ANNUAL REPORT OF PROGRAM ACTIVITIES

NATIONAL INSTITUTES OF HEALTH

1968-1969

NATIONAL HEART INSTITUTE
VOL. I

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

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NIH-NHI

THE NATIONAL HEART INSTITUTE

ANNUAL REPORT

July 1, 1968 through June 30, 1969

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OFFICE OF THE DIRECTOR

EXTRAMURAL

HEART INFORMATION

EPIDEMIOLOGY AND BIOMETRY

ARTIFICIAL HEART

MYOCARDIAL INFARCTION

NATIONAL INSTITUTES OF HEALTH
NATIONAL HEART INSTITUTE
July 1, 1968 to June 30, 1969
OFFICE OF THE DIRECTOR

The mission of the National Heart Institute is to conduct and support research to increase scientific knowledge of the cardiovascular system; to define structural and functional abnormalities occurring with cardiovascular diseases; and to develop more effective means of prevention, diagnosis, and treatment.

The backbone of the Institute's activities in fulfillment of this mission is its large, diversified research grants program, which, during FY 1969, supported nearly 2,000 research projects at universities, medical schools, and other institutions throughout the U.S.

Many of these studies yielded basic information on the cardiovascular system and the blood it carries; on the lungs and kidneys, which oxygenate the blood and purify it of waste products; and on the endocrine glands and their secretions, which influence cardiovascular performance. Some studies probed biochemical reactions occurring within individual cells and the enzyme catalysts that make these reactions go; others investigated the genetic mechanisms that dictate the form and regulate the synthesis of structural proteins and enzymes.

Many other grant-supported studies are developing information, techniques, and instrumentation directly applicable to clinical problems posed by the cardiovascular diseases. These include clinical trials of promising new drugs; safer, more sensitive diagnostic procedures for congenital or acquired cardiovascular disorders; improved surgical and life support techniques for curing or ameliorating congenital or acquired heart disorders; and improved monitoring and treatment procedures for averting or dealing effectively with life-threatening complications of heart attacks.

Still other studies, ranging from laboratory research through animal experiments to epidemiological investigations in human populations, are exploring host and environmental factors that increase susceptibility to various cardiovascular diseases in an attempt to devise more effective preventive measures.

During the past year the Institute has undertaken a detailed analysis of selected research areas in its grants program by NHI staff members and consultants. The aim is to strengthen those areas of research where new knowledge might find fruitful application in the prevention of atherosclerosis and its complications.

Dr. Gardner McMillan, of the University of Toronto, was retained as a special consultant to review NHI grant support in the broad category of atherosclerosis. His final report and recommendations were recently submitted for study by the Institute and its advisory groups.

Of crucial importance is a fuller understanding of the underlying causes of this disease; of the mechanisms by which it attacks the arterial wall; and of factors increasing susceptibility to the disease, accelerating its development, and precipitating its disabling or lethal complications. A heart attack or stroke is a culminating event--and all too often the terminating one--of a disease process that has been going on for many years. Can it be prevented from starting at all; or, if the disease process is already underway, at which points might suitable therapeutic interventions retard, arrest, or even reverse its development? In persons with advanced stages of atherosclerosis can therapeutic interventions directed against precipitating factors abort the development of heart attacks or strokes?

Other areas meriting research emphasis are the development of atraumatic instrumentation and techniques for detecting atherosclerosis in its early stages and for following the development of the disease; studies on the regression of established atherosclerotic lesions and on the pathogenesis of plaque hemorrhages; the rehabilitation of patients with arteriosclerotic conditions; and further elucidation of salient risk factors and the effectiveness of countermeasures against these amenable to modification.

One important possibility on which a lot of scientific hopes are pinned is that the reduction of blood lipid levels by diet or other means can reduce susceptibility to atherosclerosis and also the risk of such consequences as heart attacks.

Earlier feasibility studies demonstrated that palatable diets can be devised that will bring about predictable reductions in blood cholesterol. What we do not know is whether such diets, if followed by large groups of people for prolonged periods, will affect their morbidity and mortality rates from coronary heart disease. A 12-member Diet-Heart Review panel was convened to examine the various approaches to such a study and the problems inherent in each. The possibility of conducting such a study in an open, free-living population is still under consideration, but it appears that an equally definitive study might be carried out at much lower cost and with more adequate controls among institutionalized subjects. One smaller grant-supported study set up along these lines is already underway and could be expanded by gradual addition of similar study groups to achieve the numbers required to demonstrate conclusively any effect of dietary modification on CHD experience in these groups should preliminary findings indicate such expansion.

Another large field trial, whose object is secondary prevention, is the Coronary Drug Project. This study is designed to determine whether and to what extent lipid-lowering drugs will confer protection against recurrent heart attacks and other complications of pre-existing coronary heart disease in men who have previously experienced one or more heart attacks. The goal is to reduce by 25 percent or more the five-year mortality rate among treated subjects at very highest risk of death from coronary heart disease.

The drugs being evaluated are nicotinic acid, dextro-thyroxine, clofibrate, and conjugated equine estrogens at two dosage levels. Patients in each of the five treatment groups will be compared with a control group which will receive a placebo rather than drugs, but will otherwise receive the same care as the treated patients.

The study is underway at 55 participating clinics throughout the continental U.S., Puerto Rico, and Hawaii. Patient recruitment was completed in June of 1969, and the clinical phase of the Project will be completed in 1974.

Dr. Kenneth Brinkhous, of the University of North Carolina, is presently serving as a special consultant to review another important sector of the NHI research grants program --thrombosis and hemorrhagic diseases-- which has immense potential in preventive cardiology. Thrombosis is a specially important problem because it appears that clots or emboli are directly responsible for the great majority of heart attacks, more than half of all strokes, and for many other serious consequences of blood-vessel diseases. Thrombosis is also a major problem attending the use of artificial valves and most other cardiovascular prostheses. Much additional research knowledge is needed on basic coagulation mechanisms; on factors that influence coagulability; on normal and abnormal trigger factors that set the coagulation process in motion; and on the body's clot lysing system. From such knowledge may develop new or improved techniques for protecting individuals against thromboembolic complications of existing cardiovascular disease or, failing this, minimizing the damage done by clots or emboli by hastening their dissolution.

In addition to its regular research grants program, the National Heart Institute carries on a number of special research and development programs. Supported for the most part through research contracts, these programs are directed against specific, well defined health problems.

The Artificial Heart Program, which began operations in 1964, is seeking to reduce death and disability from heart disease through the development of devices and techniques for providing temporary or permanent assistance to a failing circulation and a total replacement for hearts damaged beyond salvage. To this end, it has awarded to date more than $19 million in contracts to support research attacking specific bioengineering, physiological, and related problems of artificial heart development. This research is being carried out, not only in universities and medical centers, but also by chemical and engineering firms, electronics corporations, and other elements of private industry.

During fiscal year 1969, the Program supported more than 100 contracts totalling more than $7 million. These contracts dealt with 13 key areas of bioengineering and physiology, including instrumentation, materials development and evaluation, implantable and external power sources and control mechanisms, new circulatory assist devices and blood oxygenators, various physiological problems of assisted circulation, and the planning of test and evaluation facilities for techniques and hardware developed under the program.

In June, 1969, the Program sponsored a 5-day Artificial Heart Conference in Washington to cover progress to date in the artificial heart field. The conference featured 90 presentations by scientists conducting research under contracts from NHI. The Conference Proceedings, to be published later this year, will comprise a valuable review of the current "state of the art" in this important, rapidly developing area of research.

The Myocardial Infarction Program was established in 1966 for the purpose of designing and administering a national program of biomedical research directed against acute heart attacks, our Nation's most important single cause of death and disability. The research activities of this Program also complement those of the Artificial Heart Program and provide a base of medical knowledge highly useful toward the continued development and evaluation of circulatory assist devices and techniques; for it is in the treatment of heart-attack victims that these devices are likely to achieve their greatest potential for saving and rehabilitating otherwise doomed or hopelessly disabled patients.

A major element of the Myocardial Infarction Program is the establishment of a chain of Myocardial Infarction Research Units (MIRUs) combining unexcelled patient care with intensive clinical and laboratory research on acute heart attacks and their complications. The purpose of these units is to improve medical knowledge of the acute attack itself, including identification of factors that critically affect the outcome, and to develop new or improved methods of diagnosis and treatment that will be widely applicable to the care of coronary patients.

During the past year, new MIRUs were established at the University of California, San Diego; Cedars-Sinai Medical Center, Los Angeles; the University of Chicago; and the University of Rochester. In addition, the Myocardial Infarction Program provided continuing research support for MIRUs previously established at the University of Alabama, Cornell, Duke, Johns Hopkins, and Massachusetts General Hospital.

A major series of studies to be undertaken in the near future will attack the problem of sudden, unexpected death which overtakes fully half of all heart attack patients before they can be brought to a hospital. The mechanisms bringing on such swift death in these patients are little understood and their study poses formidable problems; but if any substantial reduction in mortality from heart attacks is to be achieved, means must be found to develop information on this problem and to improve survival among such patients.

The National Blood Resource Program has as its major goals 1) to survey our Nation's blood resources and their utilization in terms of present and foreseeable needs and 2) to meet steadily accelerating demands for blood products, especially blood fractions, without undue strains on existing resources through improvements in all phases of technology relating to the acquisition, processing, storage, and distribution of blood products.

Specific goals of research and development projects currently underway or planned for the immediate future include

- the development of efficient, highly automated procedures for large-scale production of plasma and cellular fractions (red cells, white cells, platelets) from whole blood.

- the development of high yield techniques for fractionating plasma to yield albumin, gamma globulin, blood clotting factors, and other medically important protein fractions.

- investigation of chemical additives and freezing techniques for the preservation of whole blood and blood components.

- studies investigating the feasibility of computerized local, regional or national inventory systems for blood donors and blood products that, if applicable, might 1) minimize losses due to outdating in storage; 2) minimize presently avoidable problems due to fluctuations in supply and demand; and 3) forestall or meet local shortages through effective redistribution of surpluses existing elsewhere.

The Program is also supporting a cooperative clinical trial of the clot-dissolving drug urokinase against pulmonary embolism at 18 institutions. Urokinase, apparently a non-toxic, non-antigenic drug that attacks clots by activating the body's own clot lysing mechanisms, may prove to be a major advance against clotting complications so often directly responsible for the disabling or lethal consequences of cardiovascular disease. However, the therapeutic effectiveness of fibrinolytic agents remains to be convincingly demonstrated in carefully controlled clinical trials.

The present study is designed to provide definitive evidence of the drug's effectiveness against clots in the pulmonary circulation. The results of this study are an essential prelude to further trials of urokinase against coronary occlusion and other thromboembolic complications of cardiovascular disease.

The NHI Intramural Research Program blends basic research on the structure and functions of the cardiovascular system with clinical research directed against specific cardiovascular disease problems. Some accomplishments of this program that have generated a great deal of scientific and medical interest during the past year include

- the system developed at NHI over the past few years for identifying and classifying blood-lipid abnormalities on the basis of lipoprotein patterns, obtained by simple, low-cost electrophoretic techniques. NHI clinical studies in progress indicate that it is more reliable and sensitive, both for diagnosis and for evaluating the effectiveness of diet and/or drug therapy, than are conventional determinations of cholesterol, triglycerides, or total blood lipids. It is being widely adopted by clinical scientists working in this field.

