ANNUAL REPORT OF PROGRAM ACTIVITIES

NATIONAL INSTITUTES OF HEALTH

1967 - 1968

NATIONAL HEART INSTITUTE

VOL. I

NIH-NHI

THE U.S. NATIONAL HEART INSTITUTE

ANNUAL REPORT

July 1, 1967 through June 30, 1968

NIH-NHI

THE NATIONAL HEART INSTITUTE

ANNUAL REPORT

July 1, 1967 through June 30, 1968

OFFICE OF THE DIRECTOR

EPIDEMIOLOGY AND BIOMETRY

AH-MI PROGRAM

PROGRAM

RESEARCH

NATIONAL INSTITUTES OF HEALTH
NATIONAL HEART INSTITUTE
July 1, 1967 to June 30, 1968
OFFICE OF THE DIRECTOR

The special province of the National Heart Institute is the cardiovascular system and its diseases. Its primary mission is to conduct and support research aimed at increasing scientific knowledge of the structure and functions of this complex system; defining structural and functional abnormalities occurring with disease; seeking out factors that underlie or influence the development of these abnormalities; and, on the basis of this knowledge, searching for effective means of prevention, diagnosis, and treatment.

It is a complex system, vulnerable at many points and prey to a large family of diseases. In many instances, the causes of these diseases are not known, but appear to be exceedingly complex and may often involve the interplay of a whole constellation of factors. Further complicating matters are the large number of factors--within the person himself, his environment, or his mode of life--that may influence his susceptibility to certain of these diseases, accelerate their development, or trigger their often devastating complications.

The scope and complexity of the problems posed by the cardiovascular diseases make mandatory a large, broadly based, and widely diversified research program. In both its intramural and extramural programs, the Institute has deployed its resources and scientific manpower along a wide variety of research approaches. However, the steadily growing fund of basic and clinical knowledge emerging from these programs has also enabled the Institute to mount and sustain a number of special research and development programs directed against specific, well-defined health problems.

The Artificial Heart-Myocardial Infarction Program has as its primary goals 1) the development of devices and techniques for assisting a failing circulation and 2) reduction of death and disability from acute heart attacks, which strike an estimated 750,000 Americans each year and kill more than 350,000 of them. This joint program is combining biomedical and bioengineering approaches to this major health problem.

The Artificial Heart Branch continues to concentrate on the development and refinement of instrumentation and techniques for providing pumping assistance to damaged or failing hearts. During fiscal year 1967, it provided research contract support for 57 projects concerned with specific engineering, physiological, biochemical, and related problems of artificial heart development.

During 1968, nearly 100 contracts will be awarded in 14 key areas of physiology and bioengineering. These include: implantable devices for measuring blood pressure and bloodflow in arteries and veins and instrumentation for monitoring physiological functions in heart patients; blood compatible materials; evaluation of the effects of various materials on blood cells, proteins, and other components of plasma; devices for emergency, temporary, and permanent circulatory assistance; improved oxygenators for heart-lung machines; energy

systems for implantable heart-assist devices; planning of test and evaluation facilities for new instrumentation and techniques; biological fuel cells; physiological consequences of assisted circulation; factors important in the physiological regulation of circulatory assist devices; and others.

The Myocardial Infarction Branch, through its MIRU program and other biomedical research activities, is seeking more effective means of medical management of acute heart attacks. The Myocardial Infarction Research Unit, or MIRU, is a clinical unit specially equipped and staffed for the most comprehensive care and detailed study of heart-attack patients during the acute phase of their illness. Its purpose is

- to obtain precise information on the clinical course of the attack;
- to identify and define factors that favorably or unfavorably affect the patient's prospects for recovery;
- to assess the effects and effectiveness of accepted and new modes of treatment; including circulatory assist devices and techniques developed under the Artificial Heart Program;
- to improve clinical management of coronary cases by providing more rational scientific bases for all phases of diagnosis, treatment, and patient care.

During fiscal year 1967, MIRU's were established at the University of Alabama, Cornell, Duke, Johns Hopkins, and Massachusetts General Hospital. During 1968, the Myocardial Infarction Branch will establish 4 additional MIRUs toward the 10-12 units presently projected under this program.

Supplementing the clinical activities of each MIRU will be extensive laboratory research and experimental studies in animals. Animal studies permit for more detailed observations than are presently possible in patients and also extensive testing of new drugs or other therapeutic measures that may be applicable to clinical problems.

In order to expand the scope and usefulness of such animal studies, the Myocardial Infarction Branch has awarded 6 contracts for the development of more suitable animal models of myocardial infarction. The contractors are seeking techniques for producing heart attacks in animals that closely mimick human heart attacks in terms of heart-muscle damage, circulatory alterations, physiological consequences, and potential complications. The methods should produce predictable, reproducible results and should be applicable to various species.

Strong epidemiological evidence indicates that elevated blood lipid levels are consistently related to increased risk of developing coronary heart disease and its most common manifestation: the heart attack. It seems reasonable to suppose that 1) elevated blood lipid levels also affect prospects for long-term survival after recovery from a heart attack; and 2) drugs that produce sustained lowering of blood lipids should improve longevity among heart-attack

patients.

This is the principal objective of the Coronary Drug Project, a large-scale, cooperative trial involving 55 study clinics throughout the continental United States, Puerto Rico, and Hawaii. During the next two years, this study will provide opportunities for some 8,500 men who have sustained one or more heart attacks to participate in a 5-year trial of four lipid-lowering drugs: Conjugated equine estrogens, d-thyroxine, clofibrate, and nicotinic acid. The goal is to determine whether one or more of these drugs will reduce by 25 percent or more the 5-year mortality rate among treated patients.

Various studies have indicated that the cumulative 5-year mortality rate among recovered heart-attack patients is 30 percent or more. The Coronary Drug Project hopes to pare this mortality rate to 22 percent or less in one or more of the treatment groups by reducing the threat of recurrent heart attacks and other complications in patients with pre-existing coronary heart disease.

Clinic enrollment was completed during the summer of 1967 and patient recruitment is well underway. Each clinic is expected to recruit 150-160 patients toward the 8,500 total required to ensure the validity of the study findings. As of May 1968, approximately 3,781 had been assigned to one of the 5 treatment regimens or to the control group.

To assist in patient recruitment, the National Heart Institute has mailed 48,000 information packets on the Coronary Drug Project to general practitioners, cardiologists, and internists practicing in areas where study clinics are located.

Major goals of the National Blood Resource Program are 1) to survey our Nation's blood resources and their utilization in terms of present and foreseeable needs; and 2) to meet a steadily accelerating demand for blood and blood fractions without undue strains on these resources through improvements in technology that will make possible the more efficient production, storage, and distribution of blood products.

Increasingly, specific blood fractions are replacing transfusions of whole blood or plasma in clinical states caused or complicated by deficiencies of some particular blood component.

In such instances, fractions produce superior clinical results and also carry less risk of adverse reactions. As physicians have become aware of the therapeutic advantages of blood fractions, the clinical demand for them has increased rapidly during recent years and will rise still more rapidly in the future.

As a first step toward meeting the anticipated demand, the National Blood Resource Program awarded the largest of its 12 contracts let during fiscal year 1967 for the development of an integrated fractionation system for the mass production of cellular and protein components from whole blood. Support for this project will continue in 1968.

During 1968 the program will also support studies to determine the feasibility

of a computer-based donor blood inventory system. The principal object would be to make possible a more equitable distribution of the blood supply and thus to forestall the development of local shortages due to fluctuations in supply and demand. Among the additional benefits of such a system would be

- .reduction of whole blood losses due to outdating through redistribution of local surpluses;
- .closer co-ordination of civilian and military blood programs;
- .a means of summoning prospective donors during slack donation periods;
- .a means of screening and excluding donors who are probable carriers of infectious hepatitis; and
- .a means of locating rare-blood donors within a region.

Also scheduled to begin in 1968 is a cooperative clinical trial of the clot-dissolving agent urokinase against pulmonary embolism. The study will involve about 15 institutions and 225-300 subjects. Patients with pulmonary emboli will be studied intensively before, during, and after administration of urokinase to determine whether this agent will destroy the clots in the lungs. If the results are promising against pulmonary embolism, urokinase will probably be clinically tested against coronary occlusion in future studies.

Under its Cardiovascular Research and Training Center Program the National Heart Institute has awarded 10 planning grants and approved 2 others to date toward the establishment of 10-12 such Centers by 1973. Given the continued availability of planning funds, the Institute intends to award sufficient planning grants to provide a basis for competitive selection of the 10-12 that will qualify for operational support. Recipients of planning grants are: 1) the University of Washington, 2) the University of Utah, 3) Presbyterian Medical Center (San Francisco), 4) the University of Alabama, 5) University Hospital (Boston), 6) Indiana University, 7) Ohio State, 8 Duke, 9) University of Minnesota, and 10) Johns Hopkins. Planning grants have been approved for St. Louis University and Vanderbilt.

Each Center will be an organizational unit, established within a university or similar institution, for carrying out research and training related to a broad range of cardiovascular disease problems. It will be staffed by a core group of scientists representing not only the various clinical disciplines but also the physical, engineering, and social sciences, each contributing his special expertise where needed in the solution of complex problems. The Center will be heavily involved in research relevant to the solution of clinical problems and will also carry out vigorous training programs designed to attract high quality trainees in a variety of disciplines and to arm them with the finest research and clinical skills that modern science can provide.

The Heart Institute believes that the center concept will permit simplification and provide greater efficiency in the administration and use of grant funds. Specialized equipment, facilities, and other resources can be provided with

greater economy. Moreover, the sustained high level of productivity and excellence expected of each center will justify support of greater stability and continuity.

During 1968, several ad hoc advisory committees were convened. One of these, the Diet-Heart Review Panel, has been meeting since last November to consider the state of the art in diet and coronary heart disease and to advise the Director as to which, if any, clinical trials in diet and heart disease should be undertaken at this time. This twelve man committee embraces a number of different disciplines and approaches to this problem. It has augmented its expertise by several sub-groups who have dealt in depth with such specific questions as the food industry's ability to alter foodstuffs, the measurable differences between men at risk of a first, in contrast to a second, myocardial infarction and the willingness of physicians to engage in and apply the results of any proposed clinical trial. The recommendations of the Diet-Heart Feasibility Study investigators have thus been viewed by the Panel and will be viewed by the Council against this background of the entire field.

The Panel have prepared an extensive report for the Director. This has been distributed to the members of the National Advisory Heart Council and a day of the June meeting of the Council set aside for a detailed consideration of the entire problem. The Chairman of the Panel, Dr. Ahrens, will present the Panel's findings; the Principal Investigators of the Feasibility Study, Drs. Page and Stamler, will present their recommendations.

PHS - NIH
NATIONAL HEART INSTITUTE
July 1, 1967 to June 30, 1968
HEART INFORMATION CENTER

Activities of the Heart Information Center (HIC) are closely tied to the needs, activities, and goals of the various research and training programs of the Institute. An effective information program can aid materially in the achievement of Institute goals by

- .creating heightened public awareness of the immensity of the cardiovascular disease problem.
- .promoting public understanding of the National Heart Institute and enlisting public support for research and training programs directed against this disease problem.
- .disseminating to the general public and to the health professions new knowledge arising from research programs carried out or supported by the Institute.
- .publicizing and promoting new programs to generate interest and encourage participation by members of the scientific community.

HIC activities in pursuit of these goals can be grouped conveniently under the following headings: 1) publications, 2) press and media services, 3) internal reporting, 4) exhibits, 5) correspondence and 6) information resources. Currently, activities under each heading are being reviewed in an effort to improve efficiency and, where possible, to expand the output of useful information. This report summarizes activities in each of these areas during the 1968 fiscal year.

PUBLICATIONS

A strong publications program is a most effective means of reaching large audiences and this area received heavy emphasis during the year. A new section was established for the specific purpose of producing, promoting, and distributing publications and related informational materials issued by HIC.

During the 12 months ending at the time this report was prepared, 322,898 copies of HIC publications were distributed, a 11.5% increase over the previous high established the preceding similar period. Individual requests and exhibit distribution accounted for most of this business; but, as a result of promotional mailings to educational and health group associations, there was a substantial increase in bulk mailings, with their attendant advantages of speed and reduced costs. Promotional mailings, containing sample copies of HIC publications and offering new publications as they are issued, have resulted in the creation of new mailing keys; and, to cite only one recent example, led to a request for more than 2,000 copies of a single publication for distribution to employees of just two companies.

A new publication issued in fiscal year 1968 was "The Coronary Drug Project," a 12-page illustrated brochure describing the nationwide NHI-supported study of lipid-lowering drugs. Produced as part of a campaign to secure physician cooperation and to assist in the recruitment of patients; it was mailed to 50,000 physicians practicing in project clinic areas and will be used with a recently completed exhibit on the project. Also prepared as part of professional publicity materials on the study was a flyer summarizing project goals, the test drugs and patient eligibility and listing all participating centers.

Publications in special demand during the year were:

"Artificial Parts for the Heart and Blood Vessels," a 28-page publication describing the evolution of cardiovascular prostheses from the earliest blood-vessel and heart-valve replacements to artificial heart prototypes, has moved very well with exhibits and has been especially popular with high-school science students. The initial supply was quickly exhausted and it is now being reprinted.

"Epidemiology of Stroke," was prepared for use with an exhibit of the same title that describes the findings of the NHI Framingham Study with respect to factors increasing risk of stroke. It has also proved useful as a general publication. The American Heart Association requested 3,000 copies for use with one of their information kits and Ayerst Laboratories requested 750 for distribution to their medical staff and field representatives.

"Varicose Veins," which was second prize winner in the leaflet category of the Federal Editors Association's "Blue Pencil" contest for outstanding government publications produced in calendar year 1966, presents facts about the common condition and information on causes, symptoms, and treatment. Shortly after publication it became

one of HIC's five most requested publications and continues to move well.

"Emphysema," a general leaflet on the disease, was requested for a number of special distributions. Large quantities were furnished for distribution to employees of the Farmer's Insurance Group and the Kimberly-Clark Corporation. Three thousand copies were provided to the National Clearinghouse for Smoking and Health, National Center for Chronic Disease Control, for use in answering inquiries resulting from emphysema radio spot announcements issued by the Clearinghouse.

"A Living Pump," the poster graphically describing the heart and circulatory system, was reprinted to supply 40,000 copies to members of the American Druggist Association for use in drug store display racks. First printed in 1953, the poster is HIC's "Best Seller" with over a half-million copies distributed to date.

Two forthcoming publications were completed during the year. Both are now in press and will be extensively promoted and distributed during fiscal 1969:

"Cardiovascular Surgery," probably the most complete lay publication on the subject, discusses and illustrates surgical treatment of a wide variety of cardiovascular disorders, including congenital defects, rheumatic heart disease, coronary heart disease, stroke, and renal hypertension. Also covered are pacemakers, heart-assist devices, and artificial hearts.

"Hypertension" will cover mechanisms of blood pressure control, hypotheses of causation, diagnosis, and current methods of medical management of this disease.

The HIC publications program will be continuously reviewed in the future with the goal of phasing out those that have outlived their usefulness, revising and updating others, and creating new publications to broaden the coverage of NHI research and training activities.

PRESS AND MEDIA SERVICES

In the year since the last report, HIC issued a total of 57 press releases (general releases, announcements, science writer releases, and press digests) dealing with such topics as research accomplishments of NHI scientists and grantees, research grant and contract awards, staff appointments and honors, and new programs. Media interest in NHI programs was generally high during fiscal 1968, particularly with

respect to the Artificial Heart-Myocardial Infarction Program and the National Blood Resource Program.

Appointment of a new Press Officer and other organizational changes increased the press output over the preceding year, but it also pointed up several basic weaknesses: 1) preoccupation with research conducted in Bethesda to the near exclusion of the much larger extramural research and training programs, 2) a passive information posture, in which press materials were generated primarily in response to inquiries or pressures from outside HIC, and 3) excessive reliance on routine press and science-writer channels while giving but token effort to the audio-visual media.

Initial steps were taken during the year to correct these inadequacies. Several joint releases coordinated with grantee institutions were issued and closer ties were initiated between HIC and public information officers at grantee institutions. HIC became more aggressive in seeking out and publicizing NHI accomplishments and program developments. Greater use was made of the NIH features branch and other previously available, but previously untapped means of information dissemination.

Releases reporting on research results of NHI scientists were well received. Subjects included: the experimental heart valve replacement consisting of a homograft valve supported by a clot-resistant prosthetic frame; the aging effects with respect to coronary heart disease (in excess of chronological age) of smoking, high cholesterol level and high blood pressure; that ATPase activity is depressed in myofibrils from failing hearts and this may be a factor in the depressed contractility that limits pumping effectiveness in congestive heart failure; and that xanthinuria, a rare disorder characterized by deficient production of uric acid, results from the absence of xanthine oxidase, an enzyme that generates uric acid from intermediate compounds in metabolism of purines derived from dietary protein.

Others were: on the relief of intractable angina pectoris by a surgically implanted electronic device that stimulates the carotid sinus nerves; that failing heart and normal heart muscles use the same amount of ATP energy per unit of work, indicating that the failing heart converts chemical energy to mechanical work as efficiently as the normal heart, and thus the biochemical defect in heart failure is not in energy utilization; that high cholesterol or triglyceride levels in blood plasma are not necessarily a specific diagnosis, but may represent symptoms of any of at least five different lipid-transport disorders; on the new technique employing radioisotope technetium-99m and a gamma scintillation camera to visualize the heart and great vessels; and that direct current is superior to alternating current for halting effective heartbeat

during open-heart operations.

The release on relief of angina by electrical stimulation of carotid sinus nerves excited much press interest. The release, together with five pictures run in an issue of the NIH Feature Service, stimulated more call-backs, requests for information, and photographs than any HIC initiated story in recent memory. AMA News, Newsweek, Saturday Evening Post, National Observer, Medical World News, Medical World (London), New York Times, ABC News, United Press International, Associated Press, and many feature services, medical trade journals, and throwaways covered the story. Life planned a full-treatment spread on the work. Clippings from such papers as the Hongkong Standard (English), the Palm Beach (Fla.) Post, Valley Evening Monitor (McAllen, Texas), and the Fort Wayne (Ind.) Journal-Gazette testify that the wire services gave the story the widest possible circulation.

Widespread publicity resulted from releases on contract awards made by the NHI Artificial Heart-Myocardial Infarction and National Blood Resource Programs and grants for the Coronary Drug Project. Also, releases on honors accorded to Drs. Fredrickson, Nirenberg, and Udenfriend generated interest and call-backs for additional background information.

HIC prepared a number of 600-word articles for use in the "Research for Health" series of columns syndicated by the Office of Information, NIH, and many feature stories for the NIH Record. The "Young at Heart" series appearing in the NIH house organ, brief personality sketches telling of the backgrounds of young people just beginning careers in science and allied fields who work at NHI, produced a side-effect of interesting editors in receiving more news from NIH. Many of the articles were given local use in "home-town" newspapers and the NIH Information Office followed-up on these contacts to introduce other aspects of NIH research programs.

Services to the general and medical press were continuously provided by HIC in response to many requests for special information. Interviews were arranged, background materials furnished, questions answered, and photographs supplied to reporters, magazine writers, editors, and free-lance writers on a variety of subjects. Among those serviced in connection with articles or feature stories were Medical World News, Medical Bio-electronics, Hospital Practice, Reader's Digest, McCall's, Life, Changing Times, Wall Street Journal, Washington Post, New York Times, and Associated Press.

Television and radio news interest in heart transplantation following the first operations in South Africa and the United States resulted in requests and participation of NHI staff in discussions of cardiac replacement, prospects for heart transplantation, and medical aspects of transplantation. TV programs participated in included NBC (News) Network, January 2, 1968 (Dr. Fredrickson); CBS "Cadence" January 2 (Dr. Hastings); ABC "Here's Barbara," January 3 (Dr. Cooper); NBC Network January 3 (Dr. Cooper); and NBC "Today" show, April 12 (Dr. Fredrickson). On another subject, a tape was made February 12 on NHI Lipoprotein Studies for later presentation in a special program "Medicine in the year 2000." Also, four 30-second and four 60-second fill-in-the-blank radio spots for local use were prepared as part of publicity material for the Coronary Drug Project.

Since TV and other audio-visual media have begun to overshadow newspapers, magazines and semi-professional journals as the source of most people's information and ideas, HIC has made plans for use of a "treatment concept" in dealing with non-printed media. By this method, information and pictures would be collected, together with background reprints or historical references, and presented as a prospectus package to TV, radio, or film news editors to interest them in developing their own programs using their own personnel and equipment. In addition to its value to non-printed media, the prospectus package could serve as the basis for development of exhibits, publications, and more traditional press services.

INTERNAL REPORTING

During fiscal 1968, HIC prepared over 100 reports intended primarily for use within NIH, PHS, and DHEW. These ranged from routine information reports through items on research findings published by NHI scientists and grantees to special reports and supporting materials for use in conjunction with appropriations hearings.

Among materials prepared in connection with appropriations were the "Director's Opening Statement;" "Highlights of Research Progress during 1967 for the National Heart Institute;" "Progress Report on Programmed Activities of the National Heart Institute," covering Artificial Heart-Myocardial Infarction Program, Cardiovascular Research and Training Center Program, Coronary Drug Project, and National Blood Resource Program; special report on "Smoking and Cardiovascular Disease;" revised special report on "Atherosclerosis and Coronary Heart Disease: Drug and Hormone Therapy;" summary material requested for the House and the

Senate sub-committees; and material on NHI information activities for inclusion in a special NIH report.

In addition to the report prepared each week on significant research findings and program developments for the information of higher echelons, a number were prepared on special request on subjects such as "Outstanding Accomplishments of NIH Grantees," "Summaries on Research Conducted by NHI Scientists," "National Diet-Heart Feasibility Study," and others. Also, regular bibliographic reports, consisting of monthly listings of NHI staff papers submitted for publication, quarterly reports of published staff papers, and a yearly compilation for inclusion in the NIH Scientific Directory and Annual Bibliography were prepared.

The plethora of reports concerning information included one on "NHI Scientific and Technical Information" for the Office of the Assistant Secretary for Health and Scientific Affairs, DHEW; material for the "GAO Survey of DHEW Information Activities (Publications)" for the Office of the Surgeon General; monthly "Information Activities" reports, semi-annual and monthly "Radio and TV Activities" reports, and ad hoc reports on "Publications of Possible Interest to Medical Libraries," "Information Projects Planned" and "Public Inquiries Activities" for the Office of Information, NIH.

Materials for several speeches, which were in essence reporting to special audiences, were prepared for various officials during the year, as were a number of requested messages for transmittal on special occasions.

Though many of the reports HIC prepares are routine, some provide excellent grist for the press release or publications mills. Currently, the Internal Reporting Unit is being reorganized and its staff increased in order to augment their research reporting activities and to increase the coordination of their efforts with those of the press and publications units. In this way, HIC hopes to make fuller and more effective use of "routine" reports that contain information of more-than-routine interest or news value.

EXHIBITS

Exhibits presently provide HIC's best direct access to professionals in the health fields. They are also excellent vehicles for displaying and disseminating publications and related information materials. A conservatively estimated 59,375 publications were distributed during fiscal 1968 as a direct result of the exhibits program.

HIC displayed exhibits at 9 medical and scientific meetings during the year (see exhibit schedule on following page) and one was installed at the Armed Forces Institute of Pathology for an indefinite period. Four exhibits were in circulation:

"Epidemiology of Stroke," an exhibit presenting findings of the NHI Framingham Study, is one of two audience-participation exhibits on Framingham that have proved extremely popular. Members of the audience may have their ECG taken and analyzed by a cardiologist, their blood pressure and vital capacity determined, and other simple tests performed, the results of which may be indicative of relative risk of coronary heart disease or cerebrovascular disease. This exhibit received a Certificate of Merit from the American Osteopathic Association at its annual convention and scientific sessions.

"Habits and Coronary Disease" is the other audience-participation exhibit presenting Framingham findings. For the past two years, it has been used at the AMA Scientific Meeting as part of their health-screening program for physicians.

"Coronary Drug Project," a new exhibit recently completed, was scheduled for four showings this year and will be widely used next year to promote professional interest in the Project and to assist in the recruitment of patients. This exhibit, closely keyed to the needs and goals of an important NHI program, sets a precedent that will be continued in the design and employment of future exhibits.

"The Heart and Circulation" contrasts the old Galenic theory of blood circulation with the "modern" concepts first put forward by Harvey and has a center panel depicting artificial spare parts for the heart along with prototypes of several totally artificial hearts. Following showings this fiscal year at meetings of the American Academy of General Practice and the American College of Cardiology, it was installed at the Medical Museum of the Armed Forces Institute of Pathology in April. The Museum, close to the tourist center of the Nation's Capitol, is visited by thousands. HIC's most popular publications accompany the exhibit - twenty thousand were stocked initially, with replenishments to be made on a regular basis after public demands can be established. Placement of the exhibit at AFIP is part of HIC's effort to gain maximum exposure for exhibits and publications at lowest possible cost.

EXHIBIT SCHEDULE - FISCAL YEAR 1968
July 1, 1967 - June 30, 1968

ORGANIZATION	LOCATION	DATE	TITLE	PUBLICATIONS DISTRIBUTED
American Academy of General Practice	Dallas, Texas	Sept.18-21	The Heart and Circulation	7,650
American Heart Association	San Francisco, California	Oct. 20-24	Epidemiology of Stroke	14,650
American Osteopathic Assoc.	San Francisco, California	Oct. 30-Nov. 2	Epidemiology of Stroke	1,650
Regional Medical Programs Workshop Conference	Washington, D.C.	Jan. 17-19	Lipoprotein Study and Coronary Drug Project	750
American College of Cardiology	San Francisco, California	Feb. 28-Mar. 3	Heart and Circulation	3,350
Armed Forces Institute of Pathology Medical Museum	Washington, D.C.	Apr. 1	Heart and Circulation	20,000
Medical and Chirurgical Faculty of Maryland	Baltimore, Maryland	Apr. 17-19	Coronary Drug Project	325
Massachusetts Medical Assoc.	Boston, Massachusetts	May 21-23	Coronary Drug Project	Est. 500
New York Annual Health Conf.	Rochester, New York	Jun. 9-12	Coronary Drug Project	Est. 500
American Medical Association	San Francisco, California	Jun. 16-20	Habits and Coronary Heart Disease	Est. 10,000
			TOTAL PUBLICATIONS	59,375
			TOTAL ESTIMATED MEETING ATTENDANCE	75,000

CORRESPONDENCE

Of the more than 11,000 public inquiries received by HIC during the past year, the great majority were requests for specific publications or other readily available information that could be easily and quickly handled. However, some of these requested information not easily come by or else required considerable delicacy or tact in framing a suitable reply. An attempt is made to answer such letters promptly and to provide the specific information requested, even though this often requires considerable staff time. Difficult ones are assigned to highly qualified personnel. As a result, HIC's best science writers spend a lot of time answering letters; but this time and effort is believed to be justified.

INFORMATION RESOURCES

Information concerning heart disease is the commodity in which the Heart Information Center deals. Hence an activity basic to the operation of the Center is the systematic development of information resources relating to the cardiovascular field. Essential stores of data and documents must be at hand from which to draw facts for the substantive content of informational products and services. Whatever the medium used for disseminating heart information--pamphlet, report, press release, film, speech, exhibit, script, letter--authentic and adequate subject matter is the required ingredient.

The Heart Information Center collects, organizes, stores, retrieves, and makes available basic elements of information in three main categories: (1) on the various aspects of the National Heart Institute and its programs, (2) on the results and contributions of the Institute's programs to progress in the cardiovascular field, and (3) on the existing and developing knowledge of the heart and circulatory system and the diseases that affect them.

During the past year, acquisition of materials in all categories was continued and expanded. These resources provided information to the Center's staff and to other branches of the Institute, not only for program, organizational, legislative, biographical, and other types of data, but for historical applications such as the NHI Almanac.

Documentation of research conducted and supported by the National Heart Institute provided basic elements essential for research reporting and other functions of the Center. An estimated 4,200 NHI-credited scientific papers and abstracts were recorded through regular screening of approximately 400 journals. Reprints of most were quickly obtained and added to the Center's research reference materials, which now number

more than 40,000 items. This information was provided the staff of the Center for informational uses and to other parts of the Institute for other purposes, particularly the Analysis and Reports Section of Extramural Programs and the Geographic Disease Studies of the Epidemiology and Biometry Program.

Cardiovascular reference materials, comprised of index volumes, texts, reports, journals, and source files of selected items on subjects of special interest, were broadened. Frequently consulted, these materials provided ready access to subject matter needed for a variety of informational purposes.

Demands made on the information resources activity have increased. Enlargement and improvement of resources will be evolved as space, equipment, and staffing permits, and as informational program requirements are further defined.

Conclusion

In terms of publications distributed, press releases issued, public inquiries handled, and other measures of informational activity, fiscal year 1968 was a good year for HIC. But there is still far to go toward full compliance with the directives set forth for the Heart Information Center by the Congress as part of the National Heart Act.

Fiscal 1968 was also a year of reorganization aimed at increasing the output of useful information and at providing opportunities for continued development of the information staff. Reorganization has been gradual and is not yet complete. Its primary focus has been the improvement of present information programs rather than the creation of new ones; continued staff development rather than staff expansion. The goal is a nucleus of well-executed information programs and highly qualified, properly placed people that will make possible both the continued growth of on-going programs and orderly expansion into heretofore neglected areas.

EPIDEMIOLOGY AND BIOMETRY

AH-MI PROGRAM

PROGRAM

RESEARCH

ANNUAL REPORT OF EPIDEMIOLOGY AND BIOMETRY

July 1, 1967 through June 30, 1968

REPORT OF ASSOCIATE DIRECTOR FOR EPIDEMIOLOGY AND BIOMETRY

The major research activities of the Epidemiology and Biometry Program during the period July 1, 1967 through June 30, 1968 have been concerned with increased responsibilities for the professional supervision of epidemiological studies and clinical trials conducted as direct research programs or as cooperative research programs with outside investigators.

During the year, each of the major epidemiological studies in Framingham, Israel, Yugoslavia, Puerto Rico and Honolulu has reached its full operational level and these studies are beginning to provide considerable data to extend knowledge about the major cardiovascular diseases with greatest emphasis on coronary heart disease.

The Coronary Drug Project, a national clinical trial of four lipid lowering drugs to determine their effectiveness in reducing mortality and recurrences of myocardial infarction, has progressed to an enrollment of 3,781 subjects as of May 3, 1968.

The involvement in these large undertakings has absorbed the major time of the professional staff of the Epidemiology and Biometry Program, however, some added attention has been directed to extend into studies of cerebrovascular disease, hypertension and obstructive pulmonary disease where these could be incorporated with other epidemiological projects.

Some progress has also been made in the planning of new activities, such as the Urokinase-Pulmonary Embolism Clinical Trial in cooperation with the National Blood Resource Program.

Several changes in senior professional staff have occurred requiring reassignment of responsibilities. Efforts toward recruitment have been made to maintain continuity of the research programs. Mr. Jerome Cornfield retired as Chief of the Biometrics Research Branch on December 31, 1967. His position has been assumed by Dr. Max Halperin, the Acting Chief of the Branch. The loss of Mr. Dean Krueger who accepted an increased grade with the National Center for Vital Statistics has removed an additional valuable professional. His responsibilities for the U.S.-U.K.-Norway Cardiorespiratory Study have been assumed by Mr. Eugene Rogot and the project is continuing.

Other senior staff who will be leaving are Dr. David C. Miller, Deputy Chief of the Honolulu Heart Program and Dr. Ralph S. Paffenbarger, Chief, Field Epidemiological Research Section, who will be retiring August 1, 1968. No replacement has yet been identified for Dr. Miller, however, Dr. Manning Feinleib will be continuing with the Epidemiology and Biometry Program after his initial two year appointment in September and will become the Chief of the Field Epidemiological Research Section on its relocation to Bethesda after Dr. Paffenbarger's retirement.

A formally constituted Epidemiology and Biometry Advisory Committee was appointed during the year and two meetings have been held to begin a systematic review and advisory function for the Director of the National Heart Institute relating to the direct research program in Epidemiology and Biometry as well as to maintain a general assessment of research in this field. The first detailed review was undertaken to determine the future of the Framingham Study in relation to its original objectives and its further research potentials. The Committee has prepared a report on the basis of a project site visit and full committee discussion recommending continuation of the study for an additional ten years to take advantage of the high rate of new events of coronary disease in its various manifestations, cerebrovascular disease and peripheral vascular disease which can now be anticipated in the cohort which is now between the ages of 50-79. Many specific suggestions have been made regarding statistical needs, epidemiological needs and laboratory shortcomings. Some of these are already receiving attention, however, the lack of qualified personnel available for assignment to Framingham and the better salaries offered by medical schools have resulted in the loss of three superior candidates who had interest in the Framingham Study.

In addition to this general summary of activities during the report period, the following specific items are highlighted:

1. The Coronary Drug Project completed its organizational stages to bring into active participation a total of 55 clinics from which a total quota of 8,400 proven myocardial infarction patients will be sought for allocation to the four lipid lowering drugs being tested. In addition to the 3,781 subjects already allocated to one of the drug regimens or to the placebo control, there are 921 patients being assessed for entry in the baseline period. Patient recruitment remains the most difficult problem that will need to be pressed, however, the general project is proceeding with relatively few major difficulties.

The observed mortality in the placebo group is close to the six per cent per year originally calculated. The dropout rate is lower than predicted with only 31 patients having dropped out as of May 1968.

2. The final report of the Diet-Heart Feasibility Study was published in Circulation in September 1967. Biometrics staff provided the central statistical services for this study and also have been participating in further deliberations of the Diet-Heart Review Panel to consider recommendations for possible full scale primary or secondary diet studies.

3. The Biometrics staff have accepted responsibility for the Coordinating Center activities of the proposed Urokinase-Pulmonary Embolism Clinical Trial being developed by the National Blood Resource Program. The protocol, manual of operations and forms have been prepared and the preliminary test of operations is about ready to begin.

4. Active consultation of the Biometrics staff with intramural investigators, the Artificial Heart - Myocardial Infarction Program and outside investigators, has continued and the degree of this involvement is limited only by the commitments to direct or collaborative projects already under way. The specific problems identified in these consultations have resulted in purely methodological research as a valuable offshoot of the original research activities.

5. The prospective epidemiological study conducted at Framingham has accumulated 442 known deaths among men and 300 deaths among women to the date of preparation of this report. There have been 437 male cases of coronary heart disease and 237 female cases identified to this period of follow-up. The epidemiological characteristics of angina pectoris, coronary insufficiency, myocardial infarction and sudden death are beginning to be differentiated.

   By the completion of the 20 year follow-up period an estimated 960 deaths, 810 cases of coronary heart disease, 170 brain infarctions and 120 cases of intermittent claudication will be available for intensive study in relation to their antecedent characteristics in contrast with the same aged controls.

   The Framingham Study continues to provide a reference population of well established characteristics against which all of the other population studies of the Epidemiology and Biometry Program can relate for inter-study comparisons.

6. A more systematic effort was made to document the status of follow-up of the original total Framingham cohort of 5,209 subjects. This follow-up is reassuring in the degree of completeness of this follow-up. 4030 subjects representing 86.1% of the living subjects took the eighth biennial examination. An additional 531 subjects had died by the time of the eighth examination. Of the remaining living 648 subjects, 527 had taken more than one previous examination leaving a residual 121 living subjects (2%) on whom little or no further medical information has been obtainable.

7. The epidemiological studies conducted by Dr. Paffenbarger based on the original medical and scholastic records of about 50,000 former male Harvard and University of Pennsylvania students who have been followed for their subsequent morbidity and mortality experience have produced additional evidence of precursors of hypertension, suicides and accidental deaths. (The latter activities supported by NIMH).

   The six precursive characteristics found among 671 college students who subsequently developed hypertension as contrasted with matched control students who remained free of diagnosed hypertension were: higher (yet normal) systolic and diastolic levels of blood pressure during college, faster pulse rate, greater weight for height, history of parental hypertension, first born status and less participation in sports and in exercise.

   The strongest precursive characteristic of future suicide cases (379 studied) was found to be the loss of the father through death or marital separation before the student entered college. Other characteristics found more frequently among future suicide cases than in their matched controls were the history of secondary boarding school, cigarette smoking, college drop-out and self-assessed personality characteristics of insomnia, worries, self consciousness and mood swings.

   Study of 790 accident decedents from this group revealed the precursive pattern during college of boarding school background, cigarette smoking, alcohol consumption and failure to graduate from college. Death rates from accidents were lower among students who reported themselves subject to exhaustion, worries and self consciousness - the traits found for suicide cases. While these findings are not an area for further pursuit by the Heart Institute, they will be published for their potential interest to other Public Health programs.

8. The collaborative P.L. 480 project on ischemic heart disease and hypertension in Israel involving a stratified sample of 10,000 government and municipal employees aged 40 and over, has progressed to the third and last cycle of examinations from which standardized incidence data will be available for detailed analysis. The project has been approved for continuation until January 1, 1970 financed from counterpart currencies.

Problems in obtaining computer analysis of tape-recorded electrocardiograms have delayed the final classification of subjects for the standardized incidence measurements. Direct cardiologist readings of the ECG's are being returned for the current examination cycle to avoid dependence on the computer resources previously anticipated as a boon for expediting mass population studies. A substantial contribution is anticipated from the high quality data being generated in this project, however, no incidence data are yet available.

9. The prospective epidemiological studies of coronary disease, hypertension and cerebrovascular disease being conducted between the Atomic Bomb Casualty Commission (ABCC) study in Hiroshima, Japan and the staff of the Geographical Pathology Section of the Epidemiology and Biometry Program located in Honolulu have achieved closer coordination as a result of direct meetings between the responsible investigators approximately at six month intervals.

   The study protocol has been standardized in all major areas and further adjustments are still being made for areas identified to have possibly significant discrepancies.

   The Honolulu Study has now examined over 7,500 Japanese Americans of the total eligible population of 9,888 men between the ages of 45-64. A re-examination cycle has begun on the subjects who entered the study in 1966 to coincide with the two year cycle of the Hiroshima program.

   Extensive tabulations are being planned to allow inter-study comparison of data between the two ongoing projects. A possible further grant-funded study of Japanese descent subjects in the San Francisco area has been coordinated with these two population studies to allow maximum interstudy comparisons of these similar ethnic groups living in diverse natural circumstances.

10. The prospective epidemiological study of coronary heart disease and hypertension in Puerto Rico has progressed to more than 8,000 subjects examined from the census enumerated population of the rural and urban areas served by the University of Puerto Rico Medical Center. A 70 per cent overall response rate has been achieved with a goal of an 80 per cent response desired for the total population in the 45-64 age group of males in the study.

    The overall prevalence of definite myocardial infarction remains substantially lower than would be expected on the basis of the National Health Survey findings: 4.7 vs 19. per 1000 at age 45-54 and 6.0 vs 43. per 1000 at age 55-64.

    Some of the population characteristics associated with this low level of mortality and prevalence of coronary heart disease are summarized in this report. Measurement criteria will allow comparison with data from the Framingham population to link the range of biological variables to the values found in the high coronary prone population.

A substudy of lipoprotein electrophoresis characteristics in this population has been established based on the training of the medical officer by Dr. Robert Levy according to the techniques used in the Laboratory of Molecular Diseases. Over 1000 fasting subjects have had serum electrophoresis to allow classification by the Fredrickson-Types in conjunction with cholesterol and triglyceride levels. This should provide data of the prevalence and significance of these lipoprotein types in the general population.

11. The P.L. 480 project in Yugoslavia studying ischemic heart disease and hypertension in two communities, one Moslem, the other Christian, has completed the re-examination cycle for the measure of incidence of new disease within these two population groups of men aged 35-64 at the time of their first examination in 1964.

    Preliminary trends of incidence were appearing to be low, however, the most recent review of all abnormal electrocardiograms, deaths and reported clinical cases during the 2 year interval between examinations reveals an astonishingly low incidence of myocardial infarction of approximately 1 per 1000 per year or one tenth that found in the Framingham population in this age group.

    While this project lacks the access to all of the more sophisticated laboratory measurements available in the other population studies, the gross population characteristics are so clear that a more valuable contribution may be found from this project than originally anticipated. Extension of the study with counterpart currencies has been approved until December 1970.

A general criticism raised by the Epidemiology and Biometry Advisory Committee has been the almost exclusive concentration of research on the problem of coronary disease with little attention being given to cerebrovascular disease, hypertension, peripheral vascular disease, congenital heart disease or cardio-respiratory diseases. This is a valid criticism but this concentration has intentionally been made to speed the answer to existing hypotheses through use of these unusual population groups. Time trends in coronary disease are unpredictable for underdeveloped populations so that these investigations are needed before these natural differences disappear.

The existing population studies have the desired range of diversity to test present hypotheses and potentially any new ones which may appear in the near future. The extension to include cerebrovascular disease, peripheral vascular disease and obstructive pulmonary disease has been made in each of these populations where this has been compatible with the local capability and interests.

A substantial experience has been gained in conducting large scale epidemiological studies and this has provided a natural base for undertaking large scale clinical trials such as the Coronary Drug Project.

It is anticipated that substantial contributions can be forthcoming from the two areas of epidemiology and mass clinical trials. An urgent need is to build and retain a strong professional research group with interest in these areas of investigation since the difficulties of successful accomplishment of such projects have discouraged young investigators from interest in these fields.

Serial No. NHI-EB-2
1. Epidemiology and Biometry
2.
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title:	Medical Liaison with the Coronary Drug Project
Previous Serial Number:	NHI-CS-2
Principal Investigator:	Dr. Howard J. Marsh, Epidemiology and Biometry, NHI, served as Medical Liaison Officer for the Coronary Drug Project. Note: This refers only to services provided by the Epidemiology and Biometry Section. The study itself is being conducted by grantees, including Dr. Robert W. Wilkins, Chairman of the Policy Board; Dr. Jeremiah Stamler, Chairman of the Steering Committee, Dr. Christian R. Klimt, Director of the Coordinating Center and clinician-investigators in 55 participating grantee institutions.
Cooperating Units:	1) Biometrics Research Branch, NHI, (Dr. Max Halperin and Mr. Fred Ederer) for statistical liaison, 2) Extramural Programs, Special Research Projects Branch, NHI, (Dr. William H. Goldwater, Dr. Jerry T. Guy, and Dr. Edward Carey) grants management aspects, 3) Central Laboratory, National Communicable Disease Center, Public Health Service, (Dr. Gerald Cooper, Dr. Alan Mather, and Dr. Adrian Hainline) for performance of biochemical blood studies of study patients, 4) Drug Distribution Center, USPHS Supply Service Center (Mr. Salvatore Gasdia) for the procurement and distribution of study drugs, 5) Heart Information Center, NHI, (Mr. William E. Sanders and Miss Sandra L. Kamisar) for assistance in developing study publicity and stimulating patient recruitment.

Man Years:

Total:	1.5
Professional:	1.0
Other:	0.5

Project Description:

Objectives: The Medical Liaison Officer is the Epidemiology and Biometry Program's representative to the Coronary Drug Project. He serves as the chief medical link between this grant-supported study and the National Heart Institute. His function is to assure that full cooperation and communication exists between this study and the administration of the National Heart Institute.

The Medical Liaison Officer serves as recording and executive secretary for the Policy Board and Steering Committee of this study. In addition, he is a member of the Criterion Subcommittee, Subcommittee on Data Analysis, the Safety Monitoring Committee and the Editorial Review Board.

He is also responsible for working with the Coordinating Center at the University of Maryland, Baltimore, Maryland with the Central Laboratory at the National Communicable Disease Center, Atlanta, Georgia, and with the USPHS Supply Service Center at Perry Point, Maryland.

The principal objectives of this study are threefold: 1) To determine the ability of four lipid-lowering drugs to reduce mortality and recurrences from myocardial infarction among men who have already experienced one or more proven myocardial infarctions. 2) To determine whether the degree to which these drugs lower serum lipids is correlated with any effect on mortality and morbidity rates. 3) By studying the control group as intensively as the treatment groups, to gain further information on the long-term prognosis of myocardial infarction.

Methods Employed: The project is a cooperative clinical trial involving random and double-blind assignment of patients to one of six drug regimens. The patients will be men aged 30 to 64 years who have survived one or more myocardial infarctions. After allocation to treatment, patients will be followed at the participating clinics for five years or until death. It is estimated that in order to establish unequivocally a 25 percent relative reduction in five-year mortality rate, 8,400 patients will be required.

Major Findings: Recruitment of participating clinics for the Coronary Drug Project was completed on June 1, 1967. A total of 55 clinics are now operational and actively recruiting patients.

As of May 3, 1968, some 3,781 patients have been enrolled in the study and allocated to therapy. An additional 921 patients are being followed in the baseline period prior to treatment allocation.

The patient recruitment goal of this study remains to enroll 8,400 patients by June 30, 1969. Local and regional publicity originating from the individual clinics with assistance from the Medical Liaison Officer and the Heart Information Center has proven to be the most effective method for recruiting study patients.

Patient adherence to their prescribed medical regimen varies with the assigned treatment. Present experience indicates that the highest adherence (83 percent) is achieved in the placebo-treated group whereas the lowest adherence (71 percent) is achieved in the group on high doses of estrogen.

