EPIDEMIOLOGIC METHODS IN CURRENT CARDIOVASCULAR DISEASE RESEARCH

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During the six-month period ending in March, 1959, we have had opportunity to review a series of epidemiologic studies of cardiovascular diseases currently under way across the nation. Twenty-one of these studies deal with some aspect of hypertension or arteriosclerotic heart disease, and thus their study methods may be of interest to the members of this conference. An over-all view of these study methods is given, as well as brief descriptions of each of the 21 studies. Abstracts of eight, which perhaps have been less widely discussed than the well known endeavors at Framingham, Albany, etc., exemplify the range of methods employed and are incorporated in the body of this report. Abstracts of the remaining 13 are included as an addendum.

Study Methods

The application of epidemiologic methods to the study of arteriosclerotic heart disease (ASHD) and hypertensive heart disease (HHD) is taking three approaches: descriptive, analytical, and experimental. (1) In the descriptive approach, observations on recognized disease are made in terms of chronologic and geographic distributions and the characteristics of patients. Personal attributes of patients are contrasted with similar attributes determined from census figures, or some other available source, for residents in the patients' community. (2) In the analytical approach, independent variables are identified and related to the occurrence of disease. The frequency of specific host or environmental factors and the frequency of disease are each determined. Populations being studied are divided into those with and those without disease, and in each group the proportion with common personal attributes is ascertained. Also, the proportions of diseased and of nondiseased populations that engage in a common practice, encounter similar incidents, or are exposed to similar potential risks are measured. (3) In the experimental approach human volunteers are induced to change their habits, or environmental factors are altered, and the effect of these changes on disease is measured.

Regardless of the approach used, the purpose is to determine whether individuals characterized in one way, such as by a physiological or socioenvironmental factor, are differentiated in a second way, as by a disease. For example, one might determine whether a difference in the frequency of coronary heart disease (CHD) exists between a group with premature presbyopia and another group without it. The essence of the approach is comparison, and it is encouraging that investigators are greatly concerned with standardizing their observations and accurately classifying persons by the presence or absence of two variables, the factor in question and the disease, in order to make valid comparison possible. The scientific requirement of assessing the socioenvironmental variable independent of the clinico-laboratory variable is being met. For the most part, attention is given to other influencing variables through selection.
of study subjects or through adjustment by accepted statistical technics. Uncertainties in diagnosis of disease lead to use of "probable" or "borderline" classifications, and most socioenvironmental factors are measured on a gradient scale. Thus, comparison of the disease variable and the socioenvironmental variable usually is not limited to a two by two correlation.

The search for association between either ASHD or HHD and any of a number of host or environmental factors uses one of three methods. First, contemporary studies of diseased and disease-free persons are providing "snapshot" or prevalence figures of the specific factors under study. Second, studies that are longitudinal in time are picturing "flashbacks" to an earlier period by measuring (through interviews, past medical records, and similar data) the proportions in the disease group and in the disease-free group that have experienced the same specific factors. Last, longitudinal studies are following individuals through a period of time in "motion picture" fashion, and by means of appropriate clinico-laboratory tests are making initial and successive determinations of the frequencies and magnitudes of the diseases and the factors.

Populations being studied include (a) hospital or clinic patients, (b) closed populations in institutions, and (c) groups of persons in communities-at-large. These populations ordinarily are chosen to meet a specific requirement of the study design.

The abstracts of study methods reviewed here are necessarily brief. Responsibility for omissions, inconsistencies, or inaccuracies in these abstracts is ours and not that of the investigators who supplied the information.

Current Studies

1. Navajo on Reservation—The first study to be described is being conducted out of the Western Navajo Hospital in Tuba City, Ariz. The frequencies and distributions of cardiovascular diseases (CVD), particularly coronary heart disease (CHD), among the Navajo are being observed. Specific aims are to determine (a) the prevalence and incidence of CHD, (b) the serum lipid patterns of adult Navajo males, (c) the make-up of the Navajo dietary, and (d) the geographic and demographic characteristics of Navajo subgroups on the reservation. These endeavors were prompted by prevailing clinical impressions and published reports to the effect that the Navajo experience less CHD than the white or Negro races. The design of methods includes the examination of 150 adult Navajo males who were considered healthy and without clinical or laboratory evidence of diabetes, renal disease, or thyroid disease. Clinico-laboratory examinations of snapshot type are being performed, and for comparative purposes, similar measurements are being made on a selected series of healthy white males seeking routine medical checkups in a medical clinic in Albuquerque. In addition, the heart and aortas of Navajo and clinic patients coming to necropsy are being examined for atherosclerosis. (Approximately 50 per cent of the Indians who die in the Fort Defiance Navajo Medical Center or in the Western Navajo Hospital come to necropsy.)

2. An example of the motion picture method applied to an open population is the study in Evans County, Ga. The study has been activated in search of preclusive factors of atherosclerosis and its sequelae. The total county census (by age, sex, race, address, and place of birth) has been determined from vital records, lists of utility subscribers, newspaper solicitations, and house-to-house canvasses. The census is being kept current by periodic rechecks using these same counting devices. Morbidity
and mortality data are obtained through physicians, vital records, and hospital data. The county, with a population of 7,500 and a two-to-one white-to-Negro distribution, is largely rural and is served by two practicing physicians. One of the physicians is the sponsor and principal investigator in this study and the other cooperates closely. Marked rapport exists among the physicians and their patients who comprise essentially the total county population. Necropsies are requested on the death of each county resident and are performed by a consulting pathologist on approximately 50 per cent of decedents.