.continued development and refinement of a technique employing an implanted electronic carotid sinus nerve stimulator to prevent or alleviate angina pain.

.the evaluation in animals of a small, relatively atraumatic blood oxygenator that shows great promise in the treatment of infants with respiratory distress syndrome.

.the determination of the complete structure of the hormone thyrocalcitonin and clinical studies of its effectiveness in the treatment of various disorders of bone metabolism.

Of the numerous honors and awards received by NHI staff members during the year, two were of special significance:

Dr. Marshall W. Nirenberg, Chief of the Laboratory of Biochemical Genetics, became the first Federal scientist to receive the Nobel Prize. He was honored for his research on the genetic code.

Dr. Earl R. Stadtman, Chief of the Laboratory of Biochemistry, was elected to membership in the National Academy of Sciences in recognition of his distinguished research achievements in enzyme chemistry. Election to the Academy is considered one of the highest honors that can be accorded to an American scientist or engineer.

Among the important ad hoc advisory groups convened during the past year was the NHI Task Force on Cardiac Replacement. The 10-member Task Force, convened by the Director, NHI, in November of 1968, has met several times to consider medical, social, and economic problems surrounding the replacement of hopelessly diseased or damaged human hearts with heart transplants or with mechanical devices to be developed under the Artificial Heart Program. The group was charged with studying all aspects of this problem area and making recommendations to the Institute concerning foreseeable program needs in this field.

The final report has been submitted to the Institute and will be published in the near future. It covers the current medical and technical "state of the art" in heart transplantation and artificial-heart development; current costs of heart replacement procedures and present or potential sources of payment, present requirements for trained personnel and suitable facilities for the preoperative, operative, and postoperative care of candidates for heart replacement; social, ethical, and moral problems raised by the possibility of heart replacement.

The report also treats 1) projected research needs for the solution of technical problems posed by heart-transplantation and the development of clinically acceptable artificial hearts and 2) projected needs in terms of dollars, personnel, and facilities to meet foreseeable demands for heart replacement, whether through transplantation or implantation of artificial hearts, when both become established therapeutic procedures.

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July 1, 1968 to June 30, 1969
HEART INFORMATION CENTER

The Heart Information Center (HIC) seeks to assist in the attainment of NHI program 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 toward solution of 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 retrieval. This report will summarize activities in each of these areas during Fiscal Year 1969 and briefly discuss plans for the near future.

PUBLICATIONS

Because a strong publications program is perhaps the most effective means of reaching large audiences, this area continued to receive heavy emphasis during 1968-1969.

During this reporting period, HIC distributed 299,864 publications. Approximately 35,000 of these were distributed in conjunction with exhibits, the remainder through individual requests and bulk mailings. The publications unit established last year has been highly effective in publicizing new and previously existing HIC publications through press releases, radio spots and other promotional activities. An excellent example was their promotion of the new booklet "Cardiovascular Surgery," which, during the last 6 months of 1968, resulted in the distribution of nearly 50,000 of the 100,000 copies printed initially.

The unit also continues to make effective use of promotional mailings, containing sample copies of HIC publications and offering new publications as they are issued, to educational and health group associations.

The updating of existing mailing keys and the creation of new ones, such as commercial and educational radio stations, newsletters, and house organs; has provided outlets for wide distribution of HIC information materials of general interest while also enabling HIC to zero in effectively on limited, special-interest audiences. These HIC keys are also made available to any other Institute or Division of NIH that wishes to use them.

New publications issued during 1968-1969:

"Cardiovascular Surgery," a 58 page, extensively illustrated booklet covers surgical treatment of congenital heart disease, rheumatic heart disease, coronary heart disease, stroke, and renal hypertension. Also described are artificial pacemakers, heart-assist devices, and artificial hearts. The concluding section deals with facilities and services for the cardiovascular surgical patients. More than 50,000 copies of this booklet have already been distributed.

"The National Heart Institute: 1948-1968," prepared for use in conjunction with White House ceremonies commemorating NHI's twentieth birthday, is a 50 page booklet summarizing the history of NHI and describing the Institute's cardiovascular research programs.

Another publication, completed in 1968 and delivered early this year was "Hypertension," a 48 page illustrated booklet that discusses blood pressure control, hypotheses dealing with possible causes of hypertension, and current methods of treatment. Within 6 weeks of receipt of the first printing, nearly 72,000 copies had been distributed; and the continuing volume of requests indicates that this booklet may prove one of the most successful HIC has ever published. HIC has gone back to press for additional copies.

Plans for 1969 include the preparation of a series of six booklets, each dealing with a specific NHI research or training program area and, in the aggregate, providing a complete description of current NHI programs in the cardiovascular field.

PRESS AND MEDIA

A series of dramatic events and timely reporting of research and program developments led to heightened public interest in the Heart Institute during FY 1969. Triggered late in 1967 by the first technically successful human heart transplant, the entire heart field claimed the attention of the media as never before. As a result, the NHI Director as well as a number of his program chiefs were much in demand for TV, newspaper, or magazine interviews and panel appearances. Moreover, press and media inquiries rose 190 percent over the previous year, and almost any heart story with even remote clinical applications was in demand. Most of the 52 press releases issued by HIC during this period received better than adequate coverage.

The news that Dr. Marshall Nirenberg had become the first federal scientist to receive the Nobel Prize again sent press and media interest soaring. HIC was again deluged with requests for information, photos, requests for

interviews, and for almost any information that might serve as a follow-up story to this event. Virtually every media outlet world-wide carried the story and the number of media contacts during the hectic three days following the announcement is impossible to estimate. HIC recorded 237 actual media contacts for the month but many more went unrecorded. An indicator of press interest, however, may be found in the fact that HIC distributed 325 single-order photographs of Dr. Nirenberg in the one-week period immediately following the Nobel announcement.

Press interest continued high throughout the celebration of the Institute's twentieth birthday at White House ceremonies in November.

As in 1967, HIC continued where possible to key media releases to coincide with the first reporting of research findings or to ride the crest of a wave of press interest in a particular area. The intense and pervasive interest in transplantation also enabled HIC to steer the interest of inquiring reporters toward related areas, such as the Artificial Heart and Myocardial Infarction Programs. This interest also carried over into such areas as the Coronary Drug Project, the National Blood Resource Program, the Biometrics Program, and recent developments in intramural research.

As in 1967, HIC continued to use the "press package"--including releases, reports, research papers, visuals, backgrounders, or publications--as the method of choice to help fulfill its mission of identifying the National Heart Institute as the major national resource for research investigation into the causes and cures of all forms of cardiovascular disease.

INTERNAL REPORTING

During FY 1969, HIC prepared 82 reports initially intended for use within NIH, PHS, and DHEW. These ranged from routine information reports through special reports and supporting materials for use in conjunction with appropriations hearings.

There was a substantial increase in the HIC output of weekly items describing research findings of NHI scientists and grantees. Moreover, a number of these were subsequently distributed by HIC as press releases and others were picked up for distribution in "News From NIH," the "NIH Feature Service," and other information channels of the NHI Office of Information. Because research is the Institute's most important produce, this increase in research reporting coupled with wider dissemination of these reports is a trend which HIC hopes to continue.

EXHIBITS

During FY 1969, HIC displayed exhibits at 11 professional meetings, and set up a special display for the White House meeting commemorating the twentieth birthday of NHI and alumni day at Cornell Medical School.

The HIC Coronary Drug Project Exhibit continued to be shown, assisting in the recruitment of volunteers by physicians referral for an important NHI study to evaluate the effectiveness of lipid-lowering drugs in increasing longevity among men who have previously experienced heart attacks.

BLOOD PROGRAM

PROGRAMS

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ANNUAL REPORT OF EPIDEMIOLOGY AND BIOMETRY

July 1, 1968 through June 30, 1969

REPORT OF ASSOCIATE DIRECTOR FOR EPIDEMIOLOGY AND BIOMETRY

During the period July 1, 1968 through June 30, 1969, all of the major consultation, direct research and cooperative clinical trials activities reached full levels of operation requiring full commitment of professional and supporting staff. As of June 30, 1969, the total personnel of the Epidemiology and Biometry Program consisted of 33 full time professional staff, 31 full time supporting staff and 11 part time or temporary personnel. The program will begin the new fiscal year, July 1, 1969 with 11 Medical Officers or 4 less than present in the current fiscal year.

The present organizational structure no longer reflects the major added research, medical liaison and operational responsibilities in cooperative clinical trials which are being supported under the organizational name and budget of the Geographic Diseases Section. A further full time staff in the Biometrics Research Branch is occupied in the Urokinase-Pulmonary Embolism Clinical Trial so that the clinical trials activities have become a substantial on-going responsibility. While the operational responsibilities have not been impeded by the anomalous administrative labels, it is apparent that some alterations of administrative form should be made to accord better with the present functional responsibilities.

In terms of program effort directed toward specific disease areas, the proportional effort and resources of the Epidemiology and Biometry Program are allocated approximately as follows.

Disease Areas	Percent of Program Activities
Coronary Heart Disease including Angina Pectoris, Myocardial Infarction, Sudden Unexpected Death, and Pathological Studies of Atherosclerosis	60
Hypertension & Hypertensive Heart Disease	15
Cerebrovascular Disease	10
Chronic Obstructive Pulmonary Disease	10
Peripheral Vascular Disease, Diabetes, Other	5

Selected aspects of the accompanying Annual Scientific Report are summarized below:

1. The Biometrics Research Branch has maintained an active program of consultation to intramural investigators, the Office of the Director, Artificial Heart-Myocardial Infarction Program, and to a lesser degree to the Extramural Programs. Direct participation with the Blood Resources Program in a controlled clinical trial of Urokinase and Pulmonary Embolism and continued direct responsibilities in the epidemiological studies and the Coronary Drug Project have also been maintained. Four junior statisticians and a statistical assistant have joined the Branch and have been undertaking assignments of increasing responsibility under the guidance of senior Biometrics staff. The Branch is still seeking a demographer, however, the needs for general development of professional staff will require a continued internal training program.

2. The Coronary Drug Project has progressed to an enrollment of 6,672 patients by April 8, 1969. Recruitment will be continued to cut-off date of June 30, at which time an estimated 7,400 subjects are projected. This is substantially below the desired quota of 8,400 patients, however, the goals of the study should still be attainable by increasing the duration of follow-up if this turns out to be necessary.

Dr. Halperin and Mr. Cornfield have been developing new statistical methods for the analysis of the data from this large scale controlled clinical trial. A procedure has been developed which appears to cope with the problems introduced by the multiple treatments, multiple endpoints and sequential significance testing.

3. The Framingham Study has continued to delineate the epidemiology of coronary heart disease, hypertensive heart disease, congestive heart failure, cerebrovascular disease and peripheral vascular disease. The joint efforts between the Framingham staff and the Biometrics Research Branch have established a more systematic approach to the analysis of the wealth of data in the study. Mr. Tavia Gordon has produced 22 sections of a monograph providing detailed tabulations of findings encompassing the 14 year follow-up.

An important recent finding indicates that the ability to predict coronary heart disease is not diminished at the oldest age group 62-65 as formerly anticipated. The relative importance of risk factors differs at these older ages than at younger ages, but the power of prediction using seven risk factors is just as strong at age 62-65 as at age 42-45.