All critical endpoint data fromthis study are being reviewed on a quarterly basis by the Safety Monitoring Committee and the Policy Board. The primary endpoint is mortality and to date no significant differences have been found between the treatment groups. The observed mortality rate among placebo-treated patients has shown agreement with the expected rate of six percent per year which is based on the reported follow-up of patients with a presumably similar diagnosis and prognosis.

The observed dropout rate has been considerably less than the predicted rate which was also six percent per year. As of May 3, 1968 only 31 patients have been reported as study dropouts.

Significance to Bio-Medical Research and the Program of the Institute: The Coronary Drug Project has been developed to meet a specific need in the field of atherosclerosis research. Drugs are available which effectively reduce the concentration of blood cholesterol and other lipids. Although elevated levels of these blood lipids are closely associated with the occurrence of coronary heart disease, proof is lacking that active intervention to reduce the levels of cholesterol and other blood lipids will improve the survival rate of men who have coronary heart disease. The demonstration of such an effect would have significance, both for atherosclerosis research and for the therapy of coronary heart disease.

Proposed Course of the Project: The study is scheduled to complete patient enrollment by June, 1969. Each patient will be followed for a period of five years after enrollment. At present the study is on schedule.

PHS-NIH
NATIONAL HEART INSTITUTE
July 1, 1967 through June 30, 1968
EPIDEMIOLOGY AND BIOMETRY

BIOMETRICS RESEARCH BRANCH

The work of the branch continues to center about intra and extra-mural collaborative activities.

During the year Jerome Cornfield retired from government service and his place as branch chief was taken by Dr. Max Halperin in an acting capacity. Cornfield continues to be a consultant to Epidemiology and Biometry. In September 1967 Dean Krueger left the branch for a post elsewhere and his responsibilities in connection with the British-Norwegian migrant study have been assumed by Eugene Rogot. Jacob Lieberman returned from his stint as statistical advisor in residence for the Hawaii study and Harold Kahn will remain in Israel for another year (to June 1969).

Early in this fiscal year Mr. Ederer and his associates completed their efforts as Central Staff for the Diet Heart Feasibility Study. Although a final report was presented before the American Medical Association in late June 1967, there were extensive later revisions which required a sustained effort in analysis, re-writing and review through September 1967. Despite the fact that this work was terminated as a major area of effort, Fred Ederer and Max Halperin are participating in the deliberations of the Diet Heart Review Panel both as members and in providing appropriate statistical inputs for the panel. The assistance of Joan Gurian should be mentioned in this latter connection.

The NHI-GHA study of prognosis in coronary heart disease, initiated by Fred Ederer, in August 1966, was terminated in August 1967. Although it is believed there is considerable need for studies of this sort, the year's experience with GHA was most discouraging. The main difficulty was a gross underreporting of cases, which appeared to reflect a basic lack of interest of GHA physicians. This was believed serious enough and so unlikely to be overcome as to preclude pursuing further efforts at this time.

In September 1967, the branch was selected to provide coordinating center services for the proposed Urokinase-Pulmonary Embolism trial. Fred Ederer is responsible for this effort and center personnel including Zelda Federman and Christine Cole have devoted a major portion of their time since then to the design of forms and working with appropriate committees in the preparation of a manual of operations and protocol. Ederer and Dr. Max Halperin have participated extensively in the committee work required to reach the present state of near-readiness for the beginning of the trial. It is expected that a "shake-down" phase will begin shortly and that soon thereafter the trial will begin.

Dr. Max Halperin and Fred Ederer are participating in the work of several of the committees of the Coronary Drug Project, which is now well advanced with approximately 3500 patients enrolled through April 15, 1968.

Liaison is being continued with the Coronary Drug Project coordinating center. Currently, discussions in depth are being held between coordinating center personnel and the Biometrics Branch to clarify the appropriate data analysis for the study. Dr. Howard Marsh, NHI Medical Liaison Officer for the study is participating actively in these discussions. They promise to continue for some time since appropriate forms of analysis for these data do not follow from standard theory.

The Veterans Administration Study on smoking and health continues to be maintained on a routine basis. Zelda Federman, since the middle of the year, has been assisting in this task.

As mentioned last year we now have a tape record of the first seven biennial examinations at Framingham. This has allowed a considerable expansion in the tabulating program. As a result of this expansion, work on a monograph on the Framingham Study has been initiated by Tavia Gordon. Several sections have been completed covering a description of the cohort and follow-up, changes in characteristics over examinations and incidence of cardiovascular diseases. Further tabulations are in preparation. Because of continuing concern about the use of discriminant function theory in the face of the non-normality of Framingham risk factor distributions, comparison was made with a straightforward but much more laborious regression analysis; this latter analysis does not assume normality of distribution. Agreement was excellent which further justifies the use of the discriminant function approach. During the last year, Biometrics Branch personnel have been meeting monthly with Framingham investigators to review progress, discuss current problems and plan future activities. These meetings have been most helpful to the progress of the study.

Jeanne Truett and Tavia Gordon are continuing close liaison with the Puerto Rico study. A copy of the Puerto Rico data tape has been obtained allowing exploratory tabulations to be done in Bethesda. Two year follow-up examinations should begin about July 1, 1968 running concurrently with remaining initial examinations. Consultation on content of these examinations, form design and data processing continue to be an important contribution of the branch to the study.

Since his return from Hawaii, Jacob Lieberman has continued work related to the Honolulu study. He has assisted in the design of the re-examination forms for the study and has been working with the Hawaii tapes running tabulations here. Since the tape is geared to a CDC computer it has been convenient to use the CDC computer in the Clinical Center to which we have been given access. Lieberman has also been working with Dr. Al Roberts on studies of obstructive pulmonary disease. This has involved writing a general purpose computer program for both the Framingham and Honolulu studies; this program has been checked out and a number of tabulations and analyses have been run. Preliminary reports on the work should be forthcoming shortly.

Processing and analysis of British-Norwegian migrant study data continues under the supervision of Eugene Rogot. Analysis of initial data on Norwegian migrant mortality from Coronary Heart Disease shows that mortality is higher among those who migrated to the U.S. at young ages than

among those who came at older ages. This appears to reflect differing lengths of exposure to environments associated with low and high coronary disease mortality. Preliminary tabulations on British migrants do not show this gradient with age at migration. Additional analyses are being planned on prevalence of symptoms in relation to place of residence, air pollution and history of various diseases. A current difficulty related to mortality follow-up is that NCHS will no longer be able to provide copies of death certificates. This affects follow-up from 1967 onwards. Practical ways of resolving this problem are being investigated.

Eugene Rogot's study of seasonal patterns of mortality in Memphis, Tennessee is in the preliminary stages of analysis and it is anticipated that work on this project will terminate in the next fiscal year; however tentative findings to date suggest it may be desirable to do a similar study in a northern city. Preliminary analyses suggest, among other things, an inverse relationship between average temperature on day of death for coronary heart disease, stroke, and all other cardiovascular disease. The relationship for coronary heart disease appears to be independent of associated conditions whereas the relationship for stroke appears dependent on other cardiovascular disease.

Joan Gurian has spent a major part of her time this fiscal year working with NHI-LM personnel on the conversion of records of the study on familial hyperlipoproteinemia to ADP equipment. This has involved designing code sheets for recording the data in such a form that they may easily be transferred to IBM cards by CDPB personnel. It has also required an extensive programming effort of a complex nature because of the need to retrieve all familial relationship from the data file. In addition programs have been created to prepare several types of reports from these data and several such reports have been made. Miss Gurian also supervised the review of code sheets which was performed by BRB personnel prior to punching and subsequent storage on magnetic tape. Data on about two thousand individuals involving anywhere from three to fifty IBM cards (80 to 4000 items of information) per individual have been processed so far. The study continues to add more individuals and data both of which will be added to that already on tape. It is anticipated that efforts in the near future will be largely devoted to appropriate analyses of these data.

Morton Raff, in addition to his day to day duties as consultant to the Myocardial Infarction Branch, AHMI, has participated in the review of a number of research proposals for Myocardial Infarction Research Units (MIRU's) and for studies of non-atherosclerotic methods of producing myocardial infarctions in animals. He also served on a task force for the study of sudden death.

One possibility for future activity of the branch is in a cooperative effort with AHMI in setting up a circulatory assist device register (CADR). A tentative proposal for this work has been written by Fred Ederer, who has also held a number of discussions with AHMI personnel about such an enterprise. Planning has also been initiated for possible morbidity and mortality surveys in conjunction with the 1970 census by Dr. Feinleib and Tavia Gordon.

In the area of training, study seminars for BRB personnel are planned starting this summer in Stochastic Processes and Enzyme Kinetics; the latter seminar will be conducted by John Mullooly who has been quite active in assisting investigators in this area.

It is to be noted that purely methodological statistical research occupies the efforts of various members of the branch, in connection with issues raised in the course of consultation, clinical trials and epidemiological studies as well as with issues of general statistical interest. This is evidenced in the list of branch publications as well as in several of the project reports.

Finally it should be mentioned that work continues on several projects initiated last year by Dr. Feinlieb, such as the serum copper investigation and autopsy study with Framingham and the genetic study. It now appears the latter study will utilize to good advantage the NAS-NRC twin panel to evaluate the relative contribution of environmental and genetic factors to the development of cardiovascular diseases and to the level of risk factors in cardiovascular diseases. Dr. Feinlieb's projects are being nominally terminated this year due to his imminent transfer to become Chief, Field Epidemiological Research Section (FERS), Epidemiology and Biometry, NHI. Thus his projects now reported from BRB will be reported next year from FERS.

Consultation

Christine Cole consulted with:

- Dr. Eugene Braunwald of NHI on the Cooperative Study on Cardiac Catheterization. Processing of data from this study designed to evaluate the techniques, complications and hazards of right and left heart catheterization was completed in the summer of 1967, and the final report will be published as a supplement to Circulation in June 1968.

Dr. Manning Feinleib consulted with:

- Dr. Sidney J. Cutler on epidemiologic studies of hormonal factors in breast cancer.

- Dr. Jack Hall on prognosis after myocardial infarction.

- Dr. John C. Bailar on effects of estrogen therapy on cardiovascular disease mortality in men with cancer of the prostate.

- Dr. John C. Bailar on organization and progress of the Third National Cancer Survey.

- Dr. Noel D. List and Marvin Schneiderman on epidemiologic models in cancer of the breast.

Joan Gurian consulted with:

- Dr. Philippe Gignon, NHI-LCP, on determination of kinetic constants using a least square method to fit the Michaelis-Menton model, to describe sex-differences of these constants for the N-Demethylation of Ethylmorphine by rat liver microsomes.

- Dr. William G. Banfield, NCI-LP, on analyses of data describing the growth pattern of the hamster. Tables were prepared showing the body-weight and thymus weight by age, the testis weight and seminal vesicle weight by body-weight and season, and the weight of other principal organs by body-weight.

- Dr. L. Anderson, NIAID-LP, on analyses of data from several Schistosoma strains relating to egg-production per worm and time-course of such production.

- Dr. Guillermo Pachecco, NIAID-LP, on analyses of data bearing on the relationship between the concentration of Dipetalenemia Witei microfilaria in the blood of gerbils (as mammalian host) and the

intake of microfilaria by ticks (as the arthropod host) as well as subsequent concentration of larvae in the tick.

- Dr. Charles J. Glueck, NHI-LMD, on studies of the correlation between Glucose-Tolerance, Insulin Level, Triglyceride level in patients with various types of Hyperlipoproteinemia.

- Dr. Ronald G. Evens, NHI-CE, on analysis of data relating to the repression of mineral content of bone as measured in vivo by monoenergetic photon beam transmission on the width of the bone.

Dr. John Mullooly consulted with:

- Dr. John Folk, D-LB, on studies of the biochemistry and mechanism of action of transglutamase. More complete results on the role of calcium ion have been achieved by studies of the hydrolysis reaction and the trimethylacyl enzyme.

- Dr. Edgar Caldwell, University of Vermont and Dr. Ralph Powell, C-PA, on studies of experimental induction of interstitial emphysema in rabbits.

- Dr. Henry Neal Coleman, H-C, on studies of the determinants of oxygen consumption of isolated heart muscle. In particular the relative effects of tension development and external work on the energy utilization of isolated heart muscle were studied.

- Dr. Sheldon Spector, BS-LVR, on studies of the interaction between virus and antibody.

- Dr. Peter Dempsey, H-C, on studies of the effect of denervation of heart muscle on its response to various drugs such as isoprel and norepinephrine.

- Dr. R. Darryl Fisher, H-Surg., on studies of factors related to operative and postoperative survival of patients having heart valve replacement.

- Dr. Peter Pool and Dr. Lynn Skelton, H-C, on studies involving the relationship of factors involved with energy utilization in cardiac muscle, in particular chemical studies of the change in the level of ATP and CD. Normal, Heart Failure and Hypothyroid groups of muscles were compared.

Morton Raff consulted with:

- Dr. Donald S. Fredrickson, NHI-OD, on international comparisons of heart disease rates, with special attention to the effect on future U.S. population of reducing American incidence of coronary disease to that of Sweden. Material provided by Mr. Raff was used by Dr. Fredrickson in a talk before the American College of Cardiology, which is to be published in the American Journal of Cardiology. Mr. Raff is also preparing a manuscript giving details of the method of projection.

- Dr. Morrison Hodges, Johns Hopkins University School of Medicine, on methods of analyzing systolic time intervals in healthy and diseased patients. This is part of the work of the Johns Hopkins MIRU.

Eugene Rogot consulted with:

- Dr. Carol E. Steinhart, Division of Research Grants, on statistical analysis of data related to hospitals receiving grants. Factors studies as predictors of grant status were size of hospital, type of control and affiliation status.

Publications

Blackwelder, W.: On Constructing Balanced Incomplete Block Designs from Association Matrices with Special Reference to Association Schemes of Two and Three Classes. Journal of Combinatorial Theory. In press, 1968.

Feinleib, M.: Breast Cancer and Artificial Menopause: A Cohort Study. J. National Cancer Institute. In press, 1968.

Gordon, T.: Further Mortality Experience among Japanese Americans. Public Health Reports. 82: 973-84, November 1967.

White, E.L., and Gordon, T.: Selected Aspects of Health and Aging in the U.S. Proceedings of Colloquium on Health and Aging. Seventh International Congress of Gerontology.

Schumacher, H., Blake, D.A., Gurian, J., and Gillette, J.R.: A Comparison of the Teratogenic Activity of Thalidomide in Rabbits and Rats. Journal of Pharmacology and Experimental Therapeutics. Vol. 160, No. 1, 1968.

Halperin, M., Rogot, E., Gurian, J., and Ederer, F.: Sample Sizes for Medical Trials with Special Reference to Long Term Therapy. J. Chronic Dis. Vol. 21, pp. 13-24, January 1968.

Halperin, M., Rastogi, S.C., Ho, I., and Yang, Y.Y.: Shorter Confidence Bands in Linear Regression. J. Amer. Stat. Assoc. Vol. 62, pp. 1050-1067, September 1967.

Halperin, M., and Gurian, J.: Confidence Bands in Linear Regression with Constraints on the Independent Variables. J. Amer. Stat. Assoc. In press, 1968.

Folk, J.E., Cole, P.W., and Mullooly, J.P.: Mechanism of Action of Guinea Pig Liver Transglutaminase IV, The Trimethylacyl Enzyme. J. Biol. Chem. 242: 4329-333, 1967.

Folk, J.E., Cole, P.W., and Mullooly, J.P.: Mechanism of Action of Guinea Pig Liver Transglutaminase V, The Hydrolysis Reaction. J. Biol. Chem. 243: 418-27, 1968.

Mullooly, J.P.: A One Dimensional Random Space-Filling Problem. J. Applied Prob. To appear August 1968.

Truett, J., Cornfield, J., and Kannel, W.: A Multivariate Analysis of Risk of Coronary Heart Disease in Framingham. J. Chron. Dis. Vol. 20, pp. 511-24, 1967.

Unpublished Papers and Talks

Ederer, Fred: The National Diet-Heart Study. A talk given to the Washington Statistical Society, June 1968.

Feinleib, M.: Breast Cancer and Artificial Menopause: A Cohort Study. Presented at the 95th Annual Meeting of the American Public Health Association, October 22-27, 1967.

Feinleib, M.: Models of Breast Cancer. Discussion. Presented at the Annual Meeting of the American Statistical Association and Biometric Society, December 27-30, 1967.

Feinleib, M.: Epidemiologic Evidence for Hormonal Factors in Breast Cancer. Presented to the Western New York State Epidemiologic Society, January 5, 1968.

Feinleib, M.: The Stable Disease Model. Presented at the Sixth Annual Symposium on Biomathematics and Computer Science in the Life Sciences, March 14-16, 1968.

Kannel, W.B., Tedeschi, C.G., and Feinleib, M.: Overweight and Coronary Heart Disease: Epidemiologic-Autopsy Correlation. The Framingham Study. Presented at the Third Annual Joint Meeting of the Commissioned Officers Association and the Clinical Society of the U.S.P.H.S., March 25-29, 1968.

Feinleib, M.: Cancer and Fetal Mortality as a Sequel of Fetal Irradiation. Discussion. Presented at the First Meeting of the Society for Epidemiologic Research, May 10-11, 1968.

Feinleib, M.: Estrogen Therapy and Cardiovascular Disease: A Review of the VA Prostate Cancer Study.

Gordon, T.: The Framingham Study. A talk given to a Dept. of Chronic Diseases Seminar, Johns Hopkins University, School of Hygiene and Public Health, February 1968.

Halperin, M.: Confidence Bands in Linear Regression. An invited paper at the Gordon Research Conference in Statistics and Chemistry, July 1967.

Halperin, M.: Confidence Bands in Linear Regression, State University of New York at Buffalo, Dept. of Statistics Seminar, November 1967.

Halperin, M.: Confidence Bands in Linear Regression, U. of Md., Dept. of Math. Seminar, March 1968.

Mullooly, J.P.: A One Dimensional Random Space-Filling Problem. A paper presented at Institute of Math. Stat., 1967 annual meeting, December 1967.

Mullooly, J.P.: A One Dimensional Random Space-Filling Problem. A talk given to the Statistics Dept. Seminar, Oregon State U., April 1968.

Truett, J.T.: A Multivariate Analysis of Risk of Coronary Heart Disease. A talk presented at the annual meeting of the American Statistical Association, December 1967.

Participation in outside committees and organizations:

Fred Ederer:

served as a referee for the Journal of the American Statistical Association.

served as a member of the National Heart Institute Diet-Heart Review Panel.

served as a member of the Coronary Drug Project Committees on Data Analysis, Evaluation of Treatment Effects, and Safety Monitoring.

served as a member of the Urokinase-Pulmonary Embolism Study Steering Committee, Protocol Committee and Committee for Standardization of Methodology and Data Analysis.

served as a member of the NIH Equal Employment Opportunity Program Planning Council.

taught statistics at American American University.

Manning Feinleib:

served as a referee for the Journal of the American Statistical Association, Journal of the National Cancer Institute, Biometrics, and the Journal of Theoretical Biology.

Tavia Gordon:

served as a member of the Pooling Committee of the AHA Council on Epidemiology.

Max Halperin:

served on the Biostatistics Fellowship Panel of the Division of Research Grants.

served as a referee for the Journal of the American Statistical Association, Biometrics, Technometrics and The American Statistician.

served as a member of the National Heart Institute Diet-Heart Review Panel.

served as a member of the Steering Committee, Cooperative Study of Drugs and Coronary Heart Disease and the committee on Safety Monitoring.

served as a member of the Committee for Standardization of Methodology and Data Analysis on the Urokinase-Pulmonary Metabolism Study.

was elected a fellow of the Institute of Mathematical Statistics.

served as a session chairman at the Institute of Math. Stat. annual meeting.

Jack Lieberman:

served as a referee for Science.

Dr. John Mullooly:

served as a referee for the Journal of the American Statistical Association.

served as a session chairman, annual meeting of the Institute of Mathematical Statistics, Washington, D.C.

taught enzyme kinetics at Georgetown University.

Morton Raff:

served as a referee for the American Statistician.

taught Economic Statistics at Georgetown University and Probability Theory at the Dept. of Agriculture Graduate School.

Eugene Rogot:

served as a referee for the Journal of the American Statistical Association.

Serial No. NHI-BRB-1
1. Biometrics Research Branch
2. Epidemiology and Biometry, NHI
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Missing Multivariate Observations

Previous Serial Number: NHI-BRB-1

Principal Investigator: Christine M. Cole

Other Investigators: Joan Gurian, Jerome Cornfield

Cooperating Units: Imperial College of Science and Technology, University of London, University of Pittsburgh

Man Years:

Total: -
Professional: -
Other: -

Project Description:

Objectives: To develop a method of drawing conclusions about the parameters of a multivariate normal distribution when not all variables are measured on all individuals.

Methods Employed: The general principle is to use computer methods to develop the likelihood function as a function of all unknown parameters. This in general may involve a larger computer output than can be comprehended. The present attack is to evaluate the function and its derivatives at its maximum value, taking as many derivatives at that point as are necessary to reproduce the function.

Significance to Bio-Medical Research and the Program of the Institute: At present the only safe method for handling experimental or epidemiological studies with missing multivariate observations is to confine the analysis to those on whom all observations have been made. This often results in discarding a large number of expensive observations. This method should therefore permit a more efficient use of observations than is now possible.

Proposed Course: This project continued to be deferred during 1967-68 because of the press of other work. Present indications are that this situation will continue in the foreseeable future. As a consequence, this project is being terminated until further notice.

Serial No. NHI-BRB-2
1. Biometrics Research Branch
2. Epidemiology and Biometry, NHI

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Statistical consultation and liaison with the Cooperative Study of Drugs and Coronary Heart Disease

Previous Serial Number: NHI-BRB-2

Principal Investigators: Jerome Cornfield, Max Halperin and Fred Ederer (Note: The investigators for the study itself, functioning under a grant from the National Heart Institute, include L. G. Berge, M. M. Best, N. H. Galluzzi, J. Marmorston, J. Stamler and S. Baer. Grants have also been awarded to R. W. Wilkins, chairman of the Policy Board, to C. R. Klimt, director of the Coordinating Center as well as to 49 additional clinics.)

Cooperating Units: Dr. H. Marsh, Epidemiology and Biometry, NHI, Medical Liaison Officer for the study; Dr. G. R. Cooper, CDC, BSS, PHS

Man Years

Total:	.17
Professional:	.15
Other:	.02

Project Description:

Objectives: To provide statistical liaison and consultation needed for the effective administration of a multi-clinic study conducted under conditions of double-blind experimental design.

Methods Employed: Statistical consultation. Initially 5 clinics started this study. Additional clinics have been recruited as the study has progressed. A total of 55 clinics are now involved and should meet the sample size requirements (8400 patients). Multi-clinic studies pose problems in coordination, uniformity of adherence to protocol, uniformity of interpretation of instruction, follow-up procedures, forms design and completion, maintenance of quality control. A standard manual of operations, quality control standards for the production of drugs, and measurements of adherence have been developed. Patients are stratified according to pre-determined criteria and assigned, at random, to the various treatments. As the study proceeds, periodic statistical reports regarding deaths, recurrent myocardial infarctions, drop-outs, moves, adherence, etc., are being prepared by the Coordinating Center. At the conclusion of the study, the results will be

evaluated and prepared for publication. Statistical consultation is being and will continue to be provided in all these phases.

Major Findings: None. The first patient was enrolled in March 1966. Approximately 3500 patients had been enrolled through April 15, 1968.

Serial No. NHI-BRB-3
1. Biometrics Research Branch
2. Epidemiology and Biometry, NHI
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Central Staff Services for the National Diet-Heart Study

Previous Serial Number: NHI-BRB-3

Principal Investigator: Fred Ederer (Note: This refers only to Central Staff services provided by the Biometrics Research Branch, the Investigators for the Study itself, who functioned under a grant from the National Heart Institute, are Drs. Stamler, Stare, Keys, Kinsell, Baker and Frantz.)

Other Investigators: Jerome Cornfield, Jerome Green, Joseph Bragdon, Eldon Rice, Eugene Rogot, Christine M. Cole

Cooperating Units: The principal investigators of the Study and the Cleveland Clinic.

Man Years:

Total:	3.50
Professional:	2.25
Other:	1.25

Project Description:

Objectives: To provide the various statistical services needed for the effective administration of a collaborative study conducted under the conditions of a double-blind experimental design.

Methods Employed: Statistical and administrative. The course of the project was divided into four phases.

Phase 1: Statistical consultation on the study design (e.g., size of the sample required, double-blind) which is important to the validity of the inferences to be drawn. Review of proposals for the common protocol to avoid introduction of inadvertent biases and insure uniformity of methods, procedures and forms.

Phase 2: Preparation of a draft of the procedure manual, together with related forms and instructions. First draft of tabulation specifications. Arrangements for the coding and punching of cards and for computer application.

Serial No. NHI-BRB-3
1. Biometrics Research Branch
2. Epidemiology and Biometry, NHI
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Phase 3: Stratification of subjects and assignment of diet groups on a random basis. Receipt of reports and forms from investigators, laboratories and food distributors. Logging in of forms, checking for shipment completeness, editing, coding, punching and filing. The methods are those of a standard data processing operation. Correspondence to clarify discrepancies, expedite tardy reporting, issue instructions and answer questions. Field visits to investigative centers to consult on various problems and to observe adherence to the common protocol. Preparation of interim reports to investigators and to interested officials in the National Heart Institute.

Phase 4: Collaboration of Central Staff with investigators in the preparation of final reports and in the evaluation of the feasibility trial.

Major Findings: Dropouts and exclusions. The dropout rate for the First Study was 9.7 percent, and the exclusion rate (due mostly to non-cardiovascular events) 2.1 percent. The dropout decreased gradually over the first year of study. The dropout pattern for the Second Study was similar to that for the First Study. These findings indicate that the original objective of retaining at least 50% of men as active participants for 5 years is probably feasible. The dropout and exclusion rate for the Extended Study is less reassuring: 8.7 percent for a six-month period. In addition 41% of the men who completed the First Study failed to volunteer for the Extended Study. The dropout rate at the Faribault State School and Hospital was similar to that for the open centers -- largely due to unanticipated transfers -- during the First Study, and lower than that for the open centers during the Second and Extended Studies. A valid inference about the dropout rate in a 5-year study cannot be drawn.

Integrity and feasibility of double-blind design. Findings from specially designed questionnaires indicate that the integrity of the double-blind design was maintained by the open center participants and by research center personnel. The several diet groups were also very similar in body weight, smoking, and blood pressure changes, and dropout patterns. The investigators felt, however, that the double-blind design created less than optimal conditions for a large-scale field trial in an open population: the necessity of producing foods indistinguishable in taste and appearance resulted in a not fully satisfactory control diet, and lack of knowledge of the diets limited investigator, staff and participant motivation, enthusiasm and effectiveness. The double-blind design created few problems at Faribault.

Adherence. Using a subjective and two semi-objective methods, nutritionists at the open centers rated about 25 percent of First Study participants as excellent adherers, 25 percent as poor adherers, and the remaining 50

percent as fair or good adherers.

Serum cholesterol. Serum cholesterol decreases from baseline concentrations on the experimental diets averaged 10 to 11 percent at the open centers and more than 15 percent at Faribault. On the control diet the average decrease was about 2 percent both at the open centers and at Faribault.

Recommendations. Large-scale studies on the prevention of coronary heart disease by dietary means in both free-living American men and in institutional populations should be planned and started as soon as possible. Guidelines for such studies are presented in the report. If possible, studies in free-living and closed populations should be conducted under coordinated scientific and administrative leadership.

Course of Project: During 1964 the first year ("First Study") of the National Diet-Heart Feasibility Study was completed at 5 open centers (Baltimore, Boston, Chicago, Minneapolis, and Oakland), and at one mental institution (Faribault State School and Hospital, Minnesota). At each center, following a baseline period of several weeks, about 200 male volunteers aged 45-54 completed 52 weeks on one of three randomly assigned double-blind diets. The diets varied in the percentage of total calories from fat, the ratio of polyunsaturated to saturated fats, and the amount of dietary cholesterol. Two of the diets were planned to appreciably lower serum cholesterol, and the third was planned as a control diet. The open center participants bought specially manufactured foods from a food center. Periodically throughout the year the men visited a clinic for dietary instruction and a physical examination which included determination of body weight, serum cholesterol, and red blood cell fatty acids. Four times during the year the men kept 7-day food diaries.

Upon completion of the "First Study" in 1964, the subjects were invited to participate in an "Extended Study", and new volunteers were recruited for a "Second Study". The Extended and Second Studies ran concurrently and were completed by May 31, 1965 (except for the Faribault Study which was completed several months later). Some of the experimental diets from the First Study were modified with respect to fat content and cost, and made less demanding for participants and less time-consuming for the investigators.

Significance to Bio-Medical Research and the Program of the Institute:

This study provided basic information relevant to determination of the feasibility of proposed large-scale clinical trials of the effect of diet

manipulation upon incidence of Coronary Heart Disease and is thus of crucial importance in the program planning of the NHI.

Proposed Course of Project: The National Diet-Heart Study has been completed and the final report of the study was published as a supplement to Circulation in March 1968. This project has thus been terminated as such although some of the investigators continue to be involved in activities stemming from the study results.

Article Published in a Periodical:

Co-author: Ederer, Fred: The National Diet-Heart Study Final Report. Supplement Number One. Circulation, Vol. 37, No. 3, March 1968.

Serial No. NHI-BRB-4
1. Biometrics Research Branch
2. Epidemiology and Biometry, NHI
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Least Squares Estimation in Straight Line Regression

Previous Serial Number: NHI-BRB-5

Principal Investigator: Max Halperin

Other Investigators: Joan Gurian

Man Years

Total: -
Professional: -
Other: -

Project Description:

Objectives: To characterize theoretically and numerically the usual least squares estimates of slope and intercept in straight line regression when, contrary to the standard assumption, the independent variables are subject to error.

Methods Employed: Theory of moment generating functions, numerical integration.

Major Findings: No further work has been done on this project during the current year because of the press of other work. As indicated in last year's report we have obtained expressions (either in integral or closed form) for expected values of the usual least squares estimates of slope and intercept as well as of estimated variances and covariance. In addition expressions have been obtained for actual variances and covariances of the estimates and some preliminary programming and computations have been done in preparation for a numerical study of the theoretical results.

Significance to Bio-Medical Research and the Program of the Institute:

The findings mentioned along with some numerical investigations will delineate circumstances under which it is practical to utilize least squares estimates even though the independent variable is subject to error.

Proposed Course: Numerical investigation will be continued for a series of sample sizes to elucidate the relationship of bias of estimate to sample a size and the ratio of the error variance for the independent variables to the variance of true values of the independent variables. Errors incurred

by using least squares estimates of variances and covariance will also be investigated numerically. Preparation of a manuscript for publication in a statistical journal will terminate the study.

Serial No. NHI-BRB-5
1. Biometrics Research Branch
2. Epidemiology and Biometry, NHI
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Relationship of the Use of Tobacco to Health

Previous Serial Number: NHI-BRB-6

Principal Investigator: Tavia Gordon

Other Investigators: Zelda Federman

Cooperating Units: Department of Data Processing and the Veterans Benefit Office, Veterans Administration

Man Years

Total:	0.6
Professional:	0.1
Other:	0.5

Project Description:

Methods Employed: Information concerning residence, occupation, and the use of tobacco has been collected from about 249,000 persons who held U.S. Government Life Insurance policies in December 1953. As each person included in the study terminates a policy, the Biometrics Research Branch is notified by the Veterans Administration. If the policy is terminated as a result of death, the death certificate is obtained. If the policy is terminated for reasons other than death the VA is queried periodically for advice as to whether the individual is still living. Any deaths reported are processed as stated above.

Major Findings: None this period.

Significance to Bio-Medical Research and the Program of the Institute: This study continues to be one of the fundamental sources for information about smoking and health.

Proposed Course: The file is being maintained on a routine basis. Processing is scheduled for conversion from punch cards to tape. Follow-up on death certificate information has been discontinued.

Serial No. NHI-BRB-6
1. Biometrics Research Branch
2. Epidemiology and Biometry, NHI
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Monograph on Cardiovascular-Renal Disease Statistics

Previous Serial Number: NHI-BRB-7

Principal Investigator: Dean E. Krueger

Other Investigators: Jeremiah Stamler, Chicago Board of Health and
I. M. Moriyama, National Center for Health Statistics, PHS

Cooperating Units: National Vital Statistics Division, PHS, American Public Health Association Committee on Vital and Health Statistics Monograph (sponsor)

Man Years

Total: -
Professional: -
Other: -

Project Description:

Objectives: As part of a comprehensive monograph on the epidemiology of cardiovascular diseases, to analyze United States and international morbidity and mortality data on the major forms of cardiovascular-renal disease in terms of magnitude, long-time trends, differences among sub-groups of the population (the sexes, color groups, geographic subdivisions) and socio-economic characteristics related to these differences.

Methods Employed: Compute age-specific and age-adjusted mortality rates by color and sex for eight cause-of-death groups. Prepare estimates for arteriosclerotic heart disease and hypertensive heart disease mortality in the United States for the period 1940 to 1948 as approximations of the classifications used from 1949 to 1960. Analyze U.S. mortality data for 1949-51 and 1959-61 by State, metropolitan status of county of residence, nativity, country of birth, and marital status.

Proposed Course: The principal investigator left NIH early in this fiscal year so that this project was terminated at that time. It might be noted that the monograph will be published under the sponsorship of the Committee on Vital and Health Statistics, American Public Health Association.

Serial No. NHI-BRB-7
1. Biometrics Research Branch
2. Epidemiology and Biometry, NHI
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: A Random Space-Filling Problem in the Crystallization of Polymers

Previous Serial Number: NHI-BRB-8

Principal Investigator: John Mullooly

Man Years:

Total:	.10
Professional:	.10
Other:	--

Project Description:

Objectives: To characterize the semi-crystalline nature of an idealized linear polymer chain in terms of the number of crystalline segments found in a chain.

Methods Employed: Theory of probability generating functions, Theory of Volterra integral equations, Theory of Laplace transforms, Tauberian theorems, Monte Carlo simulation.

Major Findings: Results in addition to those cited last year include results on the asymptotic (i.e. for long chains) higher moments of the number of crystalline segments in a chain and results on the expected number of segments for variations in probabilistic assumptions as to how the segments are placed in the chain. A manuscript embodying principal results so far obtained has been completed and accepted for publication in a mathematical journal.

Significance to Bio-Medical Research and the Program of the Institute: A method is given which unlike methods previously given enables one to obtain asymptotic solutions of the integral equations of certain systems directly from the integral equations of the system. The results and methods employed may have applications to the quantitative characterization of biopolymers.

Proposed Course: It is believed unlikely that further theoretical investigation would be fruitful. As a consequence this project is being terminated; it is hoped to apply results obtained in this work in collaboration with experimental investigators.

Serial No. NHI-BRB-7
1. Biometrics Research Branch
2. Epidemiology and Biometry, NHI
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Article Published in a Periodical:

Mullooly, J.P.: A One Dimensional Random Space-Filling Problem. J. of Applied Probability. To appear August 1968.

Serial No. NHI-BRB-8
1. Biometrics Research Branch
2. Epidemiology and Biometry, NHI
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Cardiovascular and Respiratory diseases among British and Norwegian migrants in the United States

Previous Serial Number: NHI-BRB- 9

Principal Investigator: Professor Donald D. Reid, London School of Hygiene and Tropical Medicine

Other Investigators: Eugene Rogot, NHI, William C. Blackwelder, NHI; Jerome Cornfield, University of Pittsburgh; William Haenszel, NCI; Dr. Peter Lambert, London School of Hygiene and Tropical Medicine; Dr. Einar Pedersen, Dr. Tjorborn Mork, Norwegian Cancer Registry

Cooperating Units: Bureau of the Census; Department of Commerce; National Cancer Institute; National Vital Statistics Division; University of Pittsburgh; London School of Hygiene and Tropical Medicine General Register Office, England, Wales, and Scotland; Norwegian Cancer Registry; Central Bureau of Statistics, Norway

Man Years

Total:	8
Professional:	1
Other:	7

Project Description:

Objectives: To determine morbidity and mortality from chronic respiratory and cardiovascular diseases among British and Norwegian Migrants in the United States and to compare this with corresponding data for native born residents of Great Britain, Norway and the United States. This is part of an investigation to determine reasons for the difference in the incidence of these diseases in the three countries.

Methods Employed: Information on morbidity from cardiovascular and chronic respiratory diseases, residence history, occupation, use of tobacco, and other environmental variables has been collected by two-stage mail questionnaires (a health screen, and a detailed health query) from a sample of 50,000 British and Norwegian migrants in the United States and from a sample of 20,000 U.S. native born. Death certificates for all deaths of British and Norwegian born persons which occurred in 1963 and 1964 in the twelve states sampled for the morbidity survey, and for a 2% sample of deaths

of the native born have been secured from the National Vital Statistics Division. Personal and environmental data about the deceased have been obtained by mail questionnaire from the informant listed on the death certificate; diagnostic data and the nature of evidence supporting them have been obtained from the medical certifier of the death. Data on air pollution and water quality have been obtained from other Federal agencies.

Corresponding morbidity studies in Great Britain and Norway have been carried out on the siblings of the migrants and on representative samples of the resident native population. A sample of death certificates in Great Britain is being secured and questionnaires are being sent to a subsample of medical certifiers.

All causes of death listed on the death certificates and additional diseases reported by medical certifiers to have been present in the last year of life are being coded.

Since much of the information collected in the mortality phase is similar to that obtained in the morbidity phase, it will be possible to analyze death rates with respect to a number of factors. Under this plan, deaths in the entire migrant population rather than only those of persons included in the morbidity sample can be used. This method of analysis is being carried out for 1963 and 1964 deaths, and will include about 13,000 British, 3,000 Norwegians and 15,000 native-born deaths.

A much more detailed mortality analysis is underway for the migrant groups. Under this plan, persons queried in 1962 are considered as cohorts who may be followed for X years with survivorship experience to be measured. Since detailed information is available on cardiorespiratory symptoms, smoking, occupation, income, age at migration and many other factors from the morbidity survey in 1962, cohorts may be distinguished on the basis of these characteristics and analyzed in a prospective fashion. With sufficient numbers of deaths the cohort study will prove especially valuable in furnishing data on probabilities of death by cause for the migrant groups. It is now planned to collect copies of death certificates for the migrants for a 7-year period. These will be matched against the morbidity survey listings.

Major Findings: Preliminary findings of the morbidity survey of British and Norwegian migrants and U.S. natives were published earlier (NCI Monograph No. 19, January 1966). These included (1) prevalence of symptoms of chronic respiratory disease which is no higher among British migrants than among U.S. natives, in contrast with the much higher mortality in Britain; and (2) Prevalence of symptoms of angina and myocardial infarction which is lower among

British migrants than among U.S. natives, in accord with mortality differentials between the two countries.

Analysis of initial data on mortality of Norwegian migrants to the U.S. from coronary heart disease show that mortality is higher among those who migrated to the U.S. at young ages than among those who come at older ages. Mortality being lower in Norway than in the U.S., the gradient with age at migration appears to reflect differing lengths of exposure to environments associated with low and high coronary disease mortality. A similar preliminary tabulation of chronic respiratory disease mortality among British migrants failed to show a consistent gradient with age at migration.

Proposed Course: In the United States the morbidity survey has been completed and preliminary tabulations have been made. Additional analyses are being planned on prevalence of symptoms in relation to one place of residence, air pollution, and history of various diseases. For 32,000 deaths of migrants and natives, all death certificate data including multiple causes of death have been coded, as have the personal characteristics questionnaires from the death certificate informants. Questionnaires from medical certifiers are being coded. Nearly all morbidity questionnaire respondents who died in the years 1963-1966 have already been identified, and medical certifier and informant questionnaires secured. Death records for 1967 need to be collected.

In Britain and Norway morbidity questionnaires have been secured from the siblings of migrants and from samples of the general populations. All data have been edited, and most have been transferred to magnetic tape. A sample of deaths in the general population of Britain has been secured and multiple-cause coded. In both countries respondents to the morbidity questionnaires who die are being identified and their death certificates are being secured.

Significance to Bio-medical Research and the Program of the Institute: Data on multiple causes of death and on other diseases present in British migrant decedents will reveal whether chronic respiratory disease not apparent in official mortality statistics is more common in this group than in the U.S. native born. The morbidity surveys in Britain and Norway will show the levels of prevalence of symptoms in those countries and identify environmental and personal characteristics related to the differences. Surveys of siblings of migrants may help explain the low prevalence of symptoms among migrants to the U.S.

Serial No. NHI-BRB-9
1. Biometrics Research Branch
2. Epidemiology and Biometry, NHI
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Investigation of the Relationship Between Sequential Observations on Individuals and Subsequent Disease Incidence

Previous Serial Number: NHI-BRB-10

Principal Investigator: Jeanne Truett

Other Investigators: Jerome Cornfield

Cooperating Units: Framingham Heart Disease Epidemiology Study, University of Pittsburgh

Man Years

Total:	.1
Professional:	.1
Other:	--

Project Description:

Objectives: To investigate the pattern of change in successful biennial measurements in relation to development of coronary heart disease.

Methods Employed: A relatively simple additive, multivariate model for estimating changes over time in mean level of a variable, among eventual coronary cases prior to the event, was developed. Standard errors of the estimates of distance (from an event) effects were derived and a test for the existence of pattern proposed. The proposed test assumes a large population free of disease from which parameters of the underlying multivariate arrival distribution may be estimated with great precision. The Framingham sample satisfies this requirement.

Major Findings: As reported last year the method has been applied to transformed systolic blood pressures with the finding that in the age group 40-59 there is no pattern of change in level preceding an event. A similar analysis with respect to serum cholesterol levels is in progress.

Significance to Bio-Medical Research and the Program of the Institute: The model provides logical structure for quantification of developing patterns of change in a single variate over time with respect to discrimination of subsequent development of coronary heart disease.

Serial No. NHI-BRB-9
1. Biometrics Research Branch
2. Epidemiology and Biometry, NHI
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Proposed Course: Preparation of a manuscript for publication in an epidemiologic journal and application of the method to analyze other variables measured at Framingham.

Serial No. NHI-BRB-10
1. Biometrics Research Branch
2. Epidemiology & Biometry, NHI
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Epidemiologic Study of Coronary Atherosclerosis in Puerto Rico (This refers only to statistical services provided by Biometrics Research Branch. See general description in Epidemiology Section.)

Previous Serial Number: NHI-BRB-11

Principal Investigators: Jeanne Truett and Tavia Gordon (Study Chief is Dr. Mario Garcia-Palmieri)

Man Years

Total:	.30
Professional:	.30
Other:	--

Project Description:

Objectives: To study the factors related to development of cardiovascular diseases in a population of middle-aged men where the death rate from coronary heart disease is about one-third that in the U.S. The study has been planned to make use of the unusually high autopsy rate (50%) and to maximize the heterogeneity in mortality rates, diet and physical activity observed in preliminary surveys of rural and urban residents.

Methods Employed: Anticipating a response of 80% or better, the study area was defined to yield 4,000 mountain dwellers and 8,000 city dwellers on enumeration for a sample of 10,000 split 1:2 rural-urban. All males born in the years 1900 and 1919 and presently residing in the defined mountain areas or in specified municipios in the metropolitan area of San Juan are being enumerated by household canvass by the Puerto Rico Planning Board. An intensive effort is being made to bring in all men on the enumeration lists for examination. A follow-up to obtain supplementary data on mortality, and autopsy material for dissection of the coronary arteries has been initiated. Follow-up of hospitalizations is planned.

Data processing procedures and programming for dietary computations, quality control on examiners and interviewers, and quality control on the automated methods for recording masses of data being collected have been worked out with the Medical Center Information Processing Division. A copy of the data tape has been obtained from the project allowing for exploratory tabulations here.

Serial No. NHI-BRB-10
1. Biometrics Research Branch
2. Epidemiology and Biometry, NHI
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Significance to Bio-Medical Research and the Program of the Institute: See general description in Epidemiology Section.

Major Findings: See general description in Epidemiology Section. We remark here, however, that more than 8000 subjects have been examined now. Computer programs for tabulating basic distributions and frequency arrays of all variates by age and rural-urban group have been written and tables produced for the first half of the samples examined.

Proposed Course of Study: Follow-up examinations roughly two years after initial examination will be initiated around July 1, 1968, while the first round of examinations continues on the remaining enumerated cohort. We provide consultation on the content of these examinations, form designs, and data processing. Assistance is also provided on methodological issues relating to data collection.

Serial No. NHI-BRB-11
1. Biometrics Research Branch
2. Epidemiology & Biometry, NHI
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Framingham Heart Study (This refers only to statistical services provided by the Biometrics Research Branch. The principal investigator for the study itself is Dr. William B. Kannel.)

Previous Serial Number: NHI-BRB-12

Principal Investigators: Jeanne Truett, Dewey Shurtleff, Manning Feinleib, Jack Lieberman, Joel Verter, and Tavia Gordon (see above)

Other Investigators: (See above)

Cooperating Units: None

Man Years

Total:	7.0
Professional:	4.0
Other:	3.0

Project Description:

Objectives: To assist in data collection, tabulation and analysis for this long-term prospective study.

Methods and Findings: Completion of a tape record covering the first seven biennial examinations has allowed a considerable expansion in the tabulating program. A large body of tabulations have been made and have been assembled into monograph form. These cover the following:

(1) Description of cohort and follow-up.
(2) Changes in characteristics over seven examinations.
(3) Incidence of cardiovascular diseases.

In preparation are tabulations relating the incidence of cardiovascular diseases to repeated characteristics, and factors associated with blood pressure levels.

An assessment has been made of the predictability of a discriminant function derived from early CHD experience for later, independent experience. Prediction was fairly good. A comparison of the discriminant function with a regression function has been made: close agreement was found.

Serial No. NHI-BRB-11
1. Biometrics Research Branch
2. Epidemiology & Biometry, NHI
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Exam 11 forms are being planned. New follow-up procedures have been initiated. Consultation has been given to Framingham on a continuing basis with respect to operation, analysis of data, and specific projects undertaken by outside collaborators.

Serial No. NHI-BRB-12
1. Biometrics Research Branch
2. Epidemiology and Biometry, NHI
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: NHI-GHA Study of Prognosis in Coronary Heart Disease

Previous Serial Number: NHI-BRB-13

Principal Investigators: Fred Ederer, Dr. Hubert Loncin, Goldie Krantz

Other Investigators: Zelda Federman, Eugene Rogot

Cooperating Unit: Group Health Association of Washington, D.C.

Man Years:

Total:	.10
Professional:	.07
Other:	.03

Project Description:

Objectives: A need exists for the development of continuous long-term studies of coronary heart disease (CHD) prognosis in well-defined populations in various parts of the United States to establish baseline data against which future trends can be measured. The studies should be designed according to a uniform protocol, with standard terminology, definitions, and classifications in order to provide (1) comparability with one another and (2) the potential of data pooling. The capacity for data pooling is important because no single series is ever large enough to answer all or even many of the questions that arise in the analysis of the data.

Medical knowledge, concepts, and methods regarding the treatment and management of coronary heart disease have undergone change in recent times and will undoubtedly continue to change at an accelerated rate. Among the newer methods are anti-coagulants, continuous monitoring, and circulatory assist devices. Will these methods, or still newer methods, result in a prolongation of life for the coronary patient? The objectives of prognosis studies may be stated in terms of the following questions:

1. What is the current prognosis of coronary heart disease as measured by such end-points as immediate mortality, return to work, short- and long-term survival?

2. How does prognosis vary according to age, sex, severity of infarction, treatment, and other clinical and social variables (e.g., physical activity, smoking, diet)?

Serial No. NHI-BRB-12
1. Biometrics Research Branch
2. Epidemiology and Biometry, NHI
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

3. How will prognosis change as medical knowledge, concepts, and treatment change?

4. How are coronary heart disease patients treated (i.e., length of hospitalization, patient-monitoring, defibrillation, bed-rest, absence from work, drugs, etc.)? How will future treatment methods compare with present methods, and how will changes in prognosis relate to changes in treatment?

5. What proportion of cases result in sudden death before the patient gets to the hospital? Is there evidence of a decrease in this proportion over time?

6. How do treatment and prognosis vary among the populations studied? Can any associations be found between type of medical care and prognosis?

7. Can a standard method of severity classification be developed for comparing different series?

Past and current studies of CHD prognosis which are based on data from single hospitals exclude cases treated at home and sudden deaths. Without a standard severity classification these studies are of little value because they permit neither a valid assessment of trend nor a valid comparison of different series. Even with a standard severity classification, the exclusion of an unknown number of sudden deaths or patients not hospitalized limits comparability. Single-hospital studies also lack the element of population definition; moreover, the reports in the medical literature on these studies frequently reflect a lack of care and attention to detail as well as incomplete accounting of cases, so that the results are often not interpretable. Studies of defined populations make it possible to identify all newly diagnosed cases, whether treated at home or at the hospital, and also sudden deaths from CHD. Thus, while the principal objective is a study of prognosis, a by-product of the complete enumeration of cases in a defined population is the capacity to measure incidence and study factors related thereto through either a prospective, retrospective-prospective, or retrospective (case-control) approach.

The 57,000 members of the Group Health Association, Washington, D. C. (GHA), offered the opportunity for a study of CHD prognosis in a well-defined population. About 13,000 members are males aged 30 or more, and some 86 cases of first myocardial infarction (MI) or CHD death may be expected per year. Among women there would be some 16 cases. In addition, there would be some 49 male cases of angina pectoris (AP) or coronary insufficiency (CI),

Serial No. NHI-BRB-12
1. Biometrics Research Branch
2. Epidemiology and Biometry, NHI
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

and 28 female cases. The expected number of cases in the GHA population is only of moderate size, and, while a sufficient number of cases could be accumulated in several years for some gross appraisals of GHA experience, detailed analyses by age, sex, severity and other social and demographic factors would not be possible for a long time. A principal function of the NHI-GHA study was to provide an opportunity to learn what kinds of clinical, demographic, and social data are available and collectable on a routine basis, to develop definitions, criteria, and suitable forms for uniform collection of this information, and to work out the mechanical aspects of data collection and patient follow-up. The NHI-GHA study could then serve as a model for other population-based studies to be developed in accordance with the terms, definitions, criteria, and mechanisms of the NHI-GHA study. The data of the various studies could then be pooled to provide detailed answers.

Methods Employed: A study protocol was drafted and cardiac register was established. New cases of CHD were identified by GHA physicians, through hospital claims forms and through a GHA death register. Forms were developed for abstracting information from the hospital record, out-patient record, and for obtaining information from the patient and next-of-kin. Hospital and out-patient chart abstracts and ECG's were reviewed for the purpose of confirming CHD diagnosis according to standard criteria. Patient questionnaires were to be mailed out 3 months after an event, and then annually on the anniversary of the event.

Major Findings: The crucial goal of completeness of complete ascertainment of newly diagnosed cases of CHD could not be achieved. At most 52 new, non-recurrent cases of myocardial infarction (MI) were reported by GHA physicians during the course of the study, compared with 78 cases expected from Framingham experience. GHA physicians failed to report 15 cases of MI subsequently identified through hospital claims forms.

Course of Project: The project was terminated after 1 year in August, 1967 because of evidence of gross underreporting of cases. The study might have succeded with more direct involvement by GHA physicians. No direct contact existed between the NHI staff and the GHA physicians who were responsible for reporting new cases of disease.

Serial No. NHI-BRB-13
1. Biometrics Research Branch
2. Epidemiology and Biometry, NHI
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: A study of seasonal patterns in mortality for Memphis, Tennessee

Previous Serial Number: NHI-BRB-14

Principal Investigator: Eugene Rogot

Other Investigator: William C. Blackwelder

Man Years

Total:	.38
Professional:	.28
Other:	.10

Project Description:

Objectives: To measure seasonal variations in mortality for specified causes of death utilizing multiple cause of death data. A major aim is to measure any seasonal excess in cardiovascular mortality linked to respiratory diseases. In conjunction with this, an attempt to measure seasonal excess in cardiovascular mortality according to daily mean temperature or other weather index is to be made.

Another goal is to study seasonal patterns for 'sudden" deaths as contrasted to seasonal patterns for "non-sudden" deaths. The categories of special interest here are coronary heart disease (category 420) and stroke (330-334).

Methods Employed: Death certificates for all resident deaths occurring in Memphis, Tennessee in 1959, 1960 and 1961 are being studied. All causes of death appearing on the certificate have been coded by a single physician according to the Seventh Revision of the International Lists.

Information collected from the death certificates include: I.S.C. 4-digit codes for causes of death (up through 6 causes per certificate), month-day-year of death, interval between onset and death (for the immediate cause), age at death, sex, race as well as other information.

Information from the weather bureau includes: daily mean, high and low temperatures, precipitation data, etc.

Tabulations are in preparation by month, age, race, sex, etc. for each cause of interest. These tables should permit an evaluation of a seasonal

excess (or deficit) in mortality from a particular disease in terms of both temperature level (or other weather index) and associated conditions for sudden and non-sudden deaths.

Major Findings: (Since tabulations are still in preparation and the statistical analysis has not been completed, all findings described below are tentative).

1. An inverse relationship was observed between average temperature on day of death and average number of deaths per day for coronary heart disease (CHD). This relationship appears to be independent of associated conditions, such as respiratory disease (I.S.C. 470-527) or other diseases. The pattern is exponential with sharpest change in mortality occurring with temperature change from "under 30° days" to "30-39° days".

2. An inverse relationship was observed between average temperature and average number of deaths per day for stroke. This relationship appears to be independent of respiratory disease but is dependent on other cardiovascular disease. Specifically, combinations of stroke with general arteriosclerosis (I.S.C. 450) and stroke with hypertensive disease (I.S.C. 440-447) show patterns similar to that described for CHD. No pattern was observed for stroke alone.

3. An inverse relationship between average temperature and mortality for all other cardiovascular diseases was observed similar to the pattern described for CHD.

4. Sudden CHD deaths show a more pronounced inverse relationship with average temperature than do non-sudden CHD deaths.

5. No relationship between average temperature and mortality for cancer (I.S.C. 140-205) was discerned.

6. An approximately linear inverse pattern was observed between average temperature and respiratory disease mortality.

Significance to Bio-medical Research and the Program of the Institute: Previous investigations in temperate climates have usually shown higher mortality from cardiovascular diseases in winter months compared to summer months. On the other hand, at least 2 studies recently observed the reverse to be true in cities with very hot climates. To our knowledge, multiple cause of death data has never been used previously in a systematic way to elucidate the observed seasonal relationships. Investigations of seasonal patterns for "sudden" and "non-sudden" deaths is also believed to be novel.

Serial No. NHI-BRB-13
1. Biometrics Research Branch
2. Epidemiology and Biometry, NHI
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Proposed Course: It is anticipated that the statistical analysis will be completed in the near future and an appropriate paper (or papers) prepared for publication. Tentative findings to date indicate the need for a similar study in a large northern city.

Serial No. NHI-BRB-14
1. Biometrics Research Branch
2. Epidemiology and Biometry, NHI
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: A Model for Expected Disease Incidence in Therapeutic Trials with Incomple Adherence when Therapeutic Effect is Not Constant

Previous Serial Number: NHI-BRB-15

Principal Investigators: Max Halperin, Eugene Rogot

Other Investigators: Joan Gurian, Fred Ederer

Cooperating Units: None

Man Years

Total:	.05
Professional:	.05
Others:	.00

Project Description:

Objectives: To develop a model for expected T-year disease incidence rate in a therapeutic trial when therapy attains its maximum effect only after a period of sustained treatment, an individual can only incur the disease (or other event) once, and dropouts are non-adherers, i.e. they remain under surveillance but do not receive the maximum possible benefit of therapy. In fact, in time, the risk for dropouts reverts to a level appropriate for untreated individuals.

Methods Employed: The procedures used in this investigation involved only elementary notions of differential equations, calculus and probability to derive the appropriate "bookkeeping" for the number or proportions of "disease" events in T-years.

Major Findings: An expression was derived for expected T-year incidence in an initial cohort of size N (assumed large) under the following assumptions.

a. The T-year incidence rate without treatment and with no withdrawal is p_c.

b. The maximum benefit of therapy is achieved in f years.

c. After maximum benefit of therapy has been achieved p_c is reduced by

100 k% in a treated group with no withdrawals.

d. In the course of the study 100 d% of the cohort become non-adherers (disease cases cannot become non-adherers).

e. The instantaneous risk of an event among those remaining under treatment is a function of length of time under therapy; the risk among non-adherers is a function of the length of time under treatment as well as the length of period of non-adherence.

Tables of expected T-year incidence were computed using a high-speed computer for various specifications of p_c, f, d and k assuming the instantaneous risk functions to be linear.

Other choices of the form of the instantaneous risk function could be made and would require additional computations.

Significance to Bio-Medical Research and the Program of the Institute: This project was initiated because of the need of the Diet-Heart Feasibility Study for the incidence rate described above in determination of appropriate sample sizes for a possible definitive study. The need reflected the difference between the natural mode of definition of the improvement to be realized by therapy and the manner in which, of necessity, the data had to be gathered. The result appears applicable not only in this specific study but in a class of studies.

Proposed Course: A brief discussion of the model and the tables discussed above have been included as a part of the final report of the Diet-Heart Feasibility Study published as a special supplement to Circulation in March 1968. A fuller report appeared in the January 1968, Journal of Chronic Diseases. No further work is planned on this project.

Article Published in a Periodical:

Halperin, M., Rogot, E., Gurian, J., and Ederer, F.: Sample Sizes for Medical Trials with Special Reference to Long-Term Therapy. Journal of Chronic Diseases, Vol. 21, pp. 13-24, January 1968.

Serial No. NHI-BRB-15
1. Biometrics Research Branch
2. Epidemiology and Biometry, NHI
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Sequential Assignment of Patients to Treatment in Clinical Trials

Previous Serial Number: NHI-BRB-16

Principal Investigator: Jerome Cornfield

Other Investigators: Max Halperin, Samuel W. Greenhouse

Cooperating Units: NICHD, Biometrics Branch; University of Pittsburgh

Man Years

Total:	.10
Professional:	.05
Others:	.05

Project Description:

Objectives: To develop optimum or near optimum methods for allocation of patients to treatment in a sequential clinical trial utilizing results of the trial as they become available.

Methods Employed: Bayes Theorem, Calculus of Variations, a variety of standard methods in statistics and probability.

Major Findings: Assuming comparison of two treatments, that response to treatment is a continuous variable and that there is a cost of assigning an individual to the inferior treatment which may depend on how different the two treatments are, the following problem is solved:

If N patients are available, a two stage clinical trial is contemplated, and one has a prior distribution for the difference between treatments with a (possibly) non-zero mean, how many patients should be allocated to each stage and each treatment to minimize average cost? It is assumed that information on the first stage is available before allocation to treatment in the second stage and that averaging is over the prior distribution and all possible samples in both stages.

Serial No. NHI-BRB-15
1. Biometrics Research Branch
2. Epidemiology and Biometry, NHI
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

The solution to the problem depends on N and the standardized mean of the prior distribution and, for small N, can lead to the conclusion that no trial should be attempted. If N is large an explicit expression is found for the proportion of 1st stage patients allocated to each treatment, depending only on the standardized mean of the prior, while in the second stage (independent of N) all patients are allocated to the better treatment. An exact (asymptotic) solution to a suitable generalization of this problem to an arbitrary number of stages appears wholly intractable but a sequential solution using the 1st stage allocation probabilities mentioned above and the appropriate posterior as a prior is suggested. This suggested procedure is better (in terms of cost) than the two stage solution and is a reasonable approximation to the answer to a more general problem.

Significance to Bio-Medical Research and the Program of the Institute: The findings reported above constitute a new approach to allocation of patients in clinical trials in which the objective is to decide on the best treatment and simultaneously to maximize average patient benefit; the salient feature is the near optimum use of new information as it becomes available.

Proposed Course: No further work is contemplated on this project. A manuscript has been prepared and submitted for publication in a statistical journal.

Serial No. NHI-BRB-16
1. Biometrics Research Branch
2. Epidemiology and Biometry, NHI
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Confidence Bands in Straight Line Regression for Restricted Range of the Independent Variable

Previous Serial Number: NHI-BRB-17

Principal Investigator: Max Halperin

Other Investigators: Joan Gurian

Cooperating Units: None

Man Years

Total:	.08
Professional:	.08
Others:	--

Project Description:

Objectives: To develop interpolation or extrapolation procedures in straight line regression and associated confidence intervals such that the probability that all confidence interval statements, for a restricted range in the independent variable, are correct is a specified (in advance) value.

Methods Employed: Variations on known methods of mathematical statistics and probability.

Major Findings: The classical method of obtaining confidence bands in linear regression for an unrestricted range of the independent variable has been re-evaluated when the range is restricted to any closed interval. For a type of restriction which would be most frequent and appropriate in applications, i.e. for a range restricted to values of the independent variable used in an experiment, the relevant probability distribution is shown to be one already tabulated by the principal investigator. The results obtained show that one always can obtain narrower bands than in the classical theory, the possible reduction in width being of the order of 25% or more. Comparisons with results of other workers on this problem indicate the present results to be superior. The result described above is generalized to linear regression on several independent variables where the latter are subject to an ellipsoidal restriction.

Serial No. NHI-BRB-16
1. Biometrics Research Branch
2. Epidemiology and Biometry, NHI
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Significance to Bio-Medical Research and the Program of the Institute: In many experimental settings in which linear regression is used, one is only interested in drawing inferences for a restricted range of the independent variables, usually the range in which the experiment has been done. Our results will allow less conservative evaluation of the precision of the estimated regression plane in such cases than afforded by classical procedures.

Proposed Course: A paper has been prepared and accepted for publication in a statistical journal and no further work on the project is planned.

Article Published in a Periodical:

Halperin, M., and Gurian, J.: Confidence Bands in Linear Regression with Constraints on the Independent Variables. Journal of the American Statistical Association. To appear, September 1968.

Serial No. NHI-BRB-17
1. Biometrics Research Branch
2. Epidemiology and Biometry, NHI
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Least Squares Adjustment of Multivariate Data

Previous Serial Number: NHI-BRB-19

Principal Investigator: Dr. Manning Feinleib

Other Investigators: Jerome Cornfield and Christine M. Cole

Man Years

Total:	.05
Professional:	.05
Other:	--

Project Description:

Objective: To develop a method for adjusting frequencies in a two way classification ("rows" and "columns") to yield consistent estimates of "row" effects and "column" effects. For example, the "rows" in such a way might be different age groups, the "columns" might be cholesterol levels.

Methods Employed: A computer program has been written for fitting a least squares model to original and transformed data to give column effects. A generalized model is being developed to give simultaneous column and row effects and their variance-covariance matrix.

Major Findings: The model has given more consistent results than the indirect method of standardization for several test cases and seems to be robust for missing observations and varying sample sizes.

Significance to Bio-Medical Research and the Program of the Institute: This model seems to offer definite advantages as compared with the usual indirect method of adjustment. It tends to avoid incongruous results that may occur in the indirect method and does not require an arbitrary choice of standard populations.

Proposed Course of Project: Due to the press of other activities, this project has been put in abeyance during the present year. Further development of the method will be undertaken independently by Jerome Cornfield and will then be applied to real data from the Framingham Heart Study.

Serial No. NHI-BRB-18
1. Biometrics Research Branch
2. Epidemiology & Biometry, NHI
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: A Markov Process for Describing the Natural History of Coronary Heart Disease (CHD)

Previous Serial Number: NHI-BRB-20

Principal Investigator: Dr. Manning Feinleib

Man Years

Total:	.10
Professional:	.10
Other:	--

Project Description:

Objective: To describe the sequence of events from first evidence of CHD to death by means of a time-dependent set of transition matrices.

Methods Employed: A scoring system has been developed which uniquely classifies Framingham CHD patients according to their cumulative CHD experience and defines each patient's status at each Framingham examination.

Computer programs have been prepared for generating transition matrices and for estimating various mathematical characteristics of these matrices.

Major Findings: Despite the relatively large initial size of the Framingham cohort and the availability of 14 years of follow-up data, the available information pertinent to this problem is still relatively sparse, resulting in many empty cells in the data matrices.

Significance: There is little quantitative data about the natural history of CHD. Some questions of interest that can be answered by the present analysis are: What is the risk of a person with a given CHD status of having another CHD event? What subsequent events are most likely? What is the mean interval between events? What is the mean number of events prior to death?

Proposed Course of Project: The appropriate computer programs have been prepared and efforts are now underway to condense the available data into broader rubrics in a meaningful way to provide smaller matrices with fewer empty cells. Since the principal investigator has assumed the post of Chief, Field Epidemiological Research Section, Epidemiology and Biometry,

Serial No. NHI-BRB-18
1. Biometrics Research Branch
2. Epidemiology and Biometry, NHI
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

NHI, these projects are terminated as BRB projects and will be reported upon subsequently by the Field Epidemiology Section.

Serial No. NHI-BRB-19
1. Biometrics Research Branch
2. Epidemiology & Biometry, NHI
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Framingham Coronary Heart Disease (CHD) Autopsy Study

Previous Serial Number: NHI-BRB-21

Principal Investigator: Dr. Manning Feinleib (This refers to BRB services).

Other Investigators: Dr. George Tedeschi, Dr. William Kannel

Cooperating Units: Department of Pathology, Framingham Union Hospital, and Framingham Heart Study

Man Years

Total:	.30
Professional:	.20
Other:	.10

Project Description:

Objective: To determine whether CHD risk factors observed in life correlate with the extent of atherosclerosis observed at autopsy.

Methods Employed: A special autopsy protocol has been developed in which the coronary vessels are carefully dissected and several measures of atherosclerosis are observed. The autopsy data for Framingham patients and characteristics of the patients recorded prior to death are analyzed by means of contingency tables and regression techniques.

Significance: There is little data available to determine whether factors which are known to be related to CHD morbidity and mortality are also associated with atheromatous processes observed in the coronary vessels. This study is designed to evaluate this relation.

Major Findings: An analysis of the first 75 cases in relation to measures of obesity has shown that the autopsy material reflects the general clinical implications already established. In particular, after controlling for blood pressure and serum cholesterol, in addition to age and sex, there is no striking relation between the obesity measures (relative body weight and skin fold thickness) with left ventricular muscle thickness, atheromatous or thrombotic occlusions, degree of intimal involvement or degree of luminal insufficiency found at autopsy. Heart weight does correlate with total body weight.

Serial No. NHI-BRB-19
1. Biometrics Research Branch
2. Epidemiology & Biometry, NHI
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Proposed Course of Project: Additional data will be accumulated as Framingham patients come to autopsy. Further analyses will be done for other risk factors observed prior to death. Since the principal investigator has assumed the post of Chief, Field Epidemiological Research Section, Epidemiology and Biometry, NHI, these projects are terminated as BRB projects and will be reported upon subsequently by the Field Epidemiology Section.

Serial No. NHI-BRB-20
1. Biometrics Research Branch
2. Epidemiology & Biometry, NHI
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: A Twin Study of Genetic Factors in Cardiovascular Diseases.

Previous Serial Number: NHI-BRB-22

Principal Investigator: Dr. Manning Feinleib

Man Years

Total:	.10
Professional:	.10
Other:	--

Project Description:

Objective: To evaluate the relative contribution of environmental and genetic factors to the development of cardiovascular diseases (CVD) and to the levels of risk factors associated with CVD.

Methods Employed: A sample of 300 pairs of male twins aged 40-50 will be examined each year according to a standard protocol. Data will be gathered about past environmental, family, and medical history and measurements of physiological variables will be obtained. The data will be analyzed by correlation methods and analysis of variance techniques.

Significance: There have been relatively few studies of genetic factors in CVD. Most of these have dealt with family clinical histories or with a few specific risk factors such as blood pressure and cholesterol. Twin studies in particular have been inadequate. It is recognized that twin studies are potentially the most powerful method available for studying genetic factors in human disease. The present study will take advantage of the largest population of male twins yet assembled to study this important question in relation to cardiovascular diseases.

Major Findings: None to date.

Proposed Course of Project: A protocol has been prepared and submitted to the NAS-NRC Follow-up Agency requesting access to their Twin Panel which contains more than 8,000 pairs of male twins who are veterans of W.W.II. If approved, the twins in New England will be contacted and invited to undergo a standard examination at the Framingham Heart Program facilities during the forthcoming year. In subsequent years, twins in other geographical areas will be examined until 1500-3000 twin sets have been processed. Analyses and reports will be prepared concurrently with the examinations. Since the

principal investigator has assumed the post of Chief, Field Epidemiological Research Section, Epidemiology and Biometry, NHI, these projects are terminated as BRB projects and will be reported upon subsequently by the Field Epidemiology Section.

Serial No. NHI-BRB-21
1. Biometrics Research Branch
2. Epidemiology & Biometry, NHI
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Serum Copper in Coronary Heart Disease (CHD).

Previous Serial Number: NHI-BRB 23

Principal Investigator: Dr. Manning Feinleib (This refers to BRB services).

Other Investigators: Dr. Denham Harman, Dr. William Kannel

Cooperating Units: Department of Biochemistry, University of Nebraska Medical School, and Framingham Heart Study

Man Years

Total:	.15
Professional:	.15
Other:	--

Project Description:

Objective: To determine whether serum copper levels are related to risk of CHD, and to determine how serum copper level changes after clinical myocardial infarction.

Methods Employed: Blood samples obtained before and after the CHD events of CHD patients in the Framingham Heart Study are analyzed for copper content and compared with copper values obtained for matched controls. Serum copper levels are also determined for patients hospitalized for myocardial infarction immediately after the event and for varying periods thereafter.

Major Findings: A second sample of 35 CHD cases and 35 controls was selected and their frozen sera analyzed for copper content. The results of this run were contrary to that found in the initial sample. The possible reasons for this are currently being explored.

Significance: Copper is important in several enzyme systems related to lipid metabolism and may play a role in atherogenesis. If serum copper is proven to be related to risk of CHD, the potential of controlling copper levels by diet or drugs is possible. The post-infarction pattern of serum copper levels may prove to be useful in diagnosis or prognosis.

Serial No. NHI-BRB-21
1. Biometrics Research Branch
2. Epidemiology & Biometry, NHI
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Proposed Course of Project: Dr. Harman has applied for a grant to continue this study in relation to serum copper and other trace metals. Continuation of this project will depend on whether his grant is funded. Since the principal investigator has assumed the post of Chief, Field Epidemiological Research Section, Epidemiology and Biometry, NHI, these projects are terminated as BRB projects and will be reported upon subsequently by the Field Epidemiology Section.

Serial No. NHI-BRB-22
1. Biometrics Research Branch
2. Epidemiology and Biometry, NHI
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Coordinating Center Operations for the Urokinase-Pulmonary Embolism Trial

Previous Serial Number: None

Principal Investigator: Fred Ederer

Other Investigators: Christine Cole, Max Halperin, Howard Marsh, Peter Walsh

Cooperating Units: Johns Hopkins University School of Medicine, Marshfield Clinic, Peter Bent Brigham Hospital, University of Colorado Medical Center, West Roxbury VA Hospital, New York University Medical Center, NHI Blood Resources Program

Man Years:

Total:	2.93
Professional:	1.93
Other:	1.00

Project Description:

Objectives: To provide coordinating services required for the effective administration of a controlled cooperative clinical trial.

Methods Employed:

1. Statistical consultation on the study design, including such aspects as methods of organizing a personnel structure for decision making, delegation of authority, and the smooth operational functioning of the study; choice, methods of evaluation and quantification of endpoints; methods of random treatment assignment; methods to prevent bias in the evaluation and interpretation of results; double- or single-blind; and uniformity of procedures of observation, measurement, and data collection.

2. Preparation of a protocol, manual of operations, and forms.

3. Preparation of randomization procedures.

Major Findings: None

Course of Project: Planning for the study started in September 1967. An organizational structure was drawn up: Chairman, Policy Board, Steering

Serial No. NHI-BRB-22
1. Biometrics Research Branch
2. Epidemiology and Biometry, NHI
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Committee, Coordinating Center, Central Laboratory, various committees, subcommittees, and review panels. Coordinating Center personnel are represented on the Steering Committee, the Protocol Committee, the Committee for Standardization and Analysis of Data, on Subcommittees for Analysis of Pulmonary Angiograms, Pulmonary Photoscans and Hemodynamic Data, and Biochemical Data, and on the Hemodynamic Data Analysis Panel. Major meetings were held in September 1967 and March 1968, and committee and subcommittee meetings were held in the interim. A protocol and manual of operations were prepared and approved by the Steering Committee and Policy Board. The study was approved by primary and secondary contract review boards. It is anticipated that the study will begin during the summer or fall of 1968.

ANNUAL REPORT OF THE HEART DISEASE EPIDEMIOLOGY STUDY
FRAMINGHAM, MASSACHUSETTS
July 1, 1967 - June 30, 1968

The Framingham Study continues the longitudinal prospective investigation of cardiovascular disease as a direct National Heart Institute operation in the Section concerned with Epidemiology and Biometry. It continues to pursue the broad objectives of ascertaining the circumstances under which the major cardiovascular diseases arise, evolve, and terminate fatally in a general population sample of men and women who were characterized some 20 years ago (and also biennially since that time) according to personal attributes and living habits believed important in the development of coronary heart disease (CHD).

Research Directions

The objectives have now been broadened to include a detailed investigation of the epidemiologic features of coronary heart disease, athero-thrombotic brain infarction, and occlusive peripheral vascular disease, the major clinical manifestations of atherosclerosis. In addition, the epidemiology of hypertensive cardiovascular disease and congestive heart failure are being investigated.

In the course of pursuing these primary objectives, opportunity for the investigation of a number of other important chronic diseases has presented itself. Preliminary investigations of the epidemiology of diabetes, gout, arthritis, osteoporosis, thyroid nodules, emphysema, and gallbladder disease have been carried out. These are being continued in collaboration with interested, qualified investigators in the area including Drs. Arthur Hall and Peter Barry of the Robert Breck Brigham Hospital; Mark Hegsted, Robert McGandy and Fredrick Stare of the Harvard School of Public Health, and Albert Damon of Harvard.

Possibilities for a detailed study of aging are being explored in co-operation with Dr. Nathan Shock. It is proposed that in addition to the cardiovascular disease outcomes, osteoporosis and arthritis already being investigated, methods for assessing nerve deafness, lenticular opacity, senile mental deterioration and locomotor difficulties be added. This would make a comprehensive appraisal of the major disabling conditions which plague the aged.

A new dimension to the epidemiologic investigation of cardiovascular disease has been added by investigating biochemical and physiological parameters in the pre-morbid state not only in relation to the development of clinical manifestations of CHD, but in relation to the nature and extent

of atherosclerotic disease observed in the vessels at post-mortem as well. Thus far, Dr. C. G. Tedeschi has completed 75 coronary arterial dissections using a meticulous technique which allows grading of the nature and extent of atherosclerotic involvement. Dr. Manning Feinleib has tabulated and analyzed these in relation to a variety of antecedent personal traits and habits of these individuals during the ante-mortem period of observation in the Framingham Study. Epidemiologic-autopsy correlations involving obesity have already been reported at the last Clinical Society meeting. As anticipated by the epidemiologic findings, no relationship of the degree of adiposity and to the extent of uncomplicated atherosclerotic involvement of the coronary arterial tree was demonstrated. There was a striking association between heart weight and degree of adiposity. Epidemiologic findings previously had suggested that adiposity contributed to development of angina pectoris and sudden death independent of atherogenic factors and was unrelated to the occurrence of myocardial infarction. This suggested that the effect of adiposity derived from an associated increase in the cardiac work load, which in predisposed persons with a compromised circulation, provoked angina pectoris or the occurrence of sudden death. Plans are being made to make a series of autopsy-epidemiologic correlations exploring each of the recognized factors contributing to the occurrence of coronary heart disease.

Possibilities for relating personal attributes, living habits, and biochemical parameters to deposition of lipid in tissue cultures of endothelial cells incubated with each subject's serum are being explored with Dr. David Rutstein at Harvard Medical College.

Research and development activities designed to evaluate methods for early detection of cardiovascular disease employing atraumatic, safe, and not unpleasant diagnostic techniques are being continued. Assessment of a simplified thermographic recording device to detect extracranial vascular disease has been completed. This was found to be lacking in promise either because of the lower than anticipated prevalence of extracranial disease in the general population and among persons with established strokes, or because of lack of sensitivity of the simplified apparatus. This particular technique has been accordingly abandoned.

A device for bilateral simultaneous pulse wave oscillographic recording which allows a comparison of the character and amplitude of the pulse wave generated from the two extremities has now been employed on all subjects with intermittent claudication and found to be highly sensitive. Its specificity is now being evaluated by a study of the pulse wave in the general population sample. This technique is highly promising and is now being adopted by the Albany Study as well. Plethysmographic finger pulse wave recording using the technique and apparatus of Lax and Fineberg has also been obtained in two thousand odd subjects. These results are being evaluated.

Plans are being made to tabulate the results of 16 years of follow-up experience at the close of the fiscal year. To date we have now accumulated 442 deaths among the men and 300 deaths among the women for a total of 742. Also to date we have 437 male cases of coronary heart disease and 237 female cases for a total of 674. This of course extends beyond the 16 year follow-up. At the conclusion of the 11th biennial examination, completing 20 years of follow-up, we project that there will be a total of 960 deaths, 810 cases of coronary heart disease, 170 cases of brain infarction, and 120 cases of intermittent claudication. At the end of 14 years of follow-up, where we are at present, there were 531 deaths, 492 new cases of CHD, 86 new brain infarctions, and 125 cases of intermittent claudication. At the end of the 14 years of follow-up we had 66 cancer deaths among men and 71 among women. Dr. Feinleib plans to do some analysis of these cancer deaths.

Studies of the details of the epidemiology of coronary heart disease continue with emphasis on the epidemiologic features of each particular manifestation of the disease including myocardial infarction, angina pectoris, sudden death and coronary insufficiency. It has become increasingly clear that there are certain differences in the epidemiologic features of each manifestation of the disease and these demand further investigation. The large numbers of cases accumulating now make it possible to explore the relation of antecedent traits and living habits to the development of each manifestation of the disease. Also, with the development of a large number of cases followed for a sufficient period of time, it is now possible to begin an analysis of the natural history of the disease once developed and to explore factors related to immediate mortality, case fatality rate in recurrences and the factors related to recurrences and survival. Dr. Manning Feinleib is actively exploring this important objective.

Now that sufficient follow-up experience is beginning to accumulate since the measurements were made, plans are being made to examine in detail the hypotheses introduced after the start of the study. Thus, an examination of the relation to disease outcomes of thyroid function, physical activity status, nutrient intake, anthropometric measurements, measures of emotional stress, specific electrocardiographic abnormalities, blood type, among others, is being implemented. In keeping with the introduction of new hypotheses since the inception of the study, new measurements, new instruments and the systematic addition of greater precision in prior measurements have been implemented. Diagnostic criteria have been periodically modified as new diagnostic methods have become available including enzyme studies, pulse wave recording, angiography, etc. It was not until the 4th examination that a diet history was introduced. Physical activity assessment was also introduced at that time. Thyroid function was assessed by means of protein bound iodine determinations on examinations IV and V. A psychological questionnaire to evaluate emotional stress and personality factors was not introduced until examinations VIII and IX. Needless to say,

additional follow-up will be required before an evaluation of the relation of these factors to development of CHD, cerebrovascular disease, peripheral vascular disease and hypertension will be possible.

Now that enough cases are beginning to accumulate, an examination of the epidemiologic features of coronary heart disease in women is being undertaken. Also, an extensive undertaking to document premature surgical menopause has been completed allowing an examination of the relation of menopause to vulnerability to CHD.

Systematic examination of the epidemiologic features of other cardiovascular disease outcomes is now well established and preliminary analysis is already available for the following diseases: athero-thrombotic brain infarction, other types of cerebrovascular accident, occlusive peripheral vascular disease, congestive heart failure, hypertensive cardiovascular disease.

Follow-Up

Mr. Tavia Gordon of the Biometrics Section has completed an analysis of the follow-up. The completeness of follow-up continues to be gratifying. Of the original cohort of 5,209 persons, 4,678 were still alive at the time they were scheduled for the 8th biennial examination. Of these 4,030 or 86.1% took examination VIII. The net loss on successive examinations is now very low (about 1%). Among those who missed the 8th examination a sizeable proportion (91) returned for later examination. A large number of subjects took every possible examination; about 78% took all of the first eight examinations.

In the 648 eligible persons who did not appear for the 8th biennial examination, all but 121 took more than one preceding examination. Essentially permanent loss to follow-up has been relatively constant from one examination to another. The fact that a person fails to re-appear for examination does not mean that he is completely lost to follow-up since considerable effort is made to keep track of his clinical status through daily surveillance of hospital admissions, information obtained from spouses, local physicians and other sources. As a consequence less than 2% of the population sample has been completely lost to follow-up after 14 years. It is obvious that failure to return for examination has not yet introduced any serious bias in the counts of new coronary heart disease.

By the time of the 8th biennial examination 531 persons of the original cohort have died. The number of deaths is mounting as anticipated, with each succeeding examination. Nearly 2% of those alive at examination VI died before they were scheduled for examination VII. In the next two years mortality loss increased to 2.6%. Losses due to death between succeeding

examinations can be expected to increase rapidly. The cause of death has been determined for each fatality and this constitutes an important end point of the study.

The study has been visited and reviewed by a number of Advisory Committees to help chart the future course of the study after completion of 20 years of follow-up of the present population cohort.

These committees have emphasized the potential of the Framingham Study in relation to further elaboration of the natural history of CHD, the study of cerebrovascular and peripheral vascular disease, and have recommended that the incidence, natural history, and associated risk factors in cerebrovascular and peripheral vascular disease should be studied. These recommendations were already implemented at the time the Review Committee made its visit. Diagnostic criteria for these disease outcomes have been further revised and instrumentation to aid in the detection of early asymptomatic disease is being tested out. The capability for investigation of cerebrovascular disease is being strengthened by the addition to the staff of Dr. Philip Wolf, a neurologist from the Massachusetts General Hospital and Dr. David Poskanzer from the same institution who will provide part-time consultative services to review cases detected in the clinic, to examine cases admitted to the hospital in the acute stage and to evaluate neuropathology in cases coming to autopsy.

The Review Committees have repeatedly pointed out that a more complex sophisticated analysis of data is desirable. This has long been recognized by the Framingham staff, and the remedy, a full-time, qualified, resident statistician has long been sought. A more close working relationship with the Biometrics Section is being laboriously worked out under the considerable handicap of a 500 mile distance between the two units.

The Committee has correctly observed that "one or two associate directors should be appointed without delay". An associate director with epidemiologic and statistical experience is being sought. We will be two years in July without an associate director since that post was vacated.

The Committee points out that "the original objectives should be reemphasized, particularly with respect to the natural history of CHD". This has been done and factors related to survival, immediate mortality, recurrences and case fatality rates during attacks have been explored. Dr. Manning Feinleib has generated some additional data relevant to this and a life table analysis of subsequent experience following the initial CHD event is available.

It has also been noted by the Committee that "the physical plant is inadequate to realize fully the potential of the study. Working space should be at least doubled". Dr. Ralph Paffenbarger has moved his unit out increasing the cramped space at 123 Lincoln Street. The laboratory has been moved out of the primitive quarters in the basement to the first floor, but not without many delays and administrative difficulties. It should be operative in its new location by the end of June 1968. Space at the clinic in the hospital is adequate for current needs. Re-evaluation of space requirements may be necessary if, in addition to the present cohort, the twin studies proposed by Dr. Feinleib are to be implemented. The latter proposal may also necessitate re-evaluation of examining physician staffing.

Proposal for the Future at Framingham

In general there are three broad directions the Framingham Heart Study can take:

1. Phase out the study of the original Framingham cohort under the present protocol beginning at the end of the 11th biennial examination (June 1972). Thereafter, maintain medical surveillance of the population indefinitely on a streamlined basis making no new observations of population characteristics, but continue medical surveillance for new disease events including CHD, peripheral vascular disease, cerebrovascular disease, hypertensive cardiovascular disease, and congestive heart failure. The clinic would be maintained only to examine subjects who had been admitted to the hospital for cardiovascular disease when it is necessary to clarify the diagnosis according to established criteria. Surveillance of deaths should also be maintained. This would be supplemented by an annual mail questionnaire. An underestimate of incidence would be likely, missing unrecognized myocardial infarctions, non-hospitalized angina pectoris and some strokes and congestive heart failure managed at home or in nursing homes. Prospective study of factors related to identified bonafide disease would, however, be quite feasible. Studies of the natural history of these diseases, once established, could be carried out but would be distorted by lack of information on the unidentified, possibly milder, disease not identifiable without continued biennial examination of the entire population sample.

2. Institute new studies in the old cohort which emphasize the natural history of established coronary heart disease, cerebrovascular accident, and peripheral vascular disease. Also those related to congestive heart failure. Emphasis is to be given here to an assessment and identification of factors which precipitated attacks in vulnerable persons as well as those which herald the onset of asymptomatic and symptomatic disease and lead to recurrences and affect survival.

3. Investigate new hypotheses in a new cohort of the locally available offspring of the present cohort as they reach 30 years of age. This is desirable if the epidemiology section of the National Heart Institute would like to maintain a position of leadership and give direction to epidemiologic research in cardiovascular disease. Recent innovations in methodology for assessing physical fitness, lipid patterns, carbohydrate metabolism, body composition, urinary catecholamine excretion, androgens, clotting factors, post-exercise electrocardiographic changes, and diet assessment, among others, will have to be implemented. Latest techniques and instrumentation for the early detection of cardiovascular impairments should be employed. Twin studies as proposed by Dr. Feinleib should be implemented to assess genetics as well as environmental factors in these diseases.

New objectives may be implemented as old objectives are phased out. Planning for the implementation of each of these objectives must be undertaken simultaneously if more than one is to be attempted. An early policy decision concerning these various alternatives seems imperative. While a good many cases of these various disease outcomes of interest have accumulated in the population over the period of observation, as many cases as these appear to be, it is far from enough to answer the many questions raised by the studies completed to date and to clearly delineate the natural history of the disease once established.

Despite the large number of cases of CHD, after 14 years of follow-up there were only 42 sudden unexpected deaths to study in men, clearly not enough for a detailed examination of factors related to the occurrence of this important lethal manifestation of the disease. In 14 years of follow-up there were 135 cases of stroke with 86 cases of athero-thrombotic brain infarction for analysis. Cases to date have allowed a fruitful preliminary analysis, the results of which have been published. Before the details of the relationships established and the natural history of this disease can be adequately explored, it is clear that further follow-up experience will be required.

There are now 125 cases of intermittent claudication in the population. Preliminary analysis has also yielded useful information, but again more experience will have to be accumulated before an adequate examination of its precursors can be completed. Work with the pulse recording device now in continuous operation in the general population sample indicates that we are detecting only a small fraction of the existing peripheral vascular disease by identifying only persons with symptomatic disease.

The Framingham Study investigations over the past 18 years have raised as many questions as have been answered, for example:

(1) Age. It is well established that cardiovascular mortality rises over the age range included in the Framingham Study. In particular, the incidence of cerebrovascular disease and intermittent claudication rises without apparent break from age 29 to 76 years. Similarly the blood pressure of surviving cohorts rises throughout this age span. It is surprising to find that this includes a diastolic pressure rise to age 74, since cross-sectional data (including that from Framingham) generally levels out at about age 55. The one notable exception to the tendency for cardiovascular incidence to rise with age is coronary heart disease. In men this rises only to age 55 and then levels off. These age trends require further detailed analysis.

(2) Sex. All cardiovascular disease outcomes do not appear to have a uniform sex ratio. CHD is predominantly a male disease. Men and women are equally susceptible to cerebrovascular disease, including athero-thrombotic brain infarction. Intermittent claudication incidence has an intermediate sex ratio. This requires further investigation.

(3) Blood Pressure. Most hypertension that has appeared in the population sample has developed insidiously among persons whose initial blood pressure was just below the hypertensive range. There is little incidence of hypertension secondary to other conditions. Very few persons have had an abrupt onset of hypertension. Blood pressure elevation has proven to be the most ubiquitous of the factors leading to the development of the major cardiovascular diseases including all manifestations of coronary heart disease, stroke, peripheral vascular disease and congestive heart failure. Systolic pressure has been found to be as strikingly related to these disease outcomes as diastolic. Also, there is some indication that lability adds to risk at any blood pressure level. These findings require further investigation.

(4) Cholesterol. A relationship of serum cholesterol to development of every manifestation of coronary heart disease has been conclusively demonstrated. It is now demonstrated that several types of "hypercholesterolemia" exists. It would seem reasonable to determine whether the risk of CHD is any different depending on whether a given degree of hypercholesterolemia is associated with one or another lipoprotein pattern. Also it should be determined whether the manner in which cholesterol is transported in the lipoprotein fraction is important in atherogenesis and the development of coronary heart disease. The relationship of blood lipid content to the development of other atherosclerotic disease outcomes such as intermittent claudication and brain infarction has not been nearly as striking as that for coronary heart disease, particularly for lipids measured after the age of 50. Further examination of the relationship of blood lipid content to these disease outcomes is required to clarify the issue. Also, the role of endogenous triglyceride, diabetes, obesity and gout related both to blood lipid and to coronary heart disease needs to be explored further.

(5) Electrocardiographic Abnormalities. Electrocardiographic abnormalities have been demonstrated to be distinctly and strikingly related to the development of all of the major disease outcomes under consideration, they require more detailed analysis. Studies of left ventricular hypertrophy in particular have been undertaken with the assistance of Mr. Tavia Gordon of Biometrics, and this has been demonstrated to be indeed a lethal precursor for all major manifestations of atherosclerosis, congestive heart failure, and cerebrovascular disease. The effect of this independent often associated hypertension is being assessed. The individual ECG abnormalities including, in addition, intraventricular block, nonspecific abnormalities, and atrial fibrillation need to be explored taking into account all of these ECG abnormalities developing under the period of observation. It is possible, but not proved, that the appearance of these abnormalities in predisposed individuals heralds the onset of asymptomatic coronary heart disease with myocardial involvement. Further study is required to examine this hypothesis. Data being generated by the autopsy studies should reflect on this issue.

(6) Cigarette Habit. This established risk factor needs further study to determine why its effect is so weak in women. This appears to be attributable to the fact that so many women cigarette smokers do not inhale, and seldom smoke heavily. The effect of filters, if any, needs to be examined. Also, the effect of change in habit under observation, such as giving up the habit, switching to cigar and pipe, increase and decrease in cigarette consumption, use of cigarettes, inhaling practices, etc., need to be assessed in further detail using information gathered subsequent to the initial examination. The effect of the cigarette habit in those with an irritable myocardium as evidenced by frequent premature beats needs to be further explored in relation to sudden death.

(7) A number of major hypotheses remain to be adequately tested and should be given high priority. One, the diet hypothesis. The role of specific nutrients (including the ratio of simple to complex carbohydrate, polyunsaturated to saturated fatty acid ratio, dietary cholesterol, calories per pound, meal patterns and salt intake) in relation to development of CHD, stroke , and peripheral vascular disease, remains to be tested prospectively. Also, the relation of these dietary characteristics to degree of susceptibility to CHD and to risk factors such as lipid pattern, blood pressure, adiposity, and carbohydrate intolerance should be evaluated. Additional disease outcomes which should be examined in relation to diet include hypertensive cardiovascular disease, congestive heart failure, gout and diabetes. The determinants of diet patterns in the population are being explored, and spouse aggregation of eating habits are being examined with interesting results. A preliminary analysis of the relation of antecedent nutrient intakes to subsequent disease outcomes and to degree of susceptibility to disease has been completed. No striking relationships have been

demonstrated. Further study relating specific nutrient intakes to lipoprotein pattern are required in view of the recently described carbohydrate sensitive and saturated fat and cholesterol sensitive types of lipidemia.

(8) The relation of sedentary living to risk of fatal outcome in CHD in particular, needs further investigation. The effect of activity independent of lipids, blood pressure, and obesity remains to be clarified. Also, its effect in subjects with occult disease as regards recurrences and the case fatality rate in recurrences needs examination. The effect of activity must be differentiated from "fitness" or the ability of the organism to cope efficiently with an increased load. Re-assessment of physical activity needs to be made, and is planned for the next round of examinations (XI).

(9) Emotional factors and stress as well as personality are being analyzed in detail by Drs. Norman Scotch and Sol Levine utilizing the completed stress interview obtained over the 8th and 9th examinations. The material is now on tape and is going to be correlated with the disease outcomes and risk attributes. The interrelationship of emotional factors with lipid content, blood pressure, adiposity, and the cigarette habit needs to be explored.

(10) The role of impaired carbohydrate tolerance needs to be tested prospectively to assess the magnitude in detail of its relationship to coronary heart disease and to lethal outcome once the disease occurs. Also, its relationship to other atherosclerotic outcomes such as stroke and peripheral vascular disease as well as hypertension needs further study. The relation of impaired carbohydrate tolerance to lipid patterns prior to the subsequent development of diabetes has been explored in a preliminary fashion and indicates that the lipid abnormalities may well antedate the demonstrable impairment of carbohydrate intolerance. This requires further study.

(11) Clotting factors still need evaluation. Preliminary studies utilizing the existing techniques have not been too revealing, but are being studied and analyzed further based on a case-matched control comparison completed over the last year. It is recognized that thrombosis is an essential or prominent feature in clinically manifest atherosclerotic disease. Factors which inhance clotting tendency and the relation of an increased propensity to thrombus formation to the development of coronary disease, strokes, and peripheral vascular disease have yet to be explored definitively.

(12) The relation of blood hemoglobin and hematocrit content to risk of athero-thrombotic disease requires further evaluation. Preliminary studies have demonstrated interesting relationships of blood hemoglobin content to hypertension, to stroke, and possibly to coronary heart disease. Whether these reflect changes in viscosity of the blood, variations in blood volume, or some other phenomenon such as the elaboration of erythropoietin by the kidney, needs to be elucidated.

(13) Autopsy studies designed to provide a detailed description, grading, and assessment of the nature of athero-thrombotic involvement of the coronary vessels are being carried out. It is planned to expand this to include similar grading of the vascular disease in the brain and possibly the kidney. The aim is to relate traits and habits of individuals ante-mortem to the condition of their blood vessels as well as to clinical events.

(14) The role of impaired cardiac function in the development of strokes and peripheral vascular disease needs to be further explored. Preliminary analysis of the epidemiologic data strongly suggests that strokes may be precipitated by occult impairment of cardiac function.

(15) Factors predisposing to the development of congestive heart failure in the general population need to be explored further. Promising data are already emerging and the details of the relationships demonstrated in preliminary fashion require further exploration. The underlying basis of most congestive failure, the precipitating factors and the natural history of failure once detected has not been adequately explored previously and should be given high priority.

(16) The relation of trace metals to hypertension, atherosclerotic disease, and diabetes should be evaluated. Attempt has been made to evaluate this from frozen serum specimens before and after the event, but with respect to serum copper levels this has proven unrewarding. Plans are being made to analyze tissue specimens from vessels, atheromata, kidney, brain and heart in an effort to see if tissue trace metal levels are disturbed in persons developing disease of these organs as compared to their cohorts who die without developing involvement of these organ systems.

(17) Studies of cancer are possible in this population. It is anticipated that enough gastrointestinal and breast cancer will occur in this population to consider exploring the relation of some of the factors measured in the population to risk of these diseases.

(18) Data have been collected which allow a study of chronic bronchitis and emphysema in this population. Dr. Albert Roberts has taken steps to explore the epidemiology of these respiratory disorders in this general population sample in relation to antecedent traits and living habits. Pulmonary function studies are currently being repeated on the 10th and the 11th examinations.

(19) Genetic and familial factors are being studied in relation to the diseases under study and to traits predisposing to them. Studies of aggregation of disease and traits in spouses and siblings of subjects in the study are being explored by Drs. David Sackett and Manning Feinleib. Plans

are being considered to call in offspring of study subjects who have been identified as having certain biochemical and physiologic abnormalities to determine to what extent these may be familial. Finally, the relation of age to development of coronary heart disease and stroke among parents of subjects in the study, and in sibs of study subjects also being examined in the study should be explored. Dr. Wen-ping Tseng in collaboration with Dr. Sackett has undertaken to do a case-matched control comparison of family histories of these atherosclerotic diseases among subjects who have developed CHD while participating in the study.

The research endeavors at Framingham should yield information not now available, and information which is not a duplication of effort in the National Heart Institute or elsewhere. It is the conclusion of the Review Committees and of the Director of the Study that the Study has by no means exhausted its potential. Somewhere, sometime - and it might as well be now and at Framingham - someone should study the natural history of cardiovascular disease including the circumstances under which it develops, arises, flourishes, follows its course and terminates fatally in a general population sample followed until most of the population has expired. It would seem reasonable to keep up this study of the general population at Framingham as long as useful information is being obtained and reported. Since a good start at this has been made, it is reasonable to continue to do so.

Publications over the preceding year are listed below:

"Obesity, a hazard to health". H. E. Thomas Jr., W. B. Kannel, and P. M. McNamara. Med. Times 95:1099-1106, Oct. 1967.

"The coronary profile - 12 year follow-up in the Framingham Study". W. B. Kannel, M.D., W. P. Castelli, M. D., and Patricia M. McNamara. Jour. of Occup. Med. Vol. 9. No 12:611-619. Dec. 1967.

"Coronary heart disease. Identification of susceptible individuals". T. R. Dawber, and P. M. McNamara. In Brest, A. N. and Moyer, J. H. (Eds.) Atherosclerotic Vascular Disease. A Hahnemann Symposium. New York, Appleton-Century-Crofts, pp 130-146, 1967.

"Epidemiology of Stroke". W. B. Kannel, B. L. Troy, and P. M. McNamara. U. S. Department of Health, Education and Welfare, Public Health Service, Publ. No. 1607, Washington, D. C. U.S. Gov. Printing Office. 8 pp. 1967

"Cigarette smoking and risk of coronary heart disease. Epidemiologic clues to pathogenesis. The Framingham Study". William B. Kannel, M. D., William P. Castelli, M. D., and Patricia M. McNamara. National Cancer Institute, Monograph 28. In press.

"The early diagnosis of coronary heart disease". Thomas R. Dawber and William B. Kannel, Presymptomatic Detection and Early Diagnosis. Pitman Publishing Company, Ltd. London, W. 1, England. In press.

Progress Report of Collaborative Studies

Anthropological studies of the relation of body form to development of coronary heart disease have been completed by Dr. Albert Damon in collaboration with the Framingham Staff. These studies have revealed a relationship of mesomorphy and endomorphy, but not ectomorphy to the development of manifestations of coronary disease other than myocardial infarction. Furthermore, these relationships have proven to be independent of adiposity per se according to discriminant function analysis carried out by Dr. Damon. This paper has passed review by the National Heart Institute and has been submitted for publication in the Journal of Chronic Diseases.

Copper studies in relation to development of myocardial infarction have been analyzed by Drs. Feinleib and Harman. Unfortunately, no statistically significant relationship between serum copper levels and subsequent development of infarction could be demonstrated. This may have arisen from difficulty in using frozen serum specimens for this purpose. Plans for doing an analysis of tissues obtained at autopsy for trace metals are being considered.

In collaboration with Drs. Sackett and Feinleib, studies of spouse aggregation of disease and predisposing risk attributes are being planned.

A study of osteoporosis in collaboration with Drs. Mark Hegsted and Robert McGandy of Harvard is under way. X-ray examination of the spine to determine bone density is being obtained on subjects participating in the study. Also, urine specimens for determination of calcium, magnesium, phosphorous and creatinine are being collected and sent to Harvard for analysis. Previously collected dietary data are being analyzed for dietary calcium and other nutrients in order to examine its relation to bone density. The objectives are to examine the relation of the presence of osteoporosis and its 12 year progression by radiological estimation to appropriate antecedent data on nutritional, hormonal, and physical activity factors.

Also, the presence of calcification of the abdominal aorta as assessed on these same x-rays will be examined in relation to the various clinical

manifestations of atherosclerotic disease, as well as to the several "risk factors" associated with these clinical manifestations. In addition, the extent of arthritis in these same films may be examined by Dr. Arthur Hall of the Robert Breck Brigham Hospital. Particular interest is in the relation of dietary intake of calcium, protein, and more recently fluoride and phosphate to osteoporosis. Also endocrine changes associated with aging - especially those which are related to menopause in women will be assessed. The stresses and demands of pregnancy and lactation in women will also be considered. Detailed information on dietary practices was obtained on a subsample of approximately 900 men and women some 10 years ago. Analyses of these records may in fact be more pertinent to a study of current osteoporosis status than dietary data collected now. Lateral lumbar x-rays were obtained on a subsample of 575 men and women some 12 years ago as part of another survey. Five hundred of these subjects are still alive and in the study. Over the past 10 years several hundred 24 hour urine specimens have been analyzed for estrogens, androgens, and other steroids at the Worcester Foundation for Experimental Biology. These data also will be available for examination in relation to osteoporosis. Attempt will be made to assess the presence of and to quantitate the extent of osteoporosis on the subsample of x-rays taken 12 years ago. The same measurements will be obtained on the current x-ray film. The casual urine specimens obtained on the entire population will be analyzed for calcium, magnesium, phosphorous, and creatinine. The 900 previously obtained dietary histories have already been coded and analyzed for estimates of intake of calories, protein and fat. These analyses are being extended to include an estimate of the usual daily intake of calcium, magnesium and phosphorous. Depending on the kinds of relationships demonstrated in the 900 subjects with dietary information, it may be desirable and feasible to attempt some type of rapid assessment of mineral intake in the entire population. Aside from establishing the true prevalence of osteoporosis in a defined sample of men and women ages 48 to 77 in an American community, this proposed study offers the unique opportunity to relate this disease to various physical and environmental factors suggested as having an etiological role. Moreover, it will be possible to relate the rate of progression of osteoporosis in individuals to the above-mentioned factors. This will also allow some estimate of the incidence of this disease. Work is progressing well in the study and some 500 persons have already been processed.

Studies of gout and its relationship to atherosclerotic disease continue under the guidance of Drs. Hall and Barry of the Robert Breck Brigham Hospital in collaboration with the Framingham Staff. Eight additional cases of gout have been uncovered over the past year. Studies of rheumatoid and osteoarthritis are continuing. The relationship of hyperuricemia and gouty diathesis to development of coronary heart disease independent of the associated lipid abnormalities, obesity and hypertension common to both gout and atherosclerotic disease are being evaluated in more detail.

An extensive, in-house document comprising a monograph of data produced at Framingham over the past 14 years has been prepared by Mr. Tavia Gordon and his staff. This has provided a highly useful compilation of data including distributions of disease and predisposing traits in the entire population over each biennial examination. This will provide a valuable source for answering queries both from outside the study and within the study concerning a wide variety of variables.

Below is a listing of obligations by type in the Framingham Study.

Type		Cumulative FY 1967	Estimated total FY 1968
11	Personnel Services	$188,668.77	$202,650.00
12	Related Costs	10,798.77	21,950.00
21	Travel	7,554.21	8,000.00
22	Transportation of things	2,090.28	1,825.00
23	Rent, Communications, Utilities	6,562.00	28,750.00
24	Printing and reproduction	180.00	35.00
25	Other contractual services	7,829.28	25,000.00
26	Supplies and materials	21,166.14	23,000.00
31	Equipment	9,539.44	6,200.00
	Total	$254,388.89	$294,340.00

The Staff for the fiscal year 1967-1968 are indicated below:

Commissioned Officers
William B. Kannel, Medical Director.
William P. Castelli, Senior Asst. Surgeon.
Bart L. Troy, Surgeon (Terminated May 1968.)
Melvin J. Schwartz, Surgeon (Terminating June 1968.)
Georgiana Pearson, Dietitian.

Physicians-Civil Service
Nicholas Revotskie, GS-12, Medical Officer, 50% part-time.
H. Emerson Thomas Jr., GS-11 Medical Officer, 20% part-time, Resigned May 1968.
John S. Banas, GS-11, Medical Officer, 10% part-time.

Consultants
Dr. Lloyd E. Hawes, Radiologist.
Dr. Thomas R. Dawber, Cardiology.

Supporting Staff-Administrative
Anna S. Glennon, Administrative Officer (GS-9).
Edna B. Carboneau, Secretary (Stenographer)(GS-6)
Marguerite Beattie, Clerk, Dictating Machine Transcriber (GS-4).
Judith Sabourin, Clerk-typist (GS-2).

Statistical
Patricia M. McNamara, Statistician (GS-11).
Dorothy Costello, Statistical Clerk (GS-6).
Marilyn Sanfacon, Statistical Clerk (GS-5). Terminated March 1968.
Lorraine Girard, Statistical Coding Clerk (GS-4).
Ruth Anderson, Statistical Coding Clerk (GS-4).

Laboratory
Robert Moran, Chemist (GS-7).
Gertrude Metzger, Medical Technician (GS-6).
Frederick Uhrig, Medical Aid (GS-4).
Albina Mariano, Medical Technician (50% part-time (GS-6).
Noemia Bravo, Medical Aid (Medical) 75% part-time (GS-4).
Marianne Moran, Chemist (20% part-time) GS-5).

Clinic Staff
Mrs. Lorna P. Lyell, Project Aid (GS-8).
Mrs. Irene Renner, R. N. (GS-6).
Mrs. Carleen Simoneau, R. N. (GS-6).
Mrs. Doris Honey, Clerk-typist (GS-4).
J. William Claffey, X-ray technician (GS-7).

As of the change of fiscal year we are losing Drs. Melvin J. Schwartz and Bart L. Troy, Commissioned Officers assigned to the study. They will be replaced by Dr. Mariano Garcia, a Commissioned Officer who will enter on duty July 1, 1968.

Dr. H. Emerson Thomas, part-time Civil Service Medical Officer has resigned and is to be replaced by Dr. George L. Cohen of the Massachusetts General Hospital. Dr. Cohen will enter on duty July 1, 1968.

In addition, in order to replace the Commissioned Officer not being assigned, Dr. Robert C. Moellering formerly of The Hawaii Study, now at the Massachusetts General Hospital is being considered for a part-time position. Dr. Philip A. Wolf will provide neurological consultation. Dr. Wolf will report for duty July 1, 1968.

Senior professional staff will consist of the following:

Commissioned Officers
William B. Kannel, Medical Director.
William P. Castelli, Senior Surgeon.
Georgiana Pearson, Dietitian.

Associate physician on duty July 1, 1968
Mariano Garcia, Surgeon (R).

Part-time examining physicians
Nicholas Revotskie, GS-12 Medical Officer, 50% part-time.
John S. Banas, GS-11 Medical Officer, 10% part-time.
Philip A. Wolf, neurologist GS-12 WAE, July 1, 1968.
George L. Cohen, GS-11, Medical Officer, 25% part-time, July 1, 1968.
Robert C. Moellering, GS-11, Medical Officer, 25% part-time. May report in September 1968.

Consultants
Dr. Lloyd E. Hawes, Radiologist.
Dr. Thomas R. Dawber, Cardiology.

Supporting Staff. As mentioned previously.

Clinic Operation

The 11th biennial clinic examination of the population is being initiated, and it is anticipated this will begin in September 1968. The 10th examination is being completed. The 11th biennial examination will emphasize peripheral vascular disease, stroke, and congestive failure, as well as the continued surveillance for evidence of coronary heart disease. The medical examinations continue to be performed by full-time Commissioned Officer physicians assigned to the study, and in addition, two former full-time examiners in the study perform some of the examinations on a part-time Civil Service status. As indicated previously, two additional Civil Service part-time employees have been recruited to do examinations as well as a neurological consultant. Electrocardiograms, chest x-rays, a pulmonary function test, oscillographic peripheral vascular assessment, measurements of body fat and body build are being obtained by the nursing and technical personnel.

Abstracts Published

"Hemoglobin content and risk of athero-thrombotic brain infarction". William B. Kannel, Bart L. Troy, Patrick A. McKee, and Patricia M. McNamara. Circulation 36, No. 4. Suppl. 11:20, October 1967.

"Physical activity and risk of fatal coronary heart disease: The Framingham Study". William B. Kannel and Patricia M. McNamara Circulation 36, No. 4. Suppl. 11:154, October 1967.

"Relation of hemoglobin level to hypertension: The Framingham Study" Patrick A. McKee, William B. Kannel, and Patricia M. McNamara. Circulation 36. No. 4 Suppl. 11:178, October 1967.

Papers Presented

" Cigarette smoking and risk of coronary heart disease. Epidemiologic clues to pathogenesis: The Framingham Study". World Congress on Smoking and Health, New York City. Sept 1967. Dr. William B. Kannel.

"Obesity, a force of morbidity and mortality". American Medical Association. Boston, Mass. Oct. 1967. Dr. William B. Kannel.

"Physical activity and risk of fatal coronary heart disease: The Framingham Study."American Heart Association, San Francisco, California. October 1967. Dr. William B. Kannel.

"Blood hemoglobin content and risk of athero-thrombotic brain infarction". Council on Atherosclerosis. San Francisco, California, October 1967. Dr. William B. Kannel.

"Type of hypercholesterolemia and risk of coronary heart disease". 8th Conference on Cardiovascular Epidemiology, Atlanta, Georgia, Feb 1968. Dr. William B. Kannel.

"Overweight and coronary heart disease. Epidemiologic and autopsy correlation: The Framingham Study". Clinical Society and Commissioned Officers Association meeting. San Francisco, California. March 1968. Dr. William B. Kannel.

Manuscripts based on these papers are being prepared.

Exhibits

The study personnel continue to man on occasion two exhibits dealing with habits in relation to coronary disease, and the epidemiology of stroke. This latter exhibit has won an award at the American Osteopathic Association.

Reprints

Requests for reprints continue to pour in from world-wide areas. It is estimated that an excess of 3500 requests were honored this past year, excluding the many reprints given out with the Framingham Heart Study exhibit.

Individual Project Report

Project Title:	Blood Hemoglobin Content and Risk of Athero-thrombotic brain infarction.
Principal Investigator:	William B. Kannel, M. D.
Other Investigator:	Bart L. Troy, M. D.
Cooperating Unit:	Tavia Gordon - Biometrics.

Description:

Objectives: To examine the relation of blood hemoglobin content to risk of thrombotic strokes.

Methods Employed: Standard methods-hemoglobin and hematocrit employed. Clinical criteria employed for diagnosis of stroke. Blood hemoglobin was determined by the cyano-methemoglobin method.

Major Findings: The risk of initial development of 86 strokes attributed to athero-thrombotic brain infarction of the brain over 14 years of biennial follow-up was explored in 5,209 men and women aged 30-62 years who were classified into subgroups according to blood hemoglobin content and blood pressure status at the time of their first examination.

Persons with an "elevated" blood hemoglobin content (i. e., 15 gms. or above in men; 14 gms or above in women) on the initial examination developed almost twice as many thrombotic strokes as did their cohorts with lower hemoglobin levels. Hypertension proved to be a potent predisposing factor in the development of athero-thrombotic brain infarction, confirming prospectively the long recognized clinical observation. A distinct relationship of the blood hemoglobin concentration on the initial examination to the prevalence and subsequent incidence of hypert ension was discovered. This was particularly striking in women.

Further analysis was consequently undertaken by examining the rate of occurrence of athero-thrombotic brain infarction according to blood hemoglobin content at specified levels of blood pressure. Whether or not hypertension was present, those with higher hemoglobin levels appeared to develop an excess of strokes. Those who were both hypertensive and had a high blood hemoglobin content appeared to exhibit a substantially higher risk than did those with either abnormality alone and had about five times

the risk of their cohorts with neither abnormality. Because of the correlation between hemoglobin and blood pressure, it was not possible to demonstrate conclusively that the contribution of hemoglobin to risk was independent of the associated hypertension.

Significance to Biomedical Research: The hemoglobin content of the blood influences its viscosity, oxygen content, dynamics of flow and possibly its clotting characteristics. This could provide a number of pathogenetic mechanisms in exploration of a possible relation of blood hemoglobin level to the development of atherosclerotic disease in general, and to the occurrence of athero-thrombotic brain infarction in particular.

The blood hemoglobin content may be added to the various factors identified as predisposing to the development of thrombotic strokes. The pathogenetic mechanism remains to be elucidated, both for its association with stroke and hypertension.

Individual Project Report

Project Title:	Factors of Risk in the Development of Osteoporosis.
Principal Investigator:	Mark Hegsted, Ph. D.
Other Investigators:	Robert McGandy, M. D. Fredrick Stare, M. D.
Cooperating Unit:	W. B. Kannel, M. D. Framingham Heart Disease Epidemiology Study.

Description:

Objectives: To examine the relation of the presence of osteoporosis and to its 12 year progression by radiologic estimation to appropriate antecedent data on nutritional, hormonal, and physical activity factors.

Methods Employed: X-ray examination of the lumbosacral spine. Bone density and specified measurements of vertabrae made on subjects returning for their 9th and 10th biennial examinations. Urine specimens are being collected and analyzed for calcium, magnesium, phosphorous, and creatinine. Previously collected dietary data are being analyzed for dietary calcium and other nutrient content in order to examine its relation to bone density.

Work in Progress: Particular interest is in the relation of dietary intake of calcium, protein, fluoride and phosphate to development of osteoporosis. Also, endocrine changes associated with aging, especially those in women which are related to menopause will be assessed. The stresses and demands of frequency and lactation will also be considered.

Detailed information on dietary practices was obtained on a subsample of approximately 900 men and women some 10 years ago. Analyses of these records may in fact be more pertinent to a study of current osteoporosis status than dietary data collected now.

Lateral lumbar x-rays were obtained on a subsample of 575 men and women some 12 years ago as part of another survey. Some 500 of these subjects are still alive and being followed in the study. Over the past 10 years several 24 hour urine samples have been analyzed for estrogen,

androgen, and other steroids at the Worcester Foundation for Experimental Biology. These data will also be available for examination in relation to osteoporosis. Attempt will be made to assess the presence of, and to quantitate the extent of osteoporosis on the subsample of x-rays taken 12 years ago. The same measurements will be obtained on the current x-ray film. The casual urine specimens obtained on the entire population will be analyzed for calcium, magnesium, phosphorous and creatinine. The 900 previously obtained dietary histories have already been coded and analyzed to provide estimates of calories, protein, and fat intake. These analyses are being extended to include an estimate of the usual daily intake of calcium, magnesium and phosphorous.

Individual Project Report

Project Title:	Serum Lipid Patterns and Risk of Athero-thrombotic Brain Infarction.
Principal Investigator:	William B. Kannel, M. D.
Other Investigator:	William P. Castelli, M. D.
Cooperating Unit:	Tavia Gordon - Biometrics.

Description

Objective: To examine the relation of antecedent blood lipid pattern to risk of subsequent thrombotic strokes.

Methods Employed: Standard biochemical determinations of cholesterol, phospholipid, and triglyceride. Lipoprotein fractions were determined by ultracentrifugal analysis at Donner Laboratories by Dr. John Gofman. Diagnosis of athero-thrombotic brain infarction was based on clinical findings.

Major Findings: Lipid patterns including the lipids cholesterol and phospholipid and the triglyceride-rich Sf0-20 beta lipoprotein were measured at the time of initial examination of 5,209 men and women aged 30-62. These subjects have been followed for the development of athero-thrombotic brain infarctions since that time and 14 years of follow-up experience according to antecedent lipid characteristics can now be reported.

The risk of development of 86 athero-thrombotic brain infarctions in the period of follow-up proved to be related to the antecedent level of each of the lipids and lipoproteins under investigation, but only if measured prior to age 50. An association between serum cholesterol and development of athero-thrombotic brain infarction could not be demonstrated for the cohort as a whole, but for persons under age 50 there was a strong suggestion that the higher the serum cholesterol concentration the greater the likelihood that an athero-thrombotic brain infarction will occur. The risk gradients were similar for the two sexes.

Phospholipid was associated with the incidence of athero-thrombotic brain infarction in men under 50, but this was not statistically significant. There was no suggestion of a relationship in women of all ages, or in older men.

The beta lipoproteins (Sf0-20) were significantly associated with the incidence of athero-thrombotic brain infarction in the cohort as a whole, and in most age-sex groups.

Risk of athero-thrombotic brain infarction was also proportional to antecedent pre-beta (Sf20-400) lipoprotein level, especially for men under 55. Such an association could not be demonstrated for women.

Those with multiple lipid abnormalities appeared to be at greater risk than those with single abnormalities. This may be a statistical artifact resulting from the fact that the level of each particular lipid is also proportional to the number of lipid "abnormalities".

It would appear that lipids make a significant contribution to the development of athero-thrombotic brain infarctions, but hypertension must be assigned a substantially greater role.

Significance to Biomedical Research: Knowledge to date concerning the relation of blood lipids to the development of athero-thrombotic brain infarction, a major manifestation of atherosclerosis, is inconclusive. Most studies, comparing cases and controls of advanced age have failed to demonstrate a relationship after the event. Few studies of lipids other than cholesterol are available. Prospective studies of the relation of lipids to stroke are rare.

The data available provide no basis for selecting among these lipids and lipoproteins that one most basic to cerebral atherogenesis. No lipid is clearly superior to another for predicting brain infarctions. It is possible but not conclusively demonstrated, that a number of lipids are involved in cerebral atherogenesis accelerated by the blood pressure.

Proposed Future Research: Further investigation of the details of the relationship are warranted. More sophisticated analysis using stepwise regression discriminant function analysis to assess the contribution of each lipid to risk should be undertaken after more follow-up yields a larger number of cases with which to work.

Individual Project Report

Project Title:	Spouse Aggregation of Cardiovascular Disease Outcomes and Factors Predisposing to them.
Principal Investigator:	David Sackett, M. D.
Other Investigator:	Manning Feinleib, M. D. -Biometrics.
Cooperating Unit:	W. B. Kannel, M. D. Framingham Heart Disease Epidemiology Study.

Objective: To examine husband-wife relationships with respect to various risk factors and disease outcomes.

Methods: The Spouse Aggregation Study initiated by Dr. David Sackett will use the 1,516 pairs identified in the Framingham Heart Study to examine husband-wife relationships with respect to various risk factors and disease outcomes. The value of such a study in elucidating environmental components in the etiology of cardiovascular disease is obvious, as is its value in supplementing the knowledge of genetic factors gained in analysis of parent-offspring, sib-sib, and pedigree data.

The initial step in the study will be to identify all spouse pairs and to classify them by marital history. In particular, spouse pairs representing single, continuous marriage will form the core of the study group, other spouse pairs being analyzed separately. A roster of family numbers and blood lines has been established for all persons in the Framingham Heart Study (Decks 60, 64, 505). A list of all identified spouse pairs is available. The marital status of these pairs will be obtained from the data obtained in the Levine-Scotch study. Before the data from this latter file are incorporated into the Framingham file, a subsample of these records will be verified against the personal history records in the Framingham Study. This will involve the following procedures:

1. Marital history is obtained from L-S record.
2. Framingham record is located and marital history checked.
3. Framingham record of spouse is obtained, and marital history given by spouse is checked.
4. L-S record of spouse is located and marital history checked.
5. All of the above sources are checked against Deck 505 listing.

It is proposed that about 300 records will be checked in this way by a clerk supplied by Dr. Sackett through a pending grant from the Ontario Provincial Health Council. It was decided, arbitrarily, that if 7% or more of the records contain inconsistencies, the entire project would be re-evaluated with a view towards doing a complete verification of all spouse pair records. If less than this rate of errors is found, the study will proceed.

The second step will involve the merging of the information about marital history and family numbers with the data on risk factors and disease outcome. To this end Deck 505 (248 fields) marital data from the L-S tape (1 field), and tape 0641 (3 fields) will be combined into a new tape containing 252 fields for each patient.

Note: L-S data are available for only about 60% of the Framingham cohort. For the other members of the cohort the data obtained at Framingham will be used, with no further validation.

The third step will be the analysis of the data. Several alternative and complementary approaches will be used. In order to obtain normally distributed values of quantitative measurements, scale transformations will be used where possible. Other ordering techniques such as ranks, percentiles, and the ORDAC method will also be tried. Correlation analysis and the analysis of variance techniques will be used to measure the association of characteristics in spouse pairs and for detecting changes in the strength of the associations by duration of marriage. Various techniques will be used to adjust for age at marriage and age at examination.

There will be close communication between Drs. Sackett, Feinleib, Kannel, and Tavia Gordon at all stages of the data retrieval and analysis. Duplicate copies of the work tapes will be maintained by Drs. Sackett and Feinleib. It was mutually agreed that senior authorship on publications would go to the investigator contributing the major share of work to each publication. All manuscripts will be required to undergo National Heart Institute editorial review prior to submission for publication.

It is anticipated that Dr. Sackett's grant will be funded this Fall and the verification of the files will begin at that time. Verification is expected to take about three months. Allowing two months for creating and checking out the tapes, it is expected that analysis of the data can be done during the Spring and Summer of 1969.

ANNUAL REPORT OF THE FIELD EPIDEMIOLOGICAL RESEARCH SECTION, NATIONAL HEART INSTITUTE, NATIONAL INSTITUTES OF HEALTH

July 1, 1967 through June 30, 1968

CONTENTS

I. INTRODUCTION

This Section has been concerned with identifying patterns of living and personal characteristics in youth that might point to the development of specific chronic diseases later in life. Using predocumented data in the form of college case-taking and other records of 18 to 53 years ago, 50,000 male former students from Harvard and the University of Pennsylvania have been followed for the development of cardiovascular and other diseases. Self-administered questionnaires, follow-up case-taking, and official death certificates have identified the end-point diseases of interest.

In the past fiscal year, the activities of the Section have been sponsored equally by the National Heart Institute and the Center for Studies of Suicide Prevention, National Institute of Mental Health. Accordingly, interest and work have been divided proportionately between categorical diseases of concern to these two Institutes. Details of activities are summarized in the paragraphs that follow.

II. HYPERTENSION

Doctor-diagnosed high blood pressure was reported by 671 (8.7 per cent) of 7,685 men who had attended the University of Pennsylvania, 1931-1940, and completed a self-administered questionnaire in 1962. The incidence of hypertension was determined for the 22-31 year follow-up interval in terms of characteristics extracted from college medical and athletic records.

The University had mailed questionnaires asking for the presence of doctor-diagnosed high blood pressure and specific diseases to 9,565 former

students. An 80 per cent response was realized from three mailings. Re-examination of a small validation sample showed the sensitivity of the questionnaire for hypertension to be 80 per cent and its specificity 97 per cent.

The mean age of study subjects was 19 years at college case-taking, 36 years at recognition of hypertension, and 46 years at questionnaire response. Comparison of incidence rates between students with and students without given characteristics revealed six precursive of hypertension in middle life: higher levels of blood pressure (systolic and diastolic), faster pulse rate, greater weight for height, history of parental hypertension, first-born status, and less participation in sports and exercise. Correlations with hypertension were amplified when these precursors occurred in combinations.

The strongest precursors in college aged males were higher blood pressure and parental hypertension. These findings corroborate and extend earlier works in Army officers suggesting that transient hypertension, transient tachycardia, and obesity each increased risk of later sustained hypertension. Also, higher blood pressure, faster pulse, and overweight characterized medical students with a parental history of hypertension. The role of first-born status was not previously suspected as a precursor of hypertension, and may relate to experiences in utero or at parturition. Alternatively, childhood psychological experiences of the first-born may impose stresses traditionally (but by no means certainly) associated with hypertension. Alleviation or avoidance of the condition may involve the significance of sports or exercise.

Studies of hypertension, which occupied 35 per cent of personnel time in FY '68, are being extended to include former Harvard students and to search for other precursive elements, particularly socio-psychological characteristics. Implicit in the identification of precursors in youth is the need for intervention studies to determine the effect of altering characteristics, where possible, on risk of both hypertension and its complications.

III. SUICIDE AND ACCIDENTAL DEATH

A prior study of former students from Harvard and the University of Pennsylvania identified a complex of host and environmental characteristics that distinguished eventual suicides from their classmates. These characteristics included familial, physical, social, and psychological traits recorded during college years. Dominant among the distinguishing familial traits of eventual suicides was paternal deprivation through early loss or death of the father. Physically, the suicides tended to be of average stature (neither short nor tall), weighed less for their height, and were more prone to allergies. Socially, they were more apt to smoke cigarettes, less often joined in extracurricular activities or athletics, and more often became

college dropouts. Self-assessed psychological traits revealed configurations of self-consciousness, anxiety, and mood swings.

In FY '68 observations were updated and extended to earlier Harvard classes, affording greater sample size and age range of subjects for study of events leading to suicide. Parallel analyses were made for former students reported to have died from accidental causes. Similarities and contrasts of the suicides and accident decedents were identified in terms of social and psychological precursive traits.

A total of 379 suicides and 790 accident decedents were identified among 50,000 male former students in the 17 to 51 years since college record. Two control subjects for each decedent were randomly chosen from classmates who outlived the decedent and have not died from suicide or accidental cause. By comparing decedents with controls, precursive traits were identified and their individual and collective effects were measured. Social and psychological traits were examined for similarities and contrasts in their predisposing effects on suicide and accidental death.

As previously recognized, the strongest familial trait precursive of suicide was loss of father through death or marital separation before the son entered college. Increased suicide risks also existed for sons whose fathers attended college, were in professional occupations, and were monetarily successful. Social traits precursive of suicide included secondary boarding school, cigarette smoking, and college dropout. Suicide rates were higher among students who self-assessed their personality to include insomnia, worries, self-consciousness, and mood swings than among their classmates denying these traits.

Characteristics precursive of accidental death included college training of father, boarding school for secondary education, cigarette smoking, alcohol consumption, and failure to graduate from college. The most powerful of these predisposing elements were alcohol usage and college dropout. Death rates from accident were lower among students who reported themselves as subject to exhaustion, worries, and self-consciousness than among their counterparts who denied these traits.

Comparison of precursive patterns showed that suicides and accident decedents shared some predisposing indices and were quite in opposition on others. Translating the respective patterns into their psychological implications, anxiety and despair seemed to characterize the future suicide whereas irresponsibility and nonchalance marked the future accident decedent.

In FY '68, 50 per cent of staff time was devoted to study of suicide and accidental death. Extension of these studies will include a search for predisposing factors of all unnatural deaths (military action, homicide,

suicide, and accident) by method of death (poisoning, falls, firearms, etc.).

IV. CORONARY HEART DISEASE AND STROKE MORTALITY

A prior review of health and other records of the student population at Harvard and the University of Pennsylvania for the years 1916-1950 identified nine predisposing characteristics of fatal coronary heart disease and seven of fatal stroke. Five of these -- higher levels of blood pressure, increased weight for height, shorter stature, cigarette smoking, and failure to participate in sports -- were strong correlates of both coronary heart disease and occlusive (thromboembolic) stroke. These five have been evaluated singly and in all possible combinations for their relative predictive strengths.

Over 5,000 of the 50,000 male former students that comprise the population under study are known to be dead, while survivors of their classes range in age from 30 to 70 years. A total of 1,200 subjects have died from atherosclerotic disease and they are being contrasted with twice their number of classmates of equivalent age to derive estimated mortality ratios. These ratios express the risk of atherosclerotic mortality associated with a given precursive trait, or combination of traits, as opposed to the risk in its absence.

Preliminary findings suggest that cigarette smoking and higher levels of blood pressure, occurring together or in combination with the other three characteristics, show the strongest association with subsequent atherosclerotic mortality. Lack of participation in sports is next in an ordering of importance, and increased ponderosity and shorter stature show lesser effects.

About 15 per cent of staff time in FY '68 was spent on this project. As a case-control study involving only 3,600 subjects, it was subject to greater variability than will be the case when all 50,000 students are followed as a cohort. Thus longitudinal observations are programed for the future.

V. FUTURES

It is anticipated that Dr. Ralph S. Paffenbarger, Jr., Chief of the Section, will retire from active duty in the Commissioned Corps in the fall of 1968.

VI. PUBLICATIONS

1. Paffenbarger, R. S., Jr. and Williams, J. L.: Chronic disease in former college students V. Early precursors of fatal stroke. American Journal of Public Health, 57: 1290-1299, August, 1967.

2. Paffenbarger, R. S., Jr.: Chronic disease in former college students VI. Implications for college health programs. Journal of The American College Health Association, 16: 51-55, October, 1967.

3. Thorne, M. C., Wing, A. L., and Paffenbarger, R. S., Jr.: Chronic disease in former college students VII. Early precursors of nonfatal coronary heart disease. American Journal of Epidemiology, May, 1968.

4. Paffenbarger, R. S., Jr., Thorne, M. C., and Wing, A. L.: Chronic disease in former college students VIII. Characteristics in youth predisposing to hypertension in later years. American Journal of Epidemiology, July, 1968.

5. Kuller, L., Seltser, R., Paffenbarger, R. S., Jr., and Krueger, D. E.: Trends in cerebrovascular disease mortality based on multiple cause tabulation of death certificates 1930-1960. American Journal of Epidemiology, September, 1968.

VII. STAFF

Cambridge, Massachusetts office

Ralph S. Paffenbarger, Jr., M. D., Medical Director
Alvin L. Wing, GS-9 Statistical Assistant
Susan M. Sanford, GS-4 Clerk-Stenographer

Harvard University Employees, Boston, Massachusetts

Mary Lee Teichner, Digital Computer Systems Operator
Sandra Louie, EAM Equipment Operator
Kathleen Connolly, Statistical Code Clerk
Beverly Gifford, Statistical Code Clerk
Mary K. Hamilton, Statistical Code Clerk
Linde Ludwig, Statistical Code Clerk

Serial No. NHI-CS-3
1. Epidemiology & Biometry, NHI
2. Geographical Pathology
3. Jerusalem, Israel and Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Israel-United States Cooperative Ischemic Heart Disease Study

Previous Serial Number: NHI-CS-3

Principal Investigator: Jack H. Medalie, M.D., M.P.H. (Senior Physician, Hadassah Medical Organization and Lecturer in Social Medicine, Hebrew University-Hadassah Medical School, Jerusalem, Israel) (Not NIH)

Project Officer: William J. Zukel, M.D., D.P.H. (Associate Director for Epidemiology and Biometry, NHI)

Other Investigators: Henry Neufeld, M.D., Chief, Heart Inst., Tel Aviv
Egon Riss, M.D., M.Sc.,Director, Heart Inst., Haifa
J.J. Groen, M.D.,Prof. Int. Med., Hebrew U.
Harold Kahn, M.A., Statistician, NHI
Cesar Caceres, M.D.,Chief, Instrument., HDCP

Cooperating Units: National Heart Institute
Hadassah Medical Organization
Ministry of Health, Government of Israel
Hebrew University-Hadassah Medical School
Instrumentation Unit, Heart Disease Control Program, Bureau of State Services, PHS

Man Years:

Israel	12 Professional	17 Other	29
NHI	1.1 Professional		1.1
		TOTAL	30.1

Project Description:

Objectives: This is a prospective epidemiological study of hypertension and ischemic heart disease in a defined segment of male government and municipal employees of Israel. This population represents diverse ethnic and geographic origins and differs in prevalence of cardiovascular disease.

Serial No. NHI-CS-3

1. Epidemiology & Biometry, NHI
2. Geographical Pathology
3. Jerusalem, Israel and Bethesda, Maryland

The objectives of the study are to determine the biologic characteristics including physical measurements, biochemical, dietary and psychosocial measurements upon an adequate population sample size to allow the ascertainment of incidence of morbidity and mortality from ischemic heart disease and hypertension in relation to the measured characteristics.

Methods Employed: The study population consists of 10,232 male Israeli Civil Servants age 40 and over representing approximately 1500 subjects from each of six geographical regions, Eastern Europe, Central Europe, Southeastern Europe, Middle East, North Africa and Israel native-born.

A prevalence phase baseline examination was conducted in 1963 comprising an extensive battery of standardized physical, laboratory, dietary, and psychosocial measurements. 86.2 per cent of the invited individuals were examined. The 1644 non-respondents did not differ appreciably in age or place of birth from the respondents.

A re-examination of this population was conducted in 1965 as the first of two planned incidence measurements using standardized examination procedures. 96.9 per cent of the original 10,232 subjects were re-examined providing direct measurement data upon 9,911 males now age 42 and over. Some information on all but 20 of the remaining group has also been obtained providing useful data on 98.5 per cent of the study population.

The second re-examination cycle began in November 1967 and should be completed during the summer of 1968. This will provide incidence data representing approximately 60,000 person years of prospective follow-up. The expected number of cases of ischemic heart disease which will be available for analysis in relation to antecedent measured characteristics will be approximately 600.

Major Findings: The data analysis has thus far been limited to the analysis of prevalence of disease found among the 10,000 study subjects in relation to a variety of measured variables. Such findings are often good indicators of results that may be forthcoming from the incidence measurements, but they require cautious interpretation since they represent findings only among survivors of the disease and may be altered by conscious or unconscious changes as a result of the disease.

Serial No. NHI-CS-3
1. Epidemiology & Biometry, NHI
2. Geographical Pathology
3. Jerusalem, Israel and Bethesda, Maryland

Strongest significant positive associations of prevalence of myocardial infarction on an age-adjusted basis were found for the following variables regardless of area of birth:

Diastolic blood pressure
Total serum cholesterol
Diabetes mellitus
Intermittent claudication
Cigarette smoking
An anxiety index

Additional significant positive associations were found but not uniformly present for each area of birth:

Higher educational attainment
Systolic blood pressure
Uric acid
Hematocrit

Factors found not significantly associated with prevalence of myocardial infarction were:

Period of immigration
Height/weight ratio
ABO blood groups

Because many of the surviving subjects were already on altered diets, it was not possible to determine whether or not the dietary nutrient intake differs in myocardial infarction subjects and the general population. The relationship of dietary nutrients with myocardial infarction will, however, be obtained from the incidence data accumulated from the two re-examination cycles.

Significance to Bio-medical Research and the Program of the Institute: The extensive observations and measurements made in a uniform fashion on sizable numbers of subjects representing different ethnic backgrounds and different cultural characteristics can provide a test of the relationship of these attributes to the incidence of ischemic heart disease and hypertension. Generalizations can be developed from the confirmation of risk factors found in more limited U.S. populations and new factors are present to afford direct study. Such findings from natural population experiments strengthen or refute existing hypotheses. Quantitation of the independent contribution of the multiple risk factors appears possible from the data anticipated from these studies.

Serial No. NHI-CS-3
1. Epidemiology & Biometry, NHI
2. Geographical Pathology
3. Jerusalem, Israel and Bethesda, Maryland

Proposed Course of Project: The final examination cycle is nearing completion and the data will be prepared for extensive tabulations and analysis based upon incidence data rather than on previous prevalence data.

A multivariate procedure has been developed by Mr. Kahn and will be applied as one of the advanced statistical procedures in the future analysis of the data.

The project has been funded for the period until January 1, 1970 and every effort is being made to accomplish as much of the analysis of data as possible by that date.

Publications:

Groen, J.J., Medalie, J.H., Neufeld, H.N., Riss, E., Bachrach, C.A., Mount, F.W., and Smith, H.: An epidemiological investigation of hypertension and ischemic heart disease within a defined segment of the adult male population of Israel. Israel J. Med. Sci. 4: 177-194, 1968

Balogh, M., Medalie, J.H., Smith, H., and Groen, J.J.: The development of a dietary questionnaire for an ischemic heart disease survey. Israel J. Med. Sci. 4: 195-203, 1968.

Tzur, B., Medalie, J.H., Balogh, M., Smith, H., Bachrach, C.A., and Freeman, P.A.J.: Methods used for computer processing of dietary data in an ischemic heart disease project. Israel J. Med. Sci. 4: 204-209, 1968.

Medalie, J.H., Kahn, H.A., Groen, J.J., Neufeld, H.N., and Riss, E.: The prevalence of ischemic heart disease in relation to selected variables. Israel J. Med. Sci. In press.

Herman, J.B., and Keynan, A.: The effect of hyperglycaemia on uric acid excretion. The Lancet. In press.

Medalie, J.H., Kahn, H.A., Neufeld, H.N., Riss, E., and Groen, J.J.: Physicians Fact Book. Selected measurements on 10,000 Israeli males. Monograph

Kahn, H.A., Balogh, M. and Schlesinger, Z.: An unsuccessful attempt to validate a measure of total physical activity. J. Chr. Dis. In press.

Serial No._____
1.
2.
3.

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Honolulu Heart Disease Epidemiology Study

Previous Serial Number:

Principal Investigator: Abraham Kagan, M.D.

Other Investigator:
David C. Miller, M.D., M.P.H.
Robert M. Worth, M.D., Ph.D.
Grant N. Stemmermann, M.D.
Roland L. Phillips, M.D., M.P.H.
Gary A. Glober, M.D.
Jacob E. Lieberman

Co-operating Units:
University of Hawaii
Kuakini Hospital
Atomic Bomb Casualty Commission, Hiroshima
University of California School of Public Health, Berkeley
Heart Disease Control Program, Field and Training Station, San Francisco

Man Years:

Total:	20
Professional:	5
Other:	15

Project Description:

Objectives

The reported coronary heart disease mortality rate of men of Japanese descent in the United States is two to three times as great as that of men of the same age in Japan. Conversely, the cerebrovascular disease mortality rate in Japan exceeds that in the United States. This difference in mortality experience in two groups of men of similar ethnic origin is evidence for the importance of some environmental factor or factors in the causation of these differences.

The purpose of the present project, being carried out in co-operation with the Atomic Bomb Casualty Commission in Hiroshima and Nagasaki, Japan, with the University of California School of Public Health, Berkeley, and with the Heart Disease Control Program, Field and Training Station, San Francisco, is, first, to test and assess carefully the degree of these reported differences in disease experience with regard to morbidity as well as mortality, and, second, to delineate the environmental factor or factors responsible for the differences.

Methods Employed:

To this end parallel studies began in Honolulu and in Hiroshima-Nagasaki in January 1965, utilizing comparable self-administered questionnaires specifically devised for the purpose. Similar questionnaires were mailed by the California group, to begin their part of the tri-partite study in mid-1967. The study cohort in Hawaii was identified quite expeditiously through Selective Service registration records, with addresses being updated by use of business and telephone directories, and of state agency rolls. Because of Hawaii's geography and the United States immigration policy, in and out-migration of Japanese men has been relatively small, and these men therefore are well defined by the thorough Selective Service registration which occurred during the early 1940's.

The first phase of the study, collection of data by a self-administered questionnaire, has been completed. Of the total 12,684 questionnaires mailed out, 9,888 eventually were completed and returned. These 9,888 men constitute the cohort to be examined.

This examination, the second phase of the study, began in late October 1965, after two months of pretesting, with appropriate revision of forms and modification of procedures. In addition to routine cardiovascular measures, the subjects are being characterized according to a 24-hour diet history, various anthropometric variables and detailed blood measurements. Serum is being analyzed for glucose, one hour after a 50 gram glucose load, for uric acid, and for cholesterol and triglycerides. Serum lipoprotein analysis by paper electrophoresis has been discontinued temporarily, pending further standardization of the method. By June 30, 1968 about 7,500 subjects will have been examined. It no longer appears necessary to send a study team into outlying areas of Oahu, as originally planned, since special attention by our public relations director has resulted in an encouraging attendance at our clinic of subjects from such areas, particularly on Saturdays and evenings.

A sub-study begun in 1966 is being continued on the brothers of men in the questionnaire cohort to delineate possible familial aggregation of coronary heart disease and stroke, and of certain factors which are thought to be causally associated with these diseases. Since this study will include nearly 1,000 brothers who are not in the cohort of 9,888, it will provide valuable information for characterizing a sizeable sample of the men who were not identified through Selective Service records.

Serum samples and electrocardiograms are being interchanged with the Hiroshima investigators, and the results of these comparisons, as well as of the independent grading, by different pathologists, of atherosclerotic lesions in necropsy material from both Hiroshima and Honolulu, are now available.

The third phase of the study is the ongoing system of surveillance of disease and death of these subjects, with particular emphasis upon heart attack and stroke. This surveillance is being maintained on all Japanese men living on Oahu, born between 1900 and 1920, whether or not they responded to the initial questionnaire or were examined, in order to compare the morbidity and mortality experience of respondents and nonrespondents. Using detailed, pre-tested criteria, the staff medical record librarian carefully screens all Oahu hospital discharge records and death certificates, and these records are then regularly reviewed by the staff epidemiologists who assign most probable diagnoses in each case. In addition, the staff pathologist participates in the majority of necropsies of these men, using standardized methods for grading atherosclerotic lesions.

A program of re-examinations was initiated in October 1967, with the examination format considerably changed, omitting the 24-hour diet history but adding a brief neurological examination to provide data on the prevalence of stroke. A repeat electrocardiogram is being done, to provide data on the incidence of myocardial infarction. No oral glucose load is being given, but blood is drawn and the serum frozen for future lipid and other chemical determinations. The aim is to re-examine as many as possible of the initial cohort, at an interval of two years from their first examination. The rate of examination has been increased from some 300 per month to nearly 400 per month (first and second examinations combined) to permit completion of first examinations by the end of calendar year 1968 and to maintain second examinations at this two year interval.

Major Findings:

Preliminary analysis of a representative sub-sample, numbering 5,670 men, who were examined prior to January 1968, reveals the following findings, in comparison to findings reported from Hiroshima by the ABCC investigators at the tri-partite meetings in Honolulu, Hiroshima and San Francisco. The Hawaiian-Japanese (HHP) men are significantly heavier, and have significantly higher serum cholesterol levels than do the men living in Japan (ABCC). The prevalence of coronary heart disease, found at the time of examination of these men, in the 50-59 year age range, is 42 per 1,000, a rate over twice that reported from the ABCC, but less than the rate of 59 per 1,000 reported from the Framingham study.

Analysis of death certificates of the 350 men, age 45-64, who died during the years 1965, 66 and 67 reveals a rate of 25% for coronary heart disease (CHD) and 13% for cerebral vascular accident (CVA). Pathologic confirmation of these diagnoses, on the approximately 50% upon whom necropsy examinations were performed, reveal rates of 20% and 13%, respectively, for these conditions.

Detailed analysis of the 24-hour diet histories on 100 men in the HHP, and on 202 in the ABCC study, reveals the following figures, showing striking differences:

	HHP	ABCC
Total Calories	2,500 cal.	2,200 cal.
Total Fat	97 gm.	36 gm.
- saturated	65	16
- unsaturated	32	20
Total Protein	104 gm.	74 gm.
- animal	77	36
- vegetable	27	38
Total Carbohydrate	290 gm.	348 gm.
- simple	104	64
- complex	186	284
Total Alcohol	12 gm.	30 gm.

The tri-partite meetings in Hiroshima in October 1967 and in San Francisco in April 1968 resulted from commitments made at the Honolulu meeting in March 1967, that working conferences between the investigators of the three studies be held periodically in an effort to achieve maximum agreement on methodology and comparability of results. These conferences have been of invaluable benefit toward the achievement of these goals.

One result of the Honolulu meeting has been the initiation in all three studies of a system of identical

mounting of electrocardiograms and of their identical interpretation and coding by trained personnel in the laboratory of Dr. Blackburn in Minneapolis. Efforts continue to strive for similar comparability in laboratory methodology and in pathological grading of arterial lesions.

The initiation of the California study during the current fiscal year is an integral step in the successful consummation of the over-all study, and continued regular working meetings of the investigators are of urgent importance.

Significance to Bio-Medical Research and to the Program of the Institute:

The study represents an important component in the over-all program of the Geographic Pathology Section of the National Heart Institute. It was conceived as one portion of a tri-partite design of co-operating studies to take advantage of a unique historical and sociological circumstance, which provides a rare opportunity to explore the effect of environmental factors on the cardio and cerebrovascular disease experience and risk factors of populations with similar ethnic background, but with different ways of life.

Proposed Course:

First examinations will be completed by the end of December 1968, at which time about 3,000 second examinations also will have been completed.

The surveillance phase of the study will continue, and will become increasingly important as the subjects grow older, with ever greater man - years of health experience. Diagnostic criteria for morbidity and mortality have been pre-tested extensively and are now in final form and are as comparable as possible to those used in the other studies.

Common methods of data processing, tabulation and analysis have been developed and agreed upon, and this phase of the study will also assume increasing importance.

A sub-study is planned for the coming year, to be conducted on a sample of several hundred men, stratified according to serum cholesterol levels, to determine more quantitatively their dietary lipid intake by a seven day diet record, their adipose tissue fatty acid composition by needle biopsy and gas chromatography, and their energy expenditure by more detailed activity history.

Serial No. NHI-CS-5
1. Epidemiology & Biometry, NHI
2. Geographical Pathology
3. San Juan, Puerto Rico and Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Epidemiological Study of Coronary Atherosclerosis in Puerto Rico

Previous Serial Number: NHI-CS-5

Principal Investigator: Mario R. Garcia-Palmieri, M.D.
Professor & Head, Department of Medicine
University of Puerto Rico School of Medicine
San Juan, Puerto Rico

Project Officer: William J. Zukel, M.D., D.P.H., Associate Director for Epidemiology and Biometry, NHI

Other Investigators: Manuel Feliberti, M.D., Assoc.Prof.Epid.
Raul Costas, M.D., Asst. Prof. Med.
Mercedes Cruz Vidal, M.D., Med. Instr.
Marcelino Cortes, M.D., Assoc. Med.
Dr. Patterne (½ time)
Angel Alberto Colon, M.D., Asst. Prof. Med.
Gabriel Zamorano, M.D., Assoc. Path.
Raquel Torres Llauger, Res. Stat.

NHI: Christian Gulbrandsen, M.D., Assoc.
Jeanne Truett, Stat. Consult.
Tavia Gordon, Stat. Consult.
Jeanne Tillotson, Nutr. Consult.
William B. Kannel, M.D., Med.Liaison, Framingham

Cooperating Units: National Heart Institute
University of Puerto Rico School of Medicine
Department of Public Health
Office of Census, Puerto Rico Planning Board
Information Processing Division, Medical Center
Medico-Legal Institute
Municipalities of Bayamon, Guaynabo, Carolina, Catano(urban), Naranjito, Comerio, Corozal, Cidra, Aguas Buenas, Barranguitas(rural)

Man Years:

Puerto Rico	9½ Professional	8 Other	17½
NHI	1½ Professional		1½
		Total	19

Serial No. NHI-CS-5
1. Epidemiology & Biometry, NHI
2. Geographical Pathology
3. San Juan, Puerto Rico and Bethesda, Maryland

Project Description:

Objectives: To determine the factors which are significantly associated with an unusually low death rate from coronary heart disease and a reduced severity of coronary atherosclerosis found on autopsy among men age 45-64 living in Puerto Rico. Pilot investigations confirmed a death rate approximately one-third of that found for the same age men on the U.S. mainland. It was further found that this low mortality and reduced severity of atherosclerosis of the coronary arteries could not be explained by out-migration of the sick, errors in the statement of age, under-reporting of deaths or significant errors of diagnosis.

Further pilot field surveys in the urban and rural populations revealed a heterogeneity of diet, physical activity and lipid levels which would make possible testing of the validity of the risk factors established for the Framingham population in another U.S. population with a very low incidence of coronary disease.

A relatively high autopsy rate of 55 per cent of all deaths provides a further opportunity for direct correlations of severity of lesions in the coronary vessels with antecedent biochemical measurements in this population.

Methods Employed: A special census of all males age 45-64 living in specified rural and urban municipios has been conducted to identify a total population of 4,000 rural, 4,000 urban lower socioeconomic and 4,000 higher socio-economic subjects.

A comprehensive standardized protocol was developed and pretested, a manual of operations completed and staff trained in conducting the necessary procedures for information collection, clinical, laboratory, autopsy, data processing and quality control.

A prospective epidemiological investigation on this population began in July 1965 and has now reached full operation. It is expected that approximately 10,000 men representing the three population groups will be examined over a 3 year period and a re-examination then conducted to establish accurate incidence data and determine the relationship of the measured variables to the incidence of new coronary disease by clinical and autopsy assessment.

Serial No. NHI-CS-5
1. Epidemiology & Biometry, NHI
2. Geographical Pathology
3. San Juan, Puerto Rico and Bethesda, Maryland

Major Findings: More than 8,000 subjects from the desired study sample of urban and rural men age 45-64 were brought into the Medical Center by April 1, 1968 for the comprehensive cardiovascular examinations specified in the study protocol. A cumulative response rate of 69 per cent for the urban and 74 per cent for the rural subjects has been accomplished, with an overall 75 to 80 per cent expected at the conclusion of the first examination cycle.

Based upon the findings of this first general population sample, the following differences in attributes and in prevalence of disease has appeared.
(1) The prevalence of definite myocardial infarction continues to be considerably below the expected U.S. white level using the National Health Survey data for the same age men: 4.7 vs 19. per thousand at age 45-54, and 6.0 vs 43. per thousand at age 55-64.
(2) Prevalence of AP, CI and MI is lower among rural than urban subjects at all ages.
(3) Prevalence of definite MI is as high in urban men age 45-54 as in the age group 55-64. This may suggest an increasing prevalence of coronary disease appearing in the younger population which would be important for future trends of the disease.
(4) A number of statistically significant differences in measured characteristics are being found between rural and urban subjects:
Examples for men age 45-54 are:

	Rural	Urban
Physical activity index	39.7	31.8
Weight	141	158
Height	64.6	65.1
Metabolic equivalent	63.0	45.0
Systolic blood pressure	121.4	128.0
Heart rate	69.1	73.0
Saturated fat intake	33.8	37.5
Cholesterol intake	346	447
P/S ratio	.32	.48
% Cal. from fat	32	37
% Cal. from carbohydrate	51	46
Fasting glucose	90.9	95.1
Fasting glycerides	128.	166.
Serum cholesterol	197	207

Serial No. NHI-CS-5

1. Epidemiology & Biometry, NHI
2. Geographical Pathology
3. San Juan, Puerto Rico and Bethesda, Maryland

Significance to Bio-medical Research and the Program of the Institute: This major epidemiological study is providing direct evidence to document the current pattern of unusually low prevalence of clinically manifest forms of coronary heart disease among Puerto Rican males in the "coronary prone" ages of 45-64. This trend of prevalence data reinforces the importance of continuing the measurement of the incidence or rate of occurrence of newly manifest coronary disease as it relates to the measured levels of the variety of characteristics suspected to be determinants of coronary disease.

This is the only large U.S. population group with a documented coronary disease mortality and prevalence substantially lower than the expected experience for white males in the U.S. The significance of the findings is the more direct relevance of these findings to U.S. populations than can be obtained from studies in foreign populations where differences in medical care, lack of autopsies and competing diseases complicate the interpretation of natural patterns of coronary heart disease.

The findings from this study should provide strong evidence of the natural biological interactions which are conducive to slow development of coronary disease and can provide data needed for the establishment of future recommendations for preventive regimens.

Proposed Course of Project: The minimum further effort will be to establish the accurate incidence or rate of development of various forms of coronary heart disease as they relate to the levels of the baseline measurements now nearing completion. Approximately 10,000 subjects will have been examined by September 1968 and a re-examination cycle for subjects examined in 1965 will begin in July 1968. A two year period is the minimum needed to conduct this re-examination cycle to obtain the desired incidence data for direct relationship to the individual measured characteristics.

During F.Y. 1969 the detailed analysis of data from the complete prevalence cycle will be conducted. The pilot testing of procedures for the re-examination cycle is already in progress and a target goal of 5,000 subjects for re-examination in the order of first entry to the study will be undertaken.

Publications:

None during present stage of data collection.

Serial No. NHI-CS-6
1. Epidemiology & Biometry, NHI
2. Geographical Pathology
3. Zagreb, Yugoslavia and Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Epidemiological Investigation of Ischemic Heart Disease and Hypertension in Yugoslavia

Previous Serial Number: NHI-CS-6

Principal Investigator: Bojan Pirc, M.D., Professor of Biostatistics
Andrija Stampar School of Public Health
University of Zagreb

Co-Investigator: Djordje Kozarevic, M.D., M.P.H., Chief, Chronic Diseases Program, Federal Inst. of Public Health
Belgrade

Project Officer: William J. Zukel, M.D., D.P.H., Associate Director for Epidemiology and Biometry, NHI

Other Investigators:

Zagreb
Danimir Bartolovic, M.D.
Director of Public Health, Remetinec

P. Shalek, M.D., Cardiologist

Tuzla
Sulejman Azabagic, M.D.
Director of Public Health, Tuzla

M. Strasser, M.D., Cardiologist
Dr. Josipovic, M.D., Cardiologist

NHI
Harold A. Kahn, M.A., Senior Statistician
T.R. Dawber, M.D., Consultant

Cooperating Units:
National Heart Institute
Federal Institute of Public Health, Belgrade
Health Statistics Center, Belgrade
Public Health Center, Remetinec
Mayor and Council of Remetinec
Institute of Hygiene, Zagreb
School of Public Health, Zagreb
Institute of Hygiene, Ljubljana
Public Health Center, Tuzla
Hospitals and Medical Care Department, Tuzla
Mayor and Council of Tuzla Commune

Serial No. NHI-CS-6
1. Epidemiology & Biometry, NHI
2. Geographical Pathology
3. Zagreb, Yugoslavia and Bethesda, Maryland

Man Years:				
	Yugoslavia	4 Professional	12 Other	16
	NHI	1/3Professional		1/3
			Total	16 1/3

Project Description:

Objectives: The specific objective of this study is to determine the incidence of different forms of cardiovascular diseases in rural and industrial populations and the relationship between incidence rates and ethnic origin, diet, type of work, physical activity, physical and mental stress, body type, and personal habits such as the use of tobacco and alcohol. The principal cardiovascular diseases studied will be hypertension and coronary (ischemic) heart disease. The primary emphasis will be upon the study of the incidence of these forms of cardiovascular disease in newly industrialized populations. A unique opportunity exists in Yugoslavia to study the incidence of cardiovascular diseases in a rural population as it becomes industrialized.

Methods Employed: Selection of two cities with desired population characteristics was made and the groundwork of establishing medical and community acceptance was carried out in Remetinec near Zagreb and Tuzla in the mountains southwest of Belgrade.

A census of men aged 35 to 64 was conducted identifying 6,856 eligible subjects in Tuzla, the Moslem community and 5,018 eligible subjects in Remetinec, the Christian community.

An epidemiological study plan adopted to local circumstances was drawn up with central elements of comparability to the Framingham Study. This standardized protocol was developed and pretested. Staff were trained and interstudy comparability established including arrangements for central laboratory processing of blood for biochemical determinations.

The first examination cycle was completed in 1964 attaining 94 per cent of the eligible subjects of Tuzla and 92 per cent of eligible subjects in Remetinec.

The second examination cycle was conducted in 1966-67 and more than 90 per cent of the original subjects were re-examined. Identification of the deaths, refusals, those who have moved is in progress so that status of health will be determined in this residual group as completely as possible.

Serial No. NHI-CS-6
1. Epidemiology & Biometry, NHI
2. Geographical Pathology
3. Zagreb, Yugoslavia and Bethesda, Maryland

Major Findings: The findings from the first prevalence examination cycle encompassing 11,121 men between the ages of 35-64 have been processed for basic tabulations of distributions of measured variables. Although the objectives of the study are dependent upon measurements of incidence of new disease in this defined population, the prevalence findings are of general interest.

The low prevalence of myocardial infarction by ECG (7.6 per 1000) has been suggestive evidence that the incidence of coronary heart disease will also prove to be low. However, these low prevalence ratios create problems of small numbers of cases available for internal analysis.

Illustrative data are presented below:
(1) Prevalence of myocardial infarction by ECG (definite and probable cases) clearly increases with age but the U.S. ratios are higher than found in Yugoslav men a decade older.

	Prevalence per 1000		
Age	Yugoslavia	U.S.N.H. Survey	Yugoslavians as % of U.S.ratio
35-44	3.1	11.	28.
45-54	7.6	35.	22.
55-64	18.7	97.	20.

Small numbers prevent clear statements about internal differentials in prevalence of MI between Remetinec and Tuzla but there is some indication of a higher prevalence in urban than in rural areas above age 45.

(2) Median cholesterol level for the total population is 194, with no increase with age. Rank gradient: Remetinec urban (231)>Tuzla urban (204)>Remetinec rural (202)>Tuzla rural (160). The Remetinec urban level is equal to that found in the Framingham population.

(3) Median systolic blood pressure shows a direct gradient with age. Rural levels are lower than urban levels in Tuzla and Tuzla levels are lower than Remetinec in all subgroups except urban men age 55 and over.

(4) Physical activity index is higher in rural than in urban men. No gradient by age in urban men but a decreasing index with age in rural men. These levels of physical activity are considerably higher than found in the Framingham population.

(5) Based upon incomplete results of the Examination Cycle II of 1966-67, the incidence of new myocardial infarction in this population is proving to be very low. The incidence of new ECG documented cases of coronary heart disease among 4,500 subjects re-examined in Tuzla by September 1967 was: 1 definite MI, 3 possible MI and 3 bundle branch block possibly indicative of MI. In addition to these 7 total cases, 3 deaths from MI were identified during the same interval between examinations.

This incidence of less than 1 per 1000 per year is astonishingly low and verification will be needed, but if confirmed this will be the lowest established coronary disease incidence yet recorded in any prospective population study. Unfortunately, the low expected incidence will require a longer period of observation and follow-up of this population to accumulate sufficient new cases for internal analysis of risk factor relationships.

Significance to Bio-medical Research and the Program of the Institute: This large prospective epidemiological study of coronary heart disease and hypertension provides a natural experiment of a relatively homogeneous ethnic group which has marked contrasts in diet and biochemical characteristics yet these are associated with low prevalence of coronary heart disease.

The range of cholesterol values in urban Christian subjects is the equivalent of Framingham levels (231 mgm%) but mean values for the rural Moslem population are 160 mgm%. The standardization of measurement procedures and criteria against Framingham will allow the direct comparison of these variables with Framingham results and with future incidence of coronary heart disease. An added area of interest is the finding of a high prevalence of obstructive pulmonary disease in the Yugoslav population.

Proposed Course of Project: Continuation of the planned study design to obtain one added re-examination cycle for standardized incidence measurements is planned. The plans for tabulations and analysis are being coordinated to provide the most useful direct comparison of findings with data in the Framingham Study.

Serial No. NHI-CHD-1
1. Collaborative Studies Program Area
2.
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Correlation of Prenatal Events with Congenital Heart Disease

Previous Serial Number: NHI-CHD-1

Principal Investigator: Shiela C. Mitchell, M.D., M.P.H.

Other Investigators: Heinz Berendes, M.D., John R. Park, M.D. and Pediatric and Obstetric Project Directors in the Collaborative Study of Cerebral Palsy and Mental Retardation

Cooperating Unites: Perinatal Research Branch, NINDB

Man Years:

Total:	.40
Professional:	.30
Other:	.10

Project Description:

In cooperation with the National Institute of Neurological Diseases and Blindness' Study of Cerebral Palsy and Mental Retardation, identification of patients with congenital heart disease is continuing. Virtually all of the patients dying with congenital heart disease have been reviewed in detail and classified as to diagnosis. Identification of congenital heart disease in the living patients is now almost complete. This has been effected through small sub-contracts with some of the cooperating project directors and through unreimbursed review and examination by others.

This research resource has already yielded several explorations of interest into the etiology and production of specific lesions. Further evaluations should be possible once the lesion frequency, incidence study is completed within the coming year.

Serial No. NHI-CHD-2
1. Collaborative Studies Program Area
2.
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Scientific Liaison Activities

Previous Serial Number: NHI-CHD-2

Principal Investigator: Shiela C. Mitchell, M.D., M.P.H.

Man Years:
Total: .75
Professional: .35
Other: .40

Project Description:

Scientific Liaison has been provided for 3 cooperative or collaborative studies, the first dealing with the Natural History of congenital heart disease, the second with the development of a code classification for congenital heart defects, and the third with conferences dealing with the etiology and morphogenesis of congenital heart disease and, with the relationships between maternal viral infection and offspring malformation.

Data have now been collected in the cooperative Natural History Study (Grant No. HE 09474-9) for almost two years with 1529 patients now admitted retrospectively, 503 prospectively. The study is thus progressing on schedule and will be coming in for renewal consideration at the November 1968 Council. While a good deal of very useful ancillary information has already come from this study the real harvest for which the study was undertaken will not be available until the repeat cardiac catheterizations have been done at four and eight years of follow-up. Only then will it be possible to depict the clinical outlook for the three lesions of the study and to correlate clinical with hemodynamic parameters.

The first draft of a code classification system for congenital heart disease based on the Systematic Nomenclature of Pathology has been completed and is now being pretested both by the members of the committee and by other interested clinics here and abroad. At the end of the pretest period it is planned to bring the investigators together to make use revisions in the code for further refinement and testing. Both the domestic and foreign interest in this code system is increasing and there is real reason to believe that it will be widely adopted upon its completion.

The transcript of a two day conference dealing with Viral Etiology of Congenital Malformations has been edited and prepared for publication. This conference and the publication resulting from it are shared with NICHD. The booklet of 80-100 pages should be ready for distribution in late summer.

Serial No. NHI-CHD-3
1. Collaborative Studies Program Area
2.
3. Lancaster, Pennsylvania

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Evaluation of Pediatric Cardiology Training and Testing

Previous Serial Number:

Principal Investigator: Forrest Adams, M.D., Chairman of the Sub-specialty Board of Pediatric Cardiology

Other Investigators: Sidney Blumenthal, M.D., James W. DuShane, M.D., Paul Lurie, M.D., Dan A. McNamara, M.D. and Abraham M. Rudolph, M.D.
Subcontractor: Stephen Abrahamson, Ph.D., USC

Man Years:

Total:	3.95
Professional:	2.6
Other:	2.35

Project Description:

This project has two main points of emphasis. The first is to examine and evaluate the current methods of testing for competence in the sub-specialty of pediatric cardiology which leads to certification by the sub-specialty board. The second is through evaluation of both the subject matter and the required competence for sub-specialty certification to re-evaluate the current training programs both for content and format with a view to broadening and strengthening these programs.

The first portion of the work is now well underway through evaluation of the sub-board examinations last October and through professional diaries, workshops, and detailed personal interviews. The second portion of the contract work which is dependent upon this first portion will be undertaken next year.

AH-MI
PROGRAM

BLOOD
PROGRAM

EXTRAMURAL
RESEARCH

PHS - NIH

NATIONAL HEART INSTITUTE
July 1, 1967 through June 30, 1968

ARTIFICIAL HEART - MYOCARDIAL INFARCTION PROGRAM

ARTIFICIAL HEART BRANCH

The program of the Artificial Heart Branch has as its goal the development of clinically useful artificial heart and circulatory assist devices to assist damaged or failing hearts and to effect rehabilitation of heart disease patients. The physical and biological problems standing in the way of this goal are now being attacked both at the applied and fundamental levels. The program utilizes scientific advisory and review boards, a staff of scientists and administrators, and funding by the cost-reimbursement type of contracts. The primary monitoring of the scientific aspects of contracts is at a scientist-to-scientist level. In contrast to the research grants program of NIH, in which support is given to investigators for work on projects that they have initiated, and that need not be directly related to a solution of a problem, the Artificial Heart Program is a structured one, with an overall plan and goal, intermediate goals, and systematic approaches to solve problems and achieve the goals. Under this type of program, Requests for Proposals (RFPs) are issued in accordance with the overall plan and directed toward the resolving of specific problems. Responses to the RFPs, therefore, must offer programs which could lead to the answers being sought. Continued directed and goal-oriented research has been performed, by investigators working under contract to the Program Office, on the development of materials compatible with blood, on the physiologic effects of blood pumps in animals, on the effects of additional endogenous heat, and on the use of a biological fuel cell as a possible source of energy for circulatory assist devices. Development support was given to research teams with circulatory assist devices ready for clinical evaluation. Funds were transferred to support the work of the Harry Diamond Laboratories in the further development of the Army artificial internal heart pump, and to the Atomic Energy Commisssion to share the support of four contracts for study of radioisotopes as power sources for circulatory assist devices. New contracts were in effect during the past year for work on percutaneous leads, control systems, new pump designs, blood flow studies, improved oxygenators, materials, and on energy problems. Progress by the Artificial Heart Program in the development of a family of therapeutic artificial heart devices to meet the needs of heart disease patients is presented below. Since several different types of devices are required and the requirements for each vary considerably, progress and developments will be discussed with regard to the key areas of artificial heart development. Following are names of the Artificial Heart Program contractors and summaries of the work which has been done during the past year in each area.

RESEARCH AND DEVELOPMENT CONTRACTS OF THE ARTIFICIAL HEART BRANCH, NHI
(Active during FY 1968)

STUDIES RELATIVE TO MATERIALS SUITABLE FOR USE IN CIRCULATORY ASSIST DEVICES

The requirement in this area is to develop and test materials for use in therapeutic circulatory assist devices, oxygenators and other prostheses that satisfy physiological requirements for long-term use and engineering requirements from an operational, safety, and reliability standpoint. Over two hundred different materials have been formulated and tested in vitro and in vivo by Artificial Heart Branch contractors. From these efforts, several promising approaches have been developed that offer materials with increased resistance to thrombosis and hemolysis and provide reasonable mechanical properties for use in circulatory assist devices. These approaches include heparinized silicone, polyurethane, polyelectrolytes, modified cellulose, and flocked silicone and polyurethane (coating the surface with fibers -- diameters of 15-30 microns and length of approximately 500 microns). The materials are evaluated by subjecting each to a series of tests that become progressively more difficult. At present, approximately ten materials have passed the two-hour vena cava test, approximately six have passed the two-week implant test, approximately six of the new materials have been tested with regard to plasma protein and platelets, and four materials are currently being evaluated in blood pumps. Blood pumps have been designed utilizing these materials and are currently being tested. Any prosthetic material considered for human implantation must satisfy certain critical physiological and engineering requirements to establish its usefulness and safety as a candidate material for biological application. Implicit in Artificial Heart Branch development of materials is the fundamental necessity of obtaining basic information concerning the interaction of blood and prosthetic materials to provide safe and reliable materials for clinical application.

Materials Testing

Over the last year, six contractors have directed their primary efforts toward an evaluation of new materials developed within the Program as well as existing materials that appeared to have potential for application in the biological environment.

Johns Hopkins University School of Medicine

Tests of this contractor consist of both acute and chronic inferior vena cava ring implants; right atrial flag implantation of flexible material; and right atrial implant of rigid prosthetic swords. Approximately 200 different in vivo experiments have been performed utilizing such materials as heparinized silicone, polyelectrolytes, polyurethanes, silicone (negative surface), hydrogels and modified cellulose.
Contract No.: PH43-68-84 Contract amount: $35,200

Battelle Memorial Institute (2)

This program involves the adhesion characteristics of platelets and cells to various polymers and the culturing of cells on prosthetic surfaces. About 30 different materials have been screened by this technique. Many new materials are under evaluation at the present time. All culture work is proceeding on schedule.
Contract No.: PH43-67-1404 Contract amount: $63,600

Cordis Corporation

The Cordis test is to determine denaturation of certain plasma proteins and enzymes exposed to a single material, in the absence of an air interface. The testing techniques they use are: immunoelectrophoresis, acrylamide gel electrophoresis and plasma enzymes assay. Eight different materials have been evaluated. The results indicate that: (1) silicone-heparin caused slight changes in lipoprotein; (2) polyurethane (Dupont) caused decrease in isocitric dehydrogenase and lactic dehydrogenase; (3) polyurethane (Estane) caused changes in isocitric and lactic dehydrogenase; and (4) Teflon caused an apparent increase in lactic and isocitric dehydrogenase activity.
Contract No: PH43-66-980 Contract Amount: $63,700

University of North Carolina

The purpose of this program is to test new polymers and commercially available polymers for compatibility with whole blood in a standardized test system. The effects are reported in terms of Stypven time, partial thromboplastin time, hemoglobin and adenine nucleotide content. Twenty-four polymers have been tested. Four of the polymers tested proved superior to siliconized glass in blood compatibility as indicated by a value of 100% or greater for the Stypven time test (STT) and the partial thromboplastin time test (PTT). These four polymers are: cellulose diacetate, hydroxyethyl starch, methyl methacrylate, and poly(styrene). The remaining twenty polymers appeared to be less compatible with blood than is siliconized glass, although twelve of these gave values of 100% or greater for the STT. Two polymers, amylose and poly(acrylic acid), produced a significant degree of hemolysis. Four non-polymeric surfaces have also been tested for blood compatibility. These are uncoated glass, stainless steel, heparinized hydrin rubber, and poly(styrene) coated with graphite-benzalkonium-heparin. Elevated values for STT and PTT in tests with heparinized hydrin rubber and poly(styrene) coated with graphite-benzalkonium-heparin are most likely due to solubilization of loosely-bound heparin by plasma.
Contract No: PH43-67-1416 Contract Amount: $84,700

State University of New York

This contract, which has been in effect for only the last four months, is for investigations of materials for compatibility with human blood. Electrochemical and biophysical studies are being made aimed at the selection of materials meeting criteria for blood/materials compatibility and subsequent in vivo testing. Materials to be screened in the course of the contract are metals, alloys, semiconductors, and plastics such as modified Teflon and Dacron impregnated with various types of compounds to alter their surface characteristics.
Contract No.: PH43-68-75 Contract Amount: $89,934

Brooklyn Veterans Administration Hospital

This transfer of funds agreement is supporting extensive studies on the adsorption of proteins on various materials including nine metals supplied by the Johns Hopkins University School of Medicine. These studies will be interrelated and coordinated with the protein kinetic studies of Dr. James Allen of the Johns Hopkins University. The materials to be studied include Stellite 25, Stellite 21, titanium, aluminum, aluminum alloy, nickel, tantalum, magnesium and stainless steel.
Reimbursable agreement Amount: $13,247

Materials Development

It is apparent that significant improvements have been made over the last two years in the development of a few materials that are compatible in terms of thrombogenicity, exhibit acceptable hemolytic effects on the cellular elements, and cause limited protein and platelet denaturation over a limited time period. Nevertheless, at present, materials for chronic or long-term applications are still one of the most critical problems confronting the development of therapeutic devices, i.e., blood pumps, oxygenators, etc. Materials not only must satisfy the physical and mechanical requirements of the device with high reliability and safety for as long as required, but must not cause thrombosis or hemolysis, must not appreciably shorten the life span of other cellular components of blood, degrade or modify blood proteins, interfere with the normal clotting mechanism, modify the electrolyte composition of the blood, cause toxic or allergic reactions, interfere with normal immunologic mechanisms, have any carcinogenic effects, or otherwise harm the blood or other tissues. To effectively pursue material developments that encompass emergency, temporary and permanent cardiac systems and their various modes of operation, it is necessary that a number of different approaches be supported. The current approaches include developing more permanent heparin surfaces, bonded enzymes, specially prepared graphite surfaces, modified cellulose surfaces, endothelial surfaces, polymers with "permanent" negative surface charges, hydrogels with and without ionically charged surfaces, and new and more compatible silicones.

Below are summaries of the contract work which has been done during the past year on materials development.

Amicon Corporation (1)

This contract is for the evaluation of Amicon's Ioplex resins as antithrombogenic materials for use as coatings and components of artificial hearts. Ioplex resins are complexes of water-insoluble polyanions and polycations which may be dissolved in a patented ternary solvent system from which films of the material may be cast. By varying the ratio of polyanion to polycation used in preparation of these resins, materials containing excess polycations (electrically neutralized by microanions) or excess polyanions can be produced. The materials have shown remarkable compatibility and ability to withstand

degradation in vivo and it was thought that sulfonate-excess materials would simulate the action of heparinized surfaces in vivo and exhibit antithrombogenic behavior. Tests have given preliminary evidence of antithrombogenic activity of polyanion-excess Ioplex. Methods for producing adhesion adequate for stress-free applications in vivo were developed for Ioplex coatings on polypropylene, acrylonitrile-butadiene-styrene, Mylar or Dacron, and rubber. Good adhesion was obtained between Ioplex and stainless steel. It was established that Ioplex samples could be sterilized by bombardment with high energy electrons without suffering physical damage. Recent reports on the studies of Ioplex showed that some formulations had been obtained that remained patent in dogs for two-week chronic tests, and could be fabricated into all-Ioplex components. Less promising results have been obtained with adhesion of Ioplex to other substrates and with increasing the mechanical strength of these gels. Continued work will emphasize the development of improved methods for fabricating artificial hearts and components with Ioplex and of new Ioplex formations.
Contract No: PH43-66-1129 Contract Amount: $64,125

Battelle Memorial Institute (1)

This contract during the past year was for work on the development and refinement of heparinization techniques for composite structures, and for the study of the interaction of heparinized surfaces with blood elements. Most promising of the polymers made non-thrombogenic by attachment of heparin was hydrin rubber and polyvinyl chloride. The method of attachment of heparin by water insoluble quaternary ammonium salts looks interesting, but could lead to dimensional instability of the fabricated part because of the necessity for opening the polymeric structure with heptane. Of the reactions which have been tried for the attachment of heparin covalently, use of cyanuric chloride, carbo-diimide and diazonium salt systems were successful. A layer of 50-3000 A°thick heparin has been achieved. Future work will consider simplification of reaction sequences, attainment of reproducible uniform heparinized surfaces, and development of generally applicable covalent attachment techniques. In the studies made on protein adsorption, it was observed that the filler showed a negligible effect on protein adsorption, heparinized surfaces adsorbed as much or more of Hageman factor as preheparinized surfaces, but did not activate Hageman factor; and that heparinized silicone rubber or hydrin rubber adsorbed less Factor X than unheparinized surfaces. The data indicate that heparinized silicone surfaces cause greater loss in activity of plasma proteins, whereas for hydrin rubber, the loss in activity was approximately the same for both, heparinized or nonheparinized. The data indicate that platelets adhere more to heparinized surfaces than to unheparinized. In vivo evaluations indicated that for heparinized silicone rubber, no clotting was noted. This is also true with the silicone rubber heparinized with the water insoluble quaternary salt. Under subcontract with Tracerlabs, Inc., a pilot study has begun of the modification of surfaces of materials by the use of excited gas techniques for the improvement of adhesion, as a supplement to the work on heparinization methods.
Contract No: PH43-68-649(formerly 64-496) Contract Amount: $182,320

Carnegie-Mellon University

During the past year of this contract, work was concentrated on development of improved techniques for heparinizing silicone rubber. Silicone rubber rings treated with heparin by the solvent swelling technique have shown significant thrombo-resistance in in vivo testing; blood pumps are being coated by this process for more extensive in vivo testing.
Contract No.: PH43-66-977 Contract Amount: $101,720

Denver Research Institute

This contractor has been studying the interaction of the surfaces with prothrombin and fibrinogen, and the enzyme inhibition of clotting. Work to date has been with glass, siliconized glass, and polystyrene surfaces as standards. Polyacrylonitrile and ABS surfaces indicate short clotting times. Significant protein adsorption occurred on ABS. Polynitrostyrene gave a relatively long clotting time (1 hour).
Contract No.: PH43-67-1407 Contract Amount: $51,060

Dow Corning Corporation

This contract was for the purpose of developing better silicone elastomers, and for investigating the state-of-the-art of silicone elastomers, as used in artificial heart devices. A major portion of effort has been directed toward solving the problem of blood clotting on presently used silicone elastomers. Most of the components used in the formulations of silicone elastomers have been evaluated. It has been found that clotting is caused by the dimethyl silicone polymers and by the fillers used. Several silicone intermediates were found that did not cause clotting, but preliminary efforts to polymerize these into high polymers, using standard chemical methods, were unsuccessful. Several varieties of surface treatments and coatings were investigated. In vitro evaluation indicated that four different types of coatings and/or treatments might be satisfactory, and these are now being evaluated in dogs. Several of Dow Corning's negative surface silicones have successfully passed both the two-hour and two-week in vivo tests. The Program Office feels that these materials are very important and will make a significant contribution to the program. Investigation will continue of the permeation parameters of the 30 to 40 rubber stocks prepared under this contract to date.
Contract No.: PH43-66-979 Contract Amount: $53,517

Gulf General Atomic, Inc.

During the past year, the contractor has demonstrated the capability to produce a large variety of well-characterized carbon surfaces. Some of these, polished hydrophobic isotropic carbon, for example, have shown significant non-thrombogenicity even without benzalkonium heparin. These results are promising and will be investigated further. Some all-graphite components have remained patent in preliminary in vivo tests. It is hoped that additional information can be obtained about the in vivo mechanical

characteristics of these materials and about the effect of covalently coupled heparin on the non-thrombogenic properties of graphite. A significant potential advantage of these materials is high strength, chemical inertness, and lack of deterioration, corrosion, and chemical degradation.
Contract No.: PH43-67-1411 Contract Amount: $68,531

Harris Research Laboratories

This contractor has been working on the development of better heparin surfaces. It has been found by dipping a dry cationic surface into a heparin solution, one can prepare autoradiographically homogeneous heparin surfaces. Concentrations of heparin at 0.3 $\mu g/cm^2$ for GBH or polyvinylpyridine heparin surfaces give in vitro clotting times $\geq$ 100 minutes. A dye staining method using Azure A has been developed to determine concentration of heparin on surfaces. Using ^{35}S-labeled and tritium-labeled heparin, it was found that more heparin is removed from GBH and PVPyr H surfaces by plasma than by distilled water or isotonic saline. As yet, evaluation is not available of the several types of materials under development.
Contract No.: PH43-68-38 Contract Amount: $65,980

Melpar, Incorporated (1)

This contract is for the investigation and development of blood and tissue compatible polymers by modifying the surface of cellulose, poly(amino acids) or other biopolymers by different chemical reactions. Some of the prepared modified celluloses which were developed, especially those with negative groups, have shown great improvements in antithrombogenic properties over those of cellulose. The chemistry of cellulose is well known and permits almost unlimited variations in properties. During the first 6 months of this contract period, three basic celluloses, diethylaminoethyl (DEAE), diethylmethylaminoethyl (OA) and p-aminobenzyl and three acidic celluloses, p-hydroxybenzyl (PHB), carboxymethyl (CM), phosphate (P) and ethylsulfonate (ES) have been prepared containing 0.01 to 0.5 excess meq/g of ionic groups. In addition, cellulose has been heparinized. Clotting times in vivo increased 2 to 3-fold over that of glass. Negatively charged cellulose (ACIDIC) caused no significant change on blood components within 18-hour testing period. Glass produced 50% hemolysis in 4 days, whereas, acidic and unmodified cellulose had relatively small effect. Heparin complexed ionically to diethylaminoethyl and quaternary amine celluloses produced clotting times greater than 30 and 18 hours, respectively; whereas, unheparinized and unmodified cellulose gave a clotting time of about 0.2 hours. During the coming year, additional in vivo tests will be performed in order to obtain a more critical evaluation of these materials.
Contract No.: PH43-67-1413 Contract Amount: $96,700

Monsanto Research Corporation (1)

The investigators have made some notable progress during the past year toward the development of microcellular-anchoring devices and flocked surfaces and the progress has been sufficient to warrant fabricating, testing, and evaluation of components. This approach is very promising and aims at developing cultured "living surfaces" by first growing in them a layer of fibroblastic tissue, followed by another layer of endothelial tissue. Progress to date has been encouraging with regard to the development of special monofilament fiber that will form the basic network for anchoring the endothelial cells. The preparation of the filament and the bonding of these filaments to the substrate are very critical if uniform and structurally sound materials are to be prepared for tissue culture work. During the coming year, Monsanto will be asked to put most of its emphasis on filament weaving and substrate development.
Contract No.: PH43-67-1417 Contract Amount: $89,375

Monsanto Research Corporation (3)

This contract is for the study, evaluation and development of materials compatible with blood and tissue by altering the polarity, surface charge, and conductivity of polymers and by treating polymers with heparin and dicoumarol. The work during the past year has been productive. Test tubes, for use in the Monsanto modified Lee-White clotting tests, have been prepared from polymers of high polarity (ethylene/vinyl alcohol), high surface charge (hydrolyzed polyacrylonitrile and poly styrene/acrylonitrile), and of high conductivity (Spheron C, a conducting carbon). Rigid and flexible epoxy and urethane resins have been prepared and have been found to contain good mechanical properties. Polymers studied were ethylene/vinyl acetate, ethylene/vinyl alcohol, styrene/2-methyl-5-vinylpyridine and epoxy systems of Epon 820 and DER 732 (Dow epoxy resin). Many of these materials have been found to have excellent non-thrombogenic properties. Successful *in vitro* tests (2-hour) have been conducted with rigid and flexible epoxy resins and quaternized styrene/2-methyl-5-vinylpyridine containing from 1.5 to 2.5 phr or heparin. However, the *in vivo* studies have been too limited to allow for complete evaluation of the materials. During the coming year, an in-depth study of the epoxy, urethane, and quaternary systems is planned, with special emphasis being given to *in vivo* evaluations.
Contract No.: PH43-66-975 Contract Amount: $98,110

Polysciences, Incorporated

During the past year, this contractor has worked on the development of a polymeric hydrogel material. The *in vitro* and *in vivo* test results are very promising and it would appear to be a material very useful in artificial heart development. Greater part of work was devoted to preparation of more than 20 different polymeric hydrogels and to the covalent and physical coupling of heparin to some hydrogels. Few hydrogels had good physical and mechanical properties. Weakly basic hydrogels were found to extend clotting times. Emphasis during the coming year will be placed on the

improvement of the physical and mechanical properties of the hydrogel material and the fabrication of components for in vivo testing.
Contract No.: PH43-66-1124 Contract Amount: $59,688

Stanford Research Institute (1)

This contractor has been investigating polymers with low surface-free energy. In the past year, application of attenuated total reflection spectroscopy (ATR) has shown that albumin, gamma-globulin, and fibrogen adsorb on polystyrene, polyethylene, polydimethyl siloxane, and Teflon FEP in compact monolayers without dimensional denaturation; selective adsorption on Teflon FEP was detected but is not understood (i.e., gamma-globulin not adsorbed). Cellulose acetate electrophoresis measurements on solutions exposed to polyethylene show that adsorption is in proportion to the protein concentration; flow dependence has also been shown. The phospholipid lecithin (aqueous colloidal suspension) adsorbs in monolayers on polyethylene and polystyrene and not on silastic rubber or Teflon FEP or on polyethylene coated with albumin monolayers. On the other hand, no adsorption of cephalin occurred on polyethylene. Tests are being run to correlate this behavior with micelle size, phospholipid preparative technique, and thus in turn with specific surface free energy with a critical specific surface free energy for adsorption lying between 20 and 32 ergs/cm^2. Electron microscope work has centered on obtaining surfaces sufficiently free of background structure to permit protein examination. Results on gamma-globulin on silicone and on Teflon FEP confirm very closely the results from ATR spectroscopy on layer thickness and surface coverage. Because platelet adsorption data on various polymers showed considerable scatter, a new experimental cell and technique have been devised to eliminate any possible air-blood interface effects. Preliminary results suggest that platelet adsorption is random and competitive with plasma proteins. The real value of this effort is to the general body of information that is needed. The contractor will be encouraged to continue developing new information on the physico-chemical factors involved in blood compatibility. Synthesis of new materials will be kept at a very low level since there are already a large number of candidate polymers available for evaluation.
Contract No.: PH43-64-84 Contract Amount: $68,703

Thermo Electron Corporation (3)

This contractor has worked on a study of the relationships between electrical effects at polymer surfaces and surface thrombogenic character. This work with electret tabs has shown such promise in preliminary tests that the Program Office feels that further study is desirable. Electrets were prepared using poly vinylidene chloride and implanted in canine and rabbit tissue without showing toxic effects (3 to 30 days). Negatively charged electrets had slightly longer clotting times than positively charged ones. Study has been made on homo and heterocharge of electrets with finding that poly vinylidene chloride has a heterocharge of approximately 1000 Statcoulombs per cm square. Fluorocarbons were found to have varying values of heterocharge; poly tetrafluoroethylene and Teflon FEP copolymer

have negligibly small cocharges, while some poly chlorotrifluoroethylenes have high heterocharges. During the coming year, both the thrombogenic characteristics and the fabrication problems of electrets will be tested. Significant problems may be encountered in fabricating practical devices of the electret structure.

Contract No: PH43-66-1126 Contract Amount: $90,000

PHYSIOLOGIC EFFECTS OF CIRCULATORY ASSIST DEVICES

To determine whether a given assist device is suitable for clinical use, it is first necessary to answer certain physiologic questions in experimental animals. Each of the five contractors in this area has had the same objective during the past year, i.e., the evaluation of the physiological effects of devices (supplied by the Artificial Heart Program) according to a testing protocol generated by the Program Office in collaboration with consultants in cardiovascular physiology and instrumentation. Test protocol has been developed for each type of device under evaluation. More than sixty blood pumps have been implanted for this purpose. Emphasis has been on complete physiologic evaluation of these parameters: hemodynamic, hematologic, effect of emergency assistance on progression of ischemic area; chronic tolerance with regard to biologic control mechanisms, RBC damage, arteriolar structural changes, and changes in wave form. The testing of devices and components by these groups to date has been primarily limited to acute testing and engineering evaluation. Chronic test procedures and protocols are currently being developed by the Program Office and the various physiological effects testing groups.

Case Western Reserve University

During the past year, this group has been actively pursuing acute and chronic testing of the Avco-Kantrowitz auxiliary ventricle in experimental animals. Most of their effort has been directed toward surgical techniques, specifically the end-to-end aortic anastomosis. Preliminary physiologic data has been generated to define device performance in 10 animals during acute testing (3 - 20 hours). The chronic stage of physiologic testing is in its inception. During the coming year, emphasis will be placed on chronic testing of the Avco-Kantrowitz auxiliary ventricle, and the acute and chronic testing of an intra-aortic balloon.

Contract No. PH43-67-1424 Contract amount: $180,900

Melpar, Inc. (2)

During the past year, this contractor has been testing and obtaining physiological data on the use in animals of the Avco-Kantrowitz U-shaped auxiliary ventricle and of the Avco circular pump. The performance of these two pumps was found to be very similar, i.e., left ventricular peak pressure reduction and maintenance of normal systemic blood flow. The circular device is relatively easy to implant, the procedure requiring 10 minutes or less. This ventricle did not thrombos in a manner similar to the U-shaped ventricle, probably because of the smooth flow pattern it presents and the absence of thrombogenic graft material between the pump bladder and the aortic intima. Satisfactory placing of this pump within the thoracic cavity appears to be entirely feasible. In the case of the U-shaped ventricle, the surgical problems, while largely surmountable, are still severe. This is particularly true with regard to complete intrathoracic location of the pump. The

configuration of the pig's chest precludes satisfactory placement of this device wholly within the thoracic cavity. Another major problem associated with this pump is its tendency to promote clotting. Duration of the total surgical procedure required for proper implantation of the device is long compared to the circular shape. The increased surgical time produced animal recovery difficulties due to the anesthesia.
Contract No.: PH43-67-1418 Contract amount: $255,000

University of Minnesota (1)

During the past year, this group has been actively pursuing acute testing of the Baylor Left Ventricular Bypass both *in vitro* and in experimental animals. Physiologic data on RBC survival, hemolysis, percent of cardiac bypass, coronary flow, and left atrial pressure has been obtained, and a total of 16 implantations performed. Optimization of pump parameters has been identified and its limitations presented. The chronic stage of testing is currently underway. During the coming year, this contractor will continue testing the Baylor Left Ventricular Bypass and will soon begin evaluation of other devices supplied by the Program Office.
Contract No. PH43-66-974 Contract amount: $65,000

Thermo Electron Corporation (2)

In the course of the second year of this Physiologic Evaluation Program, the evaluation of the Avco-Kantrowitz left ventricular assist device was completed with a series of 16 chronic studies in miniature swine. Studies of the Statham-DeBakey pump and control system were undertaken next, beginning with mock loop testing. This was designed first to familiarize medical and engineering personnel with the function of the equipment and, subsequently, to perform hydrodynamic tests. Acute *in vivo* testing was conducted next, based on the findings of *in vitro* studies. Three such studies were performed, two in calves and one in a miniature pig. These studies had to be interrupted after the first and after the second experiments because of electronic control malfunction, which has been rectified. Further chronic studies are being planned.
Contract No. PH43-66-1123 Contract amount: $327,380

Travenol Laboratories

This group has concentrated its efforts on acute testing of the Avco-Kantrowitz auxiliary ventricle during the past year. Using consultants from the Department of Cardiovascular Surgery at the University of Chicago, the surgical difficulties inherent in this device have been defined, anatomic constraints delineated and proposed solutions to these problem areas have been undertaken. Physiologic and anatomic data has been generated on 22 animals during the acute phase of testing (3 hours - 3 days). The effects

of this device on left ventricular pressure, aortic pressure, blood flow, and blood elements have been defined in both acute and chronic implantations. Further chronic implantations are currently being pursued. This group has gained considerable experience and knowledge in animal surgery and physiologic monitoring during the past year and will perform acute and chronic testing of two or three circulatory assist devices during the coming year.

Contract No. PH43-67-1425 Contract amount: $308,469

STUDY OF THE EFFECTS OF ADDITIONAL ENDOGENOUS HEAT

The objective in this area is to determine the physiologic effects of heat and to define the limits on temperature and total thermal energy that may be dissipated in the body. This information must be obtained to permit the design of implantable circulatory assist devices because of their inherent inefficiency and the resultant need for dissipation of the energy in the body. During the past two years, more than sixty experiments have been performed with electrical heaters dissipating up to 80 watts of heat. This level of heating is higher than anticipated requirements. Hence, all efforts in this area at present are now directed toward determination of longer-term effects. Based on these preliminary results, it appears that several energy systems are technically feasible. Work of the current contractors is discussed below.

Battelle Northwest

This contract has continued to provide experimental data from studies using standardized pigs to demonstrate the feasibility of using circulating blood as a medium to dissipate waste heat from a totally implanted artificial heart. Continued studies will be performed in standardized pigs, with both subacute and chronic effects investigated. The organization has facilities and capability for monitoring sixteen animals. Major emphasis will be placed upon chronic studies, heat exchanger designs to improve heat transfer, and heat load tolerances under various environmental conditions.
Contract No.: PH43-66-1130 Contract Amount: $250,000

John B. Pierce Foundation

This contract has provided for investigation of the physiological and pathological effect of additional increments of endogenous heat on animals, including the local effects of the heat exchanger on surrounding tissue and effect on the total animal. Experimental procedures have been designed for control experiments without implanted equipment, control experiments with implanted equipment, control experiments with implanted materials and experimental tests of a nature and frequency to detect changes in any of the organ systems which might be affected by the additional heat. Data from the animals with implanted heat exchangers will be maintained and collected.
Contract No.: PH43-66-978 Contract Amount: $54,420

Thermo Electron Corporation (1)

This contract has provided continued studies of the feasibility of using circulating blood as a medium to dissipate waste heat from a totally implanted artificial heart. Chronic hyperthermia investigations have been made using electrically heated exchangers implanted in the abdominal aorta of dogs. This has included treadmill tests and febrile episodes induced in chronically hyperthermic animals under controlled environments. A Pu238 energized heat exchanger has been implanted in an animal to demonstrate the

feasibility of the use of this energy source. Additional animal tests are planned. Comprehensive evaluation will be made of the effects of radiation on all of the animals' organ systems.
Contract No.: PH43-66-982 Contract Amount: $228,895

BIOLOGICAL FUEL CELL DEVELOPMENT

The objective of this research area is to develop an implantable biological fuel cell that is completely implantable as an energy source within the epithelial envelope to allow maximum patient freedom and rehabilitation. Technical investigation of the concept has been limited to a study of electrodes, reactant mass transport and reaction kinetics characteristics to assess biological fuel cell feasibility. Both analytical and experimental studies have revealed pertinent information on validity of the approach. Several promising electrodes are under intensive investigation for use as oxygen and glucose catalysts. Other promising approaches are planned to investigate electrode reactions and stability and to further define mass transfer limitations. There has been one contract in this area during the past year.

Monsanto Research Corporation (2)

Monsanto has carried out a broad study of the kinetics of carbohydrate and oxygen electrodes; these include oxygen transport, oxygen reduction in neutral saline, glucose oxidation on carbon, alloys, and enzymes. These studies have elucidated many of the potential problems in biological fuel cell development. Work will continue on development of porous anodes for neutral electrolytes, and on a study of the feasibility of a solid Pd membrane anode.
Contract No.: PH43-66-976 Contract Amount: $278,505

DEVELOPMENT SUPPORT TO RESEARCH TEAMS WITH CIRCULATORY ASSIST DEVICES

Backup support has been provided, through two contracts, to medical groups to improve their effectiveness in working with and developing existing circulatory assist devices. These contracts were let originally two years ago to fund the development phase for the Baylor Left Ventricular Bypass Pump and for the Avco-Kantrowitz Mechanical Auxiliary Ventricle. The aims of the Program Office in this area have been continued during the past year. These two contracts for engineering support are listed below.

Avco-Everett Research Laboratory (1)

During the past year, this contractor has fabricated 60 auxiliary ventricles for implantation in experimental animals. They have been concerned primarily with design changes to improve hemodynamics, blood flow patterns, and compatibility of materials with blood. In addition, they have fabricated 8 pneumatic drive systems for these auxiliary ventricles. The contractor has worked with the Program's physiological effects group in testing the auxiliary ventricles and drive systems.
Contract No.: PH43-66-1131 Contract Amount: $300,000

Statham Instruments, Inc.

During the past year, this group has fabricated about 50 Baylor Left Ventricular Bypass Pumps for implantation into experimental animals at Baylor University, the University of Minnesota, and Childrens' Hospital Medical Center in Boston. They have also fabricated pneumatic drive systems and have worked on design improvements of the current pump aimed at improving hemodynamics and the blood material interface.
Contract No.: PH43-66-1125 Contract Amount: $282,320

DEVELOPMENT OF SATISFACTORY LONG-TERM PERCUTANEOUS LEADS

At this stage of artificial heart development, circulatory assist devices require tubes and wires passing through the skin. Existing percutaneous connections have not been satisfactory for long term use. For this reason, two contracts were awarded for development and testing in animals of a long-term, infection-proof percutaneous lead system, to be used for the transmission of energy into the body for control of circulatory assist devices and for the transmission of various signals from the body for the evaluation of function. Stable lead systems have been designed and fabricated during the past year and are currently being evaluated in animals.

Amicon Corporation (2)

During the past contract year, screening of various monomer-polymer pairs and catalysts was conducted in an attempt to develop a satisfactory tissue adhesive for percutaneous leads. Several polyelectrolyte complexes were developed and showed promising results in preliminary *in vivo* tests and in the coating of percutaneous lead systems supplied by Epoxylite. Future work will include optimization of tissue adhesives with respect to adhesion to lead components; preparation of functional lead systems for chronic evaluation; and acute and chronic *in vivo* evaluation of these adhesives and lead systems at Children's Hospital Medical Center.
Contract No.: PH43-67-1107 Contract Amount: $87,375

Epoxylite Corporation

During the past contract year, Dr. William Stone's artificial cornea design has been adapted for use in percutaneous leads. Various combinations of Teflon and epoxy polymers have been used to fabricate a percutaneous conduit and a subcutaneous fenestrated skirt and preliminary animal implants have been performed. It is planned that intrathoracic-percutaneous leads will soon be implanted in dogs. A prototype design will be fabricated and a limited number sent to other investigators. The investigators will continue to optimize skirt design and size in regard to tissue ingrowth and stabilization against mechanical trauma; continue to optimize adhesion of the skin and subdermal tissue to the skirt and conduit; further check the fluid and bacterial seal; revise the design of the percutaneous leads based upon animal experience; and undertake the final design for human beings.
Contract No.: PH43-67-1108 Contract Amount: $194,353

CONTROL SYSTEMS FOR CIRCULATORY ASSIST DEVICES

Most circulatory assist devices require almost continuous monitoring due to the lack of information on which to automate their control. One year ago two contracts were let to study this problem, one to Stanford University School of Medicine and the other to the University City Science Center. The purpose of this work is to identify parameters of importance for the control of the various types of circulatory assistance; the emphasis at the present time is on the physiologic requirements rather than the engineering requirements. Both literature and experimental studies have been performed to determine the modes of control that are used in the intact animal and to study the function of the heart when most control modes have been removed by autotransplantation.

Stanford University School of Medicine

This contract group conducted studies of the performance characteristics of the circulation in the absence of neural control by using dogs with autotransplanted denervated hearts. Preliminary observations showed that, in autotransplanted dogs, blood volume increases about 20% with little change in venous pressure, and renal clearances are slightly higher than normal. In response to hemorrhage and transfusion, autografts responded with a greater fall in blood pressure and cardiac output and a lesser heart rate rise than normals. The Doppler-shift principle ultrasonic flowmeter has been improved and now accurately measures both forward and retrograde flow. The left heart of the autograft has been mathematically modeled. Continued work will be on pressure and flow measurements of cardiac autotransplants with the resulting data being used to construct a cardiovascular model; telemetry of pressure and flow measurements on exercising autotransplanted dogs; development of a mathematical model and of heart rate control laws of this system; development of a computer controlled pacemaker system for monitoring of the autograft; instrumentation for the closed loop control of a Free-Roaming Autograft---the computer will analyze the transducer outputs and thus control heart rate and form a closed loop from animal to computer and back to the animal.

Contract No.: PH43-67-1109 Contract Amount: $103,300

University City Science Center

This contract was for a review of existing control models and development of an analytical model of intrinsic and extrinsic control parameters of the circulatory system. A simulated uncontrolled circulatory system was developed, with preliminary equations and analog computer circuit diagrams. The carotid chemoreceptor control loop was analyzed and found not to be required in an assist device control mechanism. An analysis of humoral and neural control loops is still being performed. The effects of exercise, physical work, hypoxia, and posture are being analyzed.

Contract No.: PH43-67-1110 Contract Amount: $174,300

NEW CIRCULATORY ASSIST DEVICES

The objective of the Program in this area is to develop promising members of the entire family of assist devices - namely, emergency, temporary, and permanent types of such devices and an artificial heart for total cardiac replacement. During the past year, temporary and permanent heart assist devices have been under development and evaluation. With the promise of these devices, initial steps are being taken to develop emergency devices to improve the probability of patients reaching the hospital, to perform diagnosis more effectively and to provide initial support in the hospital. Specific blood pumping concepts that have been designed and hardware (pumps and drive and control systems) that has been fabricated are now in initial stages of physiological evaluation and include devices that will function in-series or in parallel with the left ventricle, or that will bypass the heart (veno-arterial pumping). Over a hundred animal experiments have been performed during the last year using five different pumping concepts. The devices have demonstrated that cardiac work can be decreased and that adequate tissue perfusion pressures can be maintained.

Avco-Everett Research Laboratory (2)

This contract group, working on the development of an intra-aortic balloon catheter, has made substantial contributions.
It has been shown that occlusive long slender balloon designs tend to have instability problems leading to inflation of the ends before the center portion. This resulted in sealing of the ends and caused high pressures in the center portion. Several design changes have been investigated to solve this problem. The most promising of these is a multi-segment balloon which would operate in a peristaltic manner. A three segment balloon was tested, but still showed the stability problems. A five segment balloon is being designed at this time. A non-occlusive balloon has also been designed and tested for mechanical and chemical safety in animals. Chronic studies were done without measuring hemodynamic data.
Contract No: PH43-67-1111 Contract Amount: $245,907

Cedars-Sinai Medical Research Institute

This contract was for laboratory and clinical experiments using the veno-arterial pulsatile partial bypass (VAPPPB) pump system. The equipment has been assembled for use with dogs and humans, and a total of about 200 dogs have been pumped using the VAPPPB technique. It was shown that medium flow rates (above 30cc/Kg min) for a period of 2 hours resulted in insignificant elevation of serum lactic acid. However, at low flow rates with hemodilution, the lactic acid and pCO_2 were elevated, and pH and base excess were reduced, indicating inadequate tissue perfusion. No change was shown in hematocrit and WBC and RBC counts, except that caused by the hemodilution. Serum hemoglobin was elevated and platelet count was decreased during prolonged pumping (over 5 hours). No significant changes in total proteins or electrophoretic pattern occurred with prolonged pumping. It was concluded that medium flow rates without hemodilution resulted in adequate tissue perfusion. VAPPPB, in

contrast to arterial-arterial pumping, caused significant reductions in cardiac output and work, and increased coronary, carotid, renal and mesenteric flows. Preliminary experiments have indicated that resistant ventricular fibrillation may be converted after a period of VAPPPB. Two human patients have been treated with VAPPPB. The first patient was pumped for 2½ hours. Following pumping, the skin temperature improved, peripheral cyanosis disappeared, and urine flow began. The patient died of cardiac arrest 36 hours after pumping. The second patient was pumped for two periods of two hours. Systemic pressure was restored, the pulmonary edema was corrected, and urine flow began. During the remainder of the contract more data will be obtained in animals with induced cardiogenic shock.
Contract No. PH43-67-1112 Contract Amount: $202,555

Hamilton Standard Division (1)

This contract is for the investigation and development of a co-pulsation heart assist device. The concept of "co-pulsation" remains unique in the circulatory assist device field, since it is based on the principle that circulatory assist which mimics the normal pulse wave contour is physiologically more sound than that which reverses it (as is done with all forms of counter-pulsation). The co-pulsation concept involves pumping 360° out of phase with the natural heart rather than 180° out of phase as is used with counter-pulsation devices. This concept needs to be investigated to be able to define and compare the effects of the two techniques on flow patterns, work load of the heart, effects on baroreceptors, etc. Work to date has not as yet precluded or invalidated the potential physiological feasibility of the co-pulsation device. The pump and control systems have been designed, fabricated, and tested for conformance to specifications. The system has been assembled, and stability problems were observed. Redesign of electronic and mechanical systems is being done to correct these problems and it is expected that physiological evaluation will be started soon.
Contract No. PH43-67-1113 Contract Amount: $254,090

Massachusetts Institute of Technology

This contract is for theoretical and experimental studies of the concept of intra-aortic balloon pumping. This includes the development of an engineering knowledge of the mechanics and fluid mechanics of balloon operation and the quantitative description of balloon wall motions, fluid motions, and pressure distribution. The theory for tensed-balloon operation has been developed. For the limp balloon, the reasons for bubble blowing at each end during inflation have been explained; it is hoped that this work will lead to the ability for control of this problem. A scale model of a complete system has been assembled and tested with appropriate pressure and flow transducers. High speed photography has been used to show the detailed inflation patterns, and the bubble phenomenon has been recorded. Techniques of reinforcing the balloon wall are being studied to eliminate this problem.
Contract No. PH43-67-1114 Contract Amount: $38,812

University of Mississippi

This contract is for the development of a series assist pump with a distal active valve. The control unit has been designed, fabricated, and tested. This control unit was designed to function with other types of assist devices as well as the series pump. The coupling system has been designed to allow rotation of the animal without damage to the pneumatic and electrical leads. The surgical technique for implantation has been developed so that end-to-end anastomoses can now be performed rapidly. Acute experiments were done to test the performance of the valve. Without the valve the integrated ventricular pressure was reduced 21 to 42%; with the valve the reduction was 72 to 97%. There was no significant change in mean aortic pressure and cardiac output. The coronary flow was increased 34% without the valve and 12% with the valve. Chronic patency experiments have been done with non-functioning units. Survival time ranged from 5 days to over 165 days, with the major cause of death being thrombo-emboli. The thrombi formed on the inlet side of the pump and not within the pumping chamber itself. Redesign of the inlet has reduced, but not eliminated, the thrombus problem. The inlet tube has been redesigned to allow the use of surface heparinization techniques.
Contract No. PH43-67-1118 Contract Amount: $30,900

Physics International

This contract is for the application of a piezoelectric pump to a hydraulic ventricle assist pump. The designs are for low frequency operation and require volume amplification to drive a blood pump. One of these, a radial diaphragm pump, has been assembled and tested in prototype form. The electronic power supply, using a Marx generator, has been designed, fabricated, and tested. At the present time the emphasis in the contract is toward improvements in the performance in the piezoelectric crystals and stacks.
Contract No. PH43-67-1115 Contract Amount: $232,000

Thermo Electron Corporation (4)

This group is developing a promising left-ventricle-to-aorta bypass pump. The TECO pump is a double-valved bypass pump from the apex of the ventricle to the descending aorta. Initial studies were done to evaluate the effects of chronic implantation of an apical tube. Electrocardiograms over a period of six months showed slight changes in the vector orientation and showed no persistent arrhythmias or myocardial infarction. Their results in calves thus far have been extremely encouraging, e.g., a pump has been successfully implanted in a calf since October 23, 1967, and is still functioning properly. Acute hemodynamic studies have been done using normal calves. During pumping, up to 97% of the cardiac output was through the pump; when the pump was turned off, 28% of the cardiac output continued to flow through the pump. The pump could produce a reduction of from 60 to 90% in left ventricular pressure. The total cardiac output appeared to increase slightly during pumping. No effects were observed in atrial pressure, pulmonary pressure,

or mean aortic pressure. Chronic studies, with survival of several months have been performed using a pump lined with flocked Dacron. The hematocrit fell 5 to 10 units and then stabilized after 8 to 20 days. LDH was elevated for 7 to 14 days, and osmotic fragility was increased for 7 to 20 days. Plans are for further improvements in pump design, fabrication and performance of the left-ventricle-to-aorta assist device.
Contract No. PH43-67-1116 Contract Amount: $249,750

New England Medical Center

This contract has supported the development and study of an auxiliary ventricle that attempts to avoid the problems of intrathoracic placement by subcutaneously exteriorizing the device, which is a series assist pump with a double bladder and a distal valve. Preliminary studies were done to test the effect of the distal valve. Without the valve the peak left ventricular pressure was reduced from about 150 to 115 mm Hg; with the valve the reduction was from about 125 to 25 mm Hg. Also, the valve prevented the distal aortic pressure from dropping as severely during pump filling, presenting a more normal pressure wave form to the systemic circulation. The pumps and control systems to be used for chronic implantation have been designed and fabricated. The pump has quick-connect inlet and outlet tubes, and the blood contacting surfaces are lined with Dacron velour. The outlet valve is actively operated from the compressed air source and will have no flow obstruction when open. The control system can be triggered from the R-wave or pressure wave or from an internal pacer. Pumps will be fabricated for testing by the physiological effects contractors.
Contract No. PH43-67-1117 Contract Amount: $53,634

Westinghouse Electric Corporation

This contract was for the development of intra-aortic balloons, and the group has made significant contributions during the past year to this development. Single segment and double segment balloons have been designed, fabricated, and tested. The single segment balloon gave an 18% decrease in aortic tension-time index and a 20% increase in left circumflex flow. The double balloon, with one segment in the ascending aorta, gave effects about 50% greater than the single segment balloon. Some studies were done with oversize balloons to test the effects of the balloon on the aorta. At lateral pressures of above 200 mm Hg there was evidence of hemolysis and damage to endothelial cells. Surface heparinization was performed by another contractor, and these balloons seem to be less thrombogenic. The electronic control system has been designed, fabricated, and tested. This system features the measurement of R-wave slope and magnitude to eliminate false triggering. Plans are for continued improvement of these balloon catheters and for independent evaluation of them by the physiological effects group of the Program.
Contract No. PH43-67-1139 Contract Amount: $202,058

BLOOD FLOW IN AND ADJACENT TO BLOOD PUMPS

The objective in this area is to obtain data on the hemodynamics of various flow geometries in blood pumps and oxygenators that will permit the development of devices which cause minimum hemolysis and thrombosis and have optimum flow patterns. Both analytical and experimental programs are being conducted to define the hemodynamic characteristics of blood pumps and valves. Flow characteristics for five geometries are currently under evaluation. In addition, considerations will involve the analysis of cell and platelet interaction and different geometries.

Avco Everett Research Laboratory (3)

During the past year, studies relating blood flow to thrombus formation have been performed. The experimental apparatus consists of a flow chamber which receives blood from an everted carotid artery. Streamline flow is separated, the area of separation being called the stagnation point. This stagnation point and adjacent regions are visualized microscopically and the pattern of thrombus formation observed on various materials and under varying velocities. The Avco Everett Research Laboratories developed the flow chamber for the microscopic visualization of flow and the deposition of cellular elements on various surfaces resulting from combined actions of the flow patterns and the blood material interaction. This device has been reasonably successful. During the coming year, this group's major emphasis will be on the evaluation of transparent plastics.

Contract No.: PH43-67-1120 Contract Amount: $142,125

General Electric Company (1)

This group has been primarily involved in theoretical studies of blood flow in order to provide fundamental data and quantitative formulae for use in defining design limits for circulatory assist devices in contact with flowing blood. Continued work will aim at the development of analytical methods for predicting the presence of excessive shear, turbulence and trapped vortices which can lead to excessive red cell collisions, red cell deformation, hemolysis and clotting.

Contract No. PH43-67-1121 Contract Amount: $150,000

University of Minnesota (2)

During the past year this group has been making studies of flow through visualization experiments using suspensions of red cells and red cell ghosts. During the coming year, special emphasis will be placed on the continuation of their flow visualization experiments, the study of blood flow in the skimming layer, velocity studies using laser light scattering experiments and also the biochemical aspects of cell wall interactions.

Contract No. PH43-67-1122 Contract Amount: $74,000

IMPROVED OXYGENATORS FOR CIRCULATORY ASSIST DEVICES

Improved blood oxygenators are being developed for use in cardiovascular surgery and in general surgery and for use with circulatory assist devices. Existing blood oxygenators pose very significant limitations. The Artificial Heart Program effort is to develop and evaluate improved oxygenators with increased gas transport and decreased blood trauma. At present, three existing oxygenators have been further developed and improved during the past year, and four new concepts have been designed and fabricated. Tests on small scale devices of these designs have shown significant improvements regarding gas transport and blood trauma. More extensive evaluations are presently in progress. The seven contracts of the past year were initiated for the development of new and improved blood oxygenators for improving heart and lung bypass procedures, for use with assist circulation procedures, and for transplant organ preservation. In the development of improved oxygenators, the major emphases are placed upon the utilization of new materials with increased blood compatibility, the design for improved hemodynamics and techniques for reducing fabrication costs. New concepts in blood oxygenators involve the design and development of membrane oxygenators such as the capillary type with particular emphasis upon reducing of priming volume, overall unit size, high oxygen and carbon dioxide transport properties, good hemodynamics, disposability, easily sterilizable, and low cost.

Abcor, Incorporated

This contractor has been working on a program to develop a capillary membrane oxygenator. A computer model of the device has been developed and verified by in vitro tests with 100 tube bundles. In vivo testing has begun with 100 tube bundles. The best performance was with non-woven bundles with central gas distribution tubes. Gas exchange of up to 267 cc/min. M^2 was achieved in in vitro tests with high blood velocity. Less gas exchange was achieved in the in vivo tests, possibly due to protein deposits in the tubes. The control system design is complete except for design of the sensors. Testing of oxygenators of 500 ml/min. blood flow capacity is expected during the present contract year. During the next year the major objective is the construction of a full scale total bypass oxygenator. Other goals include studies of smaller tubes and studies of increased transport by use of coiled tubes. In vitro and in vivo testing will be done with 500 cc/min. oxygenators, and possible improvements will be studied. A total bypass system will be constructed and tested.
Contract No.: PH43-67-1405 Contract amount: $96,558

General Electric Company (3)

This contractor has been working on a program for the fabrication and testing of membrane envelopes in a flat membrane oxygenator. The goals of the present program are to: (1) design and fabricate XD polymer membrane envelopes; (2) perform in vitro gas exchange tests; (3) perform sterile in vitro tests for blood damage; (4) perform long partial and total bypass experiments. Membrane envelopes have been redesigned and fabricated. In vitro gas exchange studies are being done using envelopes of 6.0 cm path length; up to 78 cc/min. M^2 gas

exchange has been obtained. Some modifications have been made in the casting technique to give slightly higher point supports. In vitro testing for blood damage has begun. In vivo testing will be begun in the present contract, but will not be completed. During the coming year primary objectives are to make improvements in membrane envelope fabrication techniques and to perform blood damage testing. Secondary objectives are to improve gas and blood distribution, to test new silicone rubber materials, and to perform clinical testing. The major advantage of the device developed by General Electric is that it could be brought into clinical use relatively soon, and important data could be obtained. This data would be useful for testing the long-term use of a satisfactory oxygenator for long-term perfusions. The contractor's future emphasis will be on producing oxygenators for in vivo and clinical testing.
Contract No.: PH43-67-1458 Contract amount: $75,050

Institute of Medical Sciences

This contract, begun in October, 1967, is for the further development of the Bramson membrane oxygenator. A single cell model oxygenator was constructed for use in detailed flow and gas transport studies. Measurements are being made of the local depth averaged oxygen saturation using a specially designed scanning photometer. The information on oxygen saturation and blood flow will be used to improve the geometry of the oxygenator, including possible changes in diameter and local blood film thickness. Long-term perfusions have been begun with a large scale oxygenator in comparison to a bubble and disc oxygenator. Long-term veno-venous perfusions have indicated a greater tendency towards pathological lesions of the lung when using the bubble oxygenator in comparison to the membrane oxygenator. Other techniques are being developed for comparative evaluations.
Contract No.: PH43-68-67 Contract amount: $91,310

Medical College of Virginia

This contractor has been working on a program for a hollow filament oxygenator. The objectives of the present contract are to: (1) perform hydrodynamic studies with solid fibers; (2) perform blood trauma studies; (3) evaluate potential materials; (4) perform gas exchange and hydrodynamic studies with model oxygenators; (5) perform in vitro and in vivo studies with full scale oxygenators. Hydrodynamic studies have demonstrated low pressure drops, and in vitro blood trauma studies have demonstrated low trauma as evidenced by plasma hemoglobin and screen filtration. Gas exchange studies have been inconclusive due to lack of availability of highly permeable materials in the desired sizes. During the remainder of the present contract the oxygenator will be expanded in size, and more permeable materials will be investigated. In vitro and in vivo testing will be done. Additional blood trauma tests are being set up and evaluated with a disc oxygenator. During the coming year, testing will be done on the scaled up oxygenator, and improved materials will be studied. Blood trauma studies will be expanded. Improvements will be made in the fabrication techniques and in the casing design. The enlarged device will be tested on a

small dog; gas exchange and blood damage will be studied. An oxygenator will be fabricated and tested with improved materials. A final optimized oxygenator will be fabricated and tested extensively.
Contract No.: PH43-67-1426 Contract amount: $57,384

University of Minnesota (3)

The purpose of this contract is to design, construct, and test in vitro the new oxygenator concept which employs a rotating membrane. It is expected that the rotating membrane will minimize the blood boundary layer and introduce flow patterns that will result in better mixing and enhanced gas transfer. The oxygenator has been designed and fabricated, and the test loop has been assembled. Evaluation of the concept is now underway.
Contract No.: PH43-67-1419 Contract amount: $19,525

University of Minnesota (4)

This contract for a flat plate membrane oxygenator program began at the University of Minnesota and was transferred to Cornell University with the move of the principal investigator. The goals of the program were to: (1) make refinements in the molds for the membrane supports; (2) perform in vitro testing of single and multi-element oxygenators; (3) perform in vivo testing and measure parameters of blood trauma caused by the oxygenator. Flow studies have been done under subcontract. Stability of flow patterns has been demonstrated, and flow patterns in the test device have been improved by changing the cone supports. Turbidity and hemolysis studies of the membrane oxygenator compared to bubble and film oxygenators have indicated less damage with the membrane oxygenator. In vivo tests have achieved oxygen transport of 80 cc/min. M^2 when using recirculation of blood through the oxygenator. Pumping by varying gas pressure has been accomplished.
Contract No.: PH43-67-1446 Contract amount: $107,300

Monsanto Research Corporation (4)

This contractor is working to develop a grooved capillary membrane oxygenator. The objectives of the present contract are to: (1) apply CIH membrane to substrate and test gas exchange; (2) fabricate oxygenator elements and test them in vitro; (3) fabricate and test a multi-element stack in vitro; (4) fabricate and test in vivo a full scale oxygenator; (5) revise designs for full scale oxygenator. Silicone rubber has been substituted for CIH due to gas exchange problems. Groove formation has been improved, but pinholes still occur in the silicone rubber membrane, probably due to cracks in the substrate. In vitro and in vivo gas exchange studies with single elements have demonstrated adequate oxygen transport. A multi-element oxygenator has been designed using modified manifold geometry. Evaluation is planned during the present contract. Redesign of the full scale oxygenator will be done. Studies will be done on improvements in blood manifolding. Improvements will be made in capillary entrance and exit geometry. Two second generation and three third generation full scale oxygenators will be designed, fabricated and tested.
Contract No.: PH43-67-1420 Contract amount: $111,930

ENERGY SYSTEMS FOR IMPLANTABLE CIRCULATORY ASSIST DEVICES

The Program requires the development of several reliable and safe energy systems that may be effectively used with a variety of circulatory assist devices --from non-implantable systems for emergency devices to a completely implantable energy system for permanent circulatory assist devices. This means that external power must be supplied either transcutaneously or percutaneously to the internal portion of the assist device, or that energy must be generated internally by a biological fuel cell or an implanted radioisotope heat source. To minimize energy system peak requirements, it is desirable to develop energy storage devices that can be integrated into the system to satisfy sudden peak energy demands of the patient and to allow the patient to move about for a limited period without being coupled to any external source of power.

During the past year, work has been done, under 10 contracts, on energy transmission, conversion, and storage. For energy transmission systems, energy transmitting and receiver units have been designed, fabricated, and tested with an efficiency of 90 to 95 percent at the designed 50 watt level. Surgical feasibility of coil implantation has been demonstrated in chronic experiments with dogs, sheep and goats. Systems are being assembled at the present time for comprehensive long-term in vitro and in vivo testing. Both electrical and thermal energy conversion systems have been designed, fabricated and tested in the laboratory. The power output characteristics of these systems are being evaluated, i.e., efficiency, power to weight and power to volume ratios, etc. Systems for animal implantation are being designed and fabricated at present. Energy storage devices that will interface with the energy transmission and conversion subsystems have been designed and fabricated. These devices are currently undergoing rigorous testing. They include techniques for storing both electrical and thermal energy. Following is a discussion of the purpose and progress for each of the energy contractors.

Energy Transmission

Hamilton Standard Division of United Aircraft Corp. (2)

This contract was for the provision of a radio frequency system capable of transmitting electrical energy through intact human skin over long periods of time to power implanted circulatory assist devices and/or to supply power for charging an implanted energy storage system. Hamilton Standard has designed and fabricated a 50-watt transmission system. It has been successfully demonstrated under varying operational conditions, i.e., significant excursions (one inch) axially and radially in terms of alignment of the transmission coil and receiver coil with retention of high efficiency in transmission. The electronics have been designed with feedback control to permit transmission in the face of varying load requirements to minimize the total energy transmitted into the body. The polyurethane encapsulants with self-wiping connectors have been incorporated into the receiver units. Bench tests reveal that the transmission system will operate with an efficiency greater than 75 percent. Systems are being assembled at the present time for comprehensive long-term in vitro and in vivo testing. During the next year, major emphasis will be on in vivo testing, elimination of interference in the feedback channel, miniaturization, and fabrication of the system for other programs. In vivo test

protocol has been developed and test units for chronic animal experimentation have been fabricated and sent to the Yale Medical School for testing.
Contract No.: PH43-67-1406 Contract amount: $137,214

Kollsman Instrument Corporation

The work of this contractor was to design, develop, fabricate, and animal test an ultrasonic power transmission system to transmit power to an implanted load. Several ultrasonic transmission systems have been designed, fabricated and tested in vitro. The maximum efficiencies achieved have been approximately 65 percent. Performance data on the system is being developed to determine response characteristic with regard to load, rate of power transmission, circuit impedance, different piezoelectric crystal materials, and other component design parameters. Units have been encapsulated for in vivo evaluation of the transmission concept. In vivo experiments are currently being performed to validate bench test data. Testing has been done using low power transmission with various crystals at efficiencies of up to 90 percent in simulated tissues. The areas of losses and problems with alignment have been quantitated. The major problem with the ultrasonic approach is the inability to maintain acoustical contact between crystals with active test animals. The crystals must be effectively coupled at all times if acceptable transmission efficiencies are to be achieved.
Contract No.: PH43-67-1415 Contract amount: $63,256

New York University

The purpose of this contract is to develop and test an energy transmission device consisting of a transformer with a closed magnetic path through ferrite, with the skin as an air gap. It has been demonstrated that it is possible to transmit sufficient energy across intact skin to power circulatory assist devices with a device about the size and weight of an implanted cardiac pacemaker. The energy can also be transmitted without causing intolerable temperature rise in the intervening tissue, e.g., the rise in temperature at the surface of the device is approximately 3° C and at approximately three centimeters distance from the transformer is only 1° C. These temperature rises appear to be acceptable based upon controlled endogenous heat studies.

The surgical procedures for animal implantation have been worked out and the preparations appear to be very stable under chronic conditions. The effects of weight, shape and method of attachment are being evaluated in chronic animal preparations. The electronics of the transmission assembly are under evaluation to improve device efficiency and to make the system compatible with different sources of electrical energy, i.e., batteries and line sources. Component encapsulation has been studied. The procedure evolved is to apply a thin inter-coating of silicone rubber and an outer-coating of epoxy resin. The development of transcutaneous power transformers is proceeding on schedule with units being designed for higher efficiency and being evaluated under chronic conditions to determine their usefulness in long-term evaluation of circulatory assist devices. Dummy coils have been implanted for six months with no sign of rejection. In vivo testing is being performed at the present

time. The concept has been shown to be basically feasible though major problems have been position sensitivity, excess weight, and hot spots in the transformer core.
Contract No.: PH43-67-1414 Contract amount: $90,000

Stanford Research Institute (2)

The current program has been concerned with engineering, surgical, and physiological aspects of an electromagnetic energy transmission system through the skin. The most important advantages of the design are high efficiency, the lack of position sensitivity, the certainty of magnetic coupling, and the potential of operating at low frequencies. This technique of energy transmission has high promise, especially for animal experimental work in which the guaranteed coupling would be a major advantage. Test units (intact skin-transformer with a gapless magnetic core) have been designed and tested. Operational data on test units coupled to simulated loads has been obtained. The implantable coils have been redesigned several times or new information has been developed with regard to weight, size and geometry to provide a better energy transmission system. Units capable of satisfying power transmission requirements have been tested under acute conditions and no limiting problems have been uncovered, e.g., temperatures have not caused rejection. Surgical feasibility of implantation of coils by a tube pedical flap has been demonstrated in chronic experiments with dogs and goats. Six coils have been implanted and tested at a transmission of 20 watts at 60 cycles and 120 watts at 400 cycles. Tests are being conducted with a ¼ pound system capable of transmitting 30 watts at 20,000 cycles. Future emphasis of this contract work will be on surgical procedures and the generation of parametric data for interface with various energy conversion systems.
Contract No.: PH43-67-1422 Contract amount: $50,878

Energy Storage

General Electric Company (2)

This contractor's program to analyze and develop an implantable electrical energy storage system of the electrolytic/fuel cell type has been carried through the first two phases--definition of system design requirements and system design. The reversible fuel cell could result in significant advantages over other electrical storage concepts in existence. Future effort will concentrate on testing and optimizing the existing design, and could result in a stored energy density of 20 watt hours per pound and a capability for complete discharge without damage to the system. A new idea from this contractor is the single membrane concept, which has a potential for leading to increased efficiency.
Contract No.: PH43-67-1410 Contract amount: $81,221

Melpar, Inc. (3)

The objective of this contract was to optimize and test an electrical storage system, i.e., lead-silver and magnesium-silver cells, that could be used both for implantation and for external application with implantable circulatory assist devices. The battery to be designed was to have a potential of 3.2 volts, provide 5 watts of power, and have the capability of being recharged. The battery cells were to be of the thin-film, solid-electrolyte type. Thin-film cells were considered particularly suitable for this application, not only because of small physical dimensions and weight, but also because of their indicated stability, freedom from liquid electrolyte, and gas evolution. The thin-film elements could be of any reasonable surface area, could be stacked or rolled up, and hermetically sealed or potted. As prepared, they were to be ready for use and capable of being recharged, i.e., serving as secondary batteries. However, due to a lack of overall experience, the research effort on silver-magnesium cells and the project was terminated.
Contract No.: PH43-67-1421 Contract amount: $161,700

Thermo Electron Corporation (5)

The work of this contractor was to develop and test a thermal energy storage system for use with circulatory assist devices, using lithium hydride. Tests have shown that an eutectic mixture of lithium fluoride and lithium chloride appears to be the most promising material for use in a thermal energy storage system. It has good chemical and mechanical stability over the temperature range and is compatible with several containment materials. Data on the thermal system has been obtained with regard to internal and surface temperature profiles as a function, total energy storage and various energy transfer rates both into and out of the storage device. This data has provided for the design, fabrication and evaluation of a complete prototype thermal storage device. The feasibility of this system of thermal storage has been demonstrated, and the system will be incorporated into future work of this group under a different contract for development of a complete energy system.
Contract No.: PH43-67-1423 Contract amount: $97,652

Energy Conversion

Donald W. Douglas Laboratories

This is a contract to determine the feasibility of the Stirling cycle energy converter by prototype operation. Stirling engine conversion devices will be designed, fabricated, tested and analyzed during the performance of this contract. During the past year, Prototype 1 of a modified Stirling engine was designed, built, and tested to give a maximum power of 1.6 watts at 4.5 cps with an overall efficiency of 0.7%. Prototype 1A, built from parts of Prototype 1, produced 7.7 watts at 9.8 cps and 6.4% efficiency for a heat input of 100 watts. This design offers the advantage of potentially high efficiency and relatively few moving parts. This design offers a good possibility of demonstrating the efficiency required to make a decision on the thermal engine concept. Plans are that Prototype 1A will be used to test improved regenerators.

Using the computer simulation program and the results of testing, design alternatives will be investigated. Prototype 2 is being fabricated and is designed to operate at higher frequency and pressures. Future work will concentrate primarily on increasing the efficiency of the engine and estimating the heat loss.
Contract No.: PH43-67-1408 Contract amount: $182,122

Energy Research & Generation, Inc.

This contract was for work to extend the energy capabilities of stacked piezoelectric crystal energy conversion and to use this knowledge to develop efficient piezoelectric motors as implantable energy conversion systems for circulatory assist devices. Two power suppliers for operation of piezoelectric drive units have been designed, fabricated, and tested. A specialized linear dynamometer for evaluation of piezoelectric crystal characteristics has been developed. Performance characteristics of piezoelectric crystals under varying operation modes (i.e., electric field conditions, pre-load conditions, etc.) has been evaluated. Techniques have been developed for making piezoelectric stack configurations with integral electrodes employing vacuum diffusion or diffusion welding. Future work of this contractor will concentrate on the design, development, integration and testing of hardware.
Contract No.: PH43-67-1409 Contract amount: $105,562

Hamilton Standard Division of United Aircraft Corp. (3)

The contractor will design and evaluate the feasibility of a high frequency bimorph piezoelectric motor pump energy conversion system. The initial six-month period has been devoted entirely to component design and fabrication. The piezoelectric bimorph procurement design specification was prepared and bimorphs procured. The prototype pump housing design was also completed. Fabrication of the bimorph and pump housing has been completed, and component static and dynamic testing was initiated early in January. The electroviscous valve design specifications were prepared and procured. An extracorporeal pump with a bimorph crystal and four electroviscous valves has now been fabricated and is being tested. This concept for a piezoelectric energy conversion system has a high possibility of leading to a highly efficient system. Operation at high frequencies with a low frequency pulsatile output has been demonstrated. No major technical problems nor major deviations to the original program plan are identified. The project has shown significant progress to date, with the major problems being the acoustic level of the present system. Special emphasis of future work will be placed on solving the acoustic problems. The electroviscous valves have a slightly excessive pressure drop, and work will be done on this problem.
Contract No.: PH43-67-1412 Contract amount: $149,000

SUPPORT TO ARTIFICIAL HEART DEVELOPMENT WORK BY OTHER GOVERNMENT AGENCIES

Atomic Energy Commission

Funds have been transferred to the Atomic Energy Commission for the partial support of four AEC contracts for investigations into the feasibility of using radioisotopes as the power source for implantable artificial hearts and assist devices and for development of the conceptual design definition of the power source. These four contracts are with Aerojet-General Corporation, Thermo Electron Corporation, Westinghouse Electric Corporation, and Donald W. Douglas Laboratories. During the year, this work has resulted in studies and conceptual design of radioisotope-powered Rankine-cycle and Stirling-cycle engines which would serve as power sources for implantable circulatory support systems. The studies have included an evaluation of candidate radioisotopes, parametric analysis of cycle performance, blood heat exchanger design, operation of control system, selection of thermal energy storage material, and packaging in vacuum-foil thermal insulation. Pu^{238} is considered the preferred isotope as fuel for an implantable power source because its half-life is much longer than that of Pm^{147}, the other isotope considered. There was very little difference in biological dose rates between the two. The design of these two types of engines is aimed at providing enough blood pumping power for long-term in vivo testing and further development of the system.
Reimbursable agreement Amount: $275,000

Harry Diamond Laboratories

The Program Office has supported, by a reimbursable funds agreement, the further development of the Army artificial internal heart pump at the Harry Diamond Laboratories. Work during the past year has aimed at solving the position sensitive problem of the present fluid-amplifier-controlled heart and the development of an external means of control in which metered amounts of a fluid would be used to drive the heart, with special effort directed toward size reduction and clot prevention. Work was also directed toward the development of a cardiovascular simulation which would provide a convenient test set for evaluation of artificial hearts.
Reimbursable agreement Amount: $80,000

ADDITIONAL CONTRACT AREAS FOR 1969

The plan of the Artificial Heart Branch for the immediate future is to continue developments in the above areas and to initiate additional critical supportive programs to develop a family of therapeutic artificial heart devices. These additional programs are described below.

Materials Testing

The purpose of this effort is to (1) establish reliable, quick, and inexpensive standardized testing techniques as common denominators for screening new materials; (2) establish techniques for evaluation of blood proteins and cellular response in both a qualitative and quantitative manner to candidate materials; and (3) establish techniques for evaluation of the promising materials by fabricating and testing actual devices. The prime emphasis of this area is upon screening of new materials and testing of promising candidates.

Instrumentation

The objective of this program is to develop new or improve existing instrumentation that offers promise of being useful in the development, control, and regulation of circulatory assist devices, i.e., venous and arterial pressure transducers and flowmeters that are both temporarily and permanently implantable, instruments for improved monitoring of cardiac patient progress, and techniques for isolating implanted devices from the biological environment. The rationale is to initiate development efforts with a limited number of experienced and skilled organizations in pressure and flow, cardiovascular function, chemical monitoring, component isolation and telemetry; to develop instruments capable of providing quantitative data for monitoring and controlling devices on a long-term basis; to develop working relationships between instrument developers and circulatory assist device developers in the Program to insure that interface problems are clearly identified and that instruments are effectively utilized as improvements are made; and to develop working relationships between instrument developers and physiologic effects testing groups in the Program to test and evaluate the performance characteristics of the instruments and to evaluate the complete blood pump containing the instruments, as part of their normal efforts in assuring development of effective, safe, and reliable assist devices.

Test and Evaluation Facilities

The Program Office needs to develop Test and Evaluation Facilities in which circulatory assist devices, components and other prostheses under development by the Artificial Heart Branch can be expeditiously and comprehensively tested and evaluated from a biological, engineering and clinical standpoint to assure their effectiveness, safety and reliability as modes of therapy. The rationale is to provide effective modes of therapy for cardiac patients and/or patients with circulatory failure for whom contemporary cardiac surgery and chemotherapy provide little effective support for altering or reversing their condition. Test and Evaluation Facilities will provide testing and evaluation under controlled conditions. Devices will be thoroughly evaluated by competent and objective groups that have had no part in the development of the particular

device. These evaluations will be in addition to the evaluations provided by the developer himself. The Artificial Heart Program Office believes that it is imperative that devices or components satisfy rigid biological and engineering criteria before they can be considered for clinical trials. At present, there is a tendency to move too quickly from the laboratory to the clinical situation. This step is often taken before (1) there is sufficient laboratory evidence that the heart, other critical organs, and/or the body as a whole can be helped through the use of the device; (2) adequate criteria have been developed for patient selection and specific indications for the particular mode of therapy have been identified; and (3) adequate monitoring techniques have been developed which will permit evaluation of the device and comparison with other forms of therapy. These are only a few of the key considerations that point to the need for definitive action in order to meet the needs of the increasing number of investigators developing circulatory assist devices and the increasing number of these devices which are being considered ready for clinical application. In several situations, these devices are being tested only by the group which developed the concept; a few have been employed clinically under a variety of different conditions, thus increasing the difficulty in interpreting the results. Clinical application or utilization should follow acceptable biological and engineering evaluations and should be approached under controlled conditions to achieve the maximum rate of progress in accordance with considerations mentioned above.

It is the plan of the Program Office to make sure that all components, materials and devices developed under the Artificial Heart Branch are adequately and systematically tested before being considered for clinical use. When the Test and Evaluation Facilities are established they will provide the required test and evaluation, step by step, in accordance with rigorous protocols. Ad hoc, uncoordinated testing and premature use of such devices by groups not following the protocols, if allowed, would create a chaotic situation in which the efficacy and safety of devices would be in jeopardy.

July 1, 1967 through
June 30, 1968

ANNUAL REPORT
MYOCARDIAL INFARCTION BRANCH

BRANCH SUMMARY

The Myocardial Infarction Branch of the Artificial Heart - Myocardial Infarction Program has the responsibility for the design and administration of a national research program aimed at the reduction of mortality and morbidity from myocardial infarction. The Myocardial Infarction Program is also to strengthen the medical base for the Artificial Heart Program.

The operational goals of the Program, based upon the Program development described in the last annual report, include the following:

1. The attention of the scientific community must be focused upon the problem of myocardial infarction and new people and new disciplines must be attracted to work in this area.

2. Broad, multidisciplinary research programs focused upon myocardial infarction must be established.

3. Specific research projects of more limited scope must also be developed in order to answer specific questions and to fulfill needs within the overall Program plan.

4. Special resources must be developed to facilitate research on myocardial infarction.

5. Cooperation and communication must be fostered among investigators working on the problem of myocardial infarction.

6. Effective techniques must be established for targeting and structuring research upon this major clinical problem, and for utilizing the contract mechanism in this setting; a Program plan must be developed both in scientific and operational contexts.

The Myocardial Infarction Program is now in its second year. It has undertaken activities leading toward each of these operational goals. Five Myocardial Infarction Research Units are now in their first year of operation. Each has a multidisciplinary program emphasizing clinical investigation, supported by more fundamental studies; each is broadly based and has brought new investigators and new ideas to attack the problem. Communications and cooperation are taking place among the Units. The establishment of four additional Units is pending current negotiations. The Myocardial Infarction Research Units have represented the largest Branch activity in the past year, both in effort and funding.

Since laboratory investigations of myocardial infarction could be strengthened by the availability of more satisfactory animal models of the acute illness, six contracts have been funded to develop more useful and predictable

non-atherosclerotic models of myocardial infarction. These techniques will represent an important resource for future research.

Clinical research on myocardial infarction requires the development of more satisfactory instrumentation methods and data management techniques. In part, these needs are being met by projects within each Myocardial Infarction Research Unit; in part, this effort is supported by collaboration with the Biomedical Engineering and Instrumentation Branch, DRS, NIH. In addition, a contract is currently being negotiated for the further development of a promising method for the repeated and continuous measurement of cardiac output, suitable for use in patients with myocardial infarction; the proposal was submitted in response to a request for proposals from the Artificial Heart Branch, but was felt to have particular relevance to the Myocardial Infarction Program.

The development of future areas for Program activity is being examined by study contracts, by task forces, and directly by Program staff. The metabolic and electrical behavior of ischemic myocardium figure importantly in myocardial infarction. These are specialized areas with extensive relevant literature; accordingly. study contracts were instituted to review the literature, to consider current concepts, and to identify important topics for research in these two areas. Both contracts will be completed by August, 1968, and will aid in defining future Program activities.

Sudden pre-hospitalization death accounts for approximately one half of the deaths from myocardial infarction. The precipitating factors and mechanisms of myocardial infarction, the early course of the acute illness, and sudden early death are little understood and have been inadequately studied. Program staff, after considering the recommendations of a task force on this topic, have studied the problem further; a request for proposals will be ready for distribution July 1, 1968. Collaboration with the Regional Medical Programs is being established to combine research on the biology of myocardial infarction in its earliest minutes with RMP supported studies of the improved early delivery of patient care.

The sudden development of cardiac arrhythmias, particularly ventricular fibrillation, has been suspected as a frequent cause of sudden and unexpected death. To test the hypothesis that the occurrence of premature ventricular contractions both in apparently well persons and in those with known coronary heart disease represents a risk factor for sudden death, Program staff is reviewing existing data of the Framingham Heart Disease Epidemiology Section, OADEM, NHI.

To catalyze the genesis of new ideas, to aid in Program development. and to focus further attention of the scientific community upon the problem of myocardial infarction, a contract is pending with the American Heart Association for the sponsorship of a symposium on research in acute myocardial infarction and the publication of the symposium proceedings.

The internal operations of the Branch include the direction and administration of ongoing contracts, the development of requests for proposals and the review of proposals, the planning and integration of the overall Program,

a limited direct participation in research, and routine administration. In the direction and administration of contracts, emphasis is placed upon scientific excellence and Program relevance, upon the development of people and resources, and upon the fulfillment of long-term as well as early Program goals. There is recognition of the need for flexibility in the scientific content and in the operation of projects- within the bounds of Program structure and priorities -- and of the need for sound administrative and fiscal practices. The cooperation of the Research Contracts Branch, SMB, OD, in contractual matters and the cooperation of the Biomedical Engineering and Instrumentation Branch, DRS and of DCRT in technical matters are valued. In the review of proposals, primary technical review is by experts predominantly from the extramural scientific community; their recommendations are considered in light of additional study of the proposals by Program staff and in the context of Program needs; Program Office recommendations are reviewed by the Executive Committee, NHI before any contact is made with potential contractors. Substantial scientific discussions between Program staff and potential contractors precede formal contract negotiations. In addition to planning the projects already cited, Program staff is studying projects to assess the importance of psychological influences upon myocardial infarction and the mechanisms by which they may operate, the possible contribution of inappropriate reflexes to shock associated with myocardial infarction, the precipitating factors leading to myocardial infarction and the pathology and pathophysiology underlying myocardial infarction. The development of more reliable and meaningful statistics relevant to myocardial infarction and the planning of statistically more sophisticated and valuable projects are being pursued by a biostatistician assigned full time to the Myocardial Infarction Branch from Biometrics Research Branch, OADEB, NHI.

In the coming year, the Myocardial Infarction Program will continue along its present directions. Only those new activities will be implemented which are most important and seem most favorable in a cost/effectiveness sense. The inter-related problems of the very early course of myocardial infarction -- its precipitating factors, pathophysiology and pathology, and sudden death -- are of highest priority; important pilot studies of new therapy may be supported; the study contracts are identifying important areas of research on the metabolic and electrical behavior of ischemic myocardium. Program staff will work closely with Program participants to develop a more cohesive total Program. The development of the overall Program plan will continue, aided by a review of Program effectiveness.

MYOCARDIAL INFARCTION RESEARCH UNITS

A network of five Myocardial Infarction Research Units (MIRUs) was established in June, 1967, as indicated in the previous annual report. Each MIRU includes the participation of several clinical and basic science disciplines. Integrated comprehensive study of the acutely ill patient, which is the central effort of each MIRU, is enhanced by relevant laboratory studies of myocardial infarction and by the support of instrumentation, data management and biostatistics groups.

Clinical investigation is conducted in a coronary care environment, specially equipped for the conduct of research. The course of the patient's illness is characterized by a series of direct and indirect hemodynamic measurements which supplement the electrocardiographic monitoring, by regular determinations of blood chemistries and gasses, and in different MIRUs by the measurement of pulmonary, renal, metabolic, endocrine and psychological state. In addition to describing the illness more precisely, this permits the classification of patients into more homogeneous subgroups and the study of therapeutic interventions in precisely characterized patients; perhaps most importantly, this makes possible an insight into the important and complex interactions of the organ systems during this acute illness.

The MIRUs have been operational for less than one year. The research programs are underway, generally in temporary clinical facilities and without full instrumentation systems. Results to date are based upon limited numbers of patients; they are preliminary and tentative: The previously described varied hemodynamic response to myocardial infarction and the not infrequent disparity between the clinical state and the hemodynamic measurements are being confirmed. The important influences upon hemodynamic and electrophysiologic behavior of routine events in the treatment of the patient, including meals, position of the bed and the environment, are becoming more evident. Arterial hypoxemia, the severity of which tends to parallel the severity of the illness, has been previously recognized; MIRU studies are providing increased evidence that this is caused by disturbances of pulmonary ventilation and perfusion. An association between transient severe hypoxemia and transient heart block has been observed on ocassion. The factors precipitating arrhythmias are under study; while elevations of urinary catechols are frequently associated with arrhythmias, major exceptions to this finding are being observed. Studies have also confirmed the elevation of urinary catechols early in the course of the illness and in the association with the development of complications. MIRU studies are beginning to shed light upon the complex interplay of the endocrine systems in acute myocardial infarction. One group of patients seems to respond to shock predominantly by catechol release, while another group seems to respond predominantly with the renin-angiotensin mechanism. The recognized abnormality of glucose tolerance in acute myocardial infarction is being studied further; MIRU studies are demonstrating a decreased insulin utilization in association with abnormal glucose tolerance, as well as instances of paradoxical growth hormone response, the latter seeming to have unfavorable prognostic implications. In serial determinations, these alterations of endocrine response have been shown to begin regressing with a week. The importance of psychological influences upon patients with myocardial infarction has long been recognized; MIRU studies are seeking to establish the etiology of the variability of this response, to correlate findings with physiological observations and to seek methods of favorably influencing the psychological state.

Improvements in the therapy of myocardial infarction are being investigated. Presently the major effort is directed at understanding more completely the effects of existing regimens and drugs, including to a limited extent, the correlation of drug levels with their effects and their metabolism. The roles and effects of pacing techniques are being examined for the treatment of profound bradycardia and of dysrhythmias and tachycardias unresponsive to other

therapy. Pilot studies on the clinical indications and effects of circulatory assist devices are to be implemented soon. In the coming year, other new techniques for the treatment of shock will be studied -- the controlled manipulation of central blood volume by the application of positive or negative pressure to the abdomen and lower extremities, and the use of the new myocardial inotropic agents, glucagon and dopamine. The effects of beta adrenergic agents with and without alpha adrenergic blockade will be examined. An essential study, long overdue, will be initiated comparing the effects of administering or withholding sympathomimetic drugs in patients with cardiogenic shock.

Clinical studies are also being conducted upon the development of non-traumatic methods for assessing cardiac performance, for measurement of regional blood flow in the kidney and lung, and for the interpretation of surface electrocardiographic maps.

In each MIRU a substantial effort is being directed at the instrumentation and data management needs of the research program. Carefully integrated systems are being developed to include transducers, signal modifiers, display devices, recorders, on-line computers, and data storage and retrieval methods. Since the system is dependent upon its inputs, methods of obtaining more reliable signals are being developed, including the routine use of intra- atrial electrocardiograms to aid in rhythm monitoring, and refinements of cardiac output measurement using thermal indicators. The development of monitoring and on-line data analysis systems represents a major effort which is necessary for clinical research on myocardial infarction; it is expected to have wide applicability in clinical investigation.

Laboratory research is designed to augment the clinical effort in each MIRU. Studies are in progress on the effects of circulatory assist devices and electrical pacing techniques upon the experimental animal. Methods are being developed for quantifying cardiac output by ventricular ejection kinetics utilizing arterial pressure, and for mapping coronary flow by radioisotope scanning techniques. The drug therapy of cardiogenic shock, methods of protecing the myocardium during periods of decreased myocardial blood flow, and basic studies of myocardial metabolism are all under investigation.

Since the MIRUs share common goals and their research programs have important areas of overlap, their senior investigators have met formally on three ocassions to examine such common problems as core protocols, description of patients, instrumentation, data management, and pathology.

In the coming year, with the availability of renovated clinical facilities and the appropriate instrumentation and data management systems, the MIRUs will become increasingly productive. Activities will be along current lines, although in several of the MIRUs additional projects will be implemented to round out the research efforts. In the first year of operation, a few projects within some MIRUs have seemed weak or unproductive; such projects are either being strengthened or will have been terminated by the end of two years of operation. The addition of four new MIRUs, for which contracts are currently being negotiated, will further strengthen the total network.

University of Alabama Medical Center
Contract Amount: $ 1,086,478
Principal Investigator: Harold T. Dodge, M. D.

Hemodynamic, gas exchange, and other physiologic investigations are being conducted on patients with acute myocardial infarction. Studies include assessment of the effects of meals, posture, routine medications, and antiarrhythmic agents. Patients coming to autopsy are studied according to research protocols. In the laboratory, utilization of circulatory assist devices and of pacing techniques is being studied. Methods of long-term left atrial pressure measurement applicable to patients with myocardial infarction are under development. Instrumentation and data management needs are being implemented. In the coming year these activities will continue; they will be supplemented by new projects of research pathology focused on the conduction system of the heart and its clinical correlations, and by a biostatistical program directed at developing improved prognostic indices to be used on-line in patient monitoring.

Cornell Medical Center - New York University
Contract Amount: $ 1,003,242
Principal Investigator: Thomas Killip, M. D.

Hemodynamic, gas exchange, electrophysiological, psychological and other studies have been conducted on patients with acute myocardial infarction. Patients coming to autopsy have been studied by research protocols. The metabolism of digoxin is being investigated in patients with myocardial infarction. In the animal laboratory, radioisotope techniques are being developed for visualization of regional coronary flow. Laboratory studies of the metabolism of hypoxic myocardium are in progress. Instrumentation and data management needs of the Unit are being implemented. In the coming year, these activities will be continued; they will be supplemented by a study of the role of the renin-angiotensin system in acute myocardial infarction and in the pre-infarction angina stage of the illness, and by a study of the relationships of acetylcholine and cholinesterase to disrhythmias, the value of atropine homologues in the treatment of tachycardia, and studies of metabolism, actions, and hemodynamic side effects of anti-arrhythmic agents. Closer ties will be developed with the new cardiovascular surgical group.

Duke University Medical Center
Contract Amount: $ 1,070,000
Principal Investigator: Andrew G. Wallace, M. D.

Hemodynamic, gas exchange, endocrine (carbohydrate metabolism, insulin clearance, growth hormone, plasma renins, urinary catechols,), electrophysiological and psychiatric studies are being conducted on patients with acute myocardial infarction. Electrophysiological techniques utilizing intracavitary electrodes and other studies utilizing surface mapping methods are under development. Post-operative myocardial infarction is under study. Patients coming to autopsy are examined according to research protocols. In the animal laboratory, techniques are being developed for evaluating cardiac function by ventricular ejection kinetics. Data management and instrumentation needs of the Unit are being implemented. In the coming year, these activities

will continue; they will be supplemented by the development of techniques for quantifying the myocardial contractile state by coronary angiography and application of this technique to patients after recovery from myocardial infarction.

Johns Hopkins University
Contract Amount: $ 800,000
Principal Investigator: Richard Ross, M. D.

Hemodynamic, gas exchange, electrophysiologic and other studies are being conducted in patients with acute myocardial infarction and correlated with routine patient activities and events. Patients coming to autopsy are examined according to research protocols. Circulatory assist techniques utilizing diastolic augmentation will soon be ready for clinical investigation. Methods for producing myocardial infarction in animals are under study. Intrumentation and data management needs are being implemented. In the coming year, these activities will continue; they will be supplemented by the development and validation of measurement techniques applicable to the patient with acute myocardial infarction -- methods of quantifying pulmonary extravascular volume by radioisotope techniques and external methods of assessing left ventricular contractility and function by phonocardiogram, jugular pulse and apex cardiogram; by elucidating mechanisms operative in the dog subjected to experimental myocardial infarction -- the distribution of coronary blood flow during shock and the role of coronary vascular reactivity and microthrombi; and by experiemental pathology relevant to the post-infarction tissue repair process.

Massachusetts General Hospital
Contract Amount: $ 1,043,628
Principal Investigator: Charles A. Sanders, M. D.

Hemodynamic, gas exchange, electrophysiologic and psychiatric studies are being conducted in patients with acute myocardial infarction. Radioactive gas techniques for the measurement of intra-renal blood flow and for the determination of regional pulmonary blood flow are being developed. Patients coming to autopsy are being studied according to research protocols. The metabolism of vasoactive polypeptides is under investigation; in the animal laboratory, studies have been undertaken on the effects of circulatory assist devices and of pharmacological interventions to minimize extent of myocardial infarction. The instrumentation and data management needs are being met. In the coming year, these activities will continue; they will be supplemented by clinical pharmacology to assess the metabolism, actions, and hemodynamic side effects of anti-arrhythmic agents.

New Myocardial Infarction Research Units

The network of Myocardial Infarction Research Units has been envisioned as constituting twelve Units. Final negotiations are now underway for four additional MIRUs, selected from among 32 proposals. An Ad Hoc Committee of twelve extramural experts provided primary review which consisted of a meeting to consider all proposals and select the most promising ones, followed by a series of eight site visits and a final meeting to review all proposals and

make recommendations. The subsequent steps leading to contract negotiation have been described in the Branch summary. All reviewing groups were unanimous in their recommendation of the four proposers: The University of California at San Diego (John Ross, Jr., M. D., Principal Investigator), The University of Chicago (Hans Hecht, M. D., Principal Investigator; Leon Resnekov, M. D. MIRU Director), University of Rochester (Paul N. Yu, M. D., Principal Investigator), and Cedars Sinai Medical Center of Los Angeles (H. J. C. Swan, M. D. Principal Investigator).

ANIMAL MODELS OF MYOCARDIAL INFARCTION

Laboratory research on myocardial infarction is in part dependent upon satisfactory animal models of the acute illness. No model can be satisfactory for all experiments, but predictability of hemodynamic impairment, anatomic involvement and time of onset of infarction are particularly desirable features for all applications. For certain studies a model utilizing the intact conscious animal is particularly important; for some applications a model in which infarction is superimposed upon prior myocardial or coronary damage may be necessary.

Existing and potential methods of provoking myocardial infarction in experimental animals were reviewed with the aid of an ad hoc committee, as reported in the last annual report. The presently available models are sufficiently unsatisfactory or sufficiently incompletely perfected to warrant further refinement before they can become widely useful. Although in some respects an atherosclerotic model might be expected to resemble the disease in man most closely, atherosclerosis can be provoked in experimental animals only after prolonged feeding on abnormal diets, sometimes with the necessary superimposition of such important metabolic disturbances as induced hypothyroidism. Even in such animals, infarction is rare and its occurrence is totally unpredictable. Accordingly, the development of non-atherosclerotic methods of provoking infarction seems most advantageous since these techniques might be applied not only to previously healthy animals, but also to animals with induced atherosclerosis or with other induced lesions of the coronary vasculature or the myocardium.

Six contracts, selected from among 37 proposals recieved, have now been in effect for three months. Each is to develop more satisfactory and widely applicable non-atherosclerotic models of myocardial infarction in animals, models which will have predictable physiological consequences, anatomical involvement, and time of onset. Several techniques are under study and development; they are being applied to one or more coronary arteries. Surgically positioned constricting devices are being used -- a radio-controlled snare, a slowly expanding balloon, and the ameroid method (hygroscopic swelling). Using coronary catheterization techniques in the intact animal, a number of occlusive techniques are being developed -- the introduction of thrombogenic metal, the infusion of thrombogenic biological substances such as adenosine diphosphase and collagen, the temporary insertion of occluding devices, the permanent insertion of partially and slowly occluding devices, the production of endothelial damage by continuous infusion of toxic substances, and the production of thrombosis and endothelial damage by the passage of an electric

current. Most of these techniques can produce myocardial infarction in the conscious, intact animal. Some techniques obviate the thoracotomy completely, while in others a prior thoracotomy is necessary for the insertion of appropriate devices. Studies are being conducted in the rhesus monkey, the minipig, the calf, and the dog.

In each contract, one or more techniques is under study. Each requires preliminary development and refinement. It is then being applied at a variety of sites in the coronary bed and at various rates or doses. Finally, using the most favorable parameters of placement, time sequence and dose, more extensive studies will be performed to characterize the model in detail and to establish its reproducibility. In each instance, the physiological effects are assessed by hemodynamic, electrical, and biochemical techniques and the anatomic effects are evaluated by gross and microscopic analysis of the lesions.

Each contract is for one year; a six to twelve month renewal is anticipated on each.

Mallory Institute of Pathology
Contract Amount: $ 73,282
Principal Investigator: Stanley Robbins, M. D.

Utilizing coronary catheterization techniques in the minipig, four techniques are under study for producing thrombosis in small vessels and/or to serve as trigger mechanisms for the occlusion of vessels previously narrowed by surgically placed ameroid constrictors -- transient adenosine diphosphate induced thrombosis, irreversible collagen induced thrombosis, embolization with 10-20 micron diameter microspheres,and coronary endothelial injury from a piano wire scratch. In addition to developing more satisfactory models of myocardial infarction, this project is expected to shed further light upon the importance of small vessel disease in myocardial infarction and upon the importance of prior large vessel constriction.

Oregon Regional Primate Center
Contract Amount: $ 37,900
Principal Investigator: M. R. Malinow, M. D.

The technique under development is the radio-controlled gradual tightening of a snare positioned about a coronary arter at prior thoracotomy; rhesus monkeys are being studied.

Cox Coronary Heart Institute
Contract Amount: $ 28,115
Principal Investigator: E. L. Stanley, M. D.

A thrombogenic metal, magnesium aluminum alloy, formed as a helical wire is positioned within one or more coronary arteries by selective catheterization; thrombus formation occurs approximately one week later.

Harvard University (Boston City Hospital)
Contract Amount: $ 59,106
Principal Investigator: John C. Norman, M. D., and William Hood, Jr., M.D.

Two techniques are under study -- the gradual constriction of a coronary artery by a balloon cuff previously positioned at thoracotomy and the direct intra-coronary positioning of hollow metallic plugs by catheterization techniques.

New York University Medical Center
Contract Amount: $ 29,935
Principal Investigator: Jacob I. Hirsch, M. D.

An electrical current between a catheter positioned in the coronary artery and an external electrode is used to provoke thrombosis. In contrast to previous studies, a variety of external electrode configurations will be investigated; also, brief high energy electrical pulses will be studied. Experiments are being conducted in the dog.

University of Wisconsin Medical Center
Contract Amount: $ 32,540
Principal Investigator: James A. Will, D.V.M. and George Rowe, M. D.

Three techniques are under study in dogs and calves. A method for positioning and maintaining a fine catheter in the coronary bed for many hours or days is being developed in order to permit the chronic infusion of vaso-toxic and other substances into the coronary bed; catheter positioned intraluminal casein ameroid devices are being developed; the electro-thrombogenic technique is under investigation.

INSTRUMENTATION METHODS FOR MYOCARDIAL INFARCTION RESEARCH

Among the increasing number of instruments and methods available for clinical investigation and suitable for use in patients with myocardial infarction, there is presently no satisfactory method of measuring cardiac output continuously or repeatedly over prolonged periods without the withdrawl of blood. A promising proposal to develop further a technique which would fulfill these goals was submitted in a proposal responding to an RFP from the Artificial Heart Branch; because of its particular relevance to the Myocardial Infarction Program, it is being incorporated herein. It is currently in the final stages of negotiation.

Indicator Dilution Measurement of Cardiac Output with Dissolved Hydrogen
Research Foundation of the State University of New York at Buffalo
Contract Amount: Pending
Principal Investigator: Francis J. Klocke, M. D.

If hydrogen saturated saline is infused intravenously, the resultant concentration of hydrogen in the pulmonary artery is inversely proportional to the cardiac output; the elimination of the gas in the lungs obviates

problems from re-circulation. A simple, special purpose gas chromatograph has been developed with which the concentration of this gas can be quickly and accurately determined on small blood specimens; this measurement can be used intermittently for the quantification of cardiac output and for the calibration of a catheter tip platinum electrode positioned in the pulmonary artery which can yield continuous indication of hydrogen saturation without the withdrawl of blood but with a gradual drift in sensitivity. The contract being negotiated is to develop the technique further, to define its accuracy and its limitation, particularly due to alterations in pH, and pCO_2, to develop simpler, smaller and more reliable gas chromatography apparatus and more stable platinum electrodes, and to make the technique available to other investigators in the Myocardial Infarction Program. A two-year program is envisioned.

STUDY CONTRACTS

For Program design, critical review of potentially important areas is essential. The metabolism of ischemic myocardium and certain questions in electrocardiography represent two such areas and two study contracts are now active.

Metabolism of Ischemic Myocardium
St. Louis University School of Medicine
Contract Amount: $ 36,620
Principal Investigator: Robert E. Olson, M. D., Ph.D.

Available fundamental information in the area of cardiac metabolism is being reviewed in the context of myocardial ischemia and infarction. In addition to conducting an extensive review of the literature, including over 1200 references, the contractor has consulted with leaders in the field to obtain collateral evaluation of the data and suggestions for research direction, and he has conducted experimental validation of promising ideas on a pilot basis. The review is to include myocardial metabolism in the normal and in the ischemic heart, including energy production, conservation and utilization, as well as myocardial metabolism in ischemic heart disease, including atherogenesis, thrombosis and infarction. Areas for future study of pathogenesis and therapy are to be identified. The contract period is completed and the report is expected currently.

Electrocardiography and Electrophysiology in Relation to Myocardial Infarction
Research Foundation of the State University of New York at Syracuse
Contract Amount: $ 44,306
Principal Investigator: J. A. Abildskov, M. D.

The developments of recent years in fundamental electrophysiology and in electrocardiography are being considered in the context of the clinical problem of acute myocardial infarction. A review of the literature for the past decade has been conducted; two groups of six experts in the field have had two-day conferences to discuss advances and their potential implication in this field. A report is in preparation. Diagnostic electrocardiography is being considered in relation to myocardial infarction, discussing the

physiological bases of QRS and ST-T alterations, the high-frequency components of the electrocardiogram, body surface isopotential maps, vectorcardiography, and computer analysis of the electrocardiogram. The electrophysiolcgy of arrhythmias associated with myocardial infarction is being considered in terms of experimental models of arrhythmias, the re-entrant mechanisms of arrhythmias, ectopic pacemaker mechanisms and artificial pacemaker applications in myocardial infarction. Potentially fruitful areas for research are to be identified. The contract will be completed and the report is due August 31, 1968.

OTHER

Symposium on Research in Acute Myocardial Infarction
American Heart Association
Contract Amount: Pending

A contract is currently being negotiated with the American Heart Association for the sponsorship of a Symposium on Research in Acute Myocardial Infarction. Major topics are to include the etiology and pathogenesis of acute myocardial infarction, critical appraisals of what has been learned about myocardial infarction from studies on its prevention, potential improvements in means of evaluation of acute myocardial infarction,and research on the treatment of acute myocardial infarction. Approximately 70 participants are to be invited for the three-day conference; the AHA is to publish the proceedings as a supplement to the journal, Circulation. Recent advances and potential developments in many areas will be presented and discussed by the participants. The Conference is expected to catalize the genesis of new ideas, to aid in the evaluation of these ideas, to provide a background for Program development, and to focus further attention of the scientific community upon the problem of myocardial infarction.

Serial No. NHI-MI-1
1. Myocardial Infarction Branch
2. AH-MI Program, NHI
3. Bethesda, Maryland

PHS-NIH

Individual Project Report
July 1, 1967, through June 30, 1968

Project Title: Relationship of Premature Ventricular Contractions (PVCs) to Sudden Cardiac Death

Previous Serial Number: None

Principal Investigators: Charles L. Jobe, M. D.
Alan N. Weiss, M. D.

Other Investigators: Morton Raff
Tavia Gordon

Cooperating Units: Biometrics Research Branch, OADEB, NHI
Framingham Heart Study, OADEB, NHI

Man Years:

Total: .2

Professional: .1

Other: .1

Project Description: Sudden cardiac death can be considered a major public health problem if one recognizes that over half of the deaths due to atherosclerotic heart disease are sudden or pre-hospital deaths. The pathophysiologic mechanisms by which these sudden cardiac deaths occur are unclear. It is probable that a majority of these deaths are due to ventricular arrhythmias. Recognizing the importance of premature ventricular contractions (PVCs) in the development of arrhythmias following acute myocardial infarction, we have postulated that PVCs in all individuals may have a similar relationship to the development of serious arrhythmias and even predispose to sudden cardiac death. The preliminary testing of this hypothesis is an important step in the development of targeted research programs focused upon the understanding of the pathophysiology of pre-hospital deaths due to coronary artery disease and myocardial infarction. Members of the Myocardial Infarction Program Office staff have undertaken a study of the electrocardiographic tracings accumulated in the first 14 years of the Framingham Epidemiologic Study of Heart Disease.

Examination of the electrocardiograms of patients who have developed coronary heart disease in the Framingham population has been completed. Analysis of the subsequent course of patients who had PVCs on the first Framingham examination is nearing completion. These data will be compared with suitable control groups from within the Framingham study population in order to determine the prognostic significance of PVCs and the relative frequency with which PVCs occurred in patients who developed coronary heart disease or died suddenly.

Should the results of this study indicate that frequent PVCs are associated with a substantially increased incidence of sudden cardiac death, it may be advisable for the Program to undertake projects which include ECG monitoring of high-risk patients in order to determine the frequency of "high-risk" arrhythmias, their nature, and means of preventing them.

Honors and Awards: None

Publications: None

PHS-NIH
NATIONAL HEART INSTITUTE
July 1, 1967 through June 30, 1968

NATIONAL BLOOD RESOURCE PROGRAM

BACKGROUND: The National Blood Resource Program was established in FY 1967 with a 1.95 million dollar appropriation by Congress in the National Heart Institute budget. These funds were provided in response to a critical problem relative to the national supply of transfusion blood and blood components. Specifically, a rapid acquisition of scientific information regarding fractionation techniques resulted in an increasing identification of the cellular and protein components of blood as therapeutically useful. However, there was at that time and there remains today a serious technological lag which prevents the large-scale application of this knowledge. The problem is made more acute by the rapidly increasing military, as well as civilian, need for blood components. It was determined that these critical demands could be met if component blood transfusion therapy was more extensively employed and if non-utilization of whole blood due to outdating in storage could be diminished.

With these problems warranting the establishment of the National Blood Resource Program, the basic goal became to direct, through the contract mechanism, research and development activities which would assure more adequate supplies of blood and blood components. Therefore, as a start, in FY 1967 eleven contracts and one reimbursable agreement were awarded in the total amount of $1,757,477 for studies in blood preservation and fractionation. In FY 1968 the National Blood Resource Program had an appropriation of 2.792 million dollars, a part of which will go to provide for continued support of the twelve original projects as follows:

1. Buffalo General Hospital (transferred from Research Foundation of State University of New York)
   Buffalo, New York PH-43-67-1382
   Project Director: Charles Bishop, Ph.D.
   Project Title: Development of Improved Solutions for Blood Storage
   FY 1967 Support: $27,122, June 29, 1967 - June 28, 1968
   FY 1968 Recommended Support: $43,208, June 29, 1968 - June 28, 1969

ACCOMPLISHMENTS TO DATE: The investigator in his initial year adduced evidence of the superiority of preservation solutions containing phosphate, inosine and guanosine over those containing adenine alone. He showed that red cell ATP levels are maintained at a high level with time, there is less cell swelling and less acid production when phosphate and purine nucleosides are added than when the purine alone is added. Interestingly enough, however, it was demonstrated that osmotic fragility increases more rapidly under the former circumstances than under the latter. Dr. Bishop made progress in the formulation of an ideal preservative solution and in the development of electrolyte and non-electrolyte solutions to replace plasma in the storage of red cells so that platelets and AHF cryoprecipitates might be harvested shortly after blood letting.

2. Blood Research Institute, Inc.
Cambridge, Massachusetts PH-43-67-1366
Project Director: John G. Gibson II, M.D.
Project Title: Effect of Adenine on Viability of Human Red Cells Preserved in the Frozen State
FY 1967 Support: $36,205, June 27, 1967 - June 26, 1968
FY 1968 Recommended Support: $17,609, June 27, 1968 - December 26, 1968

ACCOMPLISHMENTS TO DATE: Under this contract Dr. Gibson is engaged in a comparison of ACD-adenine and CPD-adenine solutions as preservatives when red cells are stored in the frozen state. He is using both ATP levels and in vivo survival as criteria of effect. He has tentatively determined 1) that incubation at 37° of blood drawn into various concentrations of ACD-adenine and CPD-adenine does not have a beneficial effect; 2) that maximum ATP levels are attained by storing CPD-blood for 24 hours at 4° C prior to glycerolization and freezing but that adenine was not effective in raising ATP levels in ACD-blood under these circumstances; processing (glycerolization, freezing, deglycerolization) destroyed fewer red cells in CPD than ACD-blood; 3) that adenine added at the time of blood collection did not improve post-transfusion red cell survival in freeze-preserved blood. Experiments are now in progress to determine the value of adding adenine to CPD blood on resuspension after freezing and deglycerolization.

3. Cutter Laboratories, Inc.
Berkeley, California PH-43-67-1402
Project Director: Fred Johnson, Ph.D.
Project Title: Effect of Adenine ACD-A Solution on Plasma Proteins
FY 1967 Support: $93,650, June 28, 1967 - June 27, 1968
FY 1968 Support: Extension without additional funds through December 27, 1968

ACCOMPLISHMENTS TO DATE: A. Analytical procedures were developed for determining adenine in adenine-ACD anticoagulant solution and in plasma fractions. Sources of adenine sulfate were surveyed and a particular lot (Arapahoe P-575) was selected and subjected to a detailed analytical profile.

B. Two lots of adenine-ACD anticoagulant were prepared in plastic bags at a level of 0.5 micromol adenine sulfate per bag. Using this adenine sulfate a lot comprised of 1700 plastic bags was prepared and an additional lot comprised of 143 triple bags with a "half-fill" for studies to be conducted by Dr. Judith Pool of Stanford University. Both lots were subjected to all tests but were then discarded because of the reevaluation of the desired adenine concentration and because of the change from adenine sulfate to adenine free base. This change was made at the request of the Program Office in early September 1967 following a recommendation of a committee assembled to give advice on the adenine studies program.

C. The literature on the effects of adenine on red cell preservation was reviewed and an IND was compiled and submitted.

D. The reference lot of adenine base was received from the Laboratory of Comparative Biochemistry, San Diego, California, and subjected to a complete analytical profile. Two new lots of adenine-ACD anticoagulant in plastic bags were again prepared as before. This time at a level of 0.5 micromol adenine base per bag. These two lots are currently undergoing tests prior to release.

Thus, due to 1) a change in the protocol from adenine sulfate to adenine free base and 2) the unavailability of purified recrystallized adenine free base until early in calendar year 1968, progress under this contract was delayed by about six months.

4. Health Research, Inc.
Buffalo, New York PH-43-67-1366
Project Director: Julian L. Ambrus, M.D., Ph.D.
Project Title: Studies of Adenine as a Blood Preservative
FY 1967 Support: $49,555, June 22, 1967 - June 21, 1968
FY 1968 Recommended Support: $25,000, June 22, 1968 - December 21, 1968

ACCOMPLISHMENTS TO DATE: ATP/ADP ratios and total adenine nucleotides were studied in ACD and CPD-blood throughout a six-week storage period and found to be maintained consistently higher in CPD-blood. The effects of adenine and various nucleosides upon red cell enzymes, maintenance of red cell nucleotides, glycolytic intermediates shift of inorganic ions and various hematologic parameters of red cell were studied. Evidence was adduced that addition of adenine and various nucleosides such as inosine and guanosine beneficially affected the parameters measured. The effect of ATPase inhibitors upon the maintenance of red cell viability during storage were studied with negative results. Investigations were conducted of the effects of addition of adenine to ACD solutions upon autologous red cell survival in prison volunteers. Preliminary studies of in vivo red cell survival utilizing concentrated red cell packs gave inferior results to those stored as whole blood. Suggestive evidence was found that plasma may be necessary for optimal red cell preservation and that the presence of white cells may have a deleterious effect upon the viability of red cells. Studies of the effect of adenine ACD-A on the blood coagulation factors and the fibrinolysin system indicated no significant difference in the various factors measured. Platelet life span studies were conducted on prison volunteers investigating the effect of the addition of adenine, but a double-blind experimental design was employed and the code is not broken. The effect of adenine-ACD on leukocytes was hampered by technical difficulties and only preliminary results are available. No significant cardiovascular, respiratory or CNS changes were demonstrated in a study of the hemodynamic effects of adenine-ACD upon beagles.

5. Laboratory for Comparative Biochemistry
San Diego, California PH-43-67-1361
Project Director: Grant R. Bartlett, Ph.D.
Project Title: Adenine Metabolism in Man and Animals
FY 1967 Support: $17,426, June 21, 1967 - June 20, 1968
FY 1968 Recommended Support: $29,050, June 21, 1968 - June 20, 1969

ACCOMPLISHMENTS TO DATE: Dr. Bartlett attempted to purify the available adenine preparation using cation-exchange resins, in particular the Dowex-50. He also used recrystallization methods to remove various impurities. Samples of his purified preparations were sent to other investigators in this field for their analysis and experimental use. It should be pointed out that Dr. Bartlett has reduced the amount of inorganic and organic impurities in adenine preparations, but he has not eliminated the impurities entirely. He learned that only the Kay-Fries Company and the Arapahoe Company make adenine in this country and that all other commercial outlets acquire their adenine from either these companies or from foreign companies, the largest of which are in Japan. Dr. Bartlett's studies dealing with the impurities in adenine and his attempts to achieve pure adenine preparations were highly desirable, and will contribute significantly to the goals of the Blood Program.

6. Michigan Department of Public Health
Lansing, Michigan PH-43-67-1362
Project Director: James T. Sgouris, Ph.D.
Project Title: The Effects of Adenine-ACD-A Anticoagulant in Plasma Proteins
FY 1967 Support: $65,765, June 20, 1967 - June 19, 1968
FY 1968 Recommended Support: $69,584, June 20, 1968 - June 19, 1969

ACCOMPLISHMENTS TO DATE: Dr. Sgouris in his initial year searched for changes in the plasma phase of whole blood stored in adenine-ACD anticoagulant and has found that no such changes occur. Several lots of human plasma prepared in ACD and ACD-adenine were fractionated by the standard cold ethanol procedures. The effect of adenine on virus and other microorganisms in plasma was evaluated, and it was found that these microorganisms do not become a more serious hazard with the addition of adenine. AHF in cryoprecipitate form was studied with and without adenine. Also studied were the stability of serum proteins with and without adenine, the content of adenine and other related metabolites and the presence of clotting factors in plasma both with and without adenine. Blood was used that was one day, 21 days and 28 days old and stored at -6° C. The effect of adenine on plasma was determined by measuring the pH, hemoglobin, heme concentration, serum proteins, clotting factors and fibrinogen content. Eighteen separate pools of plasma were tested: half with ACD-adenine added to the whole blood from which the plasma was prepared and half with just ACD added.

In addition to the studies required by his contract, Dr. Sgouris studied the suitability of adenine sulfate for human use on the basis of its sterility, safety and pyrogenicity. Pyrogenicity tests were performed in rabbits.

A standard curve for the measurement of adenine concentrations was developed and measurements of hypoxanthine as well as adenine were performed since it appears that after adenine is added to blood the adenine concentration falls while the hypoxanthine rises. Other metabolic studies performed were plasma NH_4, glucose, phosphate and potassium.

7. The Mount Sinai School of Medicine (formerly Mt. Sinai Hospital)
New York, New York PH-43-67-1359
Project Director: Richard E. Rosenfield, M.D.
Project Title: Studies of Adenine as a Blood Preservative
FY 1967 Support: $325,000, June 12, 1967 - June 11, 1968
FY 1968 Recommended Support: $100,000, June 12, 1968 - December 12, 1968

ACCOMPLISHMENTS TO DATE: The studies of adenine in progress are divided under five headings:

A. Quantitative hemagglutination assays to determine the suitability for seriological studies of blood stored for protracted periods at 4°C.

B. The physicochemical changes in stored red cells and plasma proteins.

C. Measurements of functional red cell integrity to determine the effect of storage in ACD and ACD-adenine.

D. Coagulation assays to compare the activity of various clotting factors in stored blood collected as paired specimens in ACD and ACD-adenine.

E. The relative efficiency of ACD-adenine and ACD anticoagulant solutions (as used for the storage of whole blood) in preserving the metabolic, functional, and morphologic integrity of platelets.

The first year of contracted research was devoted to a variety of studies involving tests in vitro of parameters indicated in the above titles. Experiments were initiated only recently and preliminary data from the first four listed subdivisions is not yet available. The fifth subdivision involving the study of platelets is unaffected by lag time in storage, however, only partial data from early experiments in this area are available. Adenine in the ACD solution, used for the collection of whole blood, appears to have no effect on total platelet, magnesium, sodium, potassium, ATP-ase activity or on the maintenance of intra-platelet sodium and potassium, however some impairment of clot retraction has been observed both by gross tests and by the more sensitive method of thromboelastography.

8. Presbyterian-University of Pennsylvania Medical Center
Philadelphia, Pennsylvania PH-43-67-1384
Project Director: Frank H. Gardner, M.D.
Project Title: Platelet Preservation with Adenine-ACD Anticoagulant
FY 1967 Support: $41,405, June 27, 1967 - June 26, 1968
FY 1968 Recommended Support: $56,065, June 27, 1968 - June 26, 1969

ACCOMPLISHMENTS TO DATE: A variety of in vitro measurements of platelet functions and metabolic activity were made and platelet life spans have been determined utilizing for study platelets collected in ACD and ACD-adenine anticoagulants. Platelet yields were determined after centrifugation of whole blood collected in ACD and ACD-adenine utilizing standard Fenwal bags and in ACD-adenine utilizing a new plastic formulation bag. The addition of adenine resulted in no apparent difference in platelet yield. Platelet life span curves were determined utilizing platelet-rich plasma collected in ACD and ACD-adenine and these were not significantly different. The effect of storage temperatures was then studied and it was found that platelet viability was markedly and rapidly impaired during storage at 4°C and that the addition of adenine was not protective. On the other hand, platelet yields and life span curves after storage at 22°C were comparable to those obtained from fresh

platelets. Therefore, it would seem that the storage of platelet-rich plasma is feasible at 22°C but not at 4°C and that the addition of adenine to anticoagulant solutions neither impairs nor enhances platelet viability. However, the last point is not completely clear and will be the subject of further study now in progress. The effects of the new plastic and of adenine remain to be separated out.

9. John S. Sharpe Research Foundation of Bryn Mawr Hospital
Bryn Mawr, Pennsylvania PH-43-67-1363
Project Director: Paul V. Strumia, M.D.
Project Title: Study of Adenine as a Blood Preservative
FY 1967 Support: $16,330, June 15, 1967 - June 14, 1968
FY 1968 Recommended Action: Extension without additional funds through June 14, 1969

ACCOMPLISHMENTS TO DATE: The objective of this project is to study the clinical effectiveness and safety of ACD-adenine preserved blood in human transfusions. Dr. Strumia is measuring red cell survival (by Ashby counts and chromium 51 tagging methods), serum bilirubin, plasma hemoglobin, uric acid and other chemical determinations. He will be studying mostly surgical patients and will especially attempt to make observations in patients with liver or kidney disease, in gout and in pregnancy.

Several months of building construction interfered with progress in this laboratory. As a result only a small fraction of the work has been accomplished and only a commensurately small part of the allotted funds used. The contract period has been extended without additional funds.

10. Leland Stanford Junior University
Palo Alto, California PH-43-67-1388
Project Director: Judith G. Pool, Ph.D.
Project Title: Preparation of Cryoprecipitates from ACD-Adenine Blood
FY 1967 Support: $24,234, June 28, 1967 - June 27, 1968
FY 1968 Recommended Action: Extension without additional funds through December 27, 1968

ACCOMPLISHMENTS TO DATE: The objective of this project is to determine the effect of adenine, used in prescribed concentration, upon the antihemophilic factor found in cryoprecipitate. If adenine preservation is to be introduced as common practice in blood banking it must be demonstrated that none of the major blood components are damaged.

None of the allotted funds have been spent and work has been delayed (until recently) because of the unavailability of appropriately designed containers containing the adenine-ACD solution. However, the experiment is a very clear-cut simple one, all obstacles have been overcome and results will be forthcoming within six months.

11. Veterans Administration Hospital
Augusta, Georgia Reimbursable Agreement
Project Director: Titus H. J. Huisman, Ph.D.
Project Title: Influence of Adenine as a Blood Preservative

FY 1967 and FY 1968 Support: $47,000, May 15, 1967 - May 15, 1969
FY 1969 Recommended Support: $32,000

ACCOMPLISHMENTS TO DATE: Dr. Huisman outlined in his proposal three years of study aimed at elucidating the effects on heterogeneity and physiology of hemoglobin of various additives including adenine. His first six months were according to plan used in the development of appropriate chromatographic and other chemical methods. Since then he has been investigating sources of adenine, studying methods of purification in collaboration with Dr. Grant Bartlett and carrying out preliminary studies of the effects of adenine on hemoglobin. No definitive results are yet available.

12. American National Red Cross
Washington, D.C. PH-43-67-1364
Project Director: James H. Pert, M.D.
Project Title: Fractionating Blood for Cellular and Protein Components
FY 1967 Support: $1,013,785, June 30, 1967 - June 29, 1968
FY 1968 Recommended Action: Extension without additional funds to December 29, 1968

ACCOMPLISHMENTS TO DATE: This is a broad multifaceted program of research in blood fractionation methods. Considerable delay in progress resulted from 1) acquiring, remodeling and moving into an entirely new laboratory in Bethesda; 2) acquisition of new heavy equipment; 3) recruiting staff. As a result, less than three-fourths of the allotted funds have been spent and the contract period has been extended without additional funds.

Progress has been made on the following lines: 1) Freezemobile design and field testing. Since 85% of Red Cross blood is collected by mobile units and since some component production requires immediate separation and freezing, this is an important project and the results will be of use not only to Red Cross but to all blood agencies. 2) Red cell freezing. Dr. Pert's method has been further developed and is being adopted by other investigators in this country and abroad. 3) Anti-hemophilic factor. Dr. Alan Johnson's basic research in this field has enabled Red Cross to produce first on a pilot scale and now on a large scale two antihemophilic preparations which are proving outstandingly effective in clinical trials. His high potency preparation has been tested in this country and abroad and is the best preparation available. 4) The Prothrombin Complex (containing factors II, VII, IX and X) is developing well and promises to be a useful agent in the treatment of hemophilia B. 5) Platelet freezing studies are still in progress and have not so far resulted in a method which can serve economically as a routine one. 6) Standard preparations developed by Red Cross have been made available to WHO to serve as International Standards: alpha casein, bovine fibrinogen, AHF, plasmin, plasminogen and others.

AUTOMATED DONOR BLOOD INVENTORY AND DONOR-RECIPIENT INFORMATION SYSTEM

In pursuance of its mission to conduct a continuing study of the problem of utilization of the nation's blood supply, the National Blood Resource Program became interested in exploring the advantages, disadvantages and general applicability of an automated inventory and information system for the

management of whole blood and blood products in the United States with both a theoretical approach such as the development of hypothetical and simulated models and a practical approach which would involve the trial of sample systems.

The principal reasons for this interest are: 1) to improve the efficiency of utilization by decreasing or eliminating the waste and expense caused by the loss of blood through expiration; 2) to decrease or eliminate the hardships imposed by shortages of blood and blood products; 3) to gather adequate data on the collection, processing and distribution of blood and blood products in the United States; and 4) to promote coordination between facilities which handle blood.

With these goals in mind, contracts are being negotiated with the following six institutions:

1. Community Blood Council of Greater New York
   New York City, New York
   Project Director: Mr. Joseph S. Phelps, Jr.
   Project Title: A Computerized Blood Inventory System in the Service of the Community, the Blood Donor and the Patient Recipient
   FY 1968 Recommended Support: $372,672

2. Franklin Institute Research Laboratories
   Philadelphia, Pennsylvania
   Project Director: William M. Braybrook, M.B.A.
   Project Title: The Feasibility of Developing and Using an Automated Blood Donor Inventory and Donor-Recipient Information System
   FY 1968 Recommended Support: $89,790

3. Milwaukee Blood Center
   Milwaukee, Wisconsin
   Project Director: S. P. Masouredis, M.D., Ph.D.
   Project Title: Automated Blood Bank Information System
   FY 1968 Recommended Support: $184,841

4. University of North Carolina
   Chapel Hill, North Carolina
   Project Director: R. L. Langdell, M.D.
   Project Title: Automated Donor Blood Inventory and Donor-Recipient Information System
   FY 1968 Recommended Support: $140,286

5. Research Foundation of State University of New York
   Buffalo, New York
   Project Director: Edward L. Wallace, Ph.D.
   Project Title: Analysis and Design of a Model Regional Blood Management System
   FY 1968 Recommended Support: $182,820

6. Michael Reese Research Foundation and Blood Center
Chicago, Illinois
Project Director: Aaron Josephson, M.D.
Project Title: Automated Blood Inventory Feasibility Study
FY 1968 Recommeded Support: $318,567

UROKINASE-PULMONARY EMBOLISM TRIAL

One of the major efforts undertaken in Fiscal Year 1968 by the National Blood Resource Program was the establishment of the Urokinase-Pulmonary Embolism Trial. This will be a controlled study of approximately 200 patients with pulmonary embolism by eleven participating institutions, in order to test the efficacy of the thrombolytic agent urokinase.

The first observation of the in vitro fibrinolytic activity of human urine was made by Macfarlane in England in 1947. A group of investigators working at the Leo Company in Denmark demonstrated in 1952 that an extract of human urine when injected intravenously had the effect of activating the fibrinolytic system by converting plasminogen to plasmin. Early preparations were, however, heavily contaminated with thromboplastin and had the opposite final effect. During the ensuing years, several American pharmaceutical companies undertook studies of urokinase attempting to isolate it from thromboplastin and to purify it. Abbott Laboratories and the Sterling-Winthrop Company made the largest investment of time and money on this project and when the Committee on Thrombolytic Agents of the National Heart Institute came into being in 1963 were furthest advanced.

The Committee on Thrombolytic Agents, NHI, was established on the recommendation of the Heart Council to facilitate progress in development of thrombolytic therapy. The Committee consisting of ten basic investigators of the coagulation and fibrinolytic mechanisms was requested to identify long-range goals and stepwise objectives toward which they could work with the help of resources which the Institute could mobilize. They chose urokinase (UK), then a laboratory agent, as the most promising substance for development. Streptokinase (SK) derived from bacterial cultures was the only comparable material available. SK had been licensed and was on the market but no validated information on efficacy was available and severe febrile and antigenic reactions to it were common. Furthermore, by reason of the prevalence of streptococcal infection in the population, many patients were presensitized and dosage sufficient to exceed the body's inactivation (or immune) response was difficult to determine.

Working through appropriate subcommittees, the Committee: 1) provided a detailed description of minimum standards for a urokinase preparation which would be suitable for clinical trial; 2) developed a standard unit and assay method which has since been adopted as an international unit; 3) devised a test method to assure absence of thromboplastin; 4) carried out clinical investigations aimed at determining an appropriate dose regimen, observing toxicity and controllability of the patient response; and 5) recommended that pulmonary embolism was the lesion of choice for a controlled clinical trial of efficacy since the effect could be most clearly and quantitatively documented.

On the advice of the Committee and the National Advisory Heart Council, the Heart Institute purchased by direct contracts in 1964 678 million units of urokinase at a total cost of $144,500. Of this lot, 207.5 million units remain in storage, the rest having been used for study in patients with a variety of thromboembolic diseases.

In March 1965 the Heart Council recommended the use of $350,000 of grant funds to purchase an additional supply of urokinase. The grant was made to Washington University in the name of Dr. Sol Sherry who served as trustee of the material for use in Heart Institute-supervised experiments. The funds were expended to buy 1,374.7 million units (roughly enough to study 510 patients by present dosage schedule). The material, which shows no signs of deterioration in storage, is held on the shelves of the two companies subject to order from the Institute.

Current plans call for initiating the Urokinase-Pulmonary Embolism Trial to compare the resolution rate of pulmonary thromboemboli in patients treated with urokinase and heparin with that occurring in patients treated with the best available therapy (heparin alone). Later, a triple randomization procedure may be instituted to compare urokinase + heparin, streptokinase + heparin, and heparin alone.

The development of a Manual of Operations for the Trial has been underway since November 1966 when at a meeting in St. Louis, Missouri, held to discuss the clinical experience with the use of urokinase in 42 patients with pulmonary embolism, it was also decided to begin efforts to design a uniform study protocol. A preliminary protocol was written and submitted to a small group of interested investigators and biometricians, previously appointed by the Committee on Thrombolytic Agents. A revision of this protocol based upon the resultant recommendations was then submitted to a separate set of individuals who currently comprise the Policy Board of the Urokinase-Pulmonary Embolism Trial. Since then, several subsequent revisions of the study protocol have occurred and the Manual of Operations of the Urokinase-Pulmonary Embolism Trial has emerged under the direction of the Policy Board, the Steering Committee and the Protocol Committee of the Trial.

In order to complete the study in about two years, contracts will be awarded to the following eleven institutions qualified by reason of a) expertise and interest in pulmonary embolism; b) availability of sufficient numbers of patients; c) capability of following a fixed protocol; and d) availability of adequate catheterization, radiographic and isotopic scanning facilities. Other data-contributing units will be gradually phased into active participation during an initial "shakedown" phase during which a multiplicity of procedures and methods will be pretested. Biometric control of the experiment is to be provided by the NHI Biometry staff.

Boston City Hospital, Boston, Massachusetts
Principal Investigator: Joseph V. Messer, M.D.
Recommended FY 1968 Funding: $60,000

University of Cincinnati, Cincinnati, Ohio
Principal Investigator: Noble O. Fowler, M.D.
Recommended FY 1968 Funding: $45,000

University of Colorado Medical Center, Denver, Colorado
Principal Investigator: Edward Genton, M.D.
Recommended FY 1968 Funding: $35,000

Duke University Medical Center, Durham, North Carolina
Principal Investigator: Donald Silver, M.D.
Recommended FY 1968 Funding: $60,000

Hektoen Institute for Medical Research of the Cook County Hospital, Chicago, Illinois
Principal Investigator: Robert M. Stanzler, M.D.
Recommended FY 1968 Funding: $54,000

Johns Hopkins University, Baltimore, Maryland
Principal Investigator: Henry N. Wagner, Jr., M.D.
Recommended FY 1968 Funding $45,000

Marshfield Clinic Foundation for Medical Research and Education, Marshfield, Wisconsin
Principal Investigator: Richard D. Sautter, M.D.
Recommended FY 1968 Funding: $60,000

University of Pennsylvania Graduate Hospital, Philadelphia, Pennsylvania
Principal Investigator: Moreye I. Nusbaum
Recommended FY 1968 Funding: $48,000

Peter Bent Brigham Hospital, Boston, Massachusetts
Principal Investigators: Lewis Dexter, M.D. and James E. Dalen, M.D.
Recommended FY 1968 Funding: $44,000

Veterans Administration Hospital, West Roxbury, Massachusetts
Principal Investigator: Arthur A. Sasahara, M.D.
Recommended FY 1969 Funding: $20,000

University of Washington, Seattle, Washington
Principal Investigator: J. R. Blackmon, M.D.
Recommended FY 1968 Funding: $65,000

PHS - NIH
NATIONAL HEART INSTITUTE
Annual Report
July 1, 1967 - June 30, 1968

EXTRAMURAL PROGRAMS

The National Heart Institute through its Extramural Programs administers cardiovascular research and training programs of great scope and diversity. Grant supported research projects range from epidemiological studies of large human population groups to studies of individual cells and cellular components and the biochemical reactions that occur within them. The diversity of this research is dictated by the complexity of the problems posed by the cardiovascular diseases. For the most part, their causes are not known with certainty. In many instances, a host of complex factors -- genetic, environmental, and physiological -- seem to operate in their development and in their protean clinical manifestations. For example, atherosclerosis appears to be related not only to metabolic inbalances, but also to blood clotting mechanisms, and the dynamics of flow in vessels; susceptibility to this disease and its complications may be influenced by such factors as age, sex, diet, physical activity, psychic stress, and cigarette smoking. Congenital heart disease may arise from genetic factors or from a variety of noxious pre-natal factors affecting the fetus at critical stages of its development.

During FY 1968, the Heart Institute's research grants program will support more than 1800 research projects totaling approximately $105,000,000. Additionally an estimated 400 training grant programs totaling $17,700,000 and 400 research fellows requiring $7,400,000 will be supported in FY 1968.

PROGRAM REPORTS

A discussion of the National Heart Institute grant and award programs is presented on the following pages and is arranged according to three major subdivisions:

(1) Research including eleven major disease categories toward which research activities are directed but which encompass broadly based fundamental and applied studies.

(2) Training including graduate and undergraduate training grants, postdoctoral and special fellowships, and career development awards.

(3) Special Programs in which research and developments to reach highly focused objectives is being carried out with commitment of specific resources on a large-scale and for relatively long periods of time.

Atherosclerosis is, by far, the most prevalent of all cardiovascular disorders. If it could be entirely eliminated in the American population, or even if only some of its complications (such as heart attacks, strokes, and congestive heart failure) could be prevented, hundreds of thousands of lives would be spared or prolonged.

During the past decade, there has been nearly a tenfold increase in the number of Heart Institute supported research projects in this field; currently, in terms of research funds expended, atherosclerosis is the largest single disease category in the Heart Institute program. This emphasis is well deserved and appropriate; the long-range goal is prevention.

A large segment of this research deals with mecahnisms whereby fats are absorbed, transported, synthesized, and broken down within the body. Derangements in one or more of these processes are thought to underlie the elevated blood levels of cholesterol and other fats that predispose to atherosclerosis. Other important research is concerned with the effects of diet on blood-lipid levels and the evaluation of lipid-lowering diets and drugs as potential means of preventing atherosclerosis, retarding its development, or perhaps reversing the course of the disease.

Another area of atherosclerosis research is concerned with the body's clotting and clot-dissolving mechanisms, because clotting complications account for most heart attacks, strokes, and other lethal or crippling manifestations of the disease. This research includes basic studies on coagulation mechanisms; on elevated blood lipids and other factors that may predispose the victim of atherosclerosis to clotting complications; and on anticoagulant and clot-dissolving agents that may provide effective therapeutic measures against heart attacks, strokes, and the other thromboembolic complications of atherosclerosis.

The remainder of the research in this field involves many different disciplines and lines of attack. They vary from studies on the influence of different diets on the atherosclerotic lesion in experimental animals, to the development of new instruments for measuring arterial blood flow; and the study of the personality characteristics and "risk factors" in patients who have been victims of one or another complication of the disease.

Coronary Artery Disease. Death and disability from coronary atherosclerosis represents the greatest single challenge to modern medicine. Before the treatment of heart attack can be developed to its optimum there must be a greater understanding of the organ in its normal state, in the stress of decreased blood supply or increased metabolic demands, and in the episode of ischemia or infarction. Current research on the functions of heart muscle in health and disease will be continued. The influences of decreased blood supply on heart metabolism must be better understood. Cardiac rhythm and the many factors affecting it need further elucidation. The mechanisms by which acute cessation of blood flow injures the heart need to be more fully appreciated. The acquisition of these and other data will certainly enhance the development of interventions designed to impede or prevent coronary disaster.

Significant advances in the radiologic diagnosis of coronary disease have been made, but much remains to be done on the safer and earlier detection of impending heart failure. Surgical replacement and repair techniques have saved many lives, as have intensive care units with their resuscitative and monitoring capabilities. These require further development. Drug studies continue for the improvement of blood supply and for the management of arrhythmias.

The treatment of coronary disease and heart attack has become increasingly more effective. As a consequence there is a need to know more about cardiac invalidism. Rehabilitation of the heart attack victim, psychic as well as somatic, has become much more relevant and will require an expanded research effort.

Hypertension is the most commonly encountered form of cardiovascular disease. An estimated 17,000,000 Americans between the ages of 18 and 79 have high blood pressure, and about 10,500,000 have heart disease as a consequence of hypertension. Apparently, hypertension accelerates the development of atherosclerosis and is a major cause of strokes, heart failure, and kidney failure.

As many as 15 percent of all cases of hypertension are secondary to kidney disease or other pathologic processes that are potentially curable if promptly diagnosed and corrected. Thus, improved techniques for the diagnosis of disorders that cause secondary hypertension and for the selection of patients who may benefit from surgery are important goals. Most victims of hypertension, however, suffer from "primary" or "essential" hypertension, a disease of unknown origin. Ignorance of the cause of essential hypertension has not, however, prevented the development of a steadily growing number of drugs that are remarkably effective in reducing blood pressure in hypertensive patients. Although they do not cure the disease, a variety of drugs have now been developed for controlling hypertension of all degrees of severity. None is totally effective, and some have unpleasant and sometimes serious side effects. The quest for new and improved therapeutic agents continues.

Other important areas of study include research on fluid and electrolyte metabolism; the possible role of endocrine disturbances in hypertension; hereditary or environmental factors affecting the development or causes of the disease; and neural and hormonal mechanisms involved in blood pressure control.

Cerebrovascular Diseases. The marked vulnerability of the brain to reduction in blood supply is expressed as a "stroke", or as one of several other dysfunctions. Therefore, the measurement of cerebral blood flow; the distribution of the blood flow within the brain; the conditions which affect blood flow and the regulation of the flow are prime objectives of research. Technological developments, depending partly on bio-instrumentation and nuclear medicine, are extending such research and providing the data that are essential to understanding how an adequate cerebral blood supply is maintained and how it is affected by disease, environmental stresses, drugs and other therapies.

Research in observational techniques includes better radiological methods which more completely visualize the cerebral vessels; flow methods which permit measurements of focal, regional and total flows in the brain; and the development of non-traumatic methods which will allow repetitive observations on the patient without discomfort or hazard.

The great majority of cerebrovascular research grants deal primarily with human patients afflicted with cerebrovascular diseases, relatively few with animal studies. Research progress against stroke has been considerably hampered by the lack of a satisfactory disease model in animals. Over half of these NHI research grants involve surgical disciplines--attesting to the intensive efforts to perfect reconstructive techniques in vascular surgery; to develop better anesthetic agents and methods; and to evaluate continuous monitoring during and after cerebrovascular surgery. Most of the remaining grants are concerned with improved methods of diagnosis and medical management of cerebrovascular disease.

Although this increasing research effort has produced some noteworthy gains, certain identifiable needs and opportunities exist. To date, the preponderant investigative effort has been in the treatment and palliation of cerebrovascular diseases. Attempts to prevent these diseases, however, must await a fuller understanding of underlying processes: atherosclerosis, clot formation and lysis, and blood pressure control. Concurrently, opportunities exist for the identification of stroke-prone individuals, for the improvement of promising diagnostic methods, and for the perfection of surgical monitoring techniques.

Congenital Heart Disease is the main cause of death of infants under two years of age. One-third of all congenital heart disease patients die in the first month, and most of these in the first week of life. Although surgical treatment has continued to improve, it is still extremely risky in infants less than six months of age.

Furthermore, congenital heart disease is unquestionably one of the costliest of all diseases from the point of view of its medical care. For example, there are now over 300 surgical teams in the United States specially trained and equipped for open heart surgery of congenital heart diseases, and more than 500 diagnostic centers elaborately equipped for its diagnosis. The annual cost of this equipment, personnel, and services runs to many millions of dollars. (The cost of these services to the individual patient often exceeds $2,000.)

The Heart Institute's research program has placed heavy emphasis on the improvement of methods for the diagnosis and evaluation of congenital heart defects and on the perfection of surgical methods for correcting them.

The Institute's concern with congenital heart diseases is complemented by the categorical interests of two other Institutes. The Neurological Institute has a large organized program of perinatal research to define the prevalence and to seek the causes of various types of congenital disorders. The Heart Institute is cooperating with that Institute in the special study of congenital heart diseases that are encountered in the program. The

National Institute of Child Health and Human Development has been designated to support research that concerns human or experimental embryology prior to the heart's development into a functioning organ; research in teratology, the experimental production of congenital anomalies, is also assigned to that Institute.

Peripheral Vascular Diseases are among the commonest of diseases to afflict man and most of them are inevitably interwoven with the major causes of death--atherosclerosis and thromboembolic conditions. Progress in this area has been largely in improvement in methods of diagnosis (e.g., measurement of blood flow, angiography), and treatment. Although some of these advances have been perfected, suitably modified, and applied to other parts of the vascular system, such as the heart and brain, there still is little understanding of the mechanisms of these disorders.

Perhaps the most important advance has been the development of better angiographic techniques. Concurrently, vascular surgery has been perfected and these two developments have resulted in impressive therapeutic gains. Today, all major blood vessels can be visualized adequately and, in current practice only a few surgical procedures are undertaken without angiographic guidance. Additional improvement in angiography depends upon the continued search for better contrast dyes, improved cameras, image intensifiers, motion picture cameras, and rapid-changing film devices. The pathologic physiology of these peripheral vascular diseases, and their localization at certain sites in vessels, requires much more research. In particular, there is a real need for new insights and innovations, for there are not enough promising leads at present. The relationships between peripheral vascular diseases and diabetes, alergic states, and smoking need precise clarification. Since these diseases often occur in patients who have more serious heart disease, and since undue delay in treatment may result in amputation or death, further advances in diagnostic and therapeutic techniques are urgently needed. The usefulness of anticoagulant and clot-dissolving drugs is especially deserving of further exploration.

Rheumatic Fever and Rheumatic Heart Disease have declined steadily as causes of death and disability during the past several decades, but both continue to occur in significant enough numbers to consititute an important health problem.

The evidence associating rheumatic fever with a preceding streptococcal infection is overwhelming. Although the underlying mechanisms remain obscure, research results are most consistent with an inappropriate immunologic reaction triggered in the patient by the products of certain hemolytic streptococci. The fact that rheumatic fever develops in a very small percentage of people who become infected with these streptococci suggests that some factor or factors in the affected person are important in the development of the disease. Until highly susceptible individuals can be identified in advance and effectively protected by antibiotics or other means, rheumatic fever and rheumatic heart disease will continue to occur. A prophylactic vaccine would be of great value.

A consistently reliable test for the diagnosis of cardiac involvement in rheumatic fever victims is badly needed, as are effective techniques for preventing or reducing the severity of damage when the heart is attacked by the disease. T opportunities for this much needed research are limited in this country, but could be exploited in certain foreign countries where large untreated populations still exist.

In general, there has been a concentration of effort on the surgical treatment of these diseases. In the years to come, however, greater emphasis should be placed upon the natural and post-therapeutic history of these disorders, not merely for decisions about the relative value of various prosthetic devices (e.g., artificial heart valves) and surgical procedures, but also for the crucial decisions concerning the best time for surgery and the type of patient most likely to benefit.

Cardiopulmonary Disease. The prevalence of respiratory illnesses, and particularly that of chronic obstructive diseases such as emphysema, is increasing at an alarming rate. The Heart Institute continues to represent the single largest provider of research support in this area. Many of these diseases are complex, of uncertain etiology, and associated with a variety of factors (e.g., cigarette smoking, air pollution, allergy, infections). Research approaches have, therefore, been diverse and multidisciplinary.

The Heart Institute's cardiopulmonary research program has several major segments: pulmonary vascular disease, chronic obstructive disease, lung mechanics, and pulmonary physiology. Approximately half of these grant-supported studies are devoted to a better understanding of disease causation and approximately one-third to better diagnostic techniques.

The cardiopulmonary diseases are viewed as one of the most important program areas requiring increased research and training support. (The Institute supports, through some 30 training grants, the cardiopulmonary training of approximately 130 individuals per year.) Several new approaches and techniques that appear promising are being developed and evaluated. For example, new methods for the evaluation of ventilation-perfusion relationships in the lung are being undertaken; there is hope that regional distributions of ventilation and perfusion within the lung may be detected with new, atraumatic, isotopic techniques. The Institute is also supporting long-range prospective studies of patients who have chronic lung disease so that the natural history of these diseases may be defined more precisely.

Future prospects include a greater emphasis on experimental transplantation of the lung; in vitro preservation of lungs for elective transplantation; and new mechanical devices for patients in severe respiratory distress or failure.

Acceleration of research studies in this area is considered to be of utmost importance.

Heart Failure and Shock. The problem of congestive heart failure and shock is still a large and diffuse one. These are not discrete diseases, but rather symptom-complexes that are the end results of underlying cardiovascular diseases.

Circulatory failure may be either acute or chronic in nature. The acute form includes cardiovascular shock, fainting, and often sudden death--due to profound disturbances of heart rhythm and blood pressure. The chronic form of circulatory failure is generally known as congestive heart failure and denotes prolonged impairment of the ability of the heart to maintain an adequate blood flow to the tissues.

Most of the Heart Institute's research grant support in this disease category is concerned with causation. It is not yet known whether heart failure represents a "weakness" of the heart muscle cells or is the result of defective energy production or utilization. The answer may be found in intensive studies on the ultrastructure and arrangement of the heart muscle fibers and contractile proteins, or it may lie somewhere in the complex biochemical mechanisms by which the heart generates chemical energy and then harnesses that energy to drive the contractile process. Increasing evidence now suggests that congestive heart failure is a form of molecular pathology.

Progress in the search for effective therapeutic agents has been considerable during the past few years. Lidocaine has been added to procainamide and quinidine as a lifesaving drug for treatment of arrhythmias; powerful new diuretic drugs are avilable for combating the associated fluid retention; and drugs which block sympathetic receptors have become useful in both investigation and treatment. Digitalis, however, still remains unchallenged in its ability to improve the efficiency of cardiac contraction.

The solution of these complex problems requires greater integration of the efforts of various disciplines in both the analysis of the mechanisms causing failure and the development of better treatment methods. Because of the continued interest of scientists working on this problem, and its initial importance, extensive support will be provided for the most promising research. Multidisciplinary approaches to the problem must be strongly encouraged.

Thromboembolic and Hemorrhagic Diseases. Blood is a complex tissue of the living body that is continually changing its chemical composition; it must remain fluid in nature while being capable of coagulation when a break occurs in a blood vessel. Many chemical and cellular components are involved in the maintainance of the normal state of the blood and a more complete understanding of their relationships is necessary to prevent both hemorrhagic and thromboembolic diseases. Such knowledge is also necessary for adequate handling of other pathologic states such as anemia, leukemia, infections, trauma and the secondary complications of surgery, atherosclerosis, etc.

Continued National Heart Institute grant-supported studies in thromboembolic and hemorrhagic diseases include not only basic research but a carefully

planned development and investigation of thrombolytic and antihemophilic agents. This program has already achieved a measure of success in the identification, isolation, and purification of a substance called urokinase, which has the property of activating or assisting the body's mechanism for dissolving clots in blood vessels. Preliminary clinical investigation has indicated that this may be a promising therapeutic agent for pulmonary embolism, retinal artery thrombosis, and possibly for stroke, and a multitude of other thrombotic diseases.

Other Cardiovascular Diseases. This category includes a diverse number of cardiovascular diseases and a variety of basic research activities fundamental to an improved, more comprehensive understanding of the vascular system. A host of cardiac diseases not classified into the other major disease groups remain as challenges of considerable clinical significance.

TRAINING

Graduate and Undergraduate Training Grants. The National Heart Institute through its training grant programs aims to (1) improve the quality and quantity of research and clinical training, and (2) attract promising young students to insure a continuing and expanding supply of well trained cardiovascular scientists, teachers, and clinicians.

Undergraduate training grants are awarded to medical schools and Schools of Public Health to establish, expand, improve, or continue instruction relating to the prevention, diagnosis, and treatment of cardiovascular diseases. Presently the Heart Institute supports 110 such programs.

Graduate training grants support advanced training programs in basic and clinical cardiovascular research areas in medical schools, universities, or other research-educational organizations. These grants permit the local identification of young men and women with research potential, provide them with appropriate stipends, and assist the institution in providing high quality cardiovascular research training.

In FY 1966, the Heart Institute initiated a new graduate program to provide advanced cardiovascular clinical training. This program is directed toward the advanced training of physicians at the post-residency level and includes intensive training experience in related research disciplines. These training grants are awarded to institutions that have a distinguished history of cardiovascular research and an environment where research and clinical training can be integrated effectively.

Fellowships and Career Development Awards. The two primary objectives of the fellowships program are: (1) to increase the number of trained cardiovascular investigators, and (2) to assure the continuing flow of skilled and imaginative research workers into the cardiovascular field. Promising scientists, selected on a national competitive basis, receive these awards enabling them to obtain advanced scientific training and supervised research experience. These awards serve to encourage the research interests of young persons who show promise of becoming competent research scientists; they

serve to provide mature investigators with additional or specialized research experience and thus further develops their research skills; and they serve to provide stable support for the advanced investigator in an attempt to insure retention of the most qualified individuals within the field of cardiovascular research.

In both basic and clinical disciplines, postdoctoral fellowships help to train future research scientists. The program encourages young physicians and scientists to obtain research training and experience that will enable them to utilize their bio-medical knowledge more effectively in cardiovascular research.

In the Career Development Award Program, awards are made to the institution, not to the individual, and are designed to provide stable career opportunities for scientists of outstanding potential and competence in cardiovascular research and teaching. This award carries an implied commitment from the institution for long-term retention of the candidates. It supports the younger investigator or scientist of demonstrated ability who needs further experience to qualify for more senior positions.

SPECIAL PROGRAMS

Cardiovascular Research and Training Centers. The National Heart Institute proposes to establish approximately 12 Cardiovascular Research and Training Centers during the next six years. These are to be centers of excellence with a corps of scientists capable of imaginative and creative investigation of the diverse problems of human cardiovascular diseases. Organized under outstanding leadership, scientists from basic and clinical disciplines will work in sufficiently close proximity and with such a degree of integration of their activities, that ideas and technical advances may be continuously exchanged and evaluated in a critical environment. The stimulation to the individual scientist made possible by the physical and intellectual proximity of others dedicated to the same ultimate goal, but possessed of the special knowledge and skills of other disciplines, will foster the coordinated investigations required for the solution of difficult and challenging problems. These centers will include, or be closely allied with, personnel and facilities essential for the conduct of sophisticated diagnostic and therapeutic procedures; thus they will provide a rich environment for training both clinical and laboratory personnel. The development of such centers will accelerate and increase our capacity to meet critical manpower shortages.

During fiscal years 1966 - 1968, the NHI budget included $800,000 each year for specialized Cardiovascular Research and Training Centers. These funds have been used to award grants for planning at 12 institutions.

One possible prototype of the Cardiovascular Research and Training Center has already been developed without a formal planning grant and is currently funded as a program project grant. Many institutions, however, will require a preparatory or intermediate phase after the planning activities have been completed; this may require the construction of new facilities, the

modification of available space, and the purchase of necessary equipment and resources. The implementation of this program is, of course, dependent upon the availability of adequate facilities, and the appropriation of substantial operational funds.

The Cooperative Study of Drugs and Coronary Heart Disease aims primarily to determine whether certain drugs which reduce the concentration of blood lipids are capable of improving survival among patients with overt coronary heart disease. A second objective is to determine whether the degree to which these drugs lower serum lipids is correlated with their effect on mortality and subsequent heart attack rates. By studying just as intensively those individuals in the study who do not receive lipid-lowering agents, the investigators will also obtain valuable information concerning the outlook for men who have survived an initial myocardial infarction and are not on lipid-lowering drugs.

The study is now in its third year of operation, with a total of 55 participating clinics. These include large medical centers, small private clinics, private and community hospitals, and V.A. and PHS hospitals. Approximately 3,800 of the anticipated 8,400 patients have been entered into the study. While recruitment has been slow in the early stages, the investigators have taken steps to overcome this by a widespread publicity campaign, and it is hoped that the full complement of 8,400 patients will be recruited by June 1969.

Preliminary data are constantly being analysed and evaluated. This well-designed study continues to progress and should have an important impact on clinical care. Study leaders and Heart Institute staff are developing methods for the continuing review and evaluation of the performance of all participating clinics.

Other Cooperative Studies. A comprehensive report from the Cooperative Diet-Heart Feasibility Study was published as a Supplement to the March 1968 issue of Circulation. The investigators have detailed their findings and made a number of recommendations regarding future large-scale investigations in this important area. The report presents considerable detail regarding many alternative approaches to such studies, including recruitment of participants; statistical, chemical, clinical, and nutritional methodology; and food procurement and distribution. The results described include dietary intakes, changes in blood lipids and other coronary risk factors, factors in loss of patients from the study, and integrity of the double-blind feature of the study. From all these the investigators have formulated a number of recommendations for future studies. They suggest consideration of large-scale, long-term controlled investigations in free-living and institutionalized population groups, of the efficacy of dietary modifications in the primary and secondary prevention of coronary heart disease. In line with these recommendations, the Heart Institute has appointed a special Diet-Heart Study Panel to review these conclusions and recommendations, and to advise the Institute regarding the potential for such studies, including consideration of a variety of technical, social, and economic factors.

A Cooperative Study of Renal Disease and Hypertension is attempting to determine the efficacy of long-term suppressive anti-bacterial therapy in chronic pyelonephritis; to characterize the pathogenesis and natural history of this dis , and to characterize further relationships between pyelonephritis and hypertension. Studies involving more than 200 patients suggest that one primary objective of this study, the assessment of the efficacy of drugs in eliminating bacteriuria, should be achieved within 6-12 months. The results indicate that the control of bacteriuria is significantly better with acidifying regimens and nitrofurantoin. Also, it appears that renal function s significantly improved in those patients responding bacteriologically to chronic suppressive therapy.

A Cooperative Study of the Natural History of Congenital Heart Diseases is now midway through its third year. The investigators hope to identify the proper role of surgery in the treatment of three common forms of cardiac anomalies. The study involves five pediatric cardiology groups and a statistical coordinating center. Diagnostic cardiac catherterization data has been obtained on eight hundred patients between July 1958 and June 1965 and now annual follow-up, with re-catherterization at an eight-year interval, will provide information on anatomical and physiological changes in these patients over time. Four hundred new patients, diagnosed and admitted prospectively since July 1966, are also being studied and followed in the same way.

Increasing reliance upon cardiac catheterization as a diagnostic tool has resulted in the establishment of catheterization laboratories in many institutions. An effort was therefor made, starting in 1963, to assess the risks of various catheterization procedures, to provide data which would allow reduction of these hazards, and to make an up-to-date appraisal of procedures currently used in experienced catheterization laboratories. The results of this Cooperative Survey of Cardiac Catheterization have been reported recently. When the study terminated in the fall of 1965, a total of 12,367 procedures had been carried out in sixteen institutions during a two-year period. There had been 444 major complications (3.6%), including 55 deaths, 38 of which occurred in gravely ill infants. Cardiac arrhythmias, with 153 incidents, were the most common major complication, with ventricular fibrillation being the most frequent of these. Perforation of the heart or great vessels occurred in 100 cases, and less frequent complications developed from a variety of thrombotic, hemorragic, infections, allergic, and other causes. Experience obtained from the study has led to several improvements in procedures.

The Cooperative Study of Anti-Arrhythmic Drugs in Acute Myocardial Infarction has attempted to determine if the prophylactic use of antiarrhythmic medication in acute myocardial infarction patients results in a lower death rate and/or lower incidence of death-producing cardiac arrhythmias. This study began in 1963 with five clinical participants. Tentative conclusions, based on over 400 patients, suggest that both treatment groups (quinidine and procainamide) have a lower total ultimate mortality and a lesser incidence of serious arrhythmias than the placebo group.

The National Transfusion Hepatitis Study is a large-scale, cooperative double-blind clinical trial of the efficacy of gamma globulin in the prevention of serum hepatitis in cardiovascular surgery patients who have received multiple blood transfusions. At present, the study is in its seventeenth month of full operation and has succeeded in entering over 2,000 patients, with over 94% retention of subjects after six months of follow-up. The incidence of symptomatic hepatitis is now about 3 percent. The results of this clinical trial are under careful and continuous scrutiny.

The U.S. - U.K. Joint Study of Cardiorespiratory Disease has recently resulted in a series of articles concerning the occurrence of ischemic heart disease, chronic respiratory disease, and lung cancer in individuals who have migrated to the U.S. from the United Kingdom and Norway. Prevalence of and mortality from chronic respiratory disease in British-born migrants living in the U.S. is only one-fifth as great as that which prevails in the U.K. In contrast, coronary disease in British migrants in the U.S. surpasses the level in Britain by about 30 percent and closely approaches that of native Americans. Similar trends for coronary disease have been observed in Norwegian migrants. In contrast, mortality from lung cancer shows a much greater association with the country of origin. Thus, it appears that coronary and chronic respiratory disease are relatively susceptible to change by environmental influences during adult life, whereas proneness to lung cancer appears to be only slightly influenced by a change of environment.

The National Heart Institute Extramural Programs continue to support a wide diversity of cardiovascular research and training. However, because of the limited availability of funds to support meritorious cardiovascular research and training, there has been (1) a steep increase in the number of approved unfunded applications and (2) a substantial decrease in the number of grants and awards. Thus, for example, the number of regular research grants has decreased from approximately 2,200 in FY 1966 to an estimated 1,800 in FY 1968. Despite these limitations, the Institute has maintained a support program designed to ensure steady progress in the prevention, relief, cure, and understanding of cardiovascular and cardiopulmonary diseases.

The allocation of funds reflects, to a varying degree, a set of important considerations: prevalence, nature, and seriousness of the various cardiovascular diseases; current and anticipated research opportunities; program relevance and priorities; and, of course, scientific merit. Thus, the deployment of funds and resources remains a responsive process that reflects health needs and research opportunities.

The support of research in the area of atherosclerosis, including coronary artery disease, represents the highest program priority and approximately 27% of NHI research grant funds are allocated to this disease and its complications.

In a relative, although not absolute, sense, support of research in the area of hypertension has been decreasing.

To determine research and training needs and opportunities in the cardiopulmonary area, the Institute has established a special advisory committee of experts and an intensive analysis of the Institute's current program will be undertaken. Approximately 6% of National Heart Institute Extramural Programs funds are devoted to the problem of pulmonary diseases (and especially the chronic obstructive diseases such as emphysema).

The Institute is also engaged in an analysis of the problem of cerebrovascular diseases and, in particular, is examining the potential contribution to be made by newer, physiological techniques in the study of blood flow and hemodynamics.

Analysis of the Institute's graduate training grant program is also underway. As in the past more than half of the Institute's training funds are devoted to research training programs in basic cardiovascular disciplines; these programs relate to a variety of cardiovascular diseases. As noted in previous years, the availability of highly-trained cardiovascular research manpower is a problem of increasing urgency. Because of limited availability of funds, a number of ongoing training programs supported by the Institute have had to be terminated.

During the past year a number of special program reports have been made to the National Advisory Heart Council to keep them abreast of current research plans and progress. Several of these reports have involved ongoing cooperative studies supported by the Institute. The National Heart Institute Extramural Programs has, during the past year, benefited from closer working relationships with the Institute's Epidemiology and Biometry Program.

One of the most important problems faced by Extramural Programs has been the critical shortage of trained, qualified, professional staff. This recruitment problem derives from the national shortage of biomedical manpower and the present grade and salary structure at NIH.