Relative rates of CHD by race and sex groups are being determined longitudinally from (a) physician, hospital, autopsy, and vital records; and (b) successive censuses of Evans County. This phase of study will continue through calendar year 1960.

Blood specimens for serum lipid determinations are being drawn from approximately 1,200 adults listed on the Evans County census registry. Subjects are chosen through use of a stratified sampling technic. Laboratory testing of specimens permits comparison of lipid levels by age, race, sex, and season of the year in which the samples were collected.

For one physician’s office practice, all patients aged 35 years and over who seek medical advice or treatment for any illness are being followed over a five-year period (mid-1958 through mid-1963) for the occurrence of CHD. To the degree that a busy practice permits, the following data are being recorded on each patient at least once annually: (a) family and personal history of heart disease; (b) results of a general physical examination; and (c) findings from serum cholesterol and alpha and beta lipoprotein tests. When patients do not return within a year they will be contacted and lipid determinations repeated as a minimum examination. All overt attacks of CHD and deaths from this cause will be recorded as they are recognized. Biennially the health status of each participant will be reviewed through telephone or personal contact. Through records of such repetitive observations and laboratory determinations, it is expected that some of the precursors of CHD may come to light.

The influence of sex, race, and stress factors (physical and psychological) on serum lipid levels of children from birth through preschool ages is being determined. Umbilical cord blood samples are being collected at most deliveries in the county, and repeat blood samples are drawn at six-month intervals. These specimens are being tested for levels of cholesterol, alpha and beta lipoproteins, and the “lipid mobilizing factor.” The race, sex, and birth weight of each infant are recorded, together with weight and illness histories at each six-month interval.

Studies of school-aged cohorts are patterned after the newborn studies, with effort being made to enlist all school children in the county. More than 95 per cent have received parental approval to participate and are being entered in the study as rapidly as laboratory facilities permit. Repeat blood samples are being drawn at annual intervals and special interest centers on the influence of puberty on serum lipid levels.

3. The snapshot method is being used at Louisiana State University School of Medicine in study of atherosclerosis. Procedures have been standardized for staining arteries with Sudan IV and for preserving them in flat, transparent, durable, plastic bags. Also, a method of grading human aortas, by which different pathologists secure similar results, has been developed and used to estimate macroscopically the extent of fatty streaks, fibrous plaques, and complicating lesions (hemorrhage, ulceration,
thrombosis, and calcification). Current studies seek information on pathogenic mechanisms through description of aortas and other arteries from necropsies on individuals aged one year and over. Specimens are received from general hospitals and medico-legal services in New Orleans, Guatemala, Puerto Rico, and Colombia. Special attempts are made in these geographic areas to necropsy all deaths regardless of cause. All aortas, most coronary arteries, and, more recently, cerebral arteries are graded as to intimal lesions. Physical studies (photographic, light refraction, and colorimetric) and chemical studies (quantitative and qualitative determinations of lipid) are in progress on a sample of specimens to (a) develop a grading scheme that does not require personal judgment and (b) search for age, sex, and racial differences in pathologic lesions. An endocrine project, including urine assays, is being developed to permit correlation studies with atherosclerotic lesions.

As a second study, observations on zoo-reared baboons have suggested that this widely prevalent ape, which is first order below the anthropoids, might lend itself as an ideal experimental animal for atherogenic studies. Hence, an African expedition was undertaken in the summer of 1958 to obtain baboons from their native habitat. A total of 163 animals was captured and sacrificed for pathologic examination. Specimens permitting estimation of chronological age and degree of atherosclerosis were shipped to New Orleans for study. (Age estimates are being made from skull, teeth, and bone specimens together with measurements of body weight and size.)

4. Out of the Georgia State Health Department a motion picture study of two circumscribed populations is in progress. Since October, 1957, serial observations have been made on residents of two monasteries in study of dietary regimens as they may relate to arteriosclerotic heart disease (ASHD). One monastery quarters members of the Trappist order, whose religious dictates require a meat-free lactovegetarian diet. The second monastic population comprises Benedictine monks who are omnivorous and consume a diet essentially comparable to that of citizens-at-large in the United States. Quantitative and qualitative dietary records are collected on selected fast, feast, and regular days in order to compute average intakes per monk per day. Yearly clinicolaboratory examinations and medical records during any period of hospitalization permit evaluations of illnesses including ASHD. Blood specimens drawn quarterly are subjected to a battery of tests for lipid and protein determinations. Participation in this ongoing study is voluntary, with more than 95 per cent of the Trappist community and a comparable percentage of residence-stable Benedictines enrolled.

Eighty-two Trappists, ranging in age from 20 to 80 years (median age=35 years) are participating. These monks live rigorous lives in primitive physical settings without modern conveniences. Their work is largely of heavy manual types, which is interspersed with sedentary hours for meditation. There is essentially no verbal communication among the monks. On days selected for determination of diet intake, each monk keeps a record of his consumption by noting during meals the amounts and types of food ingested. Uniform servings and the use of standard spoon sizes facilitate accurate reporting. Tobacco and alcohol are not used by these monks.

Sixty-five Benedictine monks of an older age range (median age=40 years) than their Trappist peers, are participating. They live in modern dormitory type structures, engage in relatively less physical exercise, and are largely a teaching order. Their diet permits little freedom of choice qualitatively, but
contrary to that of the Trappists, allows for more quantitative selection. A food model demonstration is presented at the monastery to assist the monks in making quantitative estimates of their intake. A small proportion of members of this order uses tobacco and a somewhat larger proportion uses alcohol.

5. A combination of snapshot, flash-back, and progressive motion picture methods is in use at Beth-El Hospital, Brooklyn, N. Y. In progress over the past two years, this study is designed to determine whether specific somatotypes are associated with a coronary diathesis and, if so, for what reason. Members of a fraternal organization are invited to a cancer and heart disease detection clinic for specific clinico-laboratory tests that permit classification by body type, coronary heart disease status, socioeconomic stratum, and cholesterol and estrogens levels. The base population from which subjects volunteer to participate consists of 35,000 residence-stable Brooklyn males who carry health insurance. Participants are somewhat health-conscious adults who largely lead a sedentary life and eat high fat diets. Sixty per cent are salesmen and 95 per cent are married. They are queried as to dietary and social habits and classified into types of body builds by the same examiner. A second examiner evaluates their cardiac status through administration of a medical history, physical examination, and electrocardiogram (ECG) tracings. Their attack rates of CHD are being assessed through (a) annual reevaluations, and (b) reports on cardiac morbidity and mortality from their health insurance plan, which includes physician and hospital coverage. One hundred selected subjects in each of the three basic somatotypes (ectomorphs, mesomorphs, and endomorphs) are being examined for estrogen levels by analysis of 24-hour urine samples.

As an independent study the degree of coronary atherosclerosis and the type of body build are being assessed for all individuals dying suddenly and coming to medical examiner's autopsy in Westchester County, N. Y. The collection represents a 10-year experience and comprises largely deaths from automobile accidents.

6. Sometimes referred to as a human population laboratory, studies in progress at the University of Michigan School of Public Health maintain a current inventory of people, places, and things. Over an 18-month period nearly all residents of Tecumseh, Mich., and adjacent residential areas have been characterized by demographic and other factors. The prevalence of 41 chronic disease conditions has been determined for this group through self-administered questionnaire forms. The total population of approximately 8,300 persons has been identified by household (N=2,400), familial, and kindred (N=3,400) aggregations. An additional 1,000 persons from neighboring communities who are relevant to the bloodline aggregates have been identified.

Through seven consecutive monthly reports received by mail from each household, new occurrences of illness have been determined. Also, study has been made of the physical facilities and of the receptiveness of lay and medical groups to future more intensive studies in this population. The collected data have been analyzed as a lead-seeking device, and to determine the suitability of the population for subsequent epidemiologic study of a variety of chronic disease entities. On the basis of these analyses, the investigators are satisfied that the community lends itself to productive future study since (a) the single large industry in Tecumseh is relatively stable and the population is "nonmigrating"; (b) adequate numbers of individuals over the entire age spectrum are available; (c) a high prevalence of numer-
ous chronic diseases exists; and (d) new cases of CVD occur with a frequency which permits testing of many hypotheses over a several-year period.

Early identification of individuals as to their susceptible or immune status in reference to heart diseases through both snapshot and motion picture studies is under way. (Other chronic diseases will be studied in similar fashion.) Specific aims include (a) identification of individuals with heart disease and associated conditions; (b) search for associations between factors of host-environment and specific types of heart disease; (c) analysis of data by kindreds in search of familial influences and genetic patterns; (d) description of the frequencies and distributions of cerebrovascular accidents (CVA) and determination of their relationship to heart disease; (e) examination of heart disease patterns for relationships among congenital, rheumatic, arteriosclerotic, and hypertensive heart disease; and (f) initiation of similar studies of chronic diseases other than heart disease. Procedures entail the examination of Tecumseh inhabitants, residents of surrounding areas, and kindreds in neighboring communities (N=approximately 9,500). Methods include taking detailed medical histories by trained lay interviewers, review of these histories by physicians who perform physical examinations, and laboratory examinations.

As another study, blood pressure levels among Bahama Negroes have been measured to determine prevalence ratios of hypertension and to compare the findings with similar data available for Negroes living in the United States. One study is based on the clinical records of the single physician on the Grand Bahama Island and pertains to approximately 60 per cent of the inhabitants.

A third study relates to blood pressure determinations made by an epidemiologist and medical students from the University of Michigan on 3,000 individuals chosen as a probability sample of Nassau City on Providence Island. Demographic, social, and cultural data have been collected on these subjects, a large proportion of whom are Negroes. Drinking water samples from selected communities have been collected for sodium determinations since the water frequently is brackish, and association between water of high sodium content and hypertension will be looked for.

7. At the Johns Hopkins University School of Medicine and School of Hygiene and Public Health two different methods of study and two different types of population are being used in search of factors associated with CVD. Since 1946 medical students at the Johns Hopkins University have been used as subjects in a study designed to identify those characteristics which may be of value in predicting and in preventing an early onset of CVD. To date nearly 1,000 students have been classified by a variety of genetic, physiological, psychological, and metabolic characteristics in search of those traits which are associated with CHD or HHD. The CVD "heritage" of each student is assessed through family histories taken on parents, grandparents, uncles, and aunts by the students themselves in their third and fourth years at Hopkins. On the fifth and tenth anniversaries of graduation each student is reevaluated by mail questionnaires concerning his health status and sociophysical habits. The health status of his parents also is redetermined. Under the assumption that students experience greater risk of developing CVD if they have an unfavorable CVD "heritage," constitutional differences between low and high risk student groups have been identified. Based on observations to date, a four-way grouping of healthy students according to parental history and student characteristics has been proposed as a basis for selecting highly
susceptible individuals. The individual "positive traits" in this grouping include (a) higher serum cholesterol levels, (b) nonectomorphic body build, (c) higher blood pressure levels, (d) tachycardia, and (e) blood pressure hyperreactivity to cold or exercise. A student with two or more such "positive traits" is classified as having "positive individual characteristics." The parental "positive traits" signify that one or both parents has a history of coronary or hypertensive disease. Follow-up data on health will be related to these characteristics.

As an independent study, the death certificates of Baltimore residents, aged 45 years and less, who died between 1954 and 1959 have been categorized by cause of death in search of factors predisposing to ASHD. Subjects with death ascribed to ASHD have been subclassified into one of three categories following validation of death certification through review of hospital, physician, and autopsy records. These categories are: (1) definite ASHD, (2) uncertain ASHD, and (3) definitely not ASHD. In the period under study, death certificates with diagnoses of ASHD included nearly 200 subjects with a "validated" diagnosis of ASHD (Group 1), 250 with uncertain ASHD (Group 2), and approximately 100 with diseases other than ASHD (Group 3). All other Baltimore decedents in this age class (45 years and less), except those dying of accidental causes, are classified into a fourth category (Group 4). Individuals whose death was ascribed to ASHD (Groups 1, 2, and 3) are then matched by age, sex, race, and date of death on a one-to-one basis with individuals classified as having died from other than ASHD (Group 4). Survivors (spouses or siblings) of the deceased are interviewed by nurses making home surveys for specific and detailed information on family history of ASHD; alcohol and smoking; other diseases; marriage and reproduction; and psychic and physical stress. Through cross-correlation analyses those factors of host which are associated with early death from ASHD are being sought. In search of precursors of ASHD, serum cholesterol and serum uric acid determinations are being made on a sample of the decedents' children and spouses in each of the four groups.

8. Two studies are being conducted by workers affiliated with the Health Insurance Plan of Greater New York and Columbia University College of Physicians and Surgeons. The first is aimed at determining the influence of female gonadal function on the development of CHD. The method employs the measurement and comparison of CHD prevalence in oophorectomized and in a control group of non-oophorectomized, hysterectomized women. White female gynecological ward patients aged 45-65 years from the Columbia Presbyterian and Mt. Sinai Hospitals are being included in the study. Other hospitals will be added if necessary to realize the population of 700 oophorectomized and 1,300 non-oophorectomized subjects estimated to be needed in order to determine whether there is a difference in CHD prevalence. Test and control groups are being matched by (a) period of operation, within three-year groupings, (b) age at operation, and (c) nationality or country of origin. Patients with hypertension or diabetes at time of operation are eliminated from the study. Study subjects are identified through medical record review and then contacted through one or another of the following methods: (a) telephone, (b) attending gynecologist, (c) social service exchange, (d) return United States mail (Form 3547), (e) Welfare Department, or (f) visits by a retail credit agency. When notified of a death, the investigators obtain a copy of the death certificate. Survivors are invited to the hospital for medical
and laboratory examinations. A history of estrogen administration is obtained from the patient's family physician. The criteria for diagnosis of CHD rest largely on history of episodes and current ECG tracings. The study will continue until interpretable results are obtained.

The second study is that of CHD survivorship and repeat attacks. It has been activated only as a pilot undertaking thus far, utilizing new cases reported from three HIP Medical Groups. Patients are invited for examination by a single physician and for appropriate laboratory examinations. Serial medical checks are planned at six-month intervals for two years, and biennially thereafter. Attention will be given to clinical manifestations that develop as well as to mortality.

Discussion

In general, the studies reviewed here employ methods which have been developed and extensively applied in the study of infectious diseases. The process is that of measuring and comparing the frequencies and distributions of disease within defined populations. The aim is to identify or unmask those factors and conditions that cause disease. In regard to causation, it is recognized that the inability to see the dynamic processes of pathogenesis in human subjects calls for use of the epidemiologic method and the inductive reasoning on which it depends.

Of the three methods being used in search of associations between cardiovascular disease and host or environmental factors—termed "snapshot," "flashback," and "motion picture" for convenience of description—it is generally agreed that motion picture studies provide the most comprehensive and accurate data. The three study types are complementary, however, and are most effective when they are used in combination.

The investigators interviewed are aware that the mere demonstration of statistical association between a given factor and a given disease does not establish the link of causation between the two events. Rather, such an association simply indicates that a change in the frequency or magnitude of one event is accompanied by a change in the frequency or magnitude of the other. A given event shown to be directly associated with a given disease may represent only an index of a second event which is in fact a true cause.

Procedures to distinguish temporal association from causal relationship must be designed to fit specific situations and conditions. Such differentiation requires a thorough knowledge of biologic concepts of the disease, together with the conduct of studies that would test specific hypotheses. Procedures would seek to verify by further facts, to establish ancillary evidence, to reproduce results under different circumstances, or to develop alternative hypotheses.

Uncertainty exists as to whether the factors presumed to be related to CVD represent primary or secondary etiologies—that is, are they definitive causes, or in contrast, do they provoke clinical attacks in individuals harboring a primary cause? Do such factors as hypercholesterolemia, hypertension, obesity, and the like, comprise definitive or only predisposing etiologies of CHD? These questions, thus far unanswered, may prove analogous to the interactions between primary and secondary etiologies in acute poliomyelitis. In this disease three immunologically distinct viruses comprise essential causes, and such factors as pregnancy, oropharyngeal surgery, and the intramuscular inoculation of antigens have been established as contributing causes.
Current and Proposed Study Factors

The 21 studies which we have reviewed are measuring a variety of environmental and physiological characteristics, in addition to those on which information is obtained in the course of a routine diagnostic examination—medical history, social history, physical examination, and laboratory tests. Table 1 shows a partial list of these additional factors, the number of investigators currently measuring each factor, and the number of other investigators among the 21 principal investigators who were proposing, but had not yet begun to measure the respective factors at the time of our review in early 1959.

Decision to measure a particular factor implies that some hypothesis about that factor and the occurrence of disease is being tested. For any given factor, different measurements are being made from study to study.

Diet is the factor of interest to the largest number of investigators; ten are currently measuring diet and seven others propose to do so. Four are now using some measure of psychic stress, and five others plan to measure it.

The items "physical stress" and "occupation" require some explanation. Physical stress refers to the administration of some test of reaction to exertion, such as an ECG after exercise, whereas occupation refers to a job classification as an index of physical activity.

"Environment change" as used here means an attempt to alter a specific characteristic, e.g., dietary intake, and to measure the effect of this change on the occurrence of disease. A decision to undertake environmental change rests not only on confidence that an association exists between an environmental characteristic and occurrence of disease, but also on the idea that a change in the environment will be accompanied by a change in the occurrence of disease. The problems of measurement of the factor still exist, and may be made more difficult because of the fact that the investigator has induced an ecologic change.

It is apparent from this list of factors being measured in current and proposed research that the subject areas of measurement selected for attention in this Conference on Methodology are of immediate and major importance in epidemiologic studies of CVD.

Summary

The methodologies being employed in a series of epidemiologic studies have been reviewed. By means of measurement and comparison, the aims of these studies are to determine whether persons manifesting specific physiological or socioenvironmental factors experience a different risk of cardiovascular disease than do persons without such factors. Associations are sought between a specific disease and a specific factor through (a) contemporary studies providing a snapshot of the two events, (b) chronological studies picturing flashbacks to an earlier period, and (c) long-term studies of progressive motion picture type. Groups under study include closed or open populations that are chosen at random or selected on the basis of some preexisting condition.

Table 1—Environmental and Physiologic Factors Measured in 21 Selected Population Studies

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It is recognized that the success of both current and proposed epidemiologic studies will rest on standardized observations and on precise classifications of persons according to the presence or absence of two variables, a specific factor and a specific disease. Follow-up studies will attempt to distinguish between associations that are only statistical and those that reflect a causative relationship. To this end, epidemiologic studies will complement clinico-laboratory efforts by providing collateral evidence; by verifying, amplifying, or modifying prevailing concepts; or by developing alternative hypotheses. It is anticipated that application of epidemiologic methods to the study of chronic diseases will lead to evidence consistent with a causative hypothesis, as have such methods in the study of acute diseases.

Addendum

9. Framingham, Mass.—This longitudinal study began during the period of 1948 to 1950 and has run continuously to date. Serial observations have been made on over 4,000 individuals, or 69 per cent, of an initial randomly chosen sample that represented two-thirds of the Framingham population, aged 30 to 62 years. Biennial medical histories, physical examinations, and laboratory tests have provided the data for study. Reports from local practicing physicians and hospitals have complemented these records. The study’s initial aims were to obtain descriptive information on CVD and to measure prevalence and incidence of these diseases in the population. Secondary purposes were to test selected hypotheses concerning causation of heart disease, these hypotheses being constructed from clinical impressions or the epidemiologic findings of others. To date, major effort has been directed to ASHD and HHD and to associations between these diseases and specific factors of host. Foremost among these factors have been hypercholesterolemia, hypertension, and obesity. More recently other factors have been added and include dietary habits, alcohol consumption, tobacco usage, educational levels, lipoprotein measurements, and district of residence in Framingham. Plans call for extension of the study over at least ten more years.

10. Connecticut State Health Department—Studies began early in 1957 with the initial aims of (a) measuring the prevalence and incidence of CHD and CVA in Middlesex County, and (b) testing specific hypotheses concerning causation of myocardial infarction (MI) as related to particular dietary habits and to social and personality correlates of stress. Case finding has been achieved through reports from practicing physicians and hospitals, coupled with death certifications. A 10 per cent probability sample of the population was queried through Bureau of Census interviews to provide population estimates for rate denominators, an independent estimate of clinically manifest CHD, and control series for the comparison phases of the study, i.e., the nutritional and sociopsychological phases. The sociopsychological aspects of the study contrasted a sample of white male patients, aged 35-64 years, who survived an attack of MI, with an equal number of patients suffering from an acute severe illness other than heart disease and matched with the test group by: (a) age to within five years, (b) race and sex, (c) occupational level, and (d) ethnic origin traditionally similar to that of the test subject. These studies continue and are currently directed at refinement of both hypotheses and tools of measurement.

11. New York State Department of Health—A long-term project began in 1953 as repetitive observations on nearly 2,000 male Civil Service employees, aged 39-55 years, from the Albany
area. Participants represented 89 per cent of the population invited into the study. Primary objectives have been (a) to evaluate established methods of early detection of all forms of heart disease, (b) to evaluate new techniques for this purpose, and (c) to look for etiologic factors of CHD. Annual physical examinations and medical histories by physicians, as well as self-administered questionnaires, have provided the data for study. Clinico-laboratory measurements have permitted a wide search for factors associated with all types of CVD. Special emphasis has been placed on the study of potential nutritional influences on these diseases. The study proceeds in standardized fashion with more intensive clinical observations being made on subsamples of the study population.

A second project began in early 1955 and continues to date. It comprises a study of consecutive autopsies from a general hospital, and the comparison of cardiac pathology with ante-mortem characteristics and environmental exposures of the decedents. The principal purpose is to search for etiologic factors of coronary occlusion and MI. Observations at necropsy include measurements of the lumens and thicknesses of coronary vessels. Observations concerning the autopsied subjects are made through medical student interviews with a close relative of the decedent. Other social and environmental details are obtained from the usual family physician and life insurance medical records of the deceased. Selected characteristics being studied include nutritional factors, usual occupation, weight, alcohol consumption, tobacco usage, and so forth. Comparisons on these characteristics are made between individuals dying of heart disease and individuals dying of other diseases. It is expected that the study will be extended beyond the current population of approximately 900 autopsies.

A third study is being started which contrasts, by retrospective means, cases of MI with matched control subjects. The case population is being obtained by a carefully developed and vigorously monitored reporting system from all physicians in Albany County. Reporting includes cases with other manifestations of CHD, but detailed study is being limited to survivors of first infarctions. "Control subjects" matched on five characteristics (age, sex, race, socioeconomic status, and urban-rural residence) are drawn from a 5 per cent census of the population. It is estimated that 500 cases, matched with an equal number of controls, will be collected by 1961. Comparison of these populations will be directed primarily toward the variables of diet, physical activity, and chronic emotional stress, although a number of other characteristics are being studied.

12. Columbia University College of Physicians and Surgeons, Harvard Medical School, and University of British Columbia Medical School—For the past 12 years a group of 100 sympathectomized (Smithwick operation) hypertensives and an equal number of untreated hypertensives have been followed to assess the effect of this operation on survival. Pairs of test and control subjects were selected from hypertensive clinics in New York City, Boston, and Vancouver. They were matched by (a) age, race, and sex; (b) average and range of blood pressure readings; (c) cerebral symptoms and complications; (d) cardiac size and ECG patterns; (e) histories of angina or cardiac failure; and (f) other factors including degrees of proteinuria, eye ground changes, and renal damage. Each of three investigators reviewed clinical and survival data on all pairs in a "blind fashion" at two, five, and ten years after subjects were entered into the study.

Independent studies of similar
matched-control type are being undertaken at Columbia, using groups consisting of 25 patients each, to test specific hypotheses. These groups will provide information on relative survival rates of (a) patients with malignant and essential hypertension, and (b) drug-treated and untreated hypertensives.

13. New York City Health Department—This project began in February, 1957, to determine (a) if it were feasible to achieve dietary control in a free-living population, and (b) if such dietary management would reduce total cholesterolemia and lower coronary heart morbidity and mortality. Male volunteers willing to follow tailor-made dietary patterns were solicited through two newspaper announcements. They were included in the study, after attending an orientation lecture, if they expressed willingness to follow a prescribed (“prudent”) diet over many years, perhaps until age 65 years. Originally the study included males aged 50-59 years, but this has since been broadened to include age classes from 20 through 59 years.

When a subject enters the study, a medico-laboratory examination is conducted and a comprehensive diet history covering the two preceding weeks is obtained by personal interview with the subject and his wife. The interview permits an estimate of all nutrients as well as the intake of total calories and calories from fat. If the subject is judged by clinical means to be overweight, he is put on a weight-reducing diet. When a “normal” weight is achieved, the subject is placed on a prudent diet that includes a fat intake providing about 30 per cent of total calories. Fats are divided half and half into saturated and unsaturated types of fat. (Part of the latter is given in such forms as specially prepared margarine containing 80 per cent unaltered corn oil, and a “milk” constructed from a homogenized mixture of fat-free powdered milk, vegetable fat, and water.)

Serum cholesterol levels are measured at weekly intervals at the outset to establish a base line which is computed as an average of two or more determinations within 10 per cent of the lowest. Follow-through is attained by (a) annual medical examinations with ECG tracings; (b) serum cholesterol measurements and diet and weight checks every four weeks; and (c) sessions with a board of review (physicians) every ten weeks to discuss the individual’s progress. Subjects provide medical data at the ten-week check; and hospital information, where it exists, complements this. Subjects are told that they will be followed personally until age 65 years, and thereafter through Social Security records.

14. University of Pittsburgh Graduate School of Public Health—The mortality experience in (1) the Arsenal Health District of Pittsburgh during the interval 1951-1956, and (2) Donora, Pa., from 1948 to 1957 has been reviewed. Mortality has been examined in relationship to prior findings of morbidity surveys in each area. (The Donora survey of 1948 investigated the health effects of smog exposures in October of that year. The Arsenal survey was undertaken to measure the frequency of chronic illnesses and medical care in 1951.) Together with these mortality studies, the surveys of these populations have permitted prevalence estimates of various chronic conditions including heart diseases. Findings have convinced the workers of a need for (a) more detailed observations on recognized cases of all diseases, and (b) a better understanding of the timing of onset of overt heart disease and its progression. Forthcoming studies in a group of industrial employees will give attention to these problems.

15. Presbyterian-St. Luke’s Hospital
A five-year study of heart diseases among a large group of industrial employees began in the fall of 1957, with particular emphasis on CHD. Study subjects were men aged 40-55 years who had been employed two years or more in a Chicago electronic industry and who, on review of the company medical records, were believed not to have had either MI or angina pectoris when the study started. A total of over 3,000 men was randomly chosen from the complete roster of company employees and invited to participate. Over 2,100 (70 per cent) complied, have been examined, and are now in the second round of examinations. The aims are (1) to determine the cardiovascular status of subjects at the time of the initial examination, (2) to measure incidence of heart disease through four annual reexaminations, and (3) to relate the incidence of heart disease to various physiological measurements and other characteristics of the subjects. Data gathered at the initial examination included (a) a family history prepared by the subject; (b) a medical history and physical examination by one of 25 volunteer physicians assisting in the study; (c) clinico-laboratory tests including somato-typing with photography; (d) diet assessment by detailed interview with the subject and a questionnaire completed by the spouse; (e) physical activity measurement by analysis of job requirements and an interview concerning off-the-job physical exertion; and (f) personality traits determination as revealed by the Minnesota Multiphasic Personality Inventory. These procedures are being conducted in facilities at the plant and require about two half-days for which the subject is given time off with pay.

16. Tulane University—Since 1941 the influence of hot and humid (subtropical) environments on physiologic and pathologic responses in man has been under study. Observations are being made both in hospital wards and in experimental chambers using normal subjects and patients with chronic congestive heart disease. Measurements of cardiac function are being contrasted between study populations, and temporal comparisons are being made within these populations.

17. South Carolina College of Medicine—Clinico-laboratory procedures have been developed and standardized to permit screening of large numbers of subjects for (a) blood lipid levels, (b) whole blood coagulation, and (c) intravascular agglutination of erythrocytes (sludging). Interrelationships among these variables are being sought for several contrasting groups including (a) selected diseased and normal populations, and (b) samples of white and Negro residents of metropolitan Charleston. A battery of lipid tests are being run on all blood serums, including those for cholesterol, phospholipid, triglycerides, and alpha and beta lipoproteins. Microscopic observations, photographs, and closed circuit televising of the capillary circulation in the bulbar conjunctiva allow estimation of the degree of erythrocyte agglutination and arteriolar plugging with sludged masses. Blood coagulation is measured by conventional technics.

18. California State Department of Health—In 1948 a total of 577 “healthy” individuals aged 50 years or more were selected from 843 registrants who volunteered to participate in a study of nutrition as related to aging. Selection from the registrants strove to include only individuals who were physically and mentally capable of participating, in good health, not under a physician’s care within the three prior months, and not food faddists. Selection attempted to achieve an equal sex distribution and a range of age and economic classes. Initial study of this group included (a) a nutritional history and a record of seven-day food
intake; (b) a detailed medical history and complete physical examination; and (c) a series of laboratory results from blood and urine analyses, and from chest x-rays, bone density determinations, and vaginal (Papanicolaou) smears. Follow-up physical examinations and dietary evaluations of as many subjects as were available were made in 1952 and again in 1954. Data that have been analyzed pertain to mortality, morbidity, and disability (both for CVD and for total disease) in relation to the original (1948) physical findings, blood analyses, and diet patterns. The health status of subjects still available for examination and interview is being reevaluated after a total of 11 years of observation.

In 1951 a multiphasic screening examination was given to 4,000 longshoremen who volunteered to participate, out of a total of 6,000 such workers in the San Francisco Bay area. Tests included measurements of age, height, weight, hearing, blood pressure, hemoglobin, blood sugar, glycosuria, albuminuria, a chest x-ray, and an ECG tracing. The subsequent mortality of the 4,000 volunteers and the 2,000 nonparticipants has been followed through death certificate analyses and union health insurance records. This study continues as a routine operation, offering a potential for testing a series of hypotheses of causation.

A health survey of a representative sample of Californians was conducted in 1954-1955 whereby information was obtained for nearly 32,000 individuals by Bureau of the Census interviewers. A total of 250 individuals (150 males and 100 females) gave history of some form of CHD. A substantial proportion of these individuals was matched with disease-free control subjects of the same age and sex, chosen from the survey population. Interviews were held with diseased and control subjects to determine the relative frequencies of various characteristics that might be related to CHD. (Next of kin were interviewed where subjects in the sample had died.) Special attention was given to (a) smoking habits, (b) presbyopia, (c) physical exertion at work, (d) participation in athletic events, (e) occupation, (f) urban versus rural residence, and (g) native versus foreign birth.

19. Mt. Zion Hospital, San Francisco, Calif.—The role of specific behavior patterns as they may predispose to CHD among selected population groups is under study. In general, these efforts measure independently (a) personality and behavioral patterns and (b) historical experiences with CHD. Subjects, many of whom are industrial executives, were selected if they gave evidence of highly developed aggressiveness, competitiveness, and a tendency to accelerate all activities; or if, on the other hand, they seemed to lack these attributes. Evidence of previous experience with CHD was obtained from medical histories and ECG tracings. "Competitive" subjects (N=83) were matched with "noncompetitive" subjects (N=83) by similarities in age, race, ethnic group, diet, height, weight, and the amount of physical activity required by their jobs. A total of 42 unemployed blind subjects also were studied. The latter resembled the "non-competitive" group in personality pattern but had the complicating factor of continual anxiety. At the time of observations, selectees first were categorized by one examiner as to whether their behavioral patterns, which had been selected to represent the extremes of contrast between "driving" and "easy-going" personalities, were completely or incompletely developed. (This was done for purposes of subclassification.) A detailed medical history was taken and a physical examination performed. Then a second examiner drew blood for determinations of cholesterol
and clotting time, measured bleeding time, and took ECG tracings. A third examiner gave detailed instructions that would permit selectees to record qualitative and quantitative information on dietary intake by daily diary technic for one week.

Short-term studies on small groups of CHD patients and selected control subjects are under way to refine current technics and to develop new and better methods. Endocrine-CHD hypotheses are being tested through utilization of data from urinalyses. Other studies now in progress are designed to measure personality traits by objective means. A "lie detector" that simultaneously records amplitude and rate of respiration, body movement, and cardiac function is under study. Also, a psychophysiological test is being devised in search of a predictor of the occurrence of CHD in specific groups of individuals.

20. North Dakota—In 1956-1957 a longitudinal study of CHD was started in a six-county area surrounding Grand Forks, N. D., to determine the feasibility of certain investigative methods and to test specific hypotheses concerning causation of this disease. (This area was selected for study because vital records had indicated that North Dakota reported the lowest death rate from CHD in the nation.) Patients developing acute manifestations of CHD, either as new or recurrent events, were reported by practicing physicians to the study center as the primary case-finding device. Also, physicians provided clinical and ECG findings on their CHD patients to assist a review committee of internists in deciding whether reported cases should be considered CHD for purposes of the study and in classifying them into subgroups. Monthly visits were made by an epidemiologist to each physician in the study area and bimonthly visits were made to physicians in areas bordering the six counties to improve the degree of reporting and to collect collateral information. Hospital records and mortality statistics were reviewed periodically to check the completeness of this case-finding method. A 10 per cent probability sample of dwelling units was chosen and residents therein were interviewed through Bureau of the Census enumerators for demographic and selected personal characteristics. These characteristics included data on occupation, smoking, and food habits as the principal areas of interest, and were determined through personal interviews with all males aged 35 years and over who came into the probability sample. A single dietitian made detailed dietary assessments of each recognized CHD patient, together with such assessments of two age-matched control subjects chosen for each patient from the probability sample. Attempt was made to establish the dietary pattern of patients for the month preceding overt disease and of control subjects for the month preceding the interview. If the CHD patient had died, his wife or nearest kin was interviewed as, in such instances, were comparable relatives of the matched control subjects. Thereafter standardized procedures were followed in estimating qualitative and quantitative intake of specific nutrients.

21. Chicago Board of Health—An ongoing study has been conducted in a Chicago utility company in search of factors of host and environment that predispose to or precipitate cardiovascular-renal morbidity and mortality, particularly ASHD and HHD. The health status, country of birth, social class, and occupational experience of 756 employees aged 50-59 years (96 per cent of the plant employees in this age class) were determined as of January, 1954, from preexisting records. Using serial observations from annual physical examinations conducted through plant facilities, a series of determinative analyses is in progress. (In
January, 1958, the study was enlarged to include the entire labor force aged 40-59 years, approximately 2,000 individuals.) Specific aims include the testing of hypotheses concerning associations between CVD and the following host and environmental characteristics: (a) place of birth (native or foreign born), (b) dietary habits and nutrition, (c) marital status, (d) physical activity, (e) psychologic stress, and (f) other factors.

A second study concerns the comparison of Negroes and whites with respect to patterns of cholesterolemia and incidence of CHD. Other correlates include age, sex, height, weight, occupation, industry, and duration of residence in northern states.

A third study, employing methods of experimental epidemiology, is designed to measure the effect of a nutritional-hygienic regimen on risk of developing CHD. Several hundred middle-aged men without evidence of CHD, but presumed to be at high risk by virtue of high levels of (a) body weight, (b) blood pressure, and (c) serum cholesterol, have been induced to follow a prescribed regimen and are being examined serially. They are being contrasted for coronary disease with appropriately matched control subjects from the Chicago utility company.