The Framingham Study continues to be a central resource for the Epidemiology and Biometry Program and for numerous outside investigators.

4. The Field Epidemiology Research Section under Dr. Manning Feinleib has moved actively into genetic studies taking advantage of two twin rosters and also making use of the spouse and parent-offspring data at Framingham. These studies are in cooperation with the National Academy of Sciences Follow-up Agency, the Laboratory of Molecular Diseases, NHI and the Framingham Study.

5. The Epidemiological Study of Coronary Atherosclerosis in Puerto Rico has completed its first phase of examinations in December 1968 achieving an 80.5% examination response rate from the defined general populations in the urban and rural municipios under study. A total of 9,802 men aged 45-64 have been given comprehensive examination and measurements for correlation with prevalence of coronary heart disease and as a baseline for incidence measurements.

The wide range of variables makesthe population of particular interest and the further confirmation of low prevalence of myocardial infarction provides an unusual opportunity for further delineation of natural biological factors which result in low rates of coronary heart disease.

6. The P.L. 480 Cooperative Ischemic Heart Disease Study in Israel completed its final follow-up cycle of examinations with an achievement of re-examination measurements on 97 per cent of the living subjects from the original cohort of 10,232 government and municipal employees aged 40 and over.

Mr. Harold Kahn, who has been on assignment to supervise the statistical operations will be returning to Bethesda and hopefully can continue the final tasks to obtain analysis of the results of the past 7 years of work to accomplish this project.

7. The Honolulu Epidemiological Study of coronary heart disease and cerebrovascular disease among Japanese Americans has also successfully completed its first phase of baseline examinations on 8,000 men aged 45-69 achieving an 82 per cent response rate in this general population.

Marked differences in the mean value of nutrient intake are being found between the Honolulu subjects of Japanese descent and the Japanese subjects under study in Hiroshima. Systematic comparative tabulations of baseline characteristics will now be possible and also provide the basis for the incidence measurements being obtained in both populations.

Approximately 4,000 subjects have received the second cycle examination planned for establishment of accurate incidence measurements.

8. The P.L. 480 Epidemiological Study of Ischemic Heart Disease and Hypertension in Yugoslavia has maintained a morbidity and mortality surveillance on the two study populations of men aged 35-64 in Remetinec and Tuzla since completion of the second examination cycle on the approximately 11,000 participants in the defined cohorts.

The data are being prepared for analysis and of particular interest is the extremely low incidence of myocardial infarction of approximately 1 per 1000 per year. Also of interest is the high prevalence of impaired pulmonary function indicative of obstructive pulmonary disease. The overall prevalence of 22 per cent contrasts to the finding of 10 per cent in the Framingham population. Further comparative data on incidence will be possible from the coordinated collection of such data in the Framingham and two Yugoslavian communes.

The Epidemiology and Biometry Program has attempted to maintain an overview of research in epidemiology being conducted by outside investigators as well as the direct research projects conducted in the program. It participates in the Pooling Project with 5 outside studies in an attempt to overcome the limitation of numbers of cases available for analysis.

The differences in study procedures and criteria make such external pooling difficult and of limited potential. Better prospects are seen in achieving future pooling of data between the Puerto Rico-Honolulu and Framingham Studies using Framingham as the reference population.

General interest in manipulative studies to alter risk factors by artificial or natural measures is gaining momentum. The formidable nature of such controlled trials and the substantial costs require close estimates of sample sizes and proper selection of age groups for maximum probability of discriminating a therapeutic effect in the treated versus the control group. The epidemiological findings of risk factor influences at specific age groups will be increasingly needed to guide these future program decisions.

The combined biometrics, medical and epidemiological resources of the Epidemiology and Biometry Program are gaining increasing expertise in the complexities of such large scale controlled trials. This nucleus of experienced staff needs to be maintained and strengthened to assure the effective accomplishment of the direct research programs and also to provide consultation to outside investigators undertaking projects of this nature.

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

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Medical Liaison with the Coronary Drug Project

Previous Serial Number: SAME

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 53 participating grantee institutions.

Other Investigators: Dr. Richard J. Havlik, Epidemiology and Biometry, NHI, served as Assistant Medical Liaison Officer for the Coronary Drug Project.

Cooperating Units: 1) Laboratory of Molecular Diseases, NHI, (Dr. Robert I. Levy) for pharmacological consultation;
2) Laboratory of Chemical Pharmacology, NHI, (Dr. James R. Gillette) for pharmacological consultation;
3) Biometrics Research Branch, NHI, (Dr. Max Halperin and Mr. Fred Ederer) for statistical liaison;
4) Extramural Programs, Special Research Projects Branch, NHI, (Dr. William H. Goldwater and Dr. Edward D. Carey) for grants management aspects;
5) Central Laboratory, National Communicable Disease Center, U. S. Public Health Service, (Dr. Gerald Cooper, Dr. Alan Mather, and Dr. Adrian Hainline) for performance of biochemical

blood and urine studies of study patients;
6) Drug Distribution Center, USPHS Supply Service Center, (Mr. Salvatore Gasdia) for the procurement and distribution of study drugs;
7) 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:	2.0
Professional:	1.5
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-support 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: Two participating clinics have withdrawn from the Coronary Drug Project because of an inability to recruit the required minimum of 100 patients. A total of 53 clinics remain operational and are actively recruiting patients.

As of April 8, 1969, a total of 6,672 patients have been enrolled in the Coronary Drug Project. This represents 79 percent of the original goal of 8,400 patients. Fifteen clinics have exceeded their original commitment, but thirteen clinics are still fifty or more patients short of their original goal.

As of April 1, 1969, the Central Laboratory has processed specimens for 8,047 baseline patients.

The patient recruitment goal of this study remains to enroll 8,400 patients by June 30, 1969. The Medical Liaison Officer and the Heart Information Center continue to provide all clinics with assistance in local and regional publicity efforts.

The observed dropout rate continues to be less than the expected six percent per year. As of March 7, 1969, only 126 patients have been reported as study dropouts.

Patient adherence to their prescribed medical regimen varies with the assigned treatment. The mean percent adherence to maximum prescription by treatment group was as follows: placebo - 82.0%, clofibrate - 81.5%, dextrothyroxine - 78.4%, nicotinic acid - 73.2%, low estrogen - 71.8%, and high estrogen - 71.8%. These figures are essentially unchanged from last year.

All critical endpoint data are being reviewed biannually by the Safety Monitoring Committee and the Policy Board. In addition, monitoring reports are provided to all Safety Monitoring Committee and Policy Board members on a monthly basis.

The primary endpoint is mortality. To date, there has been no statistically significant differences between the five treatment groups and placebo, with respect to the primary endpoint. The observed mortality rate among placebo-treated patients was 4.8%; somewhat less than the expected rate of six percent per year. This expectation was based on the reported follow-up of patients with a presumably similar diagnosis and prognosis.

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 recruitment by June 30, 1969. Following enrollment into the study, each patient will be followed for a period of five years. At present, the study is on schedule.

A number of personnel actions during the year should be noted. Dr. Max Halperin's position was changed from Acting Branch Chief to Branch Chief. Mrs. Jeanne Truett resigned near the beginning of the fiscal year. Her role with the Puerto Rico study has been assumed by Mrs. Christine Cole who, however, continues to play a prominent part in operations of the coordinating center for the Urokinase Pulmonary Embolism trial. Dr. John Mullooly resigned shortly after the beginning of the fiscal year to accept an academic post. Dr. Manning Feinleib left the branch upon termination of his tour of duty as a commissioned officer but remained with Epidemiology and Biometry as head of the Field Epidemiology Research Section. Mrs. Esther Allen, a statistical assistant, was struck by a disabling illness and is going on medical disability retirement. New personnel coming into the branch during the year include, Mrs. Joyce Schiffman, Mr. William Fairweather, Mr. Paul Woosley, Mr. Paul Sorlie, Mrs. Ethel Black. Mrs. Schiffman, a mathematical statistician, is largely involved with quality control of comparable data from Framingham and allied studies. Mr. Fairweather, also a mathematical statistician, is working in the intra-mural consultation group. Mr. Woosley, a biostatistician, is involved with the coordinating center for the Urokinase Study. Mr. Sorlie, a biostatistician, is working on the Framingham Study and is considered a replacement for Mr. Joel Verter whose appointment as an HSO terminates at the end of this fiscal year. Mrs. Black, a statistical assistant, replaces Mrs. Allen in her work on quality control of Framingham data as well as performing other duties.

Work on the Migrant Study continues and two papers on mortality findings were presented by Dean Krueger (formerly of the NHI) and Eugene Rogot of BRB to a symposium on Migrant Populations in Hawaii. The papers have been submitted for publication to the Journal of Chronic Diseases. An unexpected finding was that chronic non-specific lung disease (CNSLD) rates for British migrants was about the same as that of U.S. native born. In addition an expected decreasing gradient for CHD mortality with increasing age at migration did not materialize except for female British migrants.

Mr. Rogot has continued his work (with the assistance of Mr. William Blackwelder) on the study of seasonal patterns of mortality in Memphis, Tennessee. The statistical analysis is virtually complete and a paper is being prepared for publication. Among the findings are an inverse relationship of number of CHD deaths to average temperature and a similar relationship for stroke, both independent of respiratory diseases. There also appears to be a direct association between wind speed and CHD mortality. Work has begun on a similar study on data from Chicago for 1967. This will allow study of the association between CHD mortality and snowfall which was not possible in the Memphis study.

Mr. Verter is in the preliminary stages of a methodological investigation comparing least squares and discriminant function estimation of non-linear

regression functions, such as the multiple logistic "risk function" being used on the Framingham data. The discriminant function approach is easier but the least squares approach is more generally valid; in view of the increasingly widespread use of the former method it is important to have some basis for assessing its appropriateness.

Tavia Gordon, in collaboration with Dr. William Kannel, has produced 22 sections of a monograph on the Framingham Study with many more to come. This work, when completed, will constitute an invaluable resource for use of the wealth of Framingham data. Mr. Gordon, along with Mrs. Schiffman and Dewey Shurtleff, continues to provide consultative services and statistical coordination and control to Framingham and allied studies.

Mrs. Cole and Mr. Tavia Gordon continue to work closely with the Puerto Rico Study providing consultation on examination content, data analysis and data processing. The first round of examinations was completed in December with a grand total of 9802 subjects, about 80.5% of these invited to participate. Data from these subjects have been edited and tabulation of basic distributions and frequency arrays of numerous variates by age and rural-urban group are currently in production. Follow-up examinations are well under way with over 2200 subjects having received a second examination.

The Urokinase Study got under way during this fiscal year and the initial group of five participating institutions has grown to eighteen institutions at the present time. The coordinating center for the study, under the direction of Fred Ederer, has participated in a number of pilot studies to develop methods for the analysis of angiographic, pulmonary photoscan and hemodynamic data. The center has also been developing a system for automatic data processing and preparing progress reports giving data on patient screening and accession, progress on pilot studies, etc; these reports are distributed to all participants. Periodic confidential analyses on treatment complications, morbidity and mortality, etc., have also been reported.

Fred Ederer has been engaged in some further analyses of the National Diet-Heart Study data with the purpose of disentangling possible statistical artifacts (regression to the mean) from the observed fact that individuals with initially high serum cholesterols have greater decreases after changing to a hypocholesterolemic diet than men with initially low values. It was found that more than fifty percent of the change was artifactual. The work is being written up for possible publication. Mr. Ederer and Mr. Woosley are also doing a small Monte Carlo study to assess the benefit, if any, of prestratification in clinical trials. This work will be completed by the end of this fiscal year and results will be presented at a statistical meeting in August 1969.

Max Halperin is continuing some research effort in collaboration with Jerome Cornfield attempting to develop new statistical methods for analysis of clinical trials like the CDP with its attendant statistical problems caused by the multiplicity of treatments, multiplicity of end-points and frequent sequential significance testing. A procedure has been developed and applied which appears to be useful in coping with the difficulties caused by multiplicity of treatments and the sequential significance testing.

Jacob Lieberman has continued working with Dr. Al Roberts on studies of obstructive pulmonary disease. Using the data of the first examination on a sample of one thousand participants of the Honolulu Heart Program, extensive tabulations have been done on the Hybrid computers. Tables are being drawn up which should shed light on: (a) which of the three measurements of air flow, (1) Total vital capacity, (2) First second vital capacity, or (3) the ratio, in percent, of these two measurements give most consistent and reproducible results; (b) which demographic, environmental and physiological variables are associated with obstructive pulmonary disease.

Lieberman has also been especially active as a reviewer of papers proposed for external publication.

Joan Gurian has continued to work with NHI-LMP personnel on the conversion of records of the study on familiilial Hyperlipoprotenemia to EDP equipment. The code sheets for recording the data have been re-designed in light of the experience gained from the originally designed code-sheets. Programming effort to create a data-file and to retrieve the information stored therein has continued. In addition, several types of reports from these data have been made. The study continues to add more individuals and data both which are being edited and added to that already on tape. Analyses of the data from the controls and from members of the kindred with propositi suffering from Type II and Type III hyperlipoproteinemia have been begun. Tabulations illustrating in a simple way the relationship between several of the variables of interest have been produced. Comparison of the cholesterol and lipid-values for the controls, the patients and their relatives have been made, taking into account the effect of age and sex on these variables. The relationship between values of the total cholesterol and its components is now being investigated.

Shortly after the departure of Dr. Mullooly, Mort Raff's duties were changed from that of full-time consultant to the Myocardial Infarction Branch to full-time intra-mural consultant and he has become very active in that area.

Along the lines of on-the-job training, an effort has been made to insure that the qualified and interested junior statisticians are given experience in statistical consultation with appropriate guidance from senior statisticians such as Mr. Raff or Mr. Lieberman. In addition, a book seminar was conducted for about six months on stochastic processes and another such seminar is under way in applied multivariate analysis.

As evidenced by some of the project reports and list of publications, some of the branch's efforts are directed toward research on statistical methodology, some of it related to questions raised in the course of our consultative work, some simply related to issues of general statistical interest. Publications listed are only those not listed in year end reports of other NIH components by the senior author.

Consultation

Mr. Blackwelder and Mr. Raff consulted with:

- Dr. Earl Stadtman, NHI-LB, on a combinatorial problem involving the number of different ways certain chemical attachments can be placed on a double hexagonal ring.

- Dr. Harriet Maling, NHI-LCP, on the inhibiting effect of ST-155 on imidazolines which stimulate the confinement motor activity of the rat.

Mr. Blackwelder consulted with:

- Dr. Jack Folk, D-LB, on studies of the kinetics of activation of transglutaminase by metal ions.

- Dr. John Baxter, A-LMB, on analysis of data measuring the extent of binding of a steroid to two strains of lymphoma cells.

Mr. Fred Ederer and Dr. Max Halperin consulted with:

- NHI extramural program staff and applicants for research grants on study design in primary and secondary prevention of coronary heart disease.

Mr. Ederer consulted with:

- Dr. Leroy Langley, NHI, on a follow-up study of recipients of NIH training grants.

Mr. William Fairweather and Mr. Morton Raff consulted with:

- Dr. Claude V. Perrier, NIAMD-MD, on the effect of certain drugs on the enzyme producing activity of different kinds of stomach tissue in the guinea pig.

Mr. Fairweather consulted with:

- Dr. Blair Bowers, NHI-LB, on analysis of volume fractions of cell bodies in the amoeba.

- Dr. Robert I. Keimowitz, NHI-LKEM, on the effects of saline on diffusion in rat kidney tubules.

- Dr. John R. Gill, Jr., NHI-CE, on albumin metabolism in patients with idiopathic edema.

Consultation

- Drs. Allen W. Cheever and Harry G. Lee, NIAID-LPD, on the susceptibility of selected schistosome worm strains to the chemotherapeutic agents niridazole, fuadin and lucanthone.

- Dr. David T. Kelly, NHI-C, on the effect of induced heart failure in dogs on measurements of left ventricular pressure and its derivative over time as a function of end diastolic pressure.

Miss Joan Gurian consulted with:

- Dr. William G. Banfield, NCI-LP, on analysis of data describing the growth pattern of the hamster, as a function of age and season.

- 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.

- Drs. Frederick H. Leitz and Francisco J. E. Stefano, NHI-LCP, comparisons of in vitro sodium and potassium concentration in the hearts from untreated animals and animals injected with oubain.

Mr. Jack Lieberman consulted with:

- Dr. David M. Fried, chief of the Rehabilitation Department of the Clinical Center, on validating the measurements of muscular force on a new apparatus designed by Dr. Fried and colleagues.

- Dr. Nicholas C. Leone, Medical Officer in Charge, Galveston PHS Hospital, on preliminary planning of a study on alcoholics.

Mr. Morton Raff consulted with:

- Dr. John G. Page, NHI-LCP, on strain and sex differences in the induction of certain enzymes in rats' livers.

- Dr. D. Luke Glancy, NHI-C, on the significance of calcium in the aortic valve in human patients.

- Dr. Bruce R. Ditzion, NHI-LCP, on the effect of various drugs on the level of cyclic AMP in the brain of the mouse.

- Dr. Joseph S. Handler, NHI-LKEM, on the effects of hormones and inhibitors on permeability and transport properties of the toad's urinary bladder.

- Drs. Frederick H. Leitz and Francisco J. E. Stefano, NHI-LCP, on the mechanism by which various drugs release norepinephrine from the adrenergic neuron in the rat heart.

- Dr. Peter L. Frommer, NHI-AHMI, and his associates on a variety of problems including an estimate of the percentage of people now alive who can expect to die of coronary heart disease before reaching age 65. A parallel estimate was made of the percentage of people now alive who can expect their cause of death, at whatever age, to be coronary heart disease.

- Mr. Peyton Stapp, DRG-SA, on the design of a sample of research grants in order to obtain information about the number and characteristics of students working on grant projects.

Publications

Gordon, T., and Kannel, W. B. (Editors): The Framingham Study. An Epidemiological Investigation of Cardiovascular Disease. Monograph, Sections 1-8, June 1968. Sections 9-22, Sept. 1968. National Heart Institute.

Cornfield, J., Halperin, M., and Greenhouse, S. W.: An Adaptive Procedure for Sequential Clinical Trials. Accepted for publication, Journal of the American Statistical Association.

Halperin, M., and Gurian, J.: Confidence Bands in Linear Regression with Constraints on the Independent Variables, Journal of the American Statistical Association, 63: 1020-27, Sept. 1968.

Unpublished Papers and Talks

Ederer, Fred: Serum Cholesterol Changes: effects of diet and regression toward the mean. A talk at the Ninth Annual Conference on Cardiovascular Disease Epidemiology, March 4, 1969.

Gordon, T.: Research for Longitudinal Studies of Chronic Disease. A talk to the American Statistical Association.

Halperin, M., and Gurian, J.: On the Expected Value of the Classical Estimate of Slope in Straight Line Regression when Both Variables are Subject to Error. Submitted for publication, Journal of the American Statistical Association, and for presentation at the annual meeting of the International Statistical Institute 1969.

Halperin, M.: Inverse Estimation in Linear Regression. Submitted for publication in Technometrics.

Krueger, D. E., Rogot, E., and Blackwelder, W. C.: Cardiorespiratory Disease Mortality among British and Norwegian Migrants to the United States. Submitted to Journal of Chronic Diseases.

Kruger, D. E., and Rogot, E.: Identification of Cardiorespiratory Disease by Morbidity Questionnaire, Death Certificate, and Questionnaire to Medical Certifier of Causes of Death. Submitted to Journal of Chronic Diseases.

Participation in outside committees and organizations

Christine Cole:

served as a member of the Urokinase Pulmonary Embolism Trial (UPET) Advisory Committee for Statistical Analysis.

Fred Ederer:

served as a member of several UPET committees. These included Steering committee, committee for Standardization of Methodology and Analysis of Data, Sub-committee for Standardization and Analyses of Pulmonary Angiograms and Hemodynamic Data, Advisory Committee for Statistical Analysis.

served as a member of the Coronary Drug Project (CDP) committees on Data Analysis, Safety Monitoring and preparation of a baseline monograph.

served as a member of the NIH Equal Employment Opportunity Program Planning council and was chairman of its committee on Data Analysis.

served on the program committee for the 1969 APHA annual meeting.

Tavia Gordon:

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

served as a member of the NHI Task Force on Cardiac Replacement.

Joan Gurian:

served as a referee for Biometrics.

Max Halperin:

served as a referee for Biometrics, Technometrics, Journal of the American Statistical Association, Annals of Mathematical Statistics.

served on the Biostatistic Fellowship Panel of DRG.

served on the CDP Steering committee, Data Analysis committee, and Safety Monitoring committee.

served on the UPET committee for standardization and analyses of pulmonary photoscans and on the Advisory Committee for Statistical Analysis.

Jack Lieberman:

served as a referee for Science.

Morton Raff:

served as a referee for the American Statistician.

taught probability at the Department of Agriculture Graduate School.

was a discussant at a Washington Statistical Society seminar on Survey Design.

served as a judge of papers by young statisticians in a competition sponsored by the Washington Statistical Society.

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2. Epidemiology and Biometry, NHI
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Statistical Problems Related to the Cooperative Study of Drugs and Coronary Heart Disease

Previous Serial Number: NHI-BRB-2

Principal Investigators: Jerome Cornfield and Max Halperin (Note: The investigators for the study itself, functioning under a grant from the National Heart Institute, include 54 clinics. Grants are also held by R. W. Wilkins, chairman of the Policy Board and C. R. Klimt, director of the Coordinating Center.)

Cooperating Units: Dr. Howard Marsh, Epidemiology and Biometry, NHI, Medical Liaison Officer for the study; Department of Biostatistics, University of Pittsburgh, CDP Coordinating Center

Man Years:

Total:	- .10
Professional:	- .08
Other:	- .02

Project Description:

Objectives: To provide statistical methods needed for the appropriate analysis of a long-term study conducted under conditions of double-blind experimental design.

Methods Employed: Long-term clinical trials with a multiplicity of endpoints and treatments as well as repetitive statistical significance testing pose fundamental problems concerning the appropriate mode of statistical inference. Investigation is being carried on in cooperation with Professor Cornfield with the goal of devising schemes for data analyses taking the above problems into account. Efforts so far have been toward the development of Bayesian methods of analysis using known mathematical and statistical ideas and methods in novel ways.

Major Findings: A method has been developed for evaluation of results on a single endpoint which attempts to take into account the multiplicity of drugs being tested as well as the repetitive testing feature mentioned above. Application of the method to some CDP data suggests the new method may be a

more useful guide to appropriate inference than methods heretofore available.

Proposed Course: Further effort is planned to extend the methods mentioned above in various ways; e.g. to analyses with sub-classifications as well as to joint evaluation of multiple endpoints.

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Individual Project Report
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Project Title: Least Squares Estimation in Straight Line Regression

Previous Serial Number: NHI-BRB-4

Principal Investigator: Max Halperin

Other Investigators: Joan Gurian

Man Years:

Total	- .06
Professional:	- .05
Other:	- .01

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: It was finally feasible, during the current fiscal year, to do the necessary numerical investigation required for this project. Investigation was focused on quantification of the percentage bias in estimation of slope (average % deviation from true slope) as a function of sample size, spread of values of the independent variable and error variance of the independent variable. A most interesting finding was that, other things being equal, bias increased as sample size increased; in particular, for sample of size three, bias was trivial for cases of practical interest. The implication of this latter fact is that by grouping data into sets of three, getting slope estimates from each set and averaging, one will get an estimate of slope which is essentially unbiased.

Significance to Bio-medical Research and Program of the Institute: Experiments in which one is concerned with linear regression and both variables are subject to error do occasionally come to our attention. In many such cases the experimental design will not allow valid estimation of slope and intercept by statistical methods available up to now.

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The results described above essentially resolve this difficulty.

Proposed Course: A manuscript deriving and discussing the results cited above has been prepared and will be presented at the 1969 meetings of the International Statistical Institute in London. The paper has also been submitted for publication to the Journal of the American Statistical Association. Further work on this problem is unlikely in the near future.

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2. Epidemiology and Biometry, NHI
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

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

Previous Serial Number: NHI-BRB-8

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

Other Investigators: Eugene Rogot, NHI, William C. Blackwelder, NHI; Dean Krueger, National Center for Health Statistics; 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 Center for Health Statistics; 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:	6.5
Professional:	2.0
Other:	4.5

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

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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 has been secured and questionnaires have been sent to a subsample of medical certifiers.

Since much of the information collected in the mortality phase is similar to that obtained in the morbidity phase, death rates are being analyzed with respect to a number of factors. In this way, deaths in the entire migrant population rather than only those of persons included in the morbidity sample are being 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 at least a 6-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 prevalence 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.

Two papers on mortality findings were presented by Dean Krueger, formerly with the NHI, to the symposium on Migrant Populations, UICC, Honolulu, Hawaii. These papers have been submitted for publication to the Journal of Chronic Diseases.

Findings of one paper were summarized as follows. Two-year mortality rates for coronary heart disease (CHD), chronic non-specific lung disease (CNSLD) and lung cancer for ages 45-74 were studied for British and Norwegian migrants to the U.S. and for a sample of U.S. native-born. The observed order for CHD and lung cancer were as anticipated, with native-born experiencing the highest CHD rate, British migrants the highest lung cancer rate and in each instance Norwegian migrants experiencing the lowest rates. For CNSLD, contrary to national comparisons, the British migrant's rates were about equal to the U.S. native-born although Norwegian migrant rates were lowest as expected. Migrants who were younger than 15 at migration experienced the highest CHD death rates but a decreasing gradient in mortality rates with increasing age at migration did not materialize except for a moderate gradient for female British migrants. CNSLD showed the same age-at-migration mortality pattern as CHD, which was unexpected. For lung cancer no clear cut age-at-migration mortality pattern emerged. Data on cigarette smoking status indicated substantial excess mortality for cigarette smokers compared to non-smokers and occasional smokers for all groups studied.

Findings of the other paper related to the success of the morbidity questionnaire as an instrument in predicting death from cardiorespiratory disease. Also findings on the usefulness of the medical certifier's information were reported.

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. Differences in cardiovascular mortality between U.S.-born and migrant groups will be studied. The 6-year cohort study should permit a wide variety of mortality analyses of British and Norwegian migrants. Prospective studies relating cardiorespiratory symptoms, smoking, occupation, income,

age-at-migration, and many other factors to cause of death are planned.

Proposed Course: In the United States the morbidity survey has been completed and preliminary findings have been published. Further analyses may be undertaken. The major emphasis however will be in completing the mortality phase of the study. Additional analyses planned for 2-year mortality rates will focus upon such factors as age-at-migration, relative weight and occupation.

Coding of medical certifier data remains to be completed for 1963 and 1964 deaths.

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 are now being scanned to identify British and Norwegian migrants, and it is expected that 1968 death records will also be secured to enable us to accumulate 6 years (1963-68) of migrant cohort deaths. The course of the study thereafter may depend upon results of earlier analyses.

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.

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PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

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

Previous Serial Number: NHI-BRB-9

Principal Investigator: Paul Sorlie

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 successive 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.

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Proposed Course: Preparation of a manuscript for publication in an epidemiologic journal and application of the method to analyze other variables measured at Framingham. This project was delayed by resignation of the original investigator but it is proposed to resume and complete it.

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2. Epidemiology and Biometry, NHI
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

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-10

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

Man Years:

Total:	.40
Professional:	.40
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. mainland population. 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 for a sample of 10,000 split 1:2 rural-urban. All males born in the years 1900 through 1919 and residing in the defined mountain areas or in specified municipios in the San Juan metropolitian area were enumerated in a 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. Home examination of a sample of non-respondents is planned. A follow-up to obtain supplementary data on mortality, and autopsy material for dissection of the coronary arteries has been initiated; and follow-up of hospitalizations is also under way.

Data processing procedures and programming for dietary computations, quality control on examiners and interviewers, and quality control on the automated methods for recording collected data have been worked out with the Medical Center Information Processing Division in San Juan. Periodically data from the project has been converted to tape compatible with the NIH computer system to allow for exploratory tabulations here.

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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. However, let us say here that the first round of examinations was completed in December, 1968 with a grand total of 9,802 subjects for an overall response rate of 80.5% of those invited to participate in the study. Data from these subjects have been subjected to comprehensive computer edit procedures, and tabulation of basic distributions and frequency arrays of numerous variates by age and rural-urban group are currently in production. Follow-up examinations, roughly two years after initial examination, were started in July, 1968; and in the first nine months more than 2,200 subjects returned for a second examination.

Proposed Course of Study: The second round of examination will continue for all remaining subjects who were examined in the first round. Efforts will also be made to characterize the non-respondents by home examination of a sample. We provide consultation on the content of these examinations, analysis of collected data, and data processing. Assistance is also provided on methodological issues relating to data collection.

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

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

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

Previous Serial Number: NHI-BRB-13

Principal Investigator: Eugene Rogot

Other Investigator: William C. Blackwelder

Man Years

Total:	.4
Professional:	.3
Other:	.1

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.

The basic statistical index employed was the average daily number of

deaths over the 3-year period.

Major Findings: Preliminary findings follow:

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 somewhat L-shaped 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 with the exception of an increase in mortality from the "70-79° days" to the "80-89° days".

7. For daily precipitation, percent of possible sunshine and barometric pressure no substantial variation in mortality could be detected for any of the disease categories studied other than what appeared to be random fluctuation resulting in generally flat or irregular patterns.

8. For wind speed there appeared to be a direct association with CHD mortality and with respiratory disease mortality.

9. For relative humidity there was a suggestion of an inverse relationship with CHD mortality but findings here were not clear-cut.

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

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

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 have 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.

Proposed Course: The statistical analysis is virtually complete and a paper is now being prepared for publication. Findings to date indicate the need for a similar study in a large northern city. Chicago has been chosen and work has begun on the new study.

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

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

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

Previous Serial Number: NHI-BRB-22

Principal Investigator: Fred Ederer

Other Investigators: Christine Cole, Peter Walsh, Paul Woosley

Cooperating Units: NHI Program Office and Medical Liaison: Blood Resources Program, NHI; New York University Medical Center: Central Laboratory, 18 clinician-investigators

Man Years:

Total:	- 4.15
Professional:	- 2.65
Other:	- 1.50

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.

4. Planning and developing systems for automatic data processing, including:

a. manual edit procedures

b. punch card layouts for data and summary cards
c. coding procedures
d. computer edit procedures
e. tabulation plans
f. writing and de-bugging computer programs for tabulations and computations

5. Data processing:

a. manual edit
b. coding punching, and verifying data
c. computer edit of data
d. data tabulation and computation

6. Preparation of periodic (monthly) progress reports containing data on patient screening and accession, information on problems encountered in implementing the protocol and how to deal with them, progress on pilot studies, schedules of meetings, etc. These reports are distributed to all participants.

7. Preparation of periodic confidential reports containing data and analyses of results on complications of treatment, morbidity, mortality, and results of radiographic and hemodynamic studies. These reports are distributed to the Policy Board and the Advisory Committee for Data Analysis.

Major Findings: None

Course of Project: Planning for the study started in September 1967. An organizational structure was drawn up: Chairman, Policy Board, Steering 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 Angiogram, Pulmonary Photoscans and Hemodynamic Data, and Biochemical Data, and on the Hemodynamic Data Analysis Panel. Major meetings were held in September 1967, March 1968, September 1968, and May 1969, 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.

In addition to the five institutions which participated in the planning in 1967-68, eight institutions joined the study in the fall of 1968, of which three later withdrew, and eight more in the spring of 1969, so that a total of 18 institutions are currently participating.

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

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

During the year ending June 30, 1969, pilot studies were started to develop methods for the analysis of angiographic, pulmonary photoscan and hemodynamic data. The first of these was satisfactorily completed, and the latter two are nearly completed.

The shakedown phase of the study began in the summer of 1968, and the official phase in the fall. Fourteen official study patients were treated in the last three months of 1968 and 46 more during the first four months of 1969. Preliminary estimates indicate that a total of 200-400 patients will be needed to complete the study.

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

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: A study of seasonal mortality in 1967 for Chicago, Illinois

Previous Serial Number: None

Principal Investigator: Eugene Rogot

Other Investigator: William C. Blackwelder

Man Years

Total:	.35
Professional:	.10
Other:	.25

Project Description:

Objectives: The objectives of this study are essentially the same as for the seasonal study of deaths in Memphis, Tennessee. We plan to study the relation of a number of climatological factors to mortality from cardiovascular disease, respiratory disease, and other diseases; multiple cause of death data will be utilized. In particular, we plan to examine the association between coronary deaths and snowfall, which we were unable to do in the Memphis study. Also, data on sudden deaths from coronary heart disease will be studied in order to evaluate seasonal patterns for these deaths.

Methods Employed: Reels of microfilm of death certificates for 1967 in Illinois have already been made available for use in the British-Norwegian migrant study. Multiple cause of death data are being coded from these microfilm reels for deaths occurring in Chicago, which total about 39,000. One advantage to using Chicago deaths is that multiple cause data are entered on these certificates routinely.

Information coded for each death includes residence (Chicago or other), age at death, race, sex, date of death, I.S.C. 4-digit code for each cause of death up through six causes, and interval between onset and death for the immediate cause. In addition, daily climatological data for Chicago have been obtained for 1967 for maximum, minimum, and average temperature; total precipitation; snowfall and sleet; average and fastest wind speed; high, low, and average relative humidity; and other variables.

Tabulations will be prepared to show variation of mortality from various causes with pertinent climatological variables, with deaths categorized by

age, sex, and race. An attempt will be made to study the interrelations of variables by means of multivariate regression techniques possibly of a non-linear nature.

Major Findings: None.

The project is in the initial phase of data processing. Mortality data for 1959-61 from Memphis, Tennessee, indicate an inverse relationship between average daily temperature and average daily number of deaths, especially for cardiovascular and respiratory deaths. These findings were based on a small number of days with low temperature. The study of mortality in Chicago should indicate whether the relationships in colder climates are the same as those found in Memphis.

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

A study of seasonal mortality patterns in a large northern city should be valuable in determining the generality of the relationships found in Memphis. It is believed that the use of multiple cause of death data from a large city to study seasonal patterns in mortality, including studies of sudden coronary deaths and of the possible association between coronary deaths and snowfall, is new.

Proposed Course: It is anticipated that the data processing and statistical analysis will be completed within the 1969-70 fiscal year and that the results will then be prepared for publication.

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

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Comparison of least squares and discriminant function approach to non-linear regression.

Previous Serial Number: None

Principal Investigator: Joel Verter

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	0.1
Professional:	0.1
Other:	0.0

Project Description:

Objectives: In analysis of Framingham data it is useful to fit incidence data by a multiple logistic function depending on several risk factors. This fitting can be accomplished by application of either discriminant function theory or non-linear regression theory. It is of interest to determine to what extent the two methods of fitting agree. Under certain assumptions both methods are valid and the discriminant function approach is computationally simpler. However, the least squares approach remains valid without some of the assumptions required for validity of the discriminant function approach and allows for generalization to more complex models.

Methods and Findings: Approach is primarily heuristic, undertaking parallel analyses by both methods and comparing the results. Early explorations indicate little difference between the two methods on these grounds but additional explorations are called for.

Significance to Bio-Medical Research and the Program of the Institute: There is a need in the analysis of epidemiological data for efficient and valid multivariate methods. This methodological inquiry is part of our search for optimum methods.

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

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Proposed Course: Due to a lack of time before I leave, it appears doubtful that I will be able to complete this project. However, it seems important enough to warrant continued study.

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

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Relationship of the Use of Tobacco to Health

Previous Serial Number: NHI-BRB-5

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:

Objectives: To evaluate the relation of tobacco usage to subsequent mortality.

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 will be maintained on a routine basis. Card to tape conversion completed. Matching against VA active file under way.

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

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

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-11

Principal Investigators: Dewey Shurtleff, Joel Verter, Tavia Gordon and Paul Sorlie. (see above)

Other Investigators: (See above)

Cooperating Units: None

Man Years

Total:	6.5
Professional:	3.5
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 disease.
(4) Distribution of 22 variables.
(5) Relation of 13 disease outcomes to these characteristics.

Exam 11 forms were prepared. New follow-up procedures have been initiated. These involve close check on the non-examined cohort and special medical examinations for study persons who have moved from Framingham. Consultation has been given to Framingham on a continuing basis with respect to operation, analysis of data for talks and papers, and specific projects undertaken by outside collaborators.

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

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

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

Proposed Course: See Epidemiology Section.

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

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Collaborative Studies (This refers only to statistical services provided by the Biometrics Research Branch. See general description in the Epidemiology Section.)

Previous Serial Number: None

Principal Investigators: Joyce Schiffman, Tavia Gordon, Dewey Shurtleff

Cooperating Units: Collaborative studies

Man Years:

Total:	1.5
Professional:	1.3
Other:	0.2

Project Description:

Objectives: To provide consultative services and statistical coordination and control to the collaborative studies which include the Framingham Study and the studies in Honolulu, Puerto Rico, Israel and Yugoslavia.

Methods: While each of the field epidemiological studies has its own objectives there is a need to compare results from the various studies. This requires work which is directed toward obtaining comparable data separate from that obtained as part of the individual studies. We have introduced inter-laboratory quality controls between Framingham, Hawaii and Puerto Rico and are coordinating ECG readings to be done at the University of Minnesota. Routine surveillance of response rates and follow-up is undertaken. In addition we supply consultative and backup statistical services.

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

Major Findings: See the Epidemiology Section.

Proposed Course: See the Epidemiology Section.

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

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Prestratification in clinical trials

Previous Serial Number: None

Principal Investigator: Fred Ederer

Other Investigator: Paul C. Woosley

Cooperating Unit: Division of Computer Research and Technology
IBM/360 computer

Man Years:

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

Project Description:

Objectives: To assess the benefit of prestratification in multiclinic trials.

Methods Employed: Assumptions were made regarding total sample size, patient accession, and the influence of the stratification variables. Two randomization schemes were developed, one using prestratification and the other not. Computer simulations of a large number of trials are being performed and the effects of prestratification measured.

Significance to Bio-medical Research and the Program of the Institute: Although widely used in clinical trials, prestratification is held to be of little benefit by some statisticians. Two possible benefits are being explored: 1) reduction of artifactual differences between treatments in unadjusted mean response; 2) improvement of balance between treatment groups within the strata.

Proposed Course: Work is to be completed by June 30, 1969. Results are to be presented before the American Statistical Association at its next annual meeting in New York City in August 1969.

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

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Serum cholesterol changes: effects of diet and regression toward the mean

Previous Serial Number: None

Principal Investigator: Fred Ederer

Other Investigators: None

Cooperating Units: None

Man Years:

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

Project Description:

Objectives: To explain why men with initially high values of serum cholesterol have greater serum cholesterol decreases after changing to a hypocholesterolemic diet than men with initially low values. Is this difference an effect of diet or due to a statistical artifact ("regression toward the mean")?

Methods Employed: Analysis of National Diet-Heart Study data.

Major Findings: When cholesterol changes are measured in natural units (mg/100ml), about half the effect is due to diet and half due to normal "regression toward the mean". When cholesterol changes are measured in logarithmic units (or percents), a major portion is explained by normal "regression toward the mean" and only a small portion by diet.

Course of Project: Most of the analytical work has been completed. Some computatations remain to be done and the work needs to be written up for publication. A paper on this project was presented at the Ninth Annual Conference on Cardiovascular Disease Epidemiology in March 1969.

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

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Inverse Estimation in Linear Regression

Previous Serial Number: None

Principal Investigator: Max Halperin

Cooperating Units: None

Man Years:

Total:	- .07
Professional:	- .06
Other:	- .01

Project Description:

Objectives: To compare a recently suggested statistical method for estimation of an independent variable by use of a linear calibration and an observed value of a dependent variable with the standard statistical procedure.

Methods Employed: Standard techniques of mathematical statistics and numerical analysis.

Major Findings: Let (x_i, y_i), $i=1,2,\ldots,n$, be the sample used to determine the calibration $y = \alpha+\beta x$. Let Y be a "new" y value and X the corresponding new x value. Then the standard method of estimating X is to take $X = (Y-\hat{\alpha})/\hat{\beta}$ where $\hat{\beta} = \Sigma(x_i-\bar{x})y_i/\Sigma(x_i-\bar{x})^2$, $\hat{\alpha} = \bar{y}-\beta\bar{x}$. The proposed new procedure is to take $X = \hat{\gamma}+\delta Y$, where $\hat{\gamma} = \bar{x}-\delta\bar{y}$, $\delta = \Sigma(x_i-\bar{x})y_i/\Sigma(y_i-\bar{y})^2$. It is found that the new procedure is more likely to give results closer to the actual value of X for many situations of practical interest but is not uniformly superior in this sense. Some numerical results are given which can be used in practice to determine which procedure is superior in the given instance.

Significance to Bio-medical Research and the Program of the Institute: In problems of bio-assay, one is interested in estimating the amount or relative amount of an active material by means of a calibration line or lines.

PHS-NIH
Individual Project Report
July 1, 1968 through June 20, 1969

The results cited above will allow estimates of improved accuracy in many such problems.

Proposed Course: A paper has been prepared deriving and discussing the results briefly described above and is under submission to a statistical journal.

ANNUAL REPORT OF THE HEART DISEASE EPIDEMIOLOGY STUDY
FRAMINGHAM, MASSACHUSETTS
July 1, 1968-June 30, 1969

The Framingham Study is now one-fourth way through its 11th cycle of biennial examinations which will provide 20 years of standardized measurements for determination of the epidemiologic factors which are precursors of coronary heart disease and hypertensive heart disease. To date, 474 cases of coronary heart disease have developed among the cohort of 2,336 men and 260 cases of coronary heart disease have developed among the 2,873 women enrolled in this prospective study.

Many of the epidemiologic factors in coronary heart disease have become delineated and its natural history, incidence and many of the personal traits and living habits related to its occurrence have been identified, particularly for men between the ages of 38-65. An important recent finding seems to indicate that the ability to predict coronary heart disease is not diminished at the oldest age group 62-65 as was formerly anticipated.

However, since the inception of the study new hypotheses have been introduced as they have emerged and as methods for pursuing them in a general population sample have been developed, they have been explored. To date, an insufficient period of follow-up has accumulated since these population attributes were measured to assess their contribution to the development of CHD under observation. Included are some of the major hypotheses concerning the causation of CHD. (1) The diet hypothesis. (2) The role of emotional stress, (3) Physical activity, (4) Body build as distinct from adiposity, (5) Thyroid function, (6) Sex and premature surgical menopause, (7) The influence of risk factors at older ages and the influence of aging per se, (8) Familial and genetic factors. A large investment in time, personnel and resources has been entailed in implementing these studies. Also, lest it be concluded that all of the answers to the etiology and epidemiology of CHD have been attained, it must be pointed out that employing all of the major factors so far identified as contributors to CHD morbidity and mortality, we can only explain 25% of the variance in the occurrence of CHD in this population. There is still much work to be done using the epidemiologic approach. There is every reason to believe that further elucidation of the circumstances under which CHD arises, evolves and terminates fatally can be achieved from further observation of this population cohort for new CHD events in relation to the aforementioned measured population characteristics.

One aspect of the natural history of CHD, in addition to the precursors of the initial event, which merits further attention is the natural history of the disease once established. The rate of recurrences, case fatality rates in recurrences, disability and survival both of cases under medical care and those cases of inapparent unrecognized disease should be determined.

Premorbid and postmorbid factors related to these should be examined. This will provide a standard of comparison for uncontrolled intervention such as surgical re-vascularization, anticoagulants, exercise programs and blood pressure, blood lipid and diet control prophylactic ventures.

In the past year a well-planned and supervised coronary care unit was introduced in the Framingham Union Hospital. Evaluation of the accomplishments of coronary care units are difficult because of a change in the population at risk with myocardial infarctions presented to the hospital and coronary care unit. We have a closed cohort and a record of the case fatality rate in patients hospitalized at the Framingham Union Hospital over the past 20 years by age and sex. We have the opportunity to make a valid evaluation of the efficacy of a coronary care unit in reducing case fatality rate in myocardial infarction by examining the case fatality rate over the next five years or more in the entire hospital in this closed cohort to see if an abrupt decrease in hospital mortality has occurred. The limited number of deaths available for analysis, however, makes this somewhat difficult.

It has been learned, largely from Framingham data, that the bulk of the high toll in mortality from CHD occurs outside the hospital as a result of sudden and unexpected death. Fully 65% of all deaths during initial coronary attacks in Framingham are sudden. One in five attacks presents with sudden death as the initial complaint. A more detailed examination of the precipitating and distant precursors of this catastrophe is needed. Since these occur out in the community and a large percentage are medical examiner cases, they cannot be studied in hospital populations. We have to date accumulated too few such cases to adequately reflect on this important issue. A substantial reduction in coronary mortality will not be achieved until we learn more about the epidemiology of these sudden deaths. To speed up the process possible collaboration with the Albany Cardiovascular Epidemiology Study is being explored.

Studies have been undertaken to broaden the clinical spectrum of CHD to include its asymptomatic phase. This is detectable atraumatically, without hazard and inexpensively by ECG examination to demonstrate evidence of unrecognized myocardial infarctions, post-exercise ECG evidence of ischemia and possibly, otherwise unexplained ECG abnormality like LVH and I-V block. A preliminary study of the unrecognized myocardial infarction has been completed. It was presented at the American Heart Association meeting November 1968 and was requested for publication in "Geriatrics". It is currently in press. It was found that at least one in five documented myocardial infarctions go unrecognized , half of these are clinically silent. A comparison of the premorbid characteristics of those sustaining clinically unrecognized versus over symptomatic attacks revealed a number of features unique to the development of

atypical or silent attacks. Persons with angina only rarely had unrecognized myocardial infarctions, but angina pectoris was not significantly less frequent after a silent myocardial infarction. Those with prior ECG abnormalities, with hypertension and with diabetes appeared more prone to silent attacks in spite of a higher index of suspicion on the part of their physician. Numbers are still too few to demonstrate statistical significance for these factors. Age, sex and the ECG location of the infarction were unrelated to whether or not the myocardial infarction was clinically inapparent. Such unrecognized myocardial infarctions proved far from innocuous. Survival curves, beginning one year after the attack, were similar to those recovering from symptomatic attacks requiring hospitalization.

A study of ECG-LVH as a possible indicator of occult CHD has been completed. Two types were contrasted: that manifested principally by increased voltage ("possible" LVH) and that including S-T and T-wave abnormalities as well ("definite" LVH). Both types were strikingly related to age and hypertension. Only 35% of the men and 50% of the women with ECG-LVH had associated cardiac enlargement on x-ray. In comparison with the general population, persons with "definite" ECG-LVH had a threefold and those with "possible" LVH had a twofold increased risk of overt CHD. Also, the outcome was more likely to be fatal in those with ECG-LVH. Adjustment for the contribution of blood pressure to risk of CHD failed to attenuate the effect of "definite" ECG-LVH but virtually obliterated the effect of "possible" ECG-LVH. A comparison of the risk of a new CHD event in those having sustained an actual myocardial infarction versus those acquiring "definite" ECG-LVH revealed the latter to be almost as serious a finding. Also, mortality subsequent to development of ECG-LVH was every bit as great as that observed following a myocardial infarction. It is tempting to hypothesize from the foregoing that only the "possible" ECG-LVH is an expression of hypertension and cardiac hypertrophy while definite ECG-LVH reflects, in addition, ischemic myocardial involvement.

It is planned to examine intraventricular block in a similar fashion over the coming year, contrasting right and left bundle branch block. Other atraumatic methods for the detection of asymptomatic CHD are being explored. (See Collaborative Studies).

In addition to a study of ECG-LVH as a possible indicator of occult CHD it has been studied in relation to mortality in general. This paper has been accepted for publication in the Annals of Internal Medicine. The incidence, prevalence and mortality of the finding has been determined. This proved to be a highly lethal finding, almost half of those developing the finding expired during the period of follow-up. The incidence of ECG-LVH rose in proportion to antecedent blood pressure level and half with systolic pressures exceeding 200 mm. Hg. developed it.

More detailed examination of the relation of blood pressure and hypertension to CHD has been carried out with the additional cases available after 14 years of follow-up. This has revealed that certain misconceptions concerning the relation of hypertension to CHD exist. Findings indicate that the cardiovascular consequences of hypertension are related to systolic as much as to the diastolic component of the blood pressure; casual pressures are a good prognosticator of risk as well as basal; hypertension is not relatively innocuous in women or in the elderly. Risk of each manifestation of CHD was proportional to the antecedent blood pressure level from the lowest to the highest recorded in the population with no evidence of any critical "hypertensive" level. The gradients of risk were similar whether subjects were classified according to systolic or diastolic pressure. In discriminant function analysis only in younger persons did the diastolic pressure discriminate potential cases of CHD better than systolic. There appears to be a declining influence of diastolic and a corresponding increase in the contribution of systolic pressure with advancing age. Both components of the blood pressure together and the mean arterial pressure discriminated potential cases no better than systolic pressure alone. Evidently, the commonly accepted notion that the cardiovascular consequences of hypertension derive principally from the diastolic component of the blood pressure requires re-evaluation as does the notion concerning the innocuous nature of systolic blood pressure elevation in the elderly. Hypertensives who developed ECG-LVH or who had associated lipid abnormalities had a very serious prognosis. Hypertension appeared to be associated with a higher case fatality rate in attacks with a higher rate of recurrences, but more follow-up will be required to demonstrate this conclusively. This paper has been accepted for publication in the Journal of the American College of Chest Physicians.

The basic nature of hypertension and its chief determinants in the general population are much in doubt. Some consider it entirely genetic. Others consider it to be primarily environmentally induced and an aging phenomenon with a relatively minor contribution of polygenic inheritance. The Framingham Study provides an opportunity for examining the determinants of blood pressure and hypertension in the general population.

Dr. Feinleib and Tavia Gordon of Biometrics have completed a detailed study of time and age trends in blood pressure in the Framingham cohort. They demonstrated that systolic blood pressure tends to rise with age at an accelerated rate as one gets older. Examination of the time-course of blood pressure in the cohort of persons at various points in time, revealed that there is a steady increase in blood pressure throughout the observed age span. There has been no sizeable secular generation or cohort effects over the past 40 years. The main determinant of the rate of rise in blood pressure appears to be associated with the phenomenon of aging and not

with the initial blood pressure level per se. No tendency can be demonstrated for the population to segregate into the bimodal distribution that would indicate a single gene determinant of a "hypertensive trait".

More detailed studies of the relation of serum cholesterol to risk of CHD, taking into account the associated lipoprotein pattern have been completed. Prospective data comparing the strength of the relationship of the major lipids and lipoproteins encountered in the blood to the incidence of CHD is scarce. Prospective data from Framingham concerning the incidence of CHD over 14 years in relation to premorbid serum lipids and their lipoprotein vehicles appears to shed some light on the role of the various lipids in the development of CHD. Given enough time everyone in the population appears to have enough lipid to produce atheromata with the risk simply proportional to the concentration of each of the major lipids from the lowest to the highest recorded in the population. This was true for cholesterol, phospholipid and endogenous triglyceride. Also, the two major lipid vehicles for cholesterol, Sf 0-20 beta and Sf20-400 pre-beta lipoprotein were good predictors of CHD. Risk appeared to increase with the number of lipid "abnormalities" (in the upper quartile) present. However, it was not clear from this that each lipid separately contributed to risk since the mean level of each particular lipid also rose with the number of lipid abnormalities. Detailed analysis of the net contribution of each lipid and its lipoprotein vehicle to risk of CHD suggests that elevated cholesterol regardless of how transported or partitioned among the lipoprotein vehicles is associated with an increased risk of CHD, the risk determined essentially by the total cholesterol concentration. After accounting for the level of Sf20-400 pre-beta lipoprotein and other factors related both to blood lipids and to CHD, there was still an appreciable gradient of risk proportional to the serum cholesterol concentration. The converse was not true. Knowledge of both the lipoprotein pattern and the serum cholesterol level proved no better in discriminating potential cases of CHD than cholesterol alone. Any particular lipid can be used for assessing vulnerability to CHD, but none would appear superior to the simple total cholesterol for this purpose. Only in older women pre-beta lipoprotein may be superior. Determination of the lipoprotein pattern in persons with "hypercholesterolemia" is apparently of more importance for diagnosing the nature of the lipid disorder and in selecting the most efficacious therapy to correct it, than for estimating the risk of CHD. It remains to be clarified whether the moderate hypercholesterolemia encountered in the general population is principally a heterozygous state for one or more inborn errors of metabolism or simply an acquired state. It may well be both.

Preparations for analysis of 16 years of follow-up are under way and scheduled to commence with the new fiscal year. We will have the following counts of disease end points for analysis:

Total deaths	605
Total CHD	537
Sudden unexpected death	59
CHD - death, not sudden	28
Coronary insufficiency	47
Uncomplicated angina	158
Myocardial infarction	225
Congestive heart failure	126
Total CVA	148
Athero-thrombotic brain infarction	83
Subarachnoid hemorrhage	20
Transient ischemic attacks	8
Cerebral embolus	24
Intracerebral hemorrhage	8

The current rate of accumulation of disease end points is accelerating markedly allowing much more detailed analysis than formerly and more precise estimates of risk associated with factors under study. The net effect and interrelated factors can now be explored in more detail. The relation of personal traits and living habits to each particular manifestation of CHD can now be examined.

Emphasis is being shifted from assessment of population attributes to careful and complete detection of disease end points including coronary heart disease, cerebrovascular disease, peripheral vascular disease, hypertensive cardiovascular disease and congestive heart failure. The natural history of the disease once established including the number and nature of recurrences over time and factors related to recurrences and to survival, can now be explored. The circumstances surrounding early mortality in general, and sudden death in particular, is being explored.

Beyond the 16 year follow-up we have to date, 850 deaths recorded, 498 men and 352 women. We have reviewed to date 734 cases of CHD (474 men and 260 women). There are also to date 249 cases of congestive heart failure (135 men and 114 women). For stroke we have 185 cases (90 men and 95 women) of which 106 are ABI and 10 transient ischemic attacks. There have been 109 autopsies with detailed assessment of the coronary circulation completed.

Follow-up

The completeness of follow-up continues to be gratifying despite the aging of the population with many of the participants retiring. Completeness of follow-up is the key to success in a longitudinal study and the adequacy of follow-up is one of the strong points of the Framingham Study.

The net loss from one examination to the next is only 1-2%. With the 11th biennial examination (20 year follow-up) measures have been taken to firm up our information on the clinical status of the non-examined respondent group to determine if we are correct in assuming that they do not contain an unusual amount of disease. We are currently having them examined by their local physician to ascertain whether this assumption is correct.

Follow-up through Exam 9 continued to be splendid. Of the original cohort of 5,209 persons, 4,553 were still alive at the time they were scheduled for the 9th examination, and 3,852 or 84.2% of those alive took Exam 9. The comparable percentage for Exam 8 was 86.1%, indicating a net decrease of less than 2% from Exam 8 to Exam 9. Of the 721 eligible persons who did not appear for Exam 9, 67 have already returned for later examination. By the time of the 8th biennial examination 656 persons in the cohort had died. Of those alive at Exam 8, 89 or 1.9%, died before they were scheduled for Exam 9.

The number of additional disease events expected in the Framingham cohort between our present level of analysis (14 years follow-up) and the end of the 11th round of examinations completing 20 years of follow-up, is projected to be: 390 deaths, 270 new cases of CHD, 60 new athero-thrombotic brain infarctions, and 40 new cases of intermittent claudication.

By Exam 11 practically all subjects participating in the study will be over the age of 50. From examination 11 on there will be a substantial number of persons in each age-sex group between age 65 and 80. As an incidental by-product of 20 years of routine follow-up we have a population with a representative balance of sick and well, institutionalized and non-institutionalized older persons. To obtain a cohort of old people like the Framingham cohort would be extraordinarily difficult and expensive. While some risk factors are less strikingly demonstrated in older persons, there is good evidence that we can predict cardiovascular disease about as well for persons 60-69 as for persons under 60. The significant predictive factors appear to be somewhat different, however, and this merits further study. Little is known concerning factors contributing to cardiovascular morbidity and mortality in persons aged 70-79. The best place to get this information is from the Framingham Study.

Stroke program

The program for the study of cerebrovascular disease is being expanded to include a yet more detailed clinical assessment, attempt to detect extracranial vascular disease and transient ischemic attacks and autopsy assessment of vessels in those who have died. Criteria for the differential diagnosis are being sharpened. A detailed autopsy protocol including anatomical and

angiographic assessment of extracranial and intracranial vessels is being developed. This will allow an assessment of premorbid personal attributes of each subject in relation to the condition of his vessels at death.

We are fortunate in having neurological consultants interested in participating in the program. Dr. Philip Wolf, now with Boston University, and Dr. David Poskanzer at the Massachusetts General Hospital are both collaborating in this endeavor. Neurological consultation is now being obtained on every identified suspected case of CVA. All stroke subjects admitted to the Framingham Union Hospital are currently being seen by a consultant neurologist during the acute stage of the disease. The number of carefully documented CVA cases continues to mount, yet it will be some time before a clear picture of the epidemiologic features of athero-thrombotic vascular disease of the brain is obtained.

The overall objective is to determine in what particulars those who develop strokes differ from those remaining free of them; the natural history of strokes including the case fatality rate, amount of residual, recurrences, and survival. We would like to attempt to: assess the role of extracranial vascular disease of the carotids in the development of strokes and factors related to its occurrence; determine the nature and frequency of transient ischemic attacks as precursors of strokes; factors related to their occurrence and risk of their having a stroke; to explore the role of emboli in "thrombotic" strokes; to attempt to differentiate "lacunar" small penetrating vessel involvement from other brain infarction and examine its epidemiology; to identify precipitating factors in strokes such as myocardial infarction, impaired myocardial function, hypertension and atrial fibrillation; and to compare the epidemiologic features of this manifestation of atherosclerosis with that of coronary artery disease and peripheral vascular disease.

An attempt has been made to involve the Institutes of Mental Disease and Neurologic Disease in collaboration in the stroke program; in developing atraumatic techniques for the detection of extracranial vascular disease; and in studying senile mental deterioration. The latter is a serious problem of major proportions in the aging population in the U.S.A. about which very little is known. A study of its epidemiology might provide clues to its pathogenesis and control. Its relationship to atherogenic precursors and vascular disease could be explored. What is entailed is the development of test procedures for evaluating mental performance so that a score on each examination could be obtained. The rate of deterioration in mental function with age and time could then be examined in relation to attributes measured over the past 20 years and factors related to rapid deterioration identified. To mount such a study from scratch would be prohibitively expensive. To pursue it now would involve only a trivial investment of re-

sources. Along with this an assessment of hearing and eyesight and neurological function would be appropriate.

In the past fiscal year a preliminary study of the relation of blood lipids to the development of athero-thrombotic brain infarction was carried out. With the limited data so far available, lipids appear to play a much less substantial role in the development of athero-thrombotic brain infarction than CHD. Its effect is overshadowed by that of hypertension. Neither cholesterol nor endogenous triglyceride made a striking contribution to risk of athero-thrombotic brain infarction in hypertensive individuals. There may be some contribution in non-hypertensive persons, but the numbers are too small to evaluate. If there is a lack of a relationship of athero-thrombotic brain infarction to lipids in the face of a striking relationship in CHD, this should be explored for its pathogenetic implications. Dr. William P. Castelli presented the findings of this study to the American Heart Association in November 1968.

Detailed studies of the relation of hypertension, the major factor in risk of stroke are being carried out. In particular, the net contribution of systolic versus diastolic pressure has been assessed. Thus far, there is no evidence to support the accepted clinical contention that the cerebrovascular consequences of hypertension derive principally from the diastolic component of the blood pressure. There was no evidence that systolic pressure was innocuous, even in the elderly, and discriminant analysis indicates, if anything, a greater net effect than diastolic pressure. Knowledge of both, systolic and diastolic, or the mean arterial pressure was no better than systolic alone in predicting athero-thrombotic brain infarctions. Evidently, the clinical assumption that systolic pressure elevation is innocuous is premature. This paper will be presented at the American Medical Association meeting in July 1969.

Inquiries for Framingham data

Both the staff at Framingham and Biometrics at Bethesda have been providing information on request to scientists around the world and to administrators (including those at the National Heart Institute) which apparently has not been obtainable elsewhere. The number of such requests continue to mount. We have had 54 such requests over the past year from Finland, New Zealand, Sweden, Scotland, Switzerland, Germany, Holland, Belgium, England and the West Indies, among others. These requests have all been for unique information not available elsewhere. Evidently Framingham provides a resource for information not currently obtainable elsewhere. The Biometrics Section at Bethesda has filled approximately 30 such requests. In the past year the Framingham Study has provided natural history information on a number of occasions vital to National Heart Institute planning in

the artificial heart program and the myocardial infarction program. With time more of this substantial, unique information concerning the natural history of atherosclerotic disease will be available for us.

Interstudy comparisons

In the past year the feasibility of making interstudy comparisons among the various ongoing epidemiologic studies under National Heart Institute supervision has been examined. The goals of such a study include: documentation of geographic differences in incidence of CHD and stroke; demonstration of the universality of established relationship of population attributes to disease outcomes; to allow an examination of rare population attributes and rare disease outcomes by pooling; to get a more complete look at the relation of factors to disease throughout the whole biologic range of variables by broadening the range of variables through pooling; to examine important hypotheses by exploration of interstudy as well as within study differences; to assess the net contribution of multiple interrelated factors in pooled data providing large numbers for analysis; to examine the determinants of risk attributes in different geographic areas.

Collaborative Studies

A number of collaborative studies are being carried out and some have been completed in the past year. In order to keep tighter control over the number and quality of collaborative studies conducted at Framingham, a more formal review procedure has been set up to evaluate proposals for collaborative ventures.

Anthropologic studies. Under the supervision of Dr. Albert Damon at Harvard, studies of the relation of body form to a variety of cardiovascular disease outcomes are under way. An analysis of anthropomorphic data in relation to subsequent CHD has been completed and published. The 198 men who developed CHD within 12 years of entry into the study were significantly more endomorphic, less ectomorphic than the 1,427 men who did not. All of the effect was confined to men under 50, and within this group to those developing manifestations of CHD other than myocardial infarction. Gynandromorphy did not distinguish among any of the age or disease categories. Using the individual body measurements it was possible to discriminate potential cases from those remaining free over a sevenfold range of risks. Physique contributed to risk of CHD independently of blood pressure and serum cholesterol. Comparison of the present findings with those in the literature disclosed a pattern which resolves many apparent contradictions. When studies are grouped according to sample characteristics, age of subjects, and manifestations of CHD, findings are quite consistent rather than inconsistent as they appear to be when not examined in the necessary detail.

Further studies relating hormone assessments to anthropometry are currently under way.

Familial aggregation of disease: This study is well under way and the data has been cleaned up and is ready for tabulation. It will examine husband-wife relationships with respect to cardiovascular risk factors and disease outcomes. The study will have value in elucidating environmental components in the etiology of cardiovascular disease and will supplement knowledge of genetic factors gained in analysis of parent-offspring, sib-sib, and pedigree data. Spouse pairs have been identified and those representing single continuous marriages will form the core of the study group. Dr. David Sackett of McMaster University is working on this with Dr. Manning Feinleib with a grant funded in Canada. The work is proceeding well. Dr. Sackett is also studying prospectively the relation of a family history of CHD and the age of its occurrence in subjects participating in the study.

Twin study. Dr. Manning Feinleib, Chief of the Field Epidemiological Research Section of the National Heart Institute, is inaugurating a twin study of factors related to the development of CHD utilizing the Framingham Study facilities. The twin roster for New England has been made available by the NAS-NRC twin panel. There is an estimated 150 sets of twins who will be contacted for examination at Framingham. It is estimated that approximately 40% are monozygous, enough to exclude hereditary factors in the study of coronary risk factors. A pre-trial has been conducted in Washington to check out the procedures to be used. This study will stretch further the shrinking resources of Framingham, particularly physician examiner resources. However, it can be done with the staff as constituted on July 1, 1969.

Osteoporosis study. The study continues smoothly at this end. The x-rays are being processed smoothly by the technicians at Harvard and measurements are being made. However, the clinical assessment by the radiologist is going very slowly. The urine specimens are being collected and assessed regularly. The diet data assessment has not yet been organized although the plan is to use already coded and collected diet data on 900 subjects interviewed with the Burke technique back on Exam 5.

Peripheral vascular disease. Plans have been made to pursue studies of peripheral vascular disease in collaboration with Albany. The Albany Heart Study has acquired the same pulse wave recording apparatus we are using to compare pulse amplitudes bilaterally simultaneously obtained at multiple counter-pressures. Uniform clinical criteria have been set up as well as a standardized examination.

Sudden death study. A collaborative venture with the Albany Heart Study is being planned to look into the circumstances surrounding sudden unexpected deaths in the Framingham and Albany studies. Both studies have to date, accumulated too few sudden unexpected deaths to allow an extensive detailed analysis. The hope is that the pooled data will allow meaningful conclusions to be drawn.

Climatic and seasonal aspects of cardiovascular disease. Dr. Eugene F. Dudley is conducting a study of the relation of climate and season to the rate of occurrence of CHD in Framingham. He has characterized the weather in the Framingham area over the period of the study using weather bureau data. He will attempt to determine if there is an increased incidence of cardiovascular attacks during or immediately following periods characterized by climatic stress; whether there is an increased incidence of attacks following significant snowstorms; and if there is a yearly pattern of attacks related to season or major holidays.

Rheumatology studies. Detailed descriptive study of persons who converted from negative to positive on serum rheumatoid factor assessment is being carried out by Dr. Arthur Hall. All cases of gout to date have also been identified for further study in relation to atherosclerosis and its precursors. This is a self-sustaining operation with clerical help supplied by Dr. Arthur Hall from funds obtained through the American Rheumatism Association.

Emotional stress study. No further progress has been made by Drs. Scotch and Levine. Tavia Gordon is trying to expedite their work by offering National Heart Institute resources for tabulation and analysis.

Post-myocardial infarction work status. Dr. Stanley Fisher of the University of Connecticut is compiling data on cases of myocardial infarction and matched controls for the purpose of comparing their work experience both prior and subsequent to the coronary event. Analysis of this material is under way. Preliminary analysis reveals surprisingly little work disability following a myocardial infarction. The principal hazard appears to be recurrences and premature death rather than symptomatic disability.

Graphic methods for evaluating cardiac function. Dr. D. H. Spodick of the Cardiology Division of the Lemuel Shattuck Hospital (Tufts University Service) proposes to test methods developed for NASA for the atraumatic assessment of cardiac function to determine if this is of predictive value in CHD. It is proposed that they will obtain on each subject a lead II ECG; carotid sphygmogram, left ventricular apexcardiogram and apical phonocardiogram. From this the electromechanical lag, isovolumetric contