

Epidemiological Approaches to Heart Disease: The Framingham Study*

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THE use of the word "epidemiology" and the concept of what epidemiology as a discipline may encompass has varied widely since the days of Peter Panum and John Snow. There are today many differing definitions of the word, but nearly all workers in the field will agree on one element of the definition: The word "epidemiology" by etymology refers to the study of something "which is thrust upon the people." There are still some who insist that epidemiology deals only with epidemics of infectious diseases, but current usage suggests that most workers would now agree that epidemiology deals with "the fundamental questions as to where a given disease is found, when it thrives, where and when it is not found . . . in other words it is the ecology of disease"¹ without regard to whether the disease is believed to be infectious.

Frost gave an analytical definition when he wrote that epidemiology "includes the orderly arrangement of facts into chains of inference which extend more or less beyond the bounds of direct observation."² His definition might be called the essence of the "epidemiological method" except for the fact that it has been used by the physician since the time of Hippocrates to arrive at his clini-

cal diagnosis. Thus, today, the epidemiological approach is used to explore certain relationships in health and disease which, with present technological methods, cannot be observed directly. In addition to the many studies of the infectious diseases, there have been epidemiological studies in the fields of nutritional imbalance, metabolic disorders, occupational hazards, accidents, cancer, and rheumatic fever—to mention only a few.

In the field of cardiovascular diseases, studies using the epidemiological method have led to findings of considerable practical importance for prevention and treatment. Mention may be made, for example, of the studies of nutritional diseases, such as beriberi, pellagra, and scurvy, and of the infectious diseases such as syphilis, hemolytic streptococcal infections, and streptococcus viridans bacteremia. Rubella and other virus diseases have been implicated as etiological factors in congenital malformations of the heart, but further epidemiological study is still required to establish these relationships beyond the possibility of reasonable doubt.³ Even in rheumatic fever, where fundamental etiology is still obscure, epidemiological studies have helped to demonstrate the relationship of streptococcal infection to subsequent rheumatic activity, and this has led to the adoption of control measures which show great promise.⁴

It should be pointed out, however,

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that except for rheumatic fever, the diseases mentioned above account for only a very small proportion of morbidity or mortality from cardiovascular disease. Of the epidemiology of hypertensive or arteriosclerotic 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 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.

These facts have long been recognized. Sir James Mackenzie, one of the great pioneers in cardiology, over 30 years ago began what was intended to be a long-term study of disease in the entire population of the town of St. Andrews, Scotland.⁵ Because of Mackenzie's retirement a few years after the start of the study, it was never completed, however, and since that time there have been no other attempts to study heart disease in a large population of normal composition over any long period of time. The expense of such a study and the necessity of guaranteeing its operation for a span of many years puts it beyond the capabilities of the individual investigator. If such a study is to be done, it is clear that it must be carried out by the community health agencies. In the light of this situation, and with the growing interest in chronic diseases, the U. S. Public Health Service began in 1947 to lay plans for setting up an epidemiological study of the cardiovascular diseases in coöperation with state and local health agencies.

At this point it is well to present in outline the principal considerations which guided the development of the study, and led ultimately to its location in Framingham, Mass.

The study is focused on arteriosclerotic and hypertensive cardiovascular disease, because these are the most important of the cardiovascular diseases and the least is known about their epidemiology. As a working hypothesis it is assumed that these diseases do not each have a single cause (as is the case in most infectious diseases), but that they are the result of multiple causes which work slowly within the individual. It is recognized that, for the most part, specific and unambiguous tests for precise diagnosis of the early stages of these diseases are lacking.

Based on these general considerations the following research plan was developed. 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 normals, and they will be observed over a period of years until a sizable 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 in the other.

As one by-product of this investigation it will also be possible to study the efficiency of various diagnostic procedures in finding heart disease or as indicators of the subsequent development of heart disease. (These findings, of course, have important bearing on the question of including tests for heart disease in mass screening programs.) A second by-product will be data on prevalence and incidence of cardiovascular diseases.

With these aims set up, it was then

necessary to define the population on which the study would be carried out. Ideally, perhaps, epidemiological investigations of cardiovascular disease should be set up in a number of widely separated areas simultaneously, so that various racial and ethnic groups will be represented, and a variety of geographic, socio-economic, and other environmental factors can be considered. The results of a study of a single area will have generality only in so far as the population of the area is representative of some larger population. Many thousands of persons should be included to allow for numerous axes of analysis, and it would be profitable to follow a cohort of individuals from birth to death. Because of the expense of examination and follow-up, however, it is not practicable to carry on studies simultaneously in several areas, nor to observe more than a few thousand persons for a limited number of years. It was concluded, therefore, that the study should be set up in a single area, and that coverage would have to be limited to approximately 6,000 persons in a limited age range, who would be observed for a period up to 20 years. A town of 25,000 to 50,000 population will supply this number of adults, and it was felt that a town of this size would be more desirable than a larger city for the type of community approach required to secure full coöperation and coverage. This limitation in geographic coverage clearly limits the generality of conclusions which can be reached. There is, however, reasonable basis for the belief that the distribution of arteriosclerosis and hypertension in the white race in the United States is such 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. This hypothesis can only be tested, of course, by similar studies in other communities.

In mid-1947, Dr. Vlado A. Getting,

State Health Commissioner for Massachusetts, offered to coöperate with the U. S. Public Health Service in setting up the study in that state, and after consideration of a number of possible areas the Town of Framingham was selected. Framingham, lying 21 miles west of Boston, is an industrial and trading center of 28,000 population, and is almost independent of Boston from the standpoint of providing suburban residence for the city. As is true of New England towns, it includes not only the built-up business and residential areas but also the outlying rural area within the town limits. Other points of interest are that Framingham has the town-meeting form of government and the people are accustomed to and well versed in the group approach to their problems. It was in Framingham that the first community study of tuberculosis was undertaken—a program sponsored by the National Tuberculosis Association and the Metropolitan Life Insurance Company, which began in 1917 and continued successfully for six years.⁶ This latter fact, together with an indication of interest in response to the initial approach influenced to some extent the selection of the town.

The problems involved in setting up the study fell into four categories: professional, administrative, organizational, and technical, and all will be discussed in some detail. A program which involves medical examination of large numbers of people requires the respect, endorsement, and support of the medical profession. The plans for the project were given the endorsement of the Massachusetts Medical Society.⁷ In Framingham the medical groups which center around the two local hospitals offered their active support to the program as proposed.

From an administrative standpoint it was necessary to secure clinic facilities and recruit a professional and technical staff. A centrally located residential

building was remodeled for clinic and laboratory space, and diagnostic equipment installed. A staff was organized, including the examining physicians; a clinic nurse; x-ray, electrocardiography and laboratory technicians; statisticians; interviewing and administrative clerks; a health educator; and visiting consultants in the fields of cardiology, electrocardiography, roentgenology, pathology, and biochemistry.

The organizational problems are those involved in bringing into the study the cross-section of the population which it is desired to study. The mechanics of selecting that cross-section are described in a later section; at this point the focus of interest is the method of bringing about community participation. The work of building a community organization began months before the start of clinic operation.

As a start, a health educator was placed in the Health Department with the assignment of studying the community. This meant not only learning about the history, resources, and government of the town but, more important, getting to know the people—their national origins, economic conditions, and lines of social stratification; their religious, fraternal, and civic organizations; and their recognized and potential leaders. From this study grew plans for the appointment, by the Town Health Officer, of an Executive Committee of 15 persons for the study—a committee which was broadly representative of the various groups in the community. Parallel to, and integrated with, the lay Executive Committee, there was organized a Professional Committee of physicians and dentists under the chairmanship of a cardiologist. Together, the Executive Committee and the Professional Committee accepted the following responsibilities:

1. To assist in planning a program which would be acceptable to the community as a whole.
2. To interpret the aims and objectives of the

study in a way which would be understandable to all elements of the community.

3. To bring recognized and potential leaders of the community into active participation in the organizational aspects of the study.

After analysis of the community organization requirements of the study by the Executive Committee, six sub-committees were set up: Arrangements, Publicity, Industry, Business, Civic Organizations, and Neighborhood Organization. The Arrangements Committee has assisted in the operation of the study by providing clerical assistance and transportation. The Publicity Committee, composed of residents who are specialists in the areas of press, radio, advertising, and associated fields developed a plan for publicity media to be used in placing the program before the community. The Industry, Business, and Civic Organizations Committees brought the study to the attention of their special publics.

Perhaps the most important of the committees, however, is the Neighborhood Organization Committee. It has been the aim that every participant in the study should come into it on the basis of an invitation from someone he knows, and in whom he has confidence, and further that the invitation should come from a person who has been through the clinic. At the start, therefore, examinations in the clinic were offered to all members of the committees and these, in turn, passed word of the study on to other members of the community who were encouraged to volunteer for examination. From these volunteers a set of neighborhood committees has been selected. To those committees falls the all-important job of inviting the initial participation of the selected individuals and later stimulating coöperation in return for follow-up observation.

Up to the present time, use has been made of standard publicity channels to inform the people about the program. However, as we discovered from sam-

pling of opinion of persons volunteering for the study, the most valuable public information has come through word of mouth. The community has accepted the program as its responsibility, and recognizes that when people participate they make a real contribution to medical research. It should be added that the nature of the examinations provides a service to the selected individuals, and this has undoubtedly motivated many in the community to participate. It should be noted parenthetically at this point, however, that the service aspects of the study are limited to diagnostic information which is furnished only to the personal physician of the person examined. Where there are abnormal findings, the individual is referred to his own physician for interpretation of the findings and treatment if necessary. The clinic staff does not provide treatment, nor offer advice on treatment.

The technical problems of the study may be considered under two headings: medical and statistical. The medical problems involve selection of diagnostic procedures and methods of measuring the various characteristics of the people, and the establishment of criteria for interpretation of these tests. Statistical problems include the development of a method for sampling the population, and of methods for recording and analyzing the data obtained.

To determine the presence or absence of cardiovascular diseases and to record those items in the patient's past history that may have a bearing on the development of disease requires a rather extensive study of each selected individual. Within the framework of this type of study, it is also necessary that the examination be organized in such a way that the whole procedure can be done in a reasonable length of time, and without discomfort or risk for the person being examined.

All medical planning for the study was done in consultation with a Technical

Advisory Committee appointed by the State Health Commissioner and made up of eleven physicians from the Boston area expert in the fields of cardiology and public health. This committee aided in setting up the broad outlines of the study by proposing hypotheses as to suspected etiological factors for testing. The committee assisted also in suggesting specific items for examination and laboratory study, and in advising on criteria for evaluating these criteria. The procedures which are carried out on each person admitted to the study may be summarized briefly as follows:

1. An extensive medical history including:
 - a. Family history of cardiovascular disease in mother and father, siblings, and children.
 - b. A detailed past medical history of diphtheria, scarlet fever, sore throat, rheumatic fever, various chronic diseases, operations, thyroid diseases, presence of transient or permanent hypertension, heart murmurs, and "heart attacks"; previous diagnoses of angina pectoris, limitation of activity due to heart disease, congenital heart disease, heart failure, vascular disease of any kind, enlarged heart, "nervous heart," pericarditis; and the history of any previous kidney disease, renal or hypertensive complications of pregnancy, or of any menopausal symptoms.
 - c. Careful questioning for any current symptoms of heart or pulmonary diseases including cough, dyspnea, hemoptysis, smothering sensation, palpitation, chest pain and discomfort, edema, and phlebitis, etc.
 - d. Personal habits of the individual, including number of hours of sleep, amount of tobacco and alcohol consumed.
 - e. Average weight at five year intervals, beginning at age 25.
 - f. History of peptic ulcer, chronic colitis, nervousness, headache, and other symptoms suggestive of emotional upset.
 - g. Use of drugs or medicines.
2. A careful, detailed physical examination performed independently by at least two physicians, aimed at detecting cardiovascular abnormalities or diseases related to the cardiovascular system, and measurement of characteristics which may be related to such disease including:
 - a. Height, sitting and standing, weight, antero-posterior diameter of chest, chest circumference, waist circumference, vital capacity, estimate of body build, color of eyes and hair,

and distribution of hair and degree of baldness.

b. Skin color and degree of freckling, the presence or absence of sweating, clubbing of fingers and toes, cyanosis, exophthalmos, arcus senilis, xanthelasma, thyroid enlargement or tumors, chest deformity, and evidence of pulmonary disease.

c. Examination of the heart itself including description of heart sounds, murmurs, abnormal rhythm, blood pressure determinations on admission and at time of discharge, and at intervals during the examination by each of the examining physicians.

d. Examination of abdomen for tumors, liver enlargement, or palpable spleen.

e. Examination of the extremities for presence or absence of femoral pulse, dorsalis pedis and posterior tibial pulsations, ankle edema, varicose veins, and phlebitis.

3. X-ray examinations, teleoroentgenogram on 14" x 17" film and on 70 mm. film with two meter target distance.

4. An electrocardiogram using twelve leads.

5. Electrokymographic tracing at 12 points on the cardiac silhouette.

6. Examination of blood sample for:

- a. Hemoglobin
- b. Serum cholesterol
- c. Serum phospholipid
- d. S_f 10-20 fraction (of Gofman)
- e. Uric acid
- f. Glucose level
- g. Serologic test for syphilis

7. A routine urinalysis

The aim of securing information on all of these items of history, physical examination or laboratory test is twofold. First, it is desired to record, in as full detail as possible, the characteristics of each individual which are considered relevant to the presence or absence, or the potential development of cardiovascular disease. Second, it is desired on the basis of this examination as a whole to classify the population studied into two groups: (1) those with definite signs of arteriosclerotic or hypertensive cardiovascular disease, and (2) those apparently free of these diseases (who may be termed "normal" for the purpose of this discussion).

It is the "normals" who are the principal focus of interest of the study. They will be brought back for reexamination

biennially for a period which it is hoped to extend for as long as 20 years. If they move from Framingham, an attempt will be made to bring them under a comparable examination elsewhere. If they die, an attempt will be made to secure autopsy data, and, at the very least, complete description of cause of death, and data as to the existence of cardiovascular diseases at time of death.

The choice of a sampling plan for this study was dictated by a number of considerations, some of which have already been suggested. The number of cases which could feasibly be studied—6,000—was much smaller than the adult population. Therefore, some method had to be introduced to select persons and avoid the unknown biases of self-selection. The total sample had to be allocated in such a way as to yield the maximum information over the period that the study was to be carried out. And the plan had to be such that it would be acceptable to the community, and could be carried out through the community organization.

One important decision which had to be reached concerned the age range of the study population. Clearly, if only a very young group was studied, only a very small number would develop arteriosclerotic or hypertensive cardiovascular disease even in 10 to 20 years' time. On the other hand, in the very old group there would be too large a proportion with preexisting cardiovascular disease. To balance these two effects, the age group 30 through 59 was selected for study. The population in this age range was approximately 10,000. If 6,000 of this group were taken into the study, with the age-sex distribution existing in the town, it could be predicted (on the basis of the criteria of the study and tentative data available from a small volunteer group) that roughly 5,000 would be free of cardiovascular disease at the time of initial examination. Of these 5,000 it was estimated that approximately 400 would be found to have

cardiovascular disease at the end of the 5th year after the initial examination, 900 at the end of the 10th year, 1,500 at the end of the 15th year, and 2,150 at the end of the 20th year. (These numbers include, of course, persons who would be dead of the disease at the end of the specified period.) These numbers appeared to be large enough to insure statistically reliable findings, though it is recognized that even this number of cases will not be sufficient to carry out all of the detailed analyses which will suggest themselves in the course of the study.

There remained the problem of securing an actual listing of persons who would form the sample. Under ordinary circumstances, it would probably have been desirable to use some form of area sampling. The Town of Framingham, however, publishes annually a listing of all residents 20 years of age and over, based on a local census, and it has been possible to use this list as a basis for sampling. (An independent check of the completeness of the listing is being made by the Bureau of the Census.)

The Executive Committee advised that it would be desirable not to break up families—that is, if one member of a family was to be brought into the sample, all other family members resident in the same household should also be brought in, provided they were within the eligible age limits. This has been arranged, and the sample has been drawn in systematic fashion from a list which is first stratified by family size and by precinct of residence, and then arranged in serial order by address.

The sampling ratio is two-thirds, which will yield approximately 6,600 names. This is 10 per cent over the number required for the study in order to provide for losses through refusal or by movement out of the town before examination.

As the description of the examination suggests, a formidable mass of data will

be available when the initial examinations have been completed early in 1952, and this will increase as follow-up examinations are carried out through the years on the normal group. Analysis of the data will proceed at each stage of data collection. When initial examinations have been completed, it will be possible to abstract prevalence data of considerable interest. It will also be possible to proceed with a study of the contribution which various elements of the total examination make in the determination of a final diagnostic impression. Analysis of this type will, for example, give a basis for determining the relative efficiency of the miniature chest x-ray, or of certain electrocardiographic leads, as diagnostic tools as compared with the total examination. In this area, some tentative data based on the group of volunteers already examined will shortly become available. Another important type of information will be data on the range of values of various diagnostic tests for "normal" populations, which have not hitherto been available in medical literature.

The more truly epidemiological parts of the analysis are essentially retrospective and must wait the passage of time. At the end of 5 years a portion of the base population, which was normal at the time of initial examination with respect to the diseases studied, will have passed the borderline into definite abnormality, and a few will have died. At that point it will 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 diseased). From this study it should be possible to test a number of hypotheses with respect to factors associated with the development of arteriosclerotic or hypertensive cardiovascular disease. As the abnormal group increases in size with the passage of time, such differences as are found to exist can be determined

with increasing statistical reliability. For the group which becomes abnormal, 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 arteriosclerotic and hypertensive cardiovascular disease for a more representative population group than has hitherto been studied.

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New Jersey Local Health Units Bill

The first bill introduced into the 1951 New Jersey State Legislature is a permissive health district bill. Developed out of the recommendations of the Governor's Committee on Local Health Administration, it gives communities a number of choices in organizing their local health services. These are:

1. Separate municipal organization as at present.
2. A consolidated health district made up of two or more municipalities. This would be independent of county government.
3. A county local health district to include some or all of the municipalities of a single county. In this case the district would be

affiliated with the county government but its jurisdiction would extend only to those municipalities included in the district.

The central idea of the bill, according to its sponsors, is that qualified, full-time public health personnel can take care of the public health needs of a population much larger than is found in most New Jersey communities. By combining with other communities and contributing its reasonable share of the cost, a community will be able to obtain the benefits of expert public health service, and often without substantially greater expenditure than at present for service that is often inadequate.