions," he writes "has begun to take form in attempts at heart transplantation. Otherwise, recurring waves of enthusiasm for

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[177] Mark E. Silverman and Walter Somerville. "To die in one's prime: the story of Paul Wood." *A J Cardiol 85 (2000):75-88*

[178] Ibid.

[179] No fourth edition of *Paul Wood's Disease of the Heart and Circulation* was ever produced.

the surgical attack on myocardial ischaemia have had a tepid response amongst critical physicians." In terms of hypertension, Somerville echoes the sentiments of those already expressed in chapter 4, when he states "the practical applications to treatment have been left hardly changed compared with a decade before. The ideal hypotensive pill, potent, cheap and free from side-effects, always a good talking point in Wood's time, still eludes the research workers."[180]

In detailing treatment of ischemic heart disease, Wood's third edition begins with a full discussion of "the intensive coronary care unit." Echoing Braunwald's words that "the world was ready for a concept of the CCU," it begins that the idea that "sudden death sometimes preceded by an arrhythmia was known for many decades to be a common hazard of acute myocardial infarction. Continuous electrocardiographic monitoring, introduced in the early 1960s, showed that arrhythmias were commoner than previously believed" and "could be the precursors of circulatory arrest." Mortality it implied could therefore be reduced if rhythm changes were detected early. According to the third edition:

> The main advantage of the intensive care unit is the constant scrutiny of the patient by trained staff who have no other commitments, and in addition to the immediate detection of critical rhythm changes, they can treat with greater efficiency other complications like shock and cardiac failure. Patients remain in the unit for three to seven days or longer depending on the call for beds…The chief promise of the intensive coronary care unit is the reduction in the early mortality of acute myocardial infarction. To what extent this is achieved is not clear although favourable reports with limited numbers of patients have appeared.[181]

Immediately following a discussion of the merits of coronary care, the book discusses bed rest stating that whether at home or in the hospital "the patient should be *confined to bed*

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[180] Walter Somerville. "Preface to Third Edition." In Paul Wood's *Diseases of the Heart and Circulation.* Philadelphia: J.B. Lippincott (1968): xxxv-xxxvi.
[181] Paul Wood. *Diseases of the Heart and Circulation.* Philadelphia: J.B. Lippincott (1968): 860-861.

at once and should remain there certainly for the first two weeks, the period of greatest risk." Thereafter policy should depend "on the progress and clinical state of the patient." Chair treatment is addressed with the following statement: "Gradual transition to armchair rest and short walks are permitted if the initial pain subsides in the usual time and arrhythmias and other complications do not develop."[182] Finally, on the status of anticoagulant therapy in the mid-1960s, the authors note "dwindling enthusiasm in the United Kingdom" for it, stating that "sharp disagreement still exists on the value of anticoagulant therapy in all forms of ischaemic heart disease, including angina pectoris, acute myocardial infarction and prophylaxis."[183]

Roman DeSanctis at the MGH, on the use of anticoagulants, believed that "the one thing it might have done is obviously if the patients were kept at bed rest for a long period of time it prevented phlebitis and pulmonary emboli and things like that."[184] Arthur Sasahara, a cardiologist and authority on pulmonary embolism, spent the majority of his professional career working at the VA Hospital in West Roxbury, Massachusetts. He told me that in the 1960s at the VA "anybody who had an acute myocardial infarction got anticoagulated. Coumadin. It was based on [a] paper out of New York. Everybody at that time in the '60s was anticoagulating patients with acute myocardial infarction to minimize recurrent infarction. And it just didn't work out that way." He then explained that the real breakthrough in terms of preventing secondary infarction was aspirin which did not come into wide spread use until later.[185] Echoing Sasahara, Braunwald told me he did not think anticoagulation made a difference in early coronary artery disease mortality noting that there was "one crude trial – crude by today's

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[182] Ibid, 862.
[183] Ibid, 863.
[184] Interview with Dr. Roman DeSanctis in his office at the Massachusetts General Hospital, October 19, 2012.
[185] Interview with Dr. Arthur Sasahara in his office at the Brigham and Women's Hospital, Boston, Massachusetts. October 18, 2012.

standards…a trial by a very famous cardiologist at the time at New York Hospital/Cornell, Irving Wright," in the early 1950s and "he was a great proponent." Although anticoagulants may have reduced the incidence of thromboembolic complications, in and of themselves, according to Braunwald, they did little to reduce the mortality related to infarction.[186]

A retrospective Professional Activity Study (PAS) data analysis, part of a medical audit program, published by the Commission on Professional and Hospital Activities, compiled death rate data on males with acute coronary occlusion from 373 PAS Hospitals in 1964. Excluding deaths within the first day of hospitalization they showed with 95% confidence intervals by age group that "for each age group, the death rate for patients without anticoagulants was higher than for patients with anticoagulants." Of further interest is that the death rate disparity in this study increased between treatment with anticoagulants and without with increasing age.[187] In any event anticoagulants for the most part were used in treating acute coronary thrombosis through at least 1968 because other and better clot busting agents were not available until much later.

The 6th edition of Harrison's textbook was published in 1970 and was distinctive for a number of reasons. It was the first in which its namesake, Tinsley Harrison, whose field of interest was cardiovascular diseases, but who was not per se a formally trained cardiologist, was not an editor. Noted hematologist Maxwell Wintrobe was editor-in-chief, and it was the first of many editions that Eugene Braunwald, already an accomplished and distinguished leader in American cardiology, was an editor, eventually becoming Editor-in-Chief of the 11th and 15th editions. For the 6th edition Braunwald was in charge of the section on cardiovascular disease

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[186] Interview with Dr. Eugene Braunwald in his office on Longwood Avenue, Boston, Massachusetts, October 18, 2012.

[187] Professional Activity Study. "Anticoagulant Therapy for Acute Coronary Occlusion: Survival Rates for Males." *The Record*. Ann Arbor: Commission on Professional and Hospital Activities 4 (1966): 1-4.

and he told me that "Dick Ross [the former chief of cardiology at Johns Hopkins and later its Dean] wrote this chapter [on coronary artery disease] for me," reiterating to me that using old textbooks of the period was "not a bad way to see what…people were thinking."[188] The section on Ischemic Heart Disease in the 6th edition represented a total revamping of what had been published in the 4th and 5th editions and written by Resnick and Harrison. In physicians hands in 1970, per Dr. Braunwald "means it was written in 1968."[189] So much had transpired between the 5th edition, probably written in 1964, and 6th editions that it was considerably longer in length than its predecessor. Ross begins the management section with discussing the CCU, emphasizing as did Braunwald, the singular significance of the innovation. He writes "Experience in coronary care units indicates that the mortality rate is highest during the first few hours; therefore, there is great urgency in bringing the patient into an environment where complications can be treated…It is possible that this scheme may prove to be the most effective way of reducing early mortality." Ross claims three major benefits of coronary care; improvement in care, reduction of mortality and a significant increase in knowledge about myocardial infarction and its natural history. This last point should not be underestimated because for the first time one could document exactly what transpired after an individual had a heart attack in terms of cardiac rhythm and function. The most important feature of the CCU writes Ross "is a staff of highly trained personnel with authority to take immediate action in emergency situations." He mentions the need for life saving equipment including defibrillators and pacemakers but emphasizes the new independent role of nurses working in the CCU backed up by highly trained cardiologists. Minimizing delay in admission to the CCU, Ross points out is the best way to discover arrhythmias and reduce the high early mortality of the disease. In

[188] Interview with Dr. Eugene Braunwald in his office on Longwood Avenue, Boston, Massachusetts, October 18, 2012.
[189] Ibid.

terms of bed rest, Ross states that it is no longer necessary to keep the patient at absolute bed rest for 6 weeks and that authorities advocate getting patients into a chair within 24 hours of admission to the CCU. It is pointed out that "the weight of evidence indicates that oxygen should be administered," but there is little evidence that anticoagulation reduces mortality and that it's only utility is in reducing thromboembolic complications that may arise after an infarct. Despite the lack of evidence, Ross points out that at the time of his writing this chapter anticoagulation is used in most patients who have had an acute myocardial infarction but the future role of this therapy awaits better studies and trials.[190] Harrison's 6th edition mirrors very closely the treatment and management of coronary artery disease patients outlined in Hurst and Logue's textbook, *The Heart,* published four years earlier.

Hospital Annual Reports

In order to fully evaluate the events and advancements occurring in the treatment of coronary artery disease in the period leading up to its initial decline in mortality I examined the hospital annual reports of four major medical centers in this country, as available, in the years between 1955 and 1970. The hospitals included: Massachusetts General Hospital (MGH), Peter Bent Brigham Hospital (PBBH), Columbia-Presbyterian Medical Center (CPMC) and Mt Sinai Hospital (MSH). Two are located in Boston and the other two are located in New York City. The bulletins were obtainable at the Countway-Harvard Medical Library in Boston. My aim was to review mortality in these hospitals and correlate it with changes in treatment and care. The endeavor was disappointing to say the least because the majority of the reports contained none of these data. However, a few points can be made from the annual bulletins reviewed.

[190] Richard Ross. "Ischemic Heart Disease." In Maxwell M. Wintrobe, et al, editors *Harrison's Principles of Internal Medicine.* Sixth Edition. New York: McGraw-Hill (1970): 1217-1226.

At the PBBH I found documentation in the Fifty-Second Annual Report (1964-1965) that the CCU had been established under the directorship of Dr. Bernard Lown. Called the "Samuel A. Levine Cardiac Center" it was conceived in spring of 1964 and "became a reality eight months later." According to the entry "the center is composed of a four-bed unit located on A-Second. Each patient is continuously monitored on bedside oscilloscopes as well as on large "slave scopes" strategically located within the unit." It outlined the training of the staff and reported that of the 100 patients admitted to the unit, 50 "had well-documented acute myocardial infarctions." Three died of intractable shock representing the "lowest mortality for coronary occlusion yet reported." No deaths were reported from cardiac arrhythmias. The report detailed a few more important facts. More than 200 physicians from other institutions had visited the unit that year and are using it as a model in constructing their own units. By the time the report was written in 1965, 550 cardioversions using the Lown DC machine were carried out in the hospital and there was not a single episode of ventricular fibrillation or cardiac stand-still as a result. It noted also that "physicians from all parts of the world [had] come to learn and observe the technique" subsequently putting it into use in their own institutions.[191]

The Fifty-Third Annual Report (1965-1966) of the PBBH reported that as of July 1966 a total of 200 patients with myocardial infarction had been treated in the CCU. The average stay was 6 days and the mortality rate during that stay was "exceptionally low (13 per cent) attesting to the success of the operation." The report specified two factors felt to be critical in this achievement: "the quality of care received by patients from the specially trained cadre of nurses and medical staff, and the philosophy which has evolved regarding prophylactic treatment of arrhythmias as they are detected by the monitoring process." The report than went onto make the astonishing pronouncement that "Death from arrhythmia has been almost completely

[191] Fifty-Second Annual Report: Peter Bent Brigham Hospital, 1964-1965, Boston, Massachusetts: 25-26

eliminated" and "most deaths [that occur after myocardial infarction at the PBBH] are a result of shock and intractable heart failure." Cardioversion had now been performed, according to the report, on 700 patients without major complication.[192]

Subsequent annual reports from the PBBH continued to document improving mortality secondary to CCU care and the control of life threatening arrhythmias. Celebrating the CCU's fifth anniversary the annual report of 1969-1970 noted a "one-third reduction in hospital mortality from this disease [coronary artery disease] at the Brigham."[193] In 1971 the CCU admitted its 1000th patient with a myocardial infarction and mortality was noted to be "about half the level previously experienced from this disease." Over the course of six years mortality of inpatients at the hospital had been reduced by 50% and the report of that year documents that the issue of "fatality from arrhythmias was almost completely abolished." Mortality now was largely from heart failure manifested either my "intractable congestion or shock," a point in line with what was written in the latest textbooks. The report of 1970-1971 also documented that over 5000 coronary care units had been established throughout the United States, many drawing on the Levine Center as their model. In addition it noted that a number of younger members of the cardiology staff from the PBBH were assuming roles of leadership in cardiology divisions of other major medical centers. [194] No further details about admissions, discharges or deaths specifically from coronary disease were noted in the PBBH annual reports.

In early 1966 Massachusetts General Hospital (MGH), observing that nearby "community hospitals" had already set up CCUs, explored the possibility of establishing such a unit on its Ward B3. After consultation with the medical and nursing staff a unit with four beds began operations in March 1966. According to the annual report of the hospital a number of

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[192] Fifty-Third Annual Report: Peter Bent Brigham Hospital, 1965-1966, Boston, Massachusetts: 19-22
[193] Fifty-Seventh Annual Report: Peter Bent Brigham Hospital, 1969-1970, Boston, Massachusetts: 57-58.
[194] Fifty-Eighth Annual Report: Peter Bent Brigham Hospital, 1970-1971, Boston, Massachusetts: 54-55.

problems arose in the beginning. MGH, founded in 1811, according to its mission, "was established by the community to satisfy a community need for skilled physicians and better medical care."[195] The physician had always been at the forefront and center of care at the institution, charged with the responsibility to attend to patient needs at what would become the flagship Hospital of Harvard Medical School and one of the premier medical facilities in the country. As the annual report of 1966 documents early problems in establishing its CCU revolved around "the role and extent of responsibility to be assumed by nurses."[196] According to Dr. Roman DeSanctis, Paul Dudley White Emeritus Professor at Harvard and MGH, "There was some controversy initially over the fact that only an MD was supposed to deliver a defibrillator shock."[197] This was not a problem though confined to the MGH alone, but the issue, like elsewhere, was soon resolved, and according to the report of that year the four bed unit began to operate smoothly. No exact estimate of the impact of the CCU at MGH on mortality is included in the report of 1966 or the report that would follow a year later but two statements in those reports would lead one to believe that the effect was profound, if somewhat understated. The "patient care" section of the 1966 report notes the following:

> How much of a contribution [the CCU] has made toward reducing the mortality from myocardial infarction has not yet been assessed, but a preliminary evaluation after the unit had been in operation for three months encouraged us to believe that it was a valuable addition to the early care of such patients.[198]

The unit on Bulfinch 3, according to DeSanctis, was a make shift unit of 4 beds in a single large room in which only general medical service (house staff) patients with myocardial infarction

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[195] One Hundred and Forty-Eighth Annual Report of the Trustees of The Massachusetts General Hospital For the Year 1961, Boston, Massachusetts: 44.
[196] One Hundred and Fifty-Third Annual Report of the Trustees of The Massachusetts General Hospital For the Year 1966, Boston, Massachusetts: 72.
[197] Email communication with Dr. Roman DeSanctis, May 27, 2014.
[198] One Hundred and Fifty-Third Annual Report of the Trustees of The Massachusetts General Hospital For the Year 1966, Boston, Massachusetts: 72.

were treated.[199] It must have been quite successful though, perhaps as an experiment, because by July 1967 it was supplanted by a new unit of 6 beds, well planned and sophisticated, which treated both private and medical service patients on the second floor of the private wing of the hospital's Phillips House.

The new unit was organized and subsequently directed for a number of years by Dr. DeSanctis. He told me that in addition to the 6-bed unit there was another bed across the corridor, in a large room, that was used for the treatment of cardiogenic shock and other clinical research on heart disease. It was his opinion and "fair to say," he believed, "that the Phillips House 2 unit offered state of the art care for MI's and what was then called 'acute coronary insufficiency.'"[200] Previously patients in Phillips House were cared for in private rooms usually by paid private duty nurses, but the report noted a "decreasing number of private duty nurses who can be depended upon for continued care" of coronary artery disease patients. By the opening of the new CCU, staff nurses at MGH were running the show receiving "intensive training in cardiac nursing in workshops developed and taught in collaboration with the cardiologists and members of other related Hospital staffs."[201] The unit was staffed only by hospital employed cardiac care nurses and no longer were privately employed nurses sitting by and witnessing complications of disease which they were untrained and ill-equipped to either handle or act upon. The initial 1966 experience inter-hospital was clear. Staff patients were surviving in the B3 CCU and private patients were succumbing to lack of such care in private rooms.

Mount Sinai Hospital (MSH) like the MGH was founded before the Civil War and also described a "heavy communal obligation" in its mission. In its 1961 Report of the President of

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[199] Interview with Dr. Roman DeSanctis, in his office at Massachusetts General Hospital, October 19, 2012.
[200] Email communication with Dr. Roman DeSanctis, May 27, 2014.
[201] One Hundred and Fifty-Fourth Annual Report of the Trustees of The Massachusetts General Hospital For the Year 1967, Boston, Massachusetts: 131.

MSH it noted the "conversion of three rooms on the seventh floor of [the original] Guggenheim [Medical Pavilion] into a five-bed intensive care unit." The report also noted that many other hospitals were also doing this to take care of their "critically ill patients" and although small, by limitation of space, it would expand with the construction of a new surgical building. The report further reported that $2,000,000 was being appropriated for "operating suites and intensive care unit."[202] Nothing further was stated in the report about the types of patients to be cared for in this new unit but the implication was clear that it was intended for surgical patients.[203] One year later in 1962, the hospital's annual report described the planning and implementation of two intensive care units, one for ward patients and one for private patients, followed in the same paragraph with a statement that a cardiac recovery room was also available for treating postoperative cardiac surgery patients.[204] The year 1964 was remarkable for MSH in a number of respects especially because in that year major steps were being taken to found its new School of Medicine. The Cardiac Intensive Care Unit was expanded in that year to eight beds, with monitoring equipment and laboratories. This expansion, according to the report, "was made necessary by the rapidly accelerating cardiac surgery program." Again no mention of the care of heart attack patients per se.[205] The 1965 report reiterated the opening in that year of the "expanded, eight-bed, Cardiac Intensive Care Unit to provide supervised care for patients who have undergone open-heart or closed-heart or thoracic surgery" noting that it was specially equipped and staffed with "the most advanced electronic and scientific laboratory facilities."[206]

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[202] Report of the President of the Mount Sinai Hospital, New York, NY: 1961, 11-13.
[203]Eugene Braunwald, did his medical training at Mt. Sinai Hospital in the 1950s, and told me that although many hospitals did not have a formal CCU until later in the 1960s not infrequently patients with heart attacks were treated in intensive care units not solely dedicated to the heart. This may have been the case here but we have no clear evidence that it was the case.
[204] Report of the President of Mount Sinai Hospital, New York, NY: 1962, 96.
[205] Report of the President of Mount Sinai Hospital, New York, NY: 1964, 11.
[206] Report of the President of Mount Sinai Hospital, New York, NY: 1965, 11.

Finally, in the 1967 MSH report one finds not only mention of the CCU but also evidence of the profound impact of Medicare and Medicaid on the hospital. According to the nursing section of the report "Nursing service administrators met intensively with members of the Planning Group to inaugurate a Coronary Care Unit which will combine beauty with a high degree of functional efficiency. The nurses will have an expanded role in caring for patients, undertaking some activities which have traditionally been relegated to the province of the physician." The program and unit was to be under the charge of Charles Friedberg.[207]

Medicare and Medicaid, it was noted in the report, resulted in a significant impact on the census of the hospital in 1967. The medical semi-private service recorded in that year its highest census to date and largely attributed it to a substantial influx to the hospital of patients covered by the two newly enacted medical assistance programs.[208] February 1968 saw the opening of the Ames Coronary Intensive Care Unit, an eight bed unit. It was touted as one of the largest of its kind in any medical center in New York exclusively dedicated to care of patients with myocardial infarctions. In making the statement at the time the '68 report made the claim "that there is evidence that more lives of patients with acute heart attacks are saved in special coronary units such as the Ames Unit, than in general intensive care units" [already in existence]. Charles Friedberg, in the same report, alludes to the fact that in years prior patients with coronary artery disease at MSH were probably cared for in non-coronary intensive care units. Now, however, these patients had a better home for the treatment of coronary disease than they did when treated in intensive care units not exclusively for patients with myocardial disease.[209]

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[207] Report of the President of Mount Sinai Hospital, New York, NY: 1967, 54.
[208] Report of the President of Mount Sinai Hospital, New York, NY: 1967, 14.
[209] Report of the President of Mount Sinai Hospital, New York, NY: 1968, 22, 117.

Statistics in the annual reports at MSH and other hospitals unfortunately give only numbers relating to admissions, surgeries, laboratory tests and the number of x-ray studies done. The eight bed CCU at MSH remains such until into the 1970s and provided care, almost exclusively, for those with evidence of acute myocardial infarction. Unfortunately, although MSH annual reports speak to improvements in care and allude to improved mortality as a result of their new CCU after 1968 they do not provide statistics documenting the impact of the CCU or other interventions on coronary artery mortality during the period.

Annual reports from Columbia-Presbyterian Medical Center (CP) are combined reports of the constituent schools and Presbyterian Hospital. They begin to be so in the late 1950s and the fifth combined report published on December 31, 1963 was the first to speak of creating a "Special Nursing Care Unit." A four-bed unit had apparently already been established by this time that was proving of great value "in increasing efficiency in the care of patients who require special devices such as cardiac monitors, mechanical respirators or pacemakers."[210] Not a true CCU but it appeared to be the first incarnation of a monitored unit for the care of patients at Columbia with heart disease. The following year the combined report of CP reported that "The Cardiac Monitoring Unit" had been approved by the Center's "Medical Board as a pilot venture in July 1964." The unit under the direction of internist Edgar Leifer appears to have grown from the four bed unit described above to 6 beds. The report notes an improvement in handling cardiac arrests; "of twenty-nine who experienced cardiac arrest (ten while in the unit), eleven have been discharged from the hospital to complete convalescence at home."[211] Such success with cardiac standstill, previously recognized only when usually too late to salvage the patient,

[210] Fifth Combined Annual Report of the Columbia-Presbyterian Medical Center, 622-630 West 168th Street, New York 32, N.Y. December 31, 1963: 44.
[211] Sixth Combined Annual Report of the Columbia-Presbyterian Medical Center, 622-630 West 168th Street, New York 32, N.Y. December 31, 1964: 40.

prompted the report of 1965 to characterize the "Special Nursing Care and Cardiac Monitoring Unit" as "an outstandingly successful undertaking."[212] By 1966 the unit was handling the care of about 25 patients per month. All beds in the unit were equipped with direct wiring to "slave oscilloscopes" where there was continuous observation at all times. In that year nurses were authorized by the medical board of the hospital to be able to defibrillate patients when physicians were not available and special training was implemented for nurses to be able to successfully do so. The unit was documented in this eighth combined report to be dealing with not only arrest but also the control of heart block and life threatening arrhythmias. The seriousness of illness appears to have increased in this interval necessitating a change in staffing with now an intern, as well as first year resident and cardiology fellow staffing the cardiac monitoring unit. The proportion of heart disease patients between 1965 and 1966 increased from 36% to 39% of the patients on the medical service at CP.[213] The trend continued and in 1967 the CP annual report noted that "The growing preponderance of cardiovascular problems among the admissions of the Medical Service has resulted in an increasing demand upon the Cardiac Monitoring Unit." Plans were made that year to expand and modernize the unit and its monitoring capabilities. An increase in the number of cardiology fellows had also been approved for the following year.[214] 1968 showed an increase to 41% the number of patients on the medical service at CP who had cardiovascular problems, almost exclusively coronary artery disease, and the expansion of both the cardiac monitoring unit and the physicians needed to

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[212] Seventh Combined Annual Report of the Columbia-Presbyterian Medical Center, 622-630 West 168th Street, New York 32, N.Y. December 31, 1965: 35.
[213] Eighth Combined Annual Report of the Columbia-Presbyterian Medical Center, 622-630 West 168th Street, New York 32, N.Y. December 31, 1966: 33.
[214] Ninth Combined Annual Report of the Columbia-Presbyterian Medical Center, 622-630 West 168th Street, New York 32, N.Y. December 31, 1967: 33.

staff it.[215] By 1969 CP was reporting that 48% of the patients on the medical service had cardiovascular disease and that both the CCU and ICU were being greatly expanded under the direction of cardiologist J. Thomas Bigger to handle the load with significant improvements as a result.[216] Columbia like the other three major hospitals reported here does not report their mortality statistics per se but it is evident from its annual reports that cardiovascular disease was being seen in increasing numbers in the hospital and that the medical center was responding with improvements and expansions of the areas in which these patients were best treated, namely the coronary care unit.

Medicare: economic empowerment and gateway to care

Congress created Medicare under title XVIII of the Social Security Act at a time of enormous social change in this country. It was signed into law by President Lyndon Johnson in 1965 in Independence, Missouri, in front of its first two beneficiaries Harry and Bess Truman. Prior to Medicare, only 65% of individuals over the age of 65 had health insurance. The rest could either not get insurance by reason of illness (pre-existing conditions) or could not afford to pay for it. A 1963 report by the Commission on Professional and Hospital Activities showed that compared to patients under 65, patients over 65 had three significant differences in how their healthcare was paid for. They had "less prepayment and insurance coverage, more private payment and more payment by [a variety of] government agencies." In addition their average length of stays were considerably longer; 14.1 days as opposed to 6.6 days for the younger cohort.[217] Until Congress passed the *Health Care and Education Reconciliation Act of 2010* (known variously as the Affordable Care Act or Obamacare) Medicare represented the "single

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[215] Tenth Combined Annual Report of the Columbia-Presbyterian Medical Center, 622-630 West 168th Street, New York 32, N.Y. December 31, 1968: 34.
[216] Annual Report of the Columbia-Presbyterian Medical Center, New York, N.Y. 1969: 46.
[217] Professional Activity Study. "Payment for the Aged." *The Record*. Ann Arbor: Commission on Professional and Hospital Activities 1 (1963): 1-3.

largest change in healthcare coverage in the United States" to date. Beyond making insurance and healthcare available for those in the age group most affected by coronary artery disease it had another important and profound social consequence. At the height of the civil rights movement, it mandated integration of healthcare facilities, from doctors' offices to hospitals, by making payment from the program conditional on desegregation and refusing to pay for care at facilities that continued a policy of segregated care.[218]

David M. Cutler and Ellen Meara, economists at Harvard, have documented a substantial and continuous decline in the mortality of the elderly almost from the moment Medicare was enacted.[219] Furthermore they and their colleagues at Harvard have studied healthcare and mortality as a function of insurance in general and have also documented that insurance and the lack of coverage impacts mortality. According to a study reported in 2004 "Lacking health insurance was associated with substantially higher adjusted mortality among adults who were white; had low incomes; or had diabetes, hypertension, or heart disease."[220]

Amy Finkelstein and Robin McKnight have studied the impact of Medicare on overall mortality and they believe that in the first ten years (1965-1975) Medicare per se "had no discernible impact on elderly mortality." They write that the introduction of Medicare "was followed by a substantial and prolonged decline in elderly mortality. Nevertheless, using several different empirical strategies, we are unable to reject the null hypothesis that, in its first 10 years, Medicare had no effect on elderly mortality." Their explanation for this conclusion rests in part on the belief that before 1965 "elderly individuals with life-threatening, treatable health

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[218] Amy Finkelstein and Robin McKnight. "What did Medicare do? The initial impact of Medicare on mortality and out of pocket medical spending." *J Pub Econ* 92 (2008): 1644-1668.
[219] David Cutler and Ellen Meara. "Changes in the age distribution of mortality over the 20th century." In: David Wise, ed. *Perspectives on the Economics of Aging.* Chicago: University of Chicago Press (2004): 333-365.
[220] J. Michael McWilliams, et al. "Health Insurance Coverage and Mortality Among the Near-Elderly." *Healt Aff* 23 (2004):223-233.

conditions sought care even if they lacked insurance, as long as they had legal access to hospitals."[221] Their argument however may not be pertinent to the impact of Medicare on coronary artery disease mortality at the time as there is no specific consistent published data addressing this matter. Cutler and Meara believe firmly in the importance of social policy as an "additional factor influencing mortality." They point to Medicare and Medicaid as "prime examples" that improved access and as social policies led to almost immediate "health improvements."[222]

As we have already demonstrated the period leading up to the introduction of Medicare was associated with great strides in the inpatient care of coronary disease, including chair treatment, CCU care, closed chest message, cardioversion and the ability to treat life-threatening arrhythmias effectively in the CCU in the acute period. It has been documented that Medicare was associated with a substantial increase in hospital utilization by the elderly. The 1966 annual report of the Trustees of The Massachusetts General Hospital reported that "in the first six months of Medicare the national figures show some 2.5 million people over 65 … received medical care under Title 18, Part A" and "some 3.5 million elderly individuals … received doctor care." Furthermore, it noted that "nationally, there [had] been a 5% increase in hospital occupancy and a change from 25% to 35% of all hospital beds occupied by those 65 and over."[223] The evidence then presented by Finkelstein and McKnight would imply "that the Medicare-induced increase in health care consumption was relatively unimportant in contributing to the overall mortality decline among the elderly" raising the question of why an

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[221] Amy Finkelstein and Robin McKnight. "What did Medicare do? The initial impact of Medicare on mortality and out of pocket medical spending." *J Pub Econ* 92 (2008): 1644-1668.
[222] David Cutler and Ellen Meara. "Changes in the age distribution of mortality over the 20th century." 360.
[223] One Hundred and Fifty-Third Annual Report of the Trustees of The Massachusetts General Hospital For the Year 1966, Boston, Massachusetts: 53-54.

increase in utilization appears to have had no significant impact on mortality of the elderly in the first ten years.[224]

For this they offer the explanation that there was a staggered timing of Medicare introduction in areas, particularly the South, that had not desegregated hospitals as required by the Medicare Act. According to the American Hospital Association's Annual Survey of Hospitals only 75% of counties in the South and 25% of counties in the Mississippi Delta had a hospital eligible to receive Medicare patients by the end of 1966. But the argument may fall short because of the work of others showing that implementation of Medicare increased access of people of color to hospitals in segregated segments of the south. Smith in his book *Health Care Divided: Race and Healing a Nation* writes in terms of "hospital care in the Medicare program, the South is the most racially integrated region in the country."[225] Also it appears that at the time of Medicare's introduction the primary effect of hospital care was in treating acute short term illness which coronary disease would include by the 1960s.[226] So there appears a conflict between the increase in utilization, the improvement in acute care and the claim that the first ten years of decline in mortality was the result of other factors outside of Medicare.

Any conclusion either way of the impact of Medicare coverage on the early decline of coronary artery disease mortality would be pure speculation based on a lack of real data but insight gained by my interview with Jack Hyland at Baylor and several others may be helpful in trying to clarify the role of Medicare in its early years. He told me that Medicare changed his life and changed the practice of medicine generally and cardiology in specific. Hyland stated to me

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[224] Amy Finkelstein and Robin McKnight. "What did Medicare do? The initial impact of Medicare on mortality and out of pocket medical spending.": 1650.
[225] David Barton Smith. *Health Care Divided: Race and Healing a Nation.* Ann Arbor: University of Michigan (1999): 221.
[226] Amy Finkelstein and Robin McKnight. "What did Medicare do? The initial impact of Medicare on mortality and out of pocket medical spending." 1652

"It changed my world. Because all of these people were now enfranchised and could come in and expect and pay for service. One third of my patients, and I think it was not different for most internists…All of a sudden I had more work than I could do and I was getting paid for it."[227] This increase in utilization of physicians and hospitals is also well documented in the literature.

According to the annual report of the MGH, already alluded to, "Doctors have never been busier, and essentially all the hospitals in the Greater Boston area have waiting lists of patients, a *far cry* from 10 and even 5 years ago when hospitals averaged 60 to 80% occupancy and there were always beds readily available." At the MGH, in the first six months of Medicare "there had been a 4% increase in the number of patients admitted over 65, from a total of 28% in 1965 to 32% of all patients in 1966." The experience of the MGH in that period, it is further pointed out, was in line with national data.[228] Many of these Medicare patients presented with cardiovascular diseases, diabetes, and hypertension. A study done in PAS Hospitals[229] compared the rate of admission of patients with a variety of diagnoses pre and post Medicare. In the period 1965-6, the rate of admission of patients with the diagnosis of "Acute Coronary Occlusion" to PAS hospitals was 89.6 per 10,000 patients. In the period 1967-8, after implementation of Medicare, it was 99.4 per 10,000[230] representing a significant and considerable increase in hospital care of those with coronary artery disease and verifying the claims of individuals like Hyland and institutions including the MGH.

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[227] Interview with Dr. John Hyland in his office at Baylor Medical Center in Dallas, Texas, November 16, 2012.

[228] One Hundred and Fifty-Third Annual Report of the Trustees of The Massachusetts General Hospital For the Year 1966, Boston, Massachusetts: 55-58.

[229] A large consortium of hospitals (995 at the time of this study) that participate in Professional Activity Studies of medical records information under the Commission on Professional and Hospital Activities (CPHA) which is sponsored by the American College of Physicians, the American College of Surgeons, the American Hospital Association, and the Southwestern Michigan Hospital Council).

[230] *Length of Stay in PAS Hospitals; United States, Pre- and Post- Medicare.* Ann Arbor: Commission on Professional and Hospital Activities, March 1969. Library of Congress Catalog Card Number 68-56603.

Conclusion – The answer appears close at hand

A thorough analysis of treatment for coronary artery disease reveals that factors and forces existed in the period from 1950 to 1965 that would appear, from a multitude of sources cited, to have had an impact on the mortality of patients with coronary artery disease. It is unlikely that any single factor related to care and treatment can alone be implicated in the decline of mortality. From a review of the literature and multiple discussions with experts of the period and inclusion of available statistics, It would appear that there were two major gale winds in this respect and perhaps a number of other minor influences that were additive in initiating a downward effect on mortality that has continued well past 1968 when it first began.

The two major factors appear to be the departure from strict bed rest to armchair therapy and from there to early ambulation and rehabilitation and the introduction of intensive coronary care units with multiple innovations for the acute treatment phase of patients sustaining a myocardial infarction or manifesting unstable angina and their sequelae. The latter brought with it not only vigilant observation of patients both technically and by skilled staff now empowered to act without hesitation or further permission, but it also ushered in the opportunity and ability to abort life threatening arrhythmias as early as possible and a new technique of closed chest resuscitation in the event of acute cardiac arrest. All of these events came together under the new rubric of the coronary care unit.

In terms of a less major determinative factor came the increasing specialization in cardiology occurring at the same time. Peter Gazes' life and experience as well as others is testimony to this fact. When he arrived in Charleston, South Carolina heart disease patients were being care for exclusively by internists. He was the first cardiologist in the state in 1950 and with him he brought experience in treating exclusively patients with heart disease. Add to this the effect of Medicare which by all available evidence had an almost immediate effect on

the availability of care for patients over the age of 65; the group with the greatest burden of coronary artery disease in this country both then and now.

Perhaps no one is better able to weigh in on the relative impact of the two major forces, armchair treatment and coronary care, than Bernard Lown who was instrumental in both, essentially co-inventing the chair with his mentor Samuel Levine, inventing DC cardioversion, an important element in resuscitation still today, and opening "a four-bed CCU" at the PBBH in 1963, "the first in New England and the fifth in the world."[231] When I spoke to Lown in his home in late 2013 he told me the CCU was important but chair treatment was the "real" key in kick starting the reduction in mortality of coronary disease and to date its contribution has not been given the credit it deserves.

In his memoir and guide to the practice of compassionate medical care Lown refers to the traditional notion of bed rest for a myocardial infarction beginning with Herrick as "not just a small error, [but rather] a colossal misjudgment."[232] Almost 50 years after his work with Levine on the chair he writes:

> I later realized that our study had been poorly carried out, since it was uncontrolled, anecdotal , and the sample was too small to permit any certain conclusions. Nonetheless, it exerted a profound effect on the care of patients with heart attack. Until our work, patients were kept in the hospital for a month or longer. Within a few years after its publication, the period of hospitalization was reduced by half. The range of activities permitted to patients was enlarged, and self-care became the norm. The hateful and dangerous bedpan was abandoned; walking was allowed earlier; hospital mortality was reduced by a third. Considering the fact that in the United States about one million people suffer heart attacks annually, perhaps as many as one hundred thousand lives were salvaged each year by this simple strategy.[233]

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[231] Bernard Lown. *The Lost Art of Healing.* 204-205
[232] Ibid, 184.
[233] Ibid, 183.

And in considering why no one has looked at the chair as revolutionary and perhaps the key element as to why mortality began to decline almost twenty years after it first came into use, and 25 years after Levine first wrote about the ills of bed rest and recumbency, Lown offers further insight. He pens:

> Curiously, I have received invitations to lecture on every subject I have researched except chair treatment for acute heart attacks. While the impact of our work was substantial and profoundly changed the treatment of coronary thrombosis, the study has rarely if ever been cited in the medical literature. Yet in number of lives saved, it was a significant medical breakthrough.[234]

The preponderance of existing evidence would suggest that the chair had an impact on mortality from the beginning. Although what we would consider good randomized control studies (RCTs) did not exist at the time for it, where used the chair did have an impact on mortality for a variety of reasons as outlined in the chapter. There is ample evidence that clinicians, not only at the PBBH, but elsewhere, from Boston to Atlanta, knew about it through the journal articles of Levine and Lown and Levine's well-read textbook and promoted its use.

There is little question that the CCU, closed chest message, continuous monitoring for fatal arrhythmias, DC cardioversion and all its other benefits for administering care contributed to the improvement in coronary artery disease mortality and that the impact was fairly immediate in nature. According to Lown, "Development of the CCU had many salutary consequences. It stimulated specialized intensive care units for other medical sub-disciplines. It promoted nurses to a central role in intensive care units. The continuous monitoring of various cardiovascular functions improved care of the critically ill, and the mortality for patients with acute myocardial infarction was reduced by 50 percent."[235] In terms of its impact over time there is no question that it caused mortality from disease to decline but in terms of its impact on

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[234] Ibid, 186.
[235] Ibid, 212.

the initial decline one must look at the totality of the situation surrounding the advent of coronary care. CCUs were springing up all over the country beginning in 1961 but many hospitals, communities, towns and small cities did not have or had not developed their CCU by the time mortality declined. Probably enough were operating to have had an impact on the decline by 1968 but this alone could not, at least on a logistical basis, have accounted for all the improvement in mortality that occurred at the beginning. Rather, the other innovations surrounding the institutionalization of the CCU, including the chair, must have added incrementally to the early improvement in mortality from the disease.

Chapter 6: Conclusion: What can and cannot be said

Does the decline demonstrate the therapeutic power of modern medicine or the impact of lifestyle change and management of risk factors?[1]

The Current Literature: What others have concluded?

In 1975 NIH Statisticians Tavia Gordon and Thomas Thom, working in the Biometrics Research Branch of what was then known as the National Heart and Lung Institute, published a ground breaking paper entitled "The Recent Decrease in CHD Mortality." Three years before the "Decline Conference" was held, it was not the first paper to note the decline, but it was one of the first to suggest possible explanations for it. In their paper they pointed first to the history of other diseases, including scarlet fever, rheumatic heart disease and tuberculosis, calling attention to the discovery of specific treatments for all but also noting that "in every instance mortality began to decline long before the specific therapies came into use." Any reasons for the apparent non-specific and hard to explain cause of these declines, they believed were speculative and lacked any real scientific proof. In terms of coronary artery disease mortality, they wrote, "While it is clear that since 1968 there has been a slight decline in CHD mortality, this decline is part of a more favorable general mortality trend." They decried the possibility that any single explanation, specific to CHD alone, can be responsible for the observed decline, citing "the recent proliferation of coronary care units," as an example. They also dismissed what they called "more general changes" as lacking "explanatory power," specifically citing tobacco use, where even though the smoking of cigarettes may have shown some decline among men, CHD mortality declined in both sexes equally, thus failing to provide a clear cause and effect relationship.[2]

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[1] David S. Jones and Jeremy A. Greene. "The Contributions of Prevention and Treatment to the Decline in Cardiovascular Mortality: Lessons from a Forty-Year Debate." *Heal Aff* 31 (2012): 2250-2258.
[2] Tavia Gordon and Thomas Thom. "The Recent Decrease in CHD Mortality." *Prev Med* 4 (1975): 115-125.

Gordon and Thom instead proposed two explanations for the decline of coronary artery mortality. The first was an "amelioration of hypertension," noting "a long term decline in mortality from hypertension and hypertensive heart disease." Complicating this assertion however they acknowledged was the change in the International Classification of Disease (ICD) with a move from ICD 7 to 8, which occurred on January 1, 1968, in which over half of the deaths assigned to hypertension and hypertensive heart disease in the former were moved to the category of chronic ischemic heart disease in the latter. Furthermore, they recognized it would not explain the fact that prior to 1968 when deaths due to hypertension were presumably decreasing, CHD mortality was still rising.[3] And finally, although hypertensive heart disease and malignant hypertension resulting in death may have been on the decline prior to the decline of CHD mortality, the evidence of this dissertation (see chapter 4) does not support any contention that essential hypertension in the majority of patients at risk for coronary artery disease was either well treated or well controlled prior to 1968.

Their second explanation draws on the fact that a significant proportion of noncardiovascular chronic disease mortality was declining at the same time, suggesting that more general causes and forces were in play. Like Michael Stern and others have done, they raised the issue of influenza but this time in the context of all respiratory diseases. Write Gordon and Thom, "It has long been recognized that mortality in general, and mortality from disease in particular, is responsive to epidemic fluctuations in these diseases and that the rise and fall in the death rate for influenza and pneumonia may reflect itself in parallel changes in deaths from other causes." A speculative explanation at best, with some basis pathophysiologically, they looked at months where mortality from lung diseases, particularly influenza and pneumonia, was the highest (November to February) and were able to show that

[3] Ibid, 121.

the decrease in CHD mortality between 1968 and 1972 was concentrated in this four month period. They therefore suspected "that most, if not all, of the decrease in CHD mortality since 1968 was a response to the epidemic fluctuations of respiratory diseases." This they felt was also supported by the fact that in 1963 an epidemic rise in influenza and pneumonia mortality seemed to account for a rise in CHD mortality. So for the period of time they examined, 1968-1973, they concluded that "most of the decrease in CHD mortality may be due to epidemic fluctuations in the incidence of the respiratory diseases," discarding their earlier contention in the paper that somehow improvements in hypertension mortality had any real impact.[4]

Stern's 1979 article in the *Annals of Internal Medicine* looked at CHD mortality between 1968 and 1976 ultimately trying "to identify and analyze the most probable factors responsible for the decline in ischemic heart disease mortality." After a thorough and exhaustive review of the data, he concluded the following:

> It is not possible at present to quantify definitively the relative extent to which the decline in ischemic heart disease mortality has been due to life-style changes with resulting improvements in cardiovascular risk factors, and the extent to which it has been due to improvements in medical care. It is likely, however, that both have played a role.[5]

Stern then went on to propose possible methods and ways to find the answers to the explanation question, including statistical analysis of secular trends in atherosclerotic lesions and examination of mortality trends in discrete segments of the population. He admits however that "few data are available to assess the possible impact" of all potential factors.[6]

Robert Levy writing on the decline in 1981 felt that one could not attribute the decline to any particular "specific events." He lists "many possible factors" that could have caused it.

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[4] Ibid, 123-125.
[5] Michael P. Stern. "The Recent Decline in Ischemic Heart Disease Mortality." *Ann Int Med* 91 (1979): 630-640.
[6] Ibid, 638.

These include, he writes, "the development of coronary care units, improved emergency medical services, cardiopulmonary resuscitation, advances in surgical and medical treatment, Medicare and Medicaid, and changes in lifestyle (less smoking, blood pressure control, dietary modification, increased leisure time exercise)." He also could not discount socioeconomic factors, a reference possibly to the work of Thomas McKeown whose work in the area was gaining much attention from theorists and other interested individuals at the time. Levy felt that more information was needed on the morbidity of CHD to determine if the disease was either being prevented or better treated. Although he believed that primary prevention played a role in the decline he "pointed out that only in those countries with an aggressive approach to risk factor change is CHD declining." According to Levy, the claim for primacy in the debate rages between cardiovascular epidemiologists, who rally around the case of prevention claiming that if all else is ignored besides changes in cholesterol, smoking habits, and blood pressure control, "one can calculate that risk factor change alone could explain the entire decline in CHD mortality" and the cardiologists who believe that "one cannot give credit to primary prevention until better morbidity data are available." The case for improved treatment, he points out, can be made on the basis that "rhythm death has been virtually eliminated as a cause of death in the coronary care units, and deaths within the units have been cut from 30% to 15%." Likewise, incipient heart failure can be treated and prevented in the CCU and similarly there have been great advances in cardiopulmonary resuscitative equipment and efforts. But he also points out that many patients continue to die before reaching the hospital and that survival rates 1, 2 and 3 years after an infarct have not changed significantly since the decline began. According to Levy, "we have too many, rather than too few, possible explanations for the decline." [7]

[7] Robert I. Levy. "Declining Mortality in Coronary Heart Disease," *Arterioscler Thromb Vasc Biol* 1 (1981): 312-325.

Another important and significant article, entitled "Cardiovascular Research: Decades of Progress, a Decade of Promise," appeared in the prestigious journal *Science* in 1982. Penned by Levy and Jay Moskowitz, it asked the question, "Why the Decline in Coronary Heart Disease and Stroke Mortality?" Citing multiple possibilities for the decline, including improvements in medical care and "socioeconomic and environmental factors" It answered the question as follows:

> Although there is general agreement that the decline in coronary heart disease mortality is real, the probable cause or causes for this decline cannot be easily identified. In fact, there are too many potential causes rather than too few.

Without explaining the cause it concluded by advocating for cardiovascular research in both areas of prevention and treatment but held out that in "the future…prevention is the major long-term goal."[8]

In 1984, Lee Goldman and E. Francis Cook published an article in the *Annals of Internal Medicine* in which they reviewed the literature looking at a variety of explanations for the decline in coronary artery disease mortality from 1968 to 1976. Citing Stern's earlier work they sought to expand on it and selected what they "considered to be the best available data to make quantitative estimates," including data not available to Stern at the time he looked at explanations for the decline in mortality. They excluded data they believed not to be representative of the nation as a whole, when it looked like that "data represented the effect of an intervention in a selected population," even if that data came from randomized controlled trials. Analyzing each potential cause for the decline "in at least two different ways" they concluded that

> More than half of the decline in ischemic heart disease mortality between 1968 and 1976 was related to changes in lifestyle,

[8] Robert I. Levy and Jay Moskowitz. "Cardiovascular Research: Decades of Progress, a Decade of Promise." *Sci* 217 (1982): 121-129.

> specifically to reductions in serum cholesterol levels and cigarette smoking. In comparison, about 40% of the decline can be directly attributed to specific medical interventions, with coronary care units and the medical treatment of clinical ischemic heart disease and hypertension being the leading estimated contributors.

When one reads carefully their article it becomes clear that the data on improvements in hypertension are imprecise and "despite the theoretical potential, existing data do not document a significant reduction in coronary heart disease mortality solely from the treatment of hypertension." In terms of serum cholesterol, Goldman and Cook use a comparison of two studies, the Health Examination Survey of 1960 to 1962 and the Health and Nutrition Examination Survey of 1971 to 1974, both "based on probability samples of persons throughout the United States," to document the best evidence for a reduction of serum cholesterol and consequently an impact on mortality despite other cited evidence to the contrary, including the much larger MRFIT study. Finally, the data they cite for "a dramatic reduction in cigarette smoking" are almost exclusively for the period beginning after 1968 and so could not have impacted an initial decline in mortality.[9]

In the same year, an article came out of the Division of Epidemiology at the University of Minnesota that credited the decline in CHD mortality to "decreasing incidence of coronary heart disease due to lowered risks brought about by lifestyle changes along with improved medical management of risk factors." They did acknowledge that "improved medical care of symptomatic coronary heart disease" may have also been a possible contributor. Although reduction in smoking might explain the trend in mortality in men, the article acknowledged it could not explain it in women where mortality rates declined despite the fact that smoking rates increased. The claim that better control of hypertension contributed to the decline revealed, on

[9] Lee Goldman and E. Francis Cook. "The Decline in Ischemic Heart Disease Mortality Rates: An analysis of the Comparative Effects of Medical Interventions and Changes in Lifestyle." *Ann Int Med* 101 (1984): 825-836.

closer examination, that is was not until the mid-1970s that a significant improvement in treatment and control of hypertension was seen in this country. In terms of better cholesterol control the data was also for much later than the initial 1968 decline and the article acknowledges that the data on cholesterol "are too scanty to allow firm conclusions." What the authors do cite is the widespread use of coronary care units, "a limited but important contribution…from emergency medical services in certain urban areas with advanced systems," and "the decline in case fatality…probably due to improved hospital care" as factors that contributed to improved mortality. They also note little influence on CHD mortality trends between 1968 and 1976 due to influenza and pneumonia mortality.[10]

In an international analysis of data on the decline in mortality, Earl Ford of the Centers for Disease Control and Prevention, and Simon Capewell of the University of Liverpool authored a review article in the *Annual Review of Public Health* entitled "Proportion of the Decline in Cardiovascular Mortality Disease due to Prevention Versus Treatment: Public Health Versus Clinical Care." The authors analyzed data from a variety of countries in terms of the contribution of both prevention and treatment to the decline in mortality. Hailing "the decrease in the U.S. CHD mortality rate…as one of ten great achievements in public health during the twentieth century" they wrote:

> The reduction in the CHD mortality rate started before powerful modern medical treatments entered mainstream medical practice, signifying that improvements in risk factors – primarily smoking, total cholesterol, and blood pressure-were key milestones to initiate decline.

Only later, after the initial decline, did they believe that "the introduction of treatments [had] contributed greatly to reducing CHD mortality rates in the United States and elsewhere."[11]

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[10] Richard F. Gillum, Aaron R. Folsom, Henry Blackburn. "Decline in Coronary Heart Disease Mortality: Old Questions and New Facts." *Am J Med* 76 (1984): 1055-1065.

[11] Earl S. Ford and Simon Capewell. "Proportion of the Decline in Cardiovascular Mortality Disease due to Prevention versus Treatment: Public Health versus Clinical Care." *Annu Rev Pub Heal* 32 (2011): 5-22.

Again, like in previous reports touting the role of risk factor mitigation in the decline of mortality from CHD the data cited here is almost all exclusively from the period following 1968 and therefore could not explain the cause for the initial decline that began in that year.

The contribution of introduced treatments to decline in mortality, reflected in Ford and Capewell's article on public health versus medical care, is seen in a much earlier *New England Journal of Medicine* special article published by these same individuals together with a number of other colleagues. In explaining the decrease in U.S. deaths from coronary disease over two subsequent decades, they concluded: "Approximately half the decline in U.S. deaths from coronary heart disease from 1980 through 2000 may be attributable to reductions in major risk factors and approximately half to evidence-based medical therapies."[12] Combining the data from this article and the later published review article, one would conclude that it was the opinion of these individuals that although both prevention and treatment ultimately contributed to the ongoing decline in CHD mortality that the initial decline was all the result of prevention and risk factor amelioration with little contribution from care and treatment.

In the same year that Ford and Capewell published their article debating the roles of public health and medical care in the decline of mortality, David S. Jones and Jeremy A. Greene presented their work entitled "Is an ounce of Prevention actually worth an ounce of Cure?" at the 2011 national meeting of the American Association for the History of Medicine (AAHM) in Philadelphia. It looked specifically at accounting for the decline in coronary heart disease mortality between 1974 and 2010 and was so subtitled. What these medical historians found was that during the period of their investigation that both prevention and treatment contributed to the decline in mortality and "probably" equally so to that decline. They

[12] Earl S. Ford, et al. "Explaining the Decrease in U.S. Deaths from Coronary Disease, 1980-2000." *NEJM* 356 (2007): 2388-98.

acknowledged however, in private conversation, that prior to 1974 they could not confidently say whether prevention or treatment played the more significant role in explaining the initial decline and failed to make any explanatory statements for the period beginning in 1968.

One year later Jones and Greene published their work in an Analysis and Commentary article in *Health Affairs* entitled "The Contributions of Prevention and Treatment to the Decline in Cardiovascular Mortality: Lessons from a Forty-Year Debate." It appears to be the latest article written in the ongoing debate between prevention and treatment. Through a careful analysis of all the data, publications and models constructed and used they came to a draw of sorts. Beginning in the mid-1970s it appears that "risk factor reductions and modern treatments contributed almost equally." According to Jones and Greene, "given the powerful interests at stake, it is no surprise that expedient results – half credit each to medicine and public health- emerged time and time again."[13] But in this and so many of the other studies in the literature the cause for the very initial decline, the events leading up to the first evidence that something had drastically changed and that the epidemic tsunami of coronary artery disease mortality had reversed and was declining, has still not been fully explained. It seems rather unlikely, given what we have in information from the period leading up to the decline, including statistics, archival information and first hand eye-witness reports (i.e. oral histories), that both prevention and treatment could have contributed equally as so many have stated and tried to convince us of or that prevention somehow lead the way in terms of the decline.

The findings of this study

This dissertation has examined the earliest period of decline and has arrived at a very different conclusion than current explanations that dominate the literature. What is critically

[13] David S. Jones and Jeremy A. Greene. "The Contributions of Prevention and Treatment to the Decline in Cardiovascular Mortality: Lessons from a Forty-Year Debate." 2250-2258.

important here is to remember the time period and the events as they occurred. As we have seen from the literature different conclusions are arrived at for different periods of time. In this study, we are looking only at the initial decline that occurred in the late 1960s and discovered very shortly thereafter. Doing this we can use all the data on prevention and treatment that occurred before 1968 and really nothing beyond it. Many other studies look at periods of time beyond the initial inception of mortality decline. This muddies the waters because so much was rapidly changing and happening, at times almost daily, in terms of interventions for risk and in treatment modalities. If we keep this in mind we quickly see that based on timing many of the factors previously invoked could not possibly have impacted the initial decline in mortality. It also bears witness to the fact that this must have been a multifactorial process and that no one single factor can by itself account for the total initial decline.

What this dissertation shows, if nothing else, is that one single factor cannot account for the initial decline in CHD mortality that occurred by consensus in 1968 and that multiple elements incrementally played a role, some that have not previously been identified in other reports and explanations for the decline. The evidence furthermore confirms that the decline in mortality was real but also appears to indicate that it is more than likely that the decline came to light, specifically in 1968, because there was a change that year in ICD classification from 7 to 8. But be that the case, it does not diminish the fact that in that year it appears that mortality due to the disease was actually starting to decline. The change in classification most probably acted to accentuate recognition of a decline that was already in motion and helped to bring it to the attention of healthcare and public health practitioners.

Why Prevention fails to explain the decline

Although prevention is critically important to improving the incidence of CHD and the epidemic it created and there is evidence from very reliable sources that as early as the mid-

1970s prevention played a key role in the declining mortality of the disease, the evidence accumulated in this dissertation argues strongly against any role for major or minor risk factors in the very early stages of the decline in mortality. The argument against prevention as a reasonable explanation for the decline in mortality does not imply that prevention and knowledge of risk factors did not exist well before the decline in CHD mortality began or that risk factors do not play a very significant role in reducing the incidence of myocardial infarction. The role that cholesterol plays in atherosclerosis has been known at least since the turn to the twentieth century and perhaps earlier. The idea that patients with hypertension had a much higher likelihood of coronary disease has been known for decades preceding the decline as well. But in both cases, skeptics as well as proponents existed and the implementation into practice of preventive measures lagged far behind existing epistemology. The data in this dissertation subscribes to the fact that both these major risk factors, as well as others, were known, but little was done timely enough to have impacted the initial decline in mortality.

Much of our knowledge about the role of risk and its substantiation has been gleaned from the Framingham Heart Study, still ongoing today, which reported its first evidence for the unequivocal role of risk in CHD in 1957. In that report a team of epidemiologists concluded that there was a clear cut association of hypertension, obesity and hypercholesterolemia with the development of CHD. Although they suspected such, they could not clearly identify, on the basis of the cohort studied, an association between smoking or educational background with the development of atherosclerotic heart disease. Subsequent studies however, have identified smoking as a risk factor for CHD and so it is included in this discussion and generally in the majority of scholarly work on the role of risk in heart disease. This dissertation has shown that although these risk factors existed and were known by the academic and medical community long before the decline in CHD mortality began, very little evidence exists that they were

mitigated against in a way meaningful enough to have played a role in the early decline of mortality in any way. One could argue that they were known, variably accepted as risk, but not implemented significantly in preventive measures, timely enough, to have impacted mortality by 1968.

Numerous authorities, as cited in this dissertation, have shown that the mortality from "hypertensive heart disease" began to decline even before that of CHD. Of all cardiovascular diseases it led the way in mortality decline in the mid-twentieth century and hypertension per se, as a cause of death, was already on the wane by the 1960s. This indeed appears to be true from all the available statistical data that exists on the subject. But malignant hypertension and hypertensive heart disease do not represent the danger we think of in terms of hypertension as a risk factor for CHD. So declining mortality due to hypertensive heart disease itself does not resonate with mitigating risk for coronary disease. The dichotomy here is nicely illustrated by Hurst and Logue in their 1966 textbook *The Heart.* They write "Although mortality has been reduced by therapy in severe hypertensive states, insufficient time has elapsed to judge the effectiveness of new drugs in the milder forms of hypertension, either upon prevention of vascular disease or upon ultimate mortality."[14]

What we are concerned about in terms of hypertension as a risk for coronary disease is the much more clandestine and less clinically evident form of hypertension, the significantly more ubiquitous and insidious entity that we often refer to as "benign essential hypertension;" an entity very different in presentation and course from malignant hypertension and that which causes hypertensive heart disease. Norman Kaplan, one of the world's leading authorities on hypertension, and W. Dallas Hall, who ran the Emory Hypertension Clinic for several decades, both agreed that although malignant hypertension was coming under greater control at mid-

[14] J. Willis Hurst and R. Bruce Logue, ed. *The Heart.* New York: McGraw-Hill (1966): 788-789.

century, treatment of essential hypertension was still in its infancy in the 1960s; neither well treated nor well controlled. The first truly effective anti-hypertensive medications for essential hypertension did not come into existence until the mid-1950s and the number of patients whose hypertension was controlled remained dismally low through the 1960s and even into the 1970s. It was not until the mid-1970s that pharmaceutical companies became interested and involved in clinical trials of medications and the promise of marketing blockbuster drugs to lower hypertension for more widespread general use.

Eugene Braunwald points out that "In 1971 blood pressure was treated and controlled in only 16 percent of all persons in the United States with a blood pressure of 160/95 mm Hg or higher."[15] Kaplan notes NHANES data in 1972 revealed that, at the time, only 12% of patients with hypertension were considered to be adequately controlled. Currently, we are treating about 80% of patients with control of hypertension in about 46%. Much of the problem in early treatment, in the days preceding the initial decline in coronary artery disease mortality, was that the medications were "not easy" according to Kaplan. Many of them carried unacceptable side effects such that patients would not take them and most physicians were loathed to prescribe them.

In the 6th edition of his book *Clinical Hypertension* published in 1994, Kaplan writes about the role of hypertension stating "we have to look elsewhere to explain much of the improvement in coronary and cerebrovascular mortality rates that have occurred since 1968." Even should adequate drug treatment have existed before 1968, which is not altogether clear, Kaplan remarks in his book that "the evidence that drug therapy protects against stroke and

[15] Eugene Braunwald. "Shattuck Lecture – Cardiovascular Medicine at the Turn of the Millennium: Triumphs, Concerns, and Opportunities." *NEJM* 337 (1997): 1360-1369.

heart failure seem strong, although doubts remain about the benefits of therapy for prevention of coronary disease."[16]

The prevailing evidence shows that control of essential hypertension probably played very little role in reducing CHD mortality because treatments prior to 1968 were not good and few patients had their hypertension well controlled. As pointed out by Kaplan and others, the belief and evidence that hypertension itself as a cause of death was declining has little to do with hypertension as a risk factor for CHD. There is just no real evidence that risk factor significant hypertension received much of the attention of clinicians and patients before at best the mid-1970s.

The role of serum cholesterol as a risk factor for CHD is a somewhat different story, one well documented here and particularly in the book *The Cholesterol Wars* by Daniel Steinberg. This is the story of greater skepticism and the struggle to convince people in the 20th century of the danger of cholesterol. In large part, even though cholesterol's role in atherosclerosis had been known since Russian scientists fed high levels of fat to rabbits in the early 1900s, the belief that it could lead to coronary artery disease was much more hotly debated and contested. Steinberg notes that, as late as 1982, the lipid hypothesis of atherosclerosis and CHD was severely set back by the MRFIT study and the ability to control serum cholesterol in a meaningful way was not easily achieved until much later. In fact numerous individuals I spoke to, including Eugene Braunwald and Jeremiah Stamler, believe that really good cholesterol control did not happen in the population at large until the first statin drugs were introduced in the mid and late 1980s. So that even though cholesterol's role in CHD as a risk factor was well documented early it was in large part not believed important or significant for a long period of

[16] Norman M. Kaplan. *Clinical Hypertension.* 6th edition. Baltimore: Williams and Wilkins (1994): 19-20.

time and where it was felt to be essential to the development of CHD hard to control until well after the initial decline in mortality began.

No matter what the belief in the saliency of cholesterol as an important, and as many have stated to me the *single most important,* factor in the development of atherosclerosis the issue is indisputable that control of cholesterol via diet and early medications was very difficult to achieve. For this reason mitigating its risk in a meaningful way was not at all evident prior to the time CHD mortality began to decline.

Finally, the role of tobacco as a risk factor for CHD has still not been convincingly sorted out. Although most believe it is a risk, some including cardiologist Richard Conti at the University of Florida are not completely convinced. Early results as well from Framingham were not able to identify it or socioeconomics as a risk factor for CHD. Reviewing "approximately 7000 articles relating to smoking and disease, the Advisory Committee to the U.S. Surgeon General concluded that cigarette smoking [was] a cause of lung and laryngeal cancer in men, a probable cause of lung cancer in women, and the most important cause of chronic bronchitis in both sexes" but failed to make any mention of its impact on the heart in what became the substance of the 1964 surgeon general's report. It was in the spirit of a general health hazard that public health efforts began to reduce "the prevalence of tobacco use" not long after the risk to the lungs was first described in 1964.[17] Many including Braunwald view it as a short lived risk for the heart without any visible "memory" or long standing risk once its use has been discontinued. But whether you believe it to be a bona-fide risk factor or not for CHD one fact is indisputable. The consumption of tobacco in this country peaked in 1963 and did not begin to decline until after 1968. It was not until 1973 that there was a steady decrease in cigarette

[17] Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion. "Tobacco Use – United States, 1990-1999." *JAMA* 282 (1999): 2202-2204. Also *MMWR* 48 (1999): 986-993.

consumption.[18] In 1965, 42.4% of the U.S. adult population 18 year and older smoked.[19] All this making the argument that Americans heeded the 1964 surgeon's general report in a timely enough fashion to help reduce the mortality of CHD most unlikely. If Americans have reduced their use of cigarettes in an attempt to reduce the ill effects of smoking on the heart it did not and, by the prevailing evidence, could not have happened before the decline in mortality began. It quite clearly has however since, with the prevalence of smoking among U.S. adults dropping in 1970 to 37.4%[20] and probably contributing to a reduction in mortality of the disease since, but not to an initial reduction.

The case for History and Treatment

Eugene Braunwald, whose sense of history, especially history of heart disease, is well known and often touted, called the coronary care unit "the single most important advance in the treatment of AMI."[21] In his office he told me that he felt even stronger about it and attributed the initial decline in mortality of CHD to the development and implementation of the CCU in the early 1960s. But the research of this dissertation traces the origins of the decline to a much earlier period. Bernard Lown, whose remarkable life journey in treating patients with heart disease is quite intimately tied to the CCU, told me emphatically "no, I was there." He said the story began much earlier than the CCU. It began with a major philosophical change in the way that patients who had sustained a myocardial infarction were initially treated and it began a full decade plus earlier than the CCU.[22]

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[18] Lawrence Garfinkel. "Trends in Cigarette Smoking in the United States." *Prev Med* 26 (1997): 447-450.
[19] Source: U.S. Centers for Disease Control and Prevention. www.cdc.gov
[20] Ibid.
[21] Eugene Braunwald. "Evolution of the management of acute myocardial infarction: a 20th century saga." *Lancet* 352 (1998): 1771-74.
[22] Interview with Dr. Bernard Lown at his home in Chestnut Hill, Massachusetts, November 4, 2013.

What Lown believes is that the idea that patients with a heart attack did not have to be condemned to bed rest and all the psychological issues that surrounded it contributed much more to the initial decline in CHD than even the CCU. He attributes the initial decline to getting patients up out of bed into a chair, reassuring them that despite the insult to their heart their lives were not over and all the other psychological and medical benefits that result from this simple maneuver. In this respect it goes all the way back to the initial work of Herrick, that having a myocardial infarction did not automatically mean death.

The initial point of departure on this remarkable journey in treatment of CHD begins with the work of Samuel Levine and Bernard Lown on the clinical wards of the Peter Bent Brigham Hospital in 1950. Levine, for reasons related to the heart as a pump, and Lown, for the fact that treating the patient to good health involved not only the body but the mind, came up with the idea that critical to improvement in mortality was the action of getting patients up from bed into a position in which the world looked better and the heart operated more smoothly. Clear evidence exists in small studies from the Harvard hospital that the chair reduced mortality, the only question being is whether it resulted in enough to have caused a nationwide decline in mortality. In speaking with other clinicians around the country and reviewing the literature, the use of the chair although not universal did have many advocates such that over a 20 year period from the time of Levine's first description that it quite reasonably could have led to a small but significant reduction in mortality; the sort of small reduction already alluded to that occurred in 1968.

The chair began a new philosophy of care of patients with a heart attack and a number of important achievements were realized on the heels of its implementation. The invention of the cardioverter, the use of medicines to control lethal arrhythmias and the adaptation of closed chest massage to resuscitative efforts were among these. But the next great achievement in

coronary care was clearly the CCU. It not only established a new standard of care, it greatly expanded the specialty of cardiology with new and greater needs for heart doctors and expanded the role of nurses, transforming them from roles of caring to ones of curing. The impact on patient mortality was almost immediate with reductions as much as 50% for patients admitted to the hospital and placed in the CCU.

The early studies and the multiple oral histories done for this dissertation attest to a very significant role played by the CCU in reducing mortality. Those critical of this view cite the fact that not all hospitals had CCUs in the 1960s. But according to Braunwald, "the concept of the CCU was proposed on July 16, 1961," and "within 5 years, CCU treatment of AMI became standard of care worldwide." This cut mortality "from about 30% to 15%."[23] Eugene H. Guthrie, Associate Surgeon General of the Public Health Service, pointed out, at a conference held in Washington, DC, in June 1967, that at the time there were "well over 300" CCUs in operation in the United States, and that "many other hospitals provide [the same] coronary care services, although without full-fledged units."[24] Intensive care units, caring for a wide diversity of patients, many with myocardial disease, as already pointed out in chapter 5, actually began in the 1950s (late 1953 and early 1954) in a variety of diverse locations across the country. Not as technologically sophisticated as the CCUs of the 1960s they nevertheless operated in similar ways with the critically ill grouped together in small units, with 24 hour "concentrated nurse staffing" and constant observation.[25] This is important to keep in mind and when I spoke with Braunwald in his office he made the same point, that even though in the early days some

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[23] Eugene Braunwald. "Evolution of the management of acute myocardial infarction: a 20th century saga." 1772.
[24] Eugene H. Guthrie, MD. "Introductory Remarks." *Proceedings of the National Conference on Coronary Care Units.* Public Health Service Publication No. 1764 (March 1968): 1.
[25] Julie Fairman and Joan E. Lynaugh. *Critical Care Nursing: A History.* Philadelphia: University of Pennsylvania (1998): 12-13.

hospitals did not call them CCUs, they provided the same close observation of patients and care environments.[26] Eliot Corday, cited earlier in this dissertation (chapter 5) spoke at the same conference in Washington, DC in 1967 pointing out the importance of resuscitation efforts in the CCU and the role of nurses. He noted that "when authority to apply countershock was delegated to nurses, up to 70 percent of patients suffering from primary cardiac arrest due to ventricular fibrillation could be resuscitated."[27]

In 1965, James Warren contributed the following to substantiating the benefit of the CCU and its accompanying components in reducing mortality: "Vigorous therapy following acute myocardial infarction might effect a saving of 40,000 lives a year." He defined this therapy as "placement of patients in special 'coronary care units' in hospitals, institution of measures to combat shock and congestive heart failure, and use of anticoagulants and vasopressor drugs;"[28] already standards of care in the CCU at the time. A two part report on the CCU appeared in May and June of the same year (1965) in *Modern Concepts of Cardiovascular Disease.* It was based on information supplied to date by the CCUs at Bethany Hospital in Kansas City, Kansas and Presbyterian Hospital in Philadelphia, Pennsylvania. Attesting to the power of the CCU in reducing mortality the report writes "Although the number of treated cases in these two units was small, the clinical data nevertheless suggest that a *significant* reduction in mortality rate in acute myocardial infarction can be expected when the patients are observed and treated in a Coronary Care Unit for an initial period of three to seven days."[29]

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[26] Interview with Dr. Eugene Braunwald in his office on Longwood Avenue, Boston, Massachusetts, October 2012.
[27] Eliot Corday, MD. "Purpose of the Conference." *Proceedings of the National Conference on Coronary Care Units.* Public Health Service Publication No. 1764 (March 1968): 5-6.
[28] W. Bruce Fye. "Resuscitating a Circulation Abstract to Celebrate the 50th Anniversary of the Coronary Care Concept." *Circ* 124(2011): 1892.
[29] Paul N. Yu, et al. "Coronary Care Unit (I, II): Specialized Intensive Care Unit for Acute Myocardial Infarction." *Mod Concepts Cardiovas Dis* 34 (1965): 23-30.

The nursing literature confirms the dramatic impact that the new era of "critical care nursing" had on life threatening illnesses like myocardial infarction. Write nurse historians Julie Fairman and Joan E. Lynaugh, "Critical care does work to save lives, maintain bodily functions, and implement complex therapies. As a treatment modality – a total technology – it has lived up to its promise that intense monitoring and correct interventions during periods of physiological instability will help many people get through otherwise deadly medical crises."[30]

Although no large scale randomized controlled trials were conducted on the efficacy of the CCU in reducing the mortality of CHD, the information that we do have from multiple sources and authorities would lead one to believe, rather convincingly, that the CCU and all its attendant benefits played a role in the early decline in coronary artery disease mortality and continued to play, perhaps an increasing role in the decline as the number of units in operation increased nationwide over time. It also forever changed the role of nurses in caring for the critically ill. Old standards and relationships were reconfigured and the critical care nurse had the opportunity to reduce mortality by implementing life saving measures in a timely fashion. This and the expansion of the profession of cardiology no doubt played a role in the continuing reduction of CHD mortality. The process was a dynamic one and according to W. Bruce Fye it was already in place in the 1960s. He notes that "between 1949 and 1960 the number of cardiology fellowship programs and trainees increased tenfold, and the trend continued during the next decade." Cardiology training programs grew from 72 to 253 and the number of fellows went from 142 to 1,409, over a 15 year period, from 1961 to 1976. The 1960s marked a new direction for medical practice in general and most graduates of medical schools in this country were going into specialties rather than general practice. Cardiology was perceived as "dynamic,

[30] Julie Fairman and Joan E. Lynaugh. *Critical Care Nursing: A History.* 112.

interesting and lucrative," and by the early 1960s it was attracting a huge following.[31] The impact on patient care, especially in life threatening situations, was obvious. Writes Jeremiah Barondess of the New York Academy of Medicine, "Without question, subspecialty expertise has offered clinical benefits to thousands of patients with uncommon disorders, critical illness, and disorders requiring special techniques."[32] This expansion of heart disease specialists in the decade preceding the decline in mortality coupled with CCUs and the expanded role of nurses all incrementally added up to improved care of patients with CHD. This view was confirmed by the oral history of Spencer King, former president of the American College of Cardiology, who credits the expanded professionalization of cardiology in the 1960s with a role in reducing CHD mortality.[33]

Coupled with improvements in treatment and care is the improvement in access that occurred during the 1960s. The introduction of Medicare and Medicaid in 1965 resulted in more people, especially the elderly, seeking care for illness. A group prone to heart disease because of age, Medicare increased access to acute care for those experiencing symptoms related to myocardial infarction. As already mentioned the bulk of the literature, hospital reports and expert oral histories all substantiate the evidence that the introduction of Medicare played a role in getting patients much needed and previously delayed care, and in this manner must have played a role in reducing the mortality of acute coronary artery disease. At age 92, Bernard Lown believed "absolutely" that Medicare had an impact, stating "Medicare improved [mortality] because it gave people hope, security about health. It made them feel good about

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[31] W. Bruce Fye. *American Cardiology: The History of a Specialty and Its College.* Baltimore: Johns Hopkins (1996): 279-282.
[32] Jeremiah A. Barondess. "Specialization and the Physician Workforce: Drivers and Determinants." *JAMA* 284 (2000): 1299-1301.
[33] Interview with Spencer B. King, III, MD in his office at St. Joseph's Medical Center, Atlanta, Georgia, July 10, 2012.

themselves. Look, I am an old man, what am I afraid of now? I am afraid of whether I will be able to afford healthcare. I have the best insurance in the world [Medicare]."[34]

But not all that involved treatment and care contributed to the decline in mortality. We know for sure that emergency medical services (EMS) could have had no effect. The data that exists shows little impact of these services prior to the 1970s. Most of the literature and oral histories obtained for this dissertation demonstrate that EMS was so primitive in the period preceding the decline that it could have played no greater role in saving life than funeral home hearses which filled the major role of ambulances in many parts of this country through the 1960s. Emergency rooms during the period were also often staffed by sleep deprived house staff or moonlighting physicians looking for additional income. State of the art in 1964, according to one authority, was a "disturbing scenario" of "untrained attendants running hearses to and from emergency rooms that were staffed by physicians assigned there against their will."[35] This view was confirmed by Dr. Robert Copeland, the first board certified cardiologist in LaGrange, Georgia. He told me that "When I first got here they were still picking them [heart attack victims] up in a hearse. The EMS concept came along in the 70s" in Lagrange.[36]

This analysis then concludes that the decline in mortality is primarily related to interventions that occurred during the acute hospitalization of patients with acute myocardial infarction. Discounting in the main, as we have done, any apparent contribution from prevention, including the lack of evidence that incidence of CHD was declining in the initial period of decline, as well as any contribution from pre-hospital intervention, that being primarily

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[34] Interview with Bernard Lown, MD at his home in Chestnut Hill, Massachusetts, November 4, 2013
[35] Carl J. Post. *Omaha Orange: A Popular History of EMS in America.* Sudbury: Jones and Bartlett (2002): 47.
[36] Interview with Dr. Robert Copeland in his home in LaGrange, Georgia on April 18, 2013.

EMS intervention following the acute event (AMI), we are left with only one other possibility contributing to reduction in mortality that has not been discussed. That last factor is an improvement in long term survivorship of patients after a myocardial infarction. Long term survival in CHD is impacted primarily by three issues, development of life threatening cardiac arrhythmias over time, the extent and progression of coronary artery disease and the degree of left ventricular function. The Decline Conference in 1978 addressed this issue concluding that the 1960s introduced no therapy that could have had an impact on either the development of arrhythmias after discharge or the preservation of functioning coronary anatomy. Furthermore, even by 1978, "treatment of pump failure" remained poor with no substantial improvements noted ten years after the decline began. What the conference concluded was "that the decline could not have resulted from changes in out-of-hospital treatment or long-term survivorship after hospital discharge."[37] Furthermore, if prevention played little role, as we have already concluded, and incidence of disease was not yet declining by the late 1960s, one is left only with a decline of "in-hospital case fatality" to explain the decline in CHD mortality on the basis of the disease itself.

Is the decline independent of treatment and prevention – Would it have happened anyway?

Can we conclusively say that the decline in CHD mortality is related only to factors related to interventions in the disease itself? There is evidence and many would argue that the initial decline in coronary artery mortality had little to do with either prevention or treatment and is rather based on evolutionary tendencies, improvements in socioeconomics, impact of simultaneous but unrelated events, and the similar experience of other diseases. In short, it was

[37] Lewis H. Kuller, Ronald E. LaPorte, and Gene B. Weinberg. "The Decline in Ischemic Heart Disease Mortality: Environmental and Social Variables." In Richard J. Havlik and Manning Feinleib. Ed. *Proceedings of the Conference on the Decline in Coronary Heart Disease Mortality.* Bethesda: NIH Publication No. 79-1610 (1979): 312-314.

destined to happen anyway! This is certainly the argument that would be put forth by individuals like Thomas McKeown and his followers. The mortality of coronary artery disease improved because mortality of almost all diseases, except cancer, were improving in the same time period. Healthier diets may have impacted this improvement, as suggested by McKeown, not in the sense that people were eating less cholesterol because clearly they weren't but because diet was impacting the population in another way, possibly epigenetically. Time wise this might also make sense. The depression of the 1920s in this country forced most people to cut back on the consumption of meat products and consumables rich in fats and proteins. If you believe in the "thrifty gene hypothesis"[38] and similar theories than this proposition in reducing factors that lead to disease may be appealing and plausible. They can it is believed lead to a "transgenerational" change in the epigenome and so impact the predisposition of vast numbers of people to coronary artery disease.

And then beyond epigenetics are the individuals who argue that the 1918 flu epidemic had a profound impact on the epidemiologic pattern of CHD mortality over the twentieth century. In effect, leading to the emergence of the CHD epidemic by modifying susceptibility, independent of any nutritional effect, risk factors or impact on treatment, and subsequently changing vastly the population dynamics and epidemiology of the disease. One might also postulate that the Influenza of 1918 was so cataclysmic in its death toll of the young that those who would have been predisposed to coronary disease later in life, and thus probably contributing to its mortality at some point, were no longer around at a time in their life to have added to that mortality. These hypotheses and theories however are, as already mentioned,

[38] Theory originally proposed by geneticist James Neel that individuals who carry thrifty genes are believed to better survive times of food scarcity.

pure hypothesis and conjecture, highly speculative in nature, but in terms of history and chronology must be viewed with some degree of potential merit.

All of these unknown, other factors, represent a “black box” of mystery in which exist a variety of explanations that can neither be proven or disproven but in many ways are persuasive arguments. Epigenetics could have changed the population at risk for CHD just as the great flu epidemic could have changed the numbers who survived to the point that they would contribute to the mortality of heart disease. We have few answers for those among us who prescribe to these theories and explanations because both are highly theoretical and very difficult to prove.

Summary

CHD appears to be very much a modern disease that came to clinical attention in a significant way only after the close of the 19th century. Unlikely a new disease, it appears to have been shielded from view while infectious diseases of past centuries raged and predominated in terms of morbidity and mortality. Once these diseases were tamed, CHD had an opportunity to reign supreme in the attention it attracted and the lives it claimed. During the early 20th century the disease appeared to manifest itself as an acute and uniformly fatal disease. Or at least so it appeared to medical practitioners. It was not until James Herrick showed the medical world, with the help of newly invented ECG technology that individuals could survive beyond the initial insult to their coronaries that the disease was recognized as a chronic one and its yearly mortality recorded. It rapidly, over the first half of the 20th century, became the leading cause of death in this country and has remained such ever since. But curiously and without warning, although rapid changes were occurring in treatment and care and knowledge about prevention was becoming more widespread, the mortality of a disease, once considered uniformly fatal, began to fall. And it has continued to decline ever since. The

explanation for its decline at present is inarguably a combination of improvements in prevention coupled with great strides in treatment and care. But does this explain the very early and initial decline in CHD mortality?

Acknowledging current contributions of both treatment and prevention to a decline in CHD mortality what can we say about the initial decline that started in 1968? I think we can safely say, and this study substantiates such, that the initial decline in CHD mortality had very little to do with prevention and the mitigation of risk factors. The evidence for a role of prevention was already quite firmly established among researchers and epidemiologists, well back to the 1950s and 1960s, if not earlier, but the acceptance and implementation of prevention was still not well transmitted into the field, to those who needed to advocate for it and put it into (healthy lifestyle) practice. Although my sample is small by necessity (many of those who could or would substantiate it no longer living) it does speak to the fact and statement that "we knew about risk factors back then but did little to implement prevention." Later on, when the treatment of essential hypertension had substantially improved, when the surgeon general's report of 1964 had been firmly embedded in the mindset of the population and consumption of tobacco across gender and racial lines had begun to decrease and finally when effective treatment had become available to lower serum cholesterol levels, then prevention no doubt played an important role in reducing CHD mortality. The data of Jones and Greene as well as others in the years beyond 1974 show clearly that these factors contributed significantly to further decreases in CHD mortality. But this was not and could not have been the case in 1968.

The evidence from this dissertation does show that the treatment of coronary artery disease was progressing with lightning speed through the late 1950s and 1960s and changes were being made that definitely and definitively impacted mortality if only in small ways. There

were not only technological changes, there were major changes in the philosophy of the way patients should be treated once they had sustained a myocardial infarction. The ill begotten notion that strict bed rest was needed for these patients, an idea that harked back to Herrick himself, with little proof or evidence that it was needed or even worked, was being changed in the 1950s to not only reduce dreaded complications in the form of pulmonary emboli and heart failure, but to also improve the sense of well-being of those who had sustained an infarction. As Lown points out one cannot underestimate the power of the psyche in terms of recovery from illness. The idea of the "chair" and early ambulation of acute patients was coming into practice in the fifties and on its heels improvements in cardiopulmonary resuscitation and defibrillation and the implementation of a brand new way of monitoring and caring for patients. If the patient with a myocardial infarction reached the hospital in the late 1960s, his or her chance of survival was improved substantially, by as much as 50% if the hospital had a CCU.

Still the improvements in treatment of the 1950s and 1960s left a large proportion of the patients, 70% by some accounts, in harm's way. What was being done in the hospital was not being replicated effectively outside. Not yet. By the 1980s rapid out of hospital medical response was becoming a reality and EMS was helping to save those who were still dying at home or in the streets of heart attacks in the 1960s. But was improving the mortality of those who made it to the hospital enough of a factor to improve the overall mortality of CHD in the late 1960s? It is hard to say but I would say, based on this research and the primary data gathered, probably. Let's do the math. If 100 patients sustained a heart attack and 30% make it to the hospital and of that 30% the mortality goes from 30% to 15% then in that group alone you have reduced the mortality from 9 patients to 4 patients. If nothing else there would have been a small reduction in mortality of about 5%.[39] Enough of a change? Again, possibly even if

[39] The same reduction Levine and Lown found between prolonged bed rest and chair treatment.

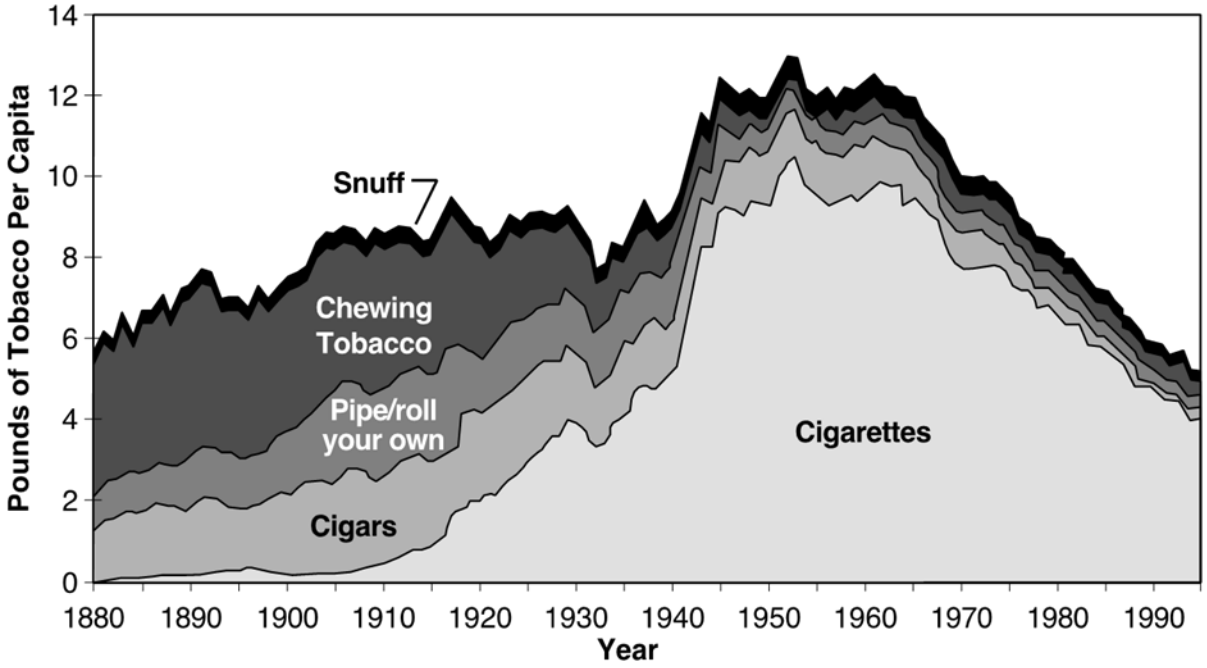
it only happened in the roughly 350 hospitals that had a CCU (or the slightly more that had a CCU equivalent) by the late 1960s.

I think it is safe to say that multiple factors outside of prevention and public health played a role in the decline of coronary artery disease mortality that began in this country in 1968. A combination of early marked improvement in treatments, the possible contribution of the 1918 influenza epidemic that changed the population dynamics and epidemiology of the disease in the 20th century, the role of epigenetic factors, and the fact that mortality of all cardiovascular diseases was improving more than likely all played a role in the early reduction of CHD mortality. No one isolated factor can be singled out alone, but multiple forces appear to have been at work, save for prevention, that helped to lower CHD mortality by 1968. In other diseases where the exact etiology is not known it would appear that altering the course of the disease would not involve a single intervention or event but would rather require the involvement of multiple interacting forces. Reducing the mortality of dreaded diseases like cancer will no doubt occur when multiple forces impacting that mortality come under control.

Appendix 1

Figure 1

Per capita consumption of different forms of tobacco in the United States, 1880-1995

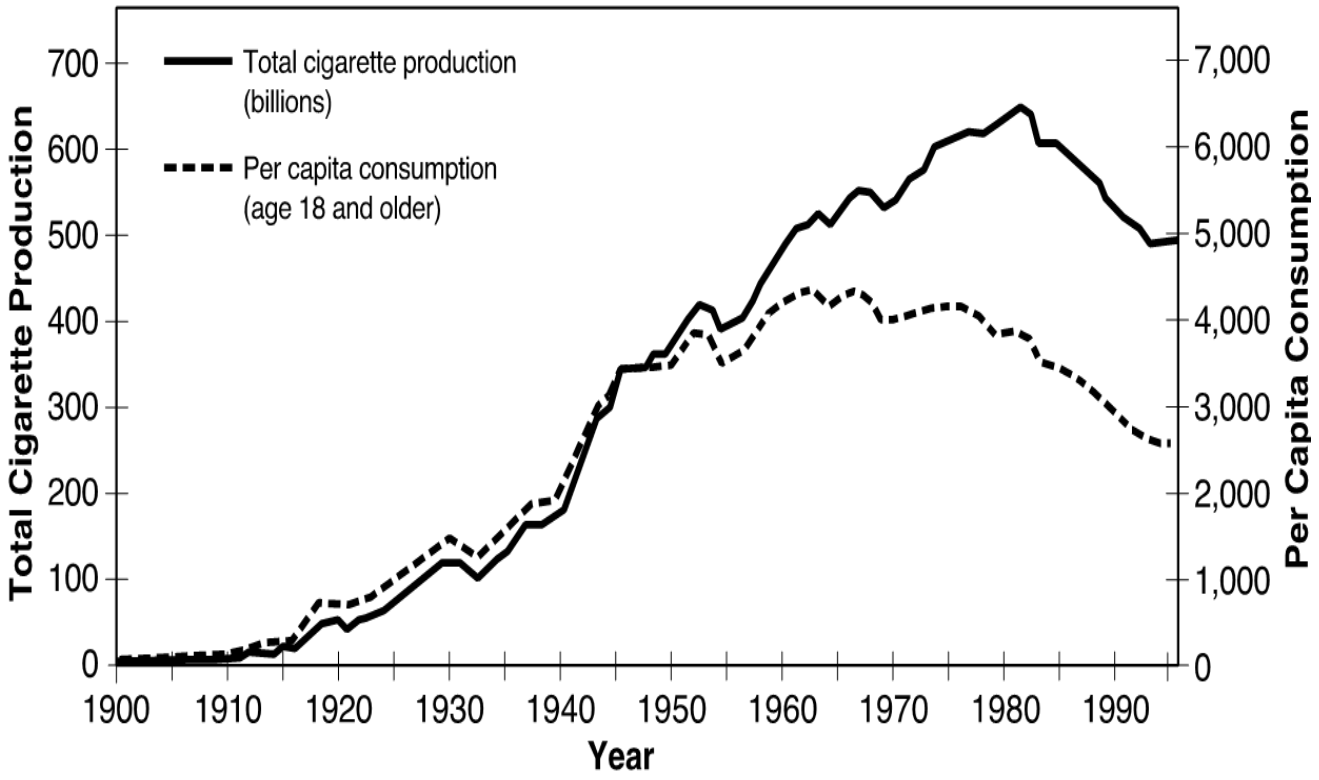


Source: U.S. Department of Agriculture, 1996.

Appendix 1

Figure 2

Total and per capita cigarette consumption in the United States, 1900-1995



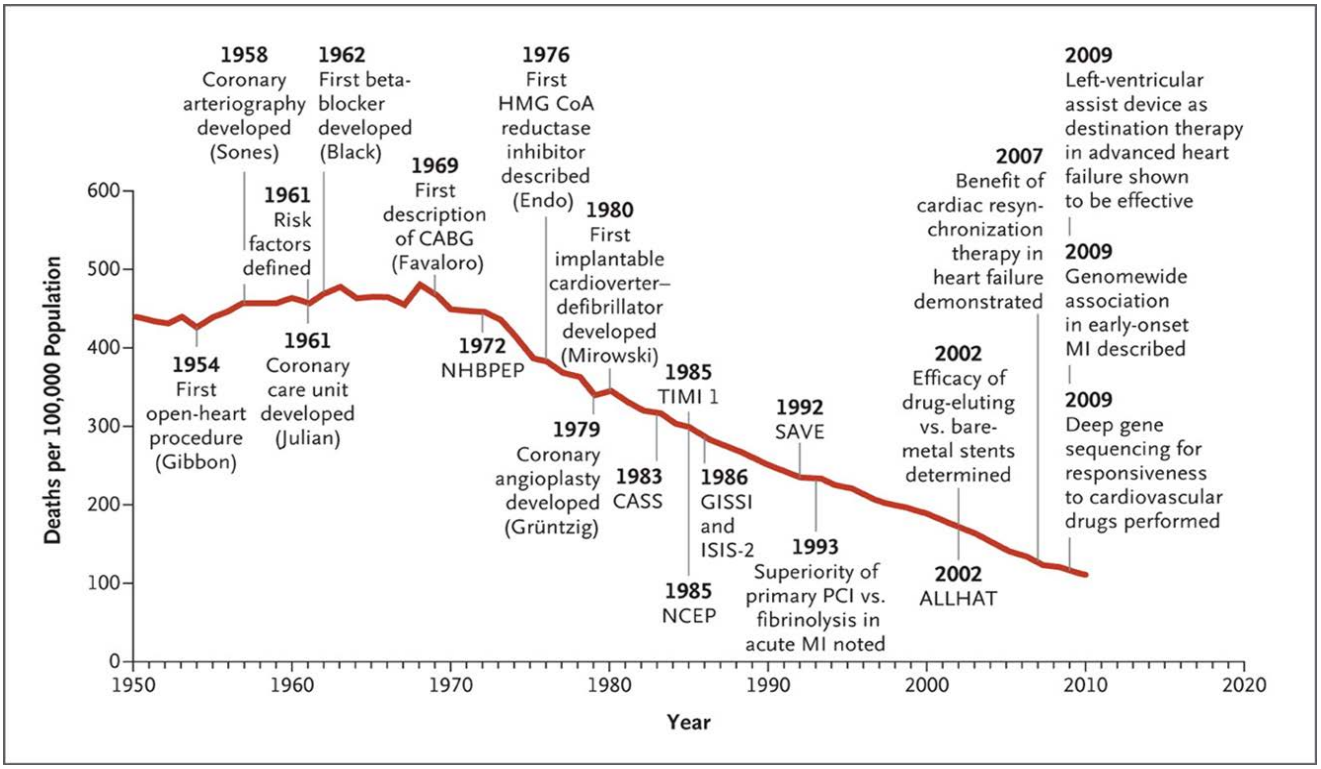
Source: U.S. Department of Agriculture, 1996.

Appendix 1

Figure 3

Decline in Deaths from Cardiovascular Disease in Relation to Scientific Advances.

Nabel, EG, Braunwald E. *N Engl J Med* 2012 (366): 54-63.



Appendix 2

Oral History Interviews
The Experts

Henry Blackburn, MD

Interviewed:	January 12, 2013
Current Address:	University of Minnesota School of Public Health Division of Epidemiology & Community Health 1300 S. 2nd Street, Suite 300 Minneapolis MN 55454
Credentials:	Professor Emeritus, University of Minnesota School of Public Health Professor, Department of Medicine, University of Minnesota Mayo Professor Emeritus of Public Health, School of Public Health, University of Minnesota Former Director, Division of Epidemiology, School of Public Health, University of Minnesota
Area of Expertise:	Cardiovascular Epidemiology, coronary heart disease prevention, Cardiac rehabilitation
DOB:	March 22, 1925

Eugene Braunwald, MD

Interviewed:	October 18, 2012
Current Address:	TIMI Study Group 350 Longwood Avenue Boston, Massachusetts 02115
Credentials:	Founding Chairman, TIMI Study Group, Brigham and Women's Hospital Senior Consultant in Medicine, Massachusetts General Hospital Senior Physician, Brigham and Women's Hospital Senior Investigator, TIMI Study Group, Brigham and Women's Hospital Distinguished Hersey Professor of Medicine, Harvard Medical School Former Chairman, Department of Medicine, Brigham and Women's Hospital

Area of Expertise: Cardiology, Coronary Artery Disease, Cardiovascular Research, History
Cardiology

DOB: August 15, 1929

Textbooks: Friedberg

Charles Richard Conti, MD, MACC, FCP (SA), FESC, FAHA

Interviewed: August 14, 2012

Current Address: University of Florida
Division of Cardiology
1600 SW Archer Road, PO Box 100277
Gainesville, Florida 32610-0277

Credentials: Eminent Scholar, University of Florida
Professor of Medicine, University of Florida
Immediate Past Medical Director, University of Florida Shands Cardiovascular Clinic

Area of Expertise: Myocardial Ischemia and reperfusion, antibiotic treatment of CAD,
Coronary angiography

DOB: October 26, 1934

Textbooks: Cecil and Loeb, Robbins Pathology, Friedberg

Robert Copeland, MD, MACP, FACC, FRCP

Interviewed: April 18, 2013

Current Address: 1551 Doctor's Drive
LaGrange, Georgia 30240

Credentials: Physician, LaGrange, Georgia
Medical Director, Georgia Heart Clinic, LaGrange, Georgia
Clinical Professor of Medicine, Emory University, Atlanta, Georgia
Former President, Southern CardioPulmonary Associates, PC, LaGrange, Georgia
Former Clinical Professor of Medicine, (Cardiology), University of Alabama at Birmingham

Area of Expertise: Clinical Cardiology

DOB: January 24, 1938

Textbooks: Harrison's, Robert Grant *EKG*

Roman DeSanctis, MD, FACC

Interviewed: October 19, 2012

Current Address: Massachusetts General Hospital
Yawkey Building
Suite 5700
55 Fruit Street
Boston, Massachusetts 02114

Credentials: James and Evelyn Jenks and Paul Dudley White Professor of Medicine

Harvard Medical School
Physician, Massachusetts General Hospital

Area of Expertise: Clinical Cardiology, Coronary Care, Myocardial Infarction

DOB: 1930

W. L. Jack Edwards, MD

Current Address: 3521 Rosedale Avenue
Dallas, Texas 75205

Credentials: Clinical Professor of Medicine, Southwestern Medical College of the

University of Texas
Attending Physician, Baylor University Medical Center, Parkland Memorial Hospital, Dallas, Texas.
Retired from Active Practice in 1993.

Area of Expertise: EKG, Clinical Cardiology, Non-invasive cardiology

DOB: September 21, 1926

Textbooks: Harrison's, Cecil, White Heart Disease 3rd edition, 1947, Thomas Lewis 1934, Levine's Clinical Heart Disease, 3rd edition, Proctor Harvey, Friedberg 1951, Cabot 1926

Arthur Roberts Errion, MD

Interviewed: January 24, 1913

Current Address: 769 Crestridge Drive, NE
Atlanta, Georgia 30306

Credentials: Retired Career Military Internist

Area of Expertise: Internal Medicine, Military Medicine

DOB: February 19, 1916

Textbooks: Could not remember

William B. Fackler, Jr., MD

Interviewed: March 21, 2012

Current Address: 829 Piney Woods Drive
Lagrange, GA 30240-2019

Credentials: Retired, Private Practice Cardiology

Area of Expertise: Clinical Cardiology, Internal Medicine

DOB: February 18, 1920

Textbooks: Harrison's, Beeson

Peter Gazes, MD

Interviewed: May 8, 2014

Current Address: 21 Country Club Drive
Charleston, South Carolina 29412

Credentials: Professor of Medicine, Medical University of South Carolina (MUSC)

Former Director, Cardiovascular Division, MUSC
Distinguished University Professor of Cardiology
First Board Certified Cardiologist in State of South Carolina

Area of Expertise: Clinical Research Cardiology

DOB: October 10, 1921

Textbooks: Levine, Friedberg

W. Dallas Hall, MD

Current Address: 3747 Peachtree Road

Atlanta, Georgia 30319

Credentials: Emeritus Professor, Emory University School of Medicine
Former Director, Division of Hypertension, Emory University School of Medicine

Area of Expertise: Hypertension

DOB: June 26, 1938

Textbooks: Harrison's Principles of Internal Medicine

Charles Ross Hatcher, Jr., MD

Interviewed: January 31, 2013

Current Address: 1105 Lullwater Drive
Atlanta, Georgia 30307

Credentials: Director Emeritus, The Robert W. Woodruff Health Sciences Center,
Emory University
Professor of Surgery, Emeritus, Emory University School of Medicine

Area of Expertise: Cardiovascular Surgery, CABG, Medical Administration

DOB: June 28, 1930

John (Jack) W. Hyland, MD

Interviewed: November 16, 2012

Current Address: Cardiology Consultants of Texas
3500 Gaston Avenue
Dallas, Texas 75246

Credentials: Private Practice of Cardiology
Former Director, H.L. and Ruth Ray Hunt Heart Center, Baylor University Medical Center, Dallas, Texas
Former Director, Cardiac Laboratory, Baylor University Medical Center, Dallas, Texas

Area of Expertise: Cardiopulmonary disease, Coronary Artery Disease, Coronary Angiography

DOB: January 13, 1929

Textbooks: Levine, Friedberg

Norman Kaplan, MD

Interviewed: November 16, 2012

Current Address: The University of Texas Southwestern Medical Center at Dallas
5323 Harry Hines Boulevard
Dallas, Texas 75390-8899

Credentials: Clinical Professor; Department of Internal Medicine; The University
of Texas Southwestern Medical School, Dallas, Texas
Former Head, Division of Hypertension, Department of Internal Medicine, University of Texas Southwestern Medical School

Area of Expertise: Clinical Hypertension

DOB: January 2, 1931

Textbooks: Friedberg

Spencer B. King, III, MD, MACC, FACP, FESC

Interviewed: July 9, 2012

Current Address: Saint Joseph's Hospital
5665 Peachtree Dunwoody Road, NE
Atlanta, Georgia 30342

Credentials: President, Heart and Vascular Institute, Saint Joseph's Hospital
Executive Director, Academic Affairs, Saints Joseph's Health System
Professor of Medicine, Emeritus, Emory University
Former Professor, Department of Medicine (Cardiology)
Former Director, Andreas Gruentzig Cardiovascular Center, Emory University
Past President, American College of Cardiology

Area of Expertise: Invasive Cardiology, coronary angiography

DOB: May 12, 1937

Textbooks: Goodman and Gilman, Friedberg, Hurst and Logue

Darwin R. LaBarthe, MD

Interviewed: January 12, 2013

Current Address: Northwestern University Feinberg School of Medicine
Department of Preventive Medicine
680 N. Lakeshore Drive
Suite 1400
Chicago, Illinois 60611

Correspondence:
Post Office Box 1406
Blanco, Texas 78606

Credentials: Professor of Preventive Medicine, Department of Preventive Medicine, Northwestern University Feinberg School of Medicine
Adjunct Professor of Epidemiology, Rollins School of Public Health,
Emory University
Former Director, Division for Heart Disease and Stroke Prevention,
National Center for Chronic Disease Prevention and Health Promotion,
CDC.

Area of Expertise: Cardiovascular Epidemiology, Cardiovascular Disease Prevention, CVD
Risk Factors

DOB: August 5, 1939

Bernard Lown, MD

Interviewed: November 4, 2013

Current Address: 194 Hobart Road
Chestnut Hill, Massachusetts 02467-1158

Credentials: Professor of Cardiology Emeritus, Department of Nutrition, Harvard
Public Health
Nobel Peace Prize recipient 1985

Area of Expertise: Coronary Artery Disease, Cardiac electrophysiology, Therapy for Arrhythmias

DOB: June 7, 1921

Textbooks: Levine, Wood

William Roberts, MD

Interviewed:	November 16, 2012
Current Address:	Baylor Heart and Vascular Institute Baylor University Medical Center 3500 Gaston Avenue, H-030 Dallas, Texas 75246
Credentials:	Executive Director, Baylor Heart and Vascular Institute, Baylor University Medical Center Dean, A. Webb Roberts Center for Continuing Medical Education, Baylor Health Care System (Dallas) Editor in Chief, *The American Journal of Cardiology* Editor in Chief, *Baylor University Medical Center Proceedings*
Area of Expertise:	Cardiology and Cardiac Pathology
DOB:	September 11, 1932
Textbooks:	Friedberg

Thomas J. Ryan, MD

Interviewed:	October 18, 2012
Current Address:	Section of Cardiology Boston Medical Center 88 East Newton Street Boston, Massachusetts 02118 Correspondence: P.O. Box 1194 18 Stageneck Road – unit 4 York Harbor, Maine 03911
Credentials:	Professor of Medicine, Boston University School of Medicine Senior Consultant in Cardiology, University Hospital, Boston University Medical Center Former Chief, Section of Cardiology, University Hospital, Boston University Medical Center
Area of Expertise:	Clinical Cardiology, Coronary Artery Disease, Congestive Heart Failure, Interventional Cardiology

DOB: December 19, 1928

Arthur Sasahara, MD

Interviewed: October 18, 2012

Current Address: 75 Francis Street
Boston, Massachusetts 02115

Correspondence:
1115 Beacon Street
The Courtyard #12
Newton, Massachusetts 02461

Credentials: Professor of Medicine, Emeritus, Harvard Medical School
Senior Physician, Department of Medicine, Brigham and Womens'
Hospital
Former Chief, Medical Service, West Roxbury VA Medical Center

Area of Expertise: Cardiopulmonary disease, Thrombosis, Pulmonary Embolism, Anticoagulation

DOB: May 11, 1927

Barry Silverman, MD

Interviewed: July 23, 2012

Current Address: Piedmont Heart Institute
95 Collier Road
Suite 2065
Atlanta, Georgia 30309

Credentials: Mark Silverman Chair of Cardiovascular Education, Piedmont Heart
Institute
Former Director of Cardiology, Northside Hospital

Area of Expertise: Non-invasive Cardiology, myocardial ischemia and infarction

DOB: November 27, 1942

Textbooks: Cecil and Loeb, Hurst, Friedberg

Jeremiah Stamler, MD

Interviewed: November 30, 2012

Current Address: 464 Riverside Drive
New York, NY 10027-6822

Credentials: Professor Emeritus and Lecturer, Department of Preventive Medicine
Feinberg School of Medicine, Northwestern University
Professor, Department of Medicine, Northwestern University
Emeritus Physician, Northwestern Memorial Hospital
Former Chairman, Department of Community Health and Preventive
Medicine, Northwestern University Medical School
Former Dingman Professor of Cardiology, Northwestern University
School of Medicine

Area of Expertise: Atherosclerosis, cardiovascular risk factor, Preventive cardiology (particularly coronary heart disease prevention), cardiovascular epidemiology

DOB: October 27, 1919

Nanette Wenger, MD

Interviewed: August 6, 2012

Current Address: Emory University School of Medicine
49 Jesse Hill Jr. Drive
Atlanta, Georgia 30303

Credentials: Professor of Medicine (Cardiology) Emeritus, Emory University
Consultant, Emory Heart and Vascular Center
Director, Cardiac Clinics, Grady Memorial Hospital
Director, Ambulatory Electrocardiographic Laboratory, Grady Memorial Hospital

Area of Expertise: Clinical Cardiology, Electrocardiography, Coronary Artery Disease,
Cardiovascular rehabilitation, Clinical cardiology research

DOB: September 3, 1930

Textbooks: Friedberg

Peter Wilson, MD

Interviewed:	September 24, 2012
Current Address:	Emory Clinical Cardiovascular Research Institute 1462 Clifton Road Room 505 Atlanta, Georgia 30322
Credentials:	Director, Epidemiology and Genomic Medicine, Atlanta VAMC Professor of Medicine (Cardiology Section), Professor of Public Health (Global Health, Epidemiology), Emory University, Atlanta, Georgia Director of Laboratories, Framingham Heart Study, Framingham, Massachusetts, 1983-2003
Area of Expertise:	Cardiac Epidemiology, Cardiovascular Research, Framingham Heart Study
DOB:	1948

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