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EPIDEMIOLOGICAL BACKGROUND AND DESIGN: THE FRAMINGHAM STUDY

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1. INTRODUCTION

The Framingham Heart Study is widely acknowledged as a premier longitudinal study. Several historical reviews of its background and design already exist (Dawber, 1980; Dawber, Kannel and Lyell, 1963; Dawber, Meadors and Moore, 1951; Dawber and Moore, 1952; Dawber, Moore and Mann, 1957; Feinlieb, 1983; Gordon and Kannel, 1968a; Gordon and Kannel, 1972 and Higgins, 1984). These were often written by the original investigators or those close to the origins of the study. They present the background facts and clarify the chronology. They give the warriors' statements of their battles or they give an informative and authoritative backdrop for understanding the scope and limitations of the study. In many ways little can be added. Nevertheless, we now proceed to present another history. We will attempt to satisfy the objectives of the previous histories. We will review the historical background and needs that gave rise to the study. We will also review the various components and stages, both chronological and conceptual, that ultimately resulted in this widely quoted study. These will be done not only in a chronological fashion detailing the study as it historically evolved, but also in a retrospective manner taking advantage of the insights which retrospective review can furnish. This latter perspective may be unique from some of the previous reviews. Finally, we will attempt to give a history sufficient to supply the correct context for the other papers in this session.

2. HISTORICAL BACKGROUND

2.1 Epidemiological Prelude to the Study

During the decades of the 1930s to 1950s infectious diseases came under control. The major efforts of public health prior to World War II were directed at the control of these diseases, for they were the major causes of morbidity and mortality. These efforts produced results. Improved sanitation greatly decreased diarrheal diseases. Substantial strides were made in controlling tuberculosis and pneumococcal pneumonia and with the introduction of penicillin in 1942 still further dramatic reductions were made in the prevalence and incidence of the latter.

The scourge of the infectious diseases was replaced in the 1940s and 1950s by a mounting epidemic of cardiovascular disease (CVD). With World War II over the alarming rise of CVD became increasingly evident. By 1950 one out of every three men in the United States developed CVD before reaching age sixty. Its prevalence was twice as common as cancer. It had become the leading cause of death and the reason why life expectancy beyond age forty-five did not increase. Further there was no known treatment capable of prolonging life, even in those who managed to survive an attack. Also statistics from around the world, while often crude and inaccurate, clearly demonstrated a world wide atherosclerotic CVD problem. Added to these distresses was the fact that little was known about the determinants of the disease process itself, so that methods for reversing the epidemic were not even conjectured.

2.2 The Need for Action

Something had to be done. The secrets of the etiology of CVD were not being uncovered by basic laboratory and clinical research, so a continued search for methods to treat and reverse the process was in order. Some believed a primary preventive approach was more promising than a search for cures (Dawber, 1980, p.2).

Some of these prevention-minded individuals occupied positions of influence and were able to translate their beliefs into actions.

The thought process that led to this conclusion presumably had various components and was not entirely homogeneous. One sequence that can be reconstructed from Dawber (1980) runs as follows. Most people eventually succumb to what was then considered degenerative diseases, including CVD. Consequently complete avoidance was considered not possible. However, it was deemed reasonable to hypothesize that the onset of these diseases might be delayed and the delay could come via a preventive approach. If a practical preventive approach was developed, physicians and public health officials would adopt it and so have a widespread impact. The key was to develop this preventive approach. To do it the characteristics of the "host and environment" that lead to the early appearance of the disease had to be determined. In particular, preventable or modifiable predisposing factors had to be identified. The study that ultimately was the Framingham Study was given the charge to identify these modifiable characteristics of host and environment.

3. AN EPIDEMIOLOGICAL STUDY -THE APPROPRIATE TYPE OF STUDY

The type of study deemed necessary to achieve the above was an epidemiological study. In Dawber, Meadors and Moore (1951) the epidemiological approach was described as one which explores "certain relationships in health and disease which, with present technological methods, cannot be observed directly." In broader terms an epidemiological study attempts to determine the natural history of a disease, explore the behavior of the disease and identify factors that might explain its behavior and relate to its development. While there is always the desire to understand the fundamental pathogenesis of the disease, the epidemiological approach often does not resolve questions at this level. It is at the second order level that the epidemiological approach works. And this was what was needed in the 1940s. There was a need to determine in what particulars those who developed CVD differed from those who escaped it.

At this point, it is useful to consider in more detail the nature of an epidemiological study and why it was deemed appropriate for the study of CVD. Epidemiology relates etymologically to the study of something which is "thrust upon us." Originally it referred to the study of epidemics, in particular, the study of the prevalence and incidence of a disease in excess of that customarily observed. In time it became the study of the natural history of any disease, often with the final objective of generating ways to control it. In summary, the objective of an epidemiological study is to root out all the underlying causes of the disease, that is all the factors that act to increase the incidence of the disease. Further such a study should involve quantification of the importance of each contributing factor both individually and jointly with the other factors. Finally, on the basis of these an explanation of the pathogenesis and plans for control of the disease may be formulated.

There had been striking examples where epidemiological investigations had amazing successes. For example, John Snow (1936) showed cholera could be stopped by cutting off the water supply from contaminated wells despite incomplete knowledge of the pathogenesis of the disease. Observations of the time and place where the disease occurred and the source of the water supply were sufficient to pinpoint the major environmental factor inducing the disease. The preventive action of cutting off the contaminated water supply by the removal of the handle of the water pumps controlled the disease. Further investigations into the nature of the offending water could uncover the precise etiology. This indicated that an epidemic could be controlled without knowledge of the precise etiology, by interrupting the chain of circumstances leading to the disease.

By the mid 1940s other striking examples of successful epidemiological studies were in the fields of nutritional imbalance, metabolic disorders, occupational hazards, accidents, cancer and rheumatic fever (Dawber, Meadors and Moore, 1951). Thus for CVD the approach had promise and the need was obvious. What was needed were the design and implementation.

4. DEVELOPMENT OF THE STUDY

A study that could best satisfy the above objective of necessity had to be long and expensive. This was beyond the capabilities of anyone investigator or private institution. Fortunately, in the 1947-49 period the opportunity

presented itself for a feasible serious epidemiological study under Federal government auspices.

4.1 Chronological History of the Start of the Study

In October 1947 at the initiative of Dr. Joseph W. Mountin, Assistant Surgeon General, Drs. Lewis C. Robinson and Gilcin Meadors were sent to organize a heart disease study in the Boston area. This was done as part of a cooperative project involving the Massachusetts State Department of Health (Dr. Vlado A. Getting, Health Commissioner), Harvard Medical School's Department of Preventive Medicine (Dr. David D. Rutstein, Chairman) and the Health Disease Demonstration Section of the United States Public Health Service (Dr. Bert R. Boone, Chief). By December 1947 it was decided to begin two projects, the Cardiovascular Hygiene Demonstration in Newton, Mass. under the direction of Dr. Robbins and the Heart Disease Epidemiology Study under the direction of Dr. Meadors in Framingham. The latter study started as a demonstration program designed to develop case finding procedures for heart disease. It began accepting volunteers. The first exam was conducted on September 29, 1948. By 1949 it became clear that it should pursue more epidemiological goals as discussed above. On July 1, 1949 the study was transferred to the newly created National Heart Institute. At that time Dr. Meadors and Felix E. Moore, Jr., the head of the Biometry Unit at the Heart Institute, developed a formal study protocol and sampling plan to change the study into a prospective epidemiological investigation. In April 1950 Dr. Thomas R. Dawber became the first Director of the Framingham Study. The Study was formally underway.

5. RESEARCH DESIGN: AIMS AND HYPOTHESES

The study was to focus on arteriosclerotic (e.g. coronary heart disease, angina pectoris and stroke) and hypertensive CVD. Arteriosclerotic refers to diseases characterized by thickening and loss of elasticity of the walls of the arteries. It and hypertension were the most important of the CVDs and the least was known about them. A research plan began to emerge which consisted of the following. A randomly selected group of subjects in the age where these forms of CVD were known to develop would be selected. Based on a complete examination those subjects free of definite signs of the disease would then be selected for reexamination at periodic intervals and observation over a period of years. This would continue over a period of years until a sizable number were found to have acquired the disease. At that time a search would be made to identify the factors which influenced the development of the disease (Dawber, Meadors and Moore, 1951). In the vocabulary of the 1980s the Framingham Heart Study as designed would be called a longitudinal cohort study. In the 1940s this terminology did not exist. The attempt to label the Framingham Study and those studies that copied features of its design were important factors in generating it.

5.1 Study Aims

The study as developed had one main aim and two subsidiary aims (Dawber and Moore, 1952):

First, to secure epidemiological data on arteriosclerotic and hypertensive CVD.

Second, to secure data on the prevalence of all forms of CVD in a representative population sample.

Third, to test the efficiency of various diagnostic procedures.

The first aim was major. The other two were viewed as by products.

5.2 Hypotheses

It was assumed from the start that the CVDs did not each have a single cause. Rather they were the result of multiple causes which worked slowly on the individual to produce the disease. Factors which potentially may be

related to CVD were listed in terms of hypotheses. These were generated by the Framingham investigators in consultation with an advisory committee composed of specialists representing several branches of medical sciences. The medical history and physical examination that would be obtained on the study subjects would generate data to test these hypotheses. The major hypotheses generated were as follows (Dawber, 1980):

1. CVD increases with age. It occurs earlier and more frequently in males.

2. Persons with hypertension develop CVD at a greater rate than those who are not hypertensive.

3. Elevated blood cholesterol level is associated with an increased risk of CVD.

4. Tobacco smoking is associated with an increased occurrence of CVD.

5. Habitual use of alcohol is associated with increased incidence of CVD.

6. Increased physical activity is associated with a decrease in the development of CVD.

7. An increase in thyroid function is associated with a decrease in the development of CVD.

8. A high blood hemoglobin or hematocrit level are associated with an increased rate of the development of CVD.

9. An increase in body weight predisposes to CVD.

10. There is an increased rate of the development of CVD in people with diabetes mellitus.

11. There is a higher incidence of CVD in people with gout.

These hypotheses were used directly to determine the medical history obtained and the physical examination taken during the repeated exams of the study. There were continued growth and modification in the research hypotheses as medical science evolved. A number of predisposing factors were introduced at intervals. For examples, the smoking question took 4 exams before it was standardized, questions of alcohol use were asked on exam 2 and then not again until exam 7, and questions on physical activity were not introduced until exam 4 and then not again until exam 11. New items which were introduced at later exams included fibrinogen, apolipoproteins: HDL and LDL lipid fractions, echocardiograms and exercise ECGs among others.

6. RESEARCH DESIGN: STUDY SITE AND POPULATION

Why Framingham? As is clear from the above the selection of Framingham as the study site was decided before the decision to perform an epidemiological study. The justification of it is post-hoc. This was recognized from the start. Dawber, Meadors and Moore (1951) stated that ideally the study should have been "set up in a number of widely separated areas simultaneously, so that the various radical and ethnic groups will be represented, and a variety of geographic, socioeconomic and other environmental factors can be considered." In fact in 1948 Framingham was basically middle class white. However, as the first investigators put it, "it was a place where such a study could be done, and it was not grossly atypical in any respect that appeared relevant" (Dawber and Moore, 1952, p. 242).

While Framingham was neither a random nor entirely representative sample, it did have certain characteristics that made it eminently suitable for a long-term epidemiological study. These are listed in Feinlieb (1983):

1. The town was of adequate size to provide enough individuals for the study.

2. It was compact enough that the study population could be observed conveniently.

3. It contained a variety of socioeconomic and ethnic subgroups to provide contrasting groups for analysis.

4. The population was relatively stable to enable adequate follow-up for a long time. This was partly due to stable economy supported by a diversity of employment opportunities.

5. The town was located near a medical center which could provide consultations and the opportunity for educational development of the staff.

6. The physicians and other medical professionals in the town were highly supportive of the study and cooperated fully with its objectives.

7. Framingham contained 2 general hospitals at the beginning of the study. However, one closed shortly after the study began, SQ that a major portion of the medical care was provided by a single hospital.

8. Framingham, like most towns in Massachusetts, maintained an annual list of its residents.

9. The staff of a well organized health department helped to provide death certificate information and other vital statistics.

10. Framingham had been the sight of a community study of tuberculosis nearly 30 years before that had had successful participation by the townspeople. It was believed that this spirit of cooperation was still present in 1948.

It should also be mentioned that the Framingham investigators have always been aware that the site may not be representative of the United States and have made repeatedly comparisons with other regions to test its generalizability.

7. RESEARCH DESIGN: ROLE OF THE STATISTICIAN

Since its inception statisticians have played a major role in the study. The major areas of activity at the beginning were development of the sampling plan, determination of the sample size and length of the study, data processing and data analysis. The first two items are appropriate items for the present discussion.

7.1 Sampling Plan, Sample Size and Length of Study

The investigators decided that examinations would be given every two years. Data from the volunteer study indicated that 6,000 exams could be given in this two year cycle. So 6,000 became the desired sample size. Subjects between the ages of 30 and 59 were deemed the appropriate target population. They developed CVD with a high frequency and also would not have a large proportion with pre-existing CVD. The town population in this age group was approximately 10,000. The investigators applied a two-thirds sampling ratio to yield the 6,000. With this size sample they estimated that 5,000 would be free of CVD at the baseline exam. Of the 5,000 it was estimated that 400 would develop CVD within five years of the first exam, 900 by ten years, 1,500 by 15 years and 2,150 by the end of twenty years. The investigators decided that these numbers were large enough to produce statistically stable data. At the end of 20 years the study would end (Gordon and Kannel, 1968a).

The official sampling frame was the population aged 30 to 59 as of January 1, 1950, according to the town census. A separate list was drawn up for each of the 8 precincts in the town. Within each precinct, the lists were arranged by family size and then in serial order by address. Two of every 3 families were then selected for the sample. The sample was a systematic sample. In each family all residents in the eligible age range were invited to have an examination. The recruitment effort was organized with 6 committees set up (Arrangements, Publicity, Industry, Business, Civic Organizations and Neighborhood Organizations) to organize the logistical and publicity aspects of the effort. The Neighborhood Organizations committee developed a network where every selected individual was contacted by someone he knew personally and urged to participate in the study (Dawber, Meadors and Moore, 1951; Feinlieb, 1983 and Gordon and Kannel, 1968a).

8. RESEARCH DESIGN: UNIQUENESS OF THE FRAMINGHAM HEART STUDY

The elaboration of the detailed hypotheses of Section 5.2 representing multifactorial causes of CVD and the commitment to a longitudinal study represented major advances in the design and implementation of epidemiological studies. In 1949 they were unique to the Framingham Heart Study. Previous epidemiological

studies sought single causes or agents responsible for the epidemic under investigation. Further, the time period allocated for the identification of the cause was always short term.

9. THE FRAMINGHAM COHORT

From 1948 through the first part of 1950 participation in the program was completely voluntary. Any adult aged 20 to 70 who wished a CVD examination was given one. In total 2,941 individuals were examined.

9.1 Response of the Selected Sample

The formal sampling plan generated a sample of 6,587 subjects. Of these 80 were duplicate names, so the potential sample size was 6,507 subjects. Approximately 68.7% or 4,469 of these came in for an examination by the end of the recruitment period in 1952. Gordon and Kannel (1972) refer to this initial response as being poor and biased. On both counts they were correct. A response less than 70% is far from ideal. Also the respondents had a better mortality experience than the nonrespondents from the onset. They were healthier than the nonrespondents.

9.2 Addition of Volunteers

Of the 4,469 respondents 4,393 were free of CVD. To achieve the desired 5,000 an additional 888 volunteers who had been examined but were not included in the drawn sample and who were 30 to 59 years old were identified. These were invited into the clinic for an examination. Seven hundred forty (740) or 83.3% of these returned for a second visit and were added to the cohort. In total 5,209 (=4,469 + 740) were taken into the cohort. These constituted the official "Framingham Cohort." Of the 5,209 there were 5,127 free of coronary heart disease.

9.3 Biases in the Framingham Cohort

The Framingham investigators anticipated that they would obtain all their sample via random selection. They had to use volunteers to obtain their desired sample. The investigators anticipated finding I in 6 of the respondents with CVD. They found I in 50. The final cohort was not random and it was healthier than the general population. Further the response rate of the selected sample was 68.7%. This is not a good rate and it plus the inclusion of volunteers may have introduced biases beyond the obvious one of a cohort healthier than the general population. The Framingham investigators have been aware of these problems and have continued to discuss them (Dawber, 1980; Friedman, Kannel, Dawber and McNamara, 1967; Gordon and Kannel, 1968a; Gordon and Kannel, 1970 and Gordon, Moore, Shurtleff and Dawber 1959).

10. CHANGES TO THE DESIGN -THE EARLY YEARS

The major change to the design of the study was the addition of the volunteers. This was discussed above. Another important change was related to the inclusion of those with CVD in future examinations. The original plan was to follow only those without CVD. It became apparent that some forms of CVD were precursors for other forms (e.g. coronary heart disease often precedes stroke) and all 5,209 subjects were followed (Gordon and Kannel, 1968b). Other changes were made regarding data collected at the exams (e.g. the addition of questions on smoking behavior). These are well documented in the Framingham literature and are not proper topics of this presentation.

11. USES OF THE FRAMINGHAM HEART STUDY

Given the above discussion, there remains the question concerning what uses can be made of data collected from the Framingham Heart Study.

For example, at the start of the study it could not be used to yield valid prevalence rates of the various types of CVD. Prevalence is the rate of individuals who, at a given time period of interest, have a certain characteristic, such as at least one manifestation of CVD. Because the Framingham cohort was healthier than the general population, prevalence rates estimated from it would have been underestimates.

On the other hand, the Framingham Study was and is well suited for the estimation of incidence rates. Incidence is the rate of individuals who develop a condition within a given time period, for example, develop CVD over a two year period. The major contribution of the study has come in detailing incidence rates, in particular relating risk factors such as age, systolic blood pressure, cholesterol and cigarette smoking to the probability of developing CVD. The study has collected excellent data on risk factors and with its careful longitudinal follow-up it has near complete data on the development of diseases. Further, much of these data were collected in periods of time when medical interventions such as anti-hypertension therapies were not actively used. This has given us the "natural history" of the risk factors and the diseases that followed them. All this is ideal for the estimation and study of incidence rates. Few other studies have been in such optimal positions.

12. CLOSING COMMENTS

We reviewed the background of the Framingham Study. It did not develop without problems. However, it did develop and it has continued to yield valuable information for over 40 years. The combined efforts of federal, state and local agencies have no better example of how well they can work together and how productive they can be.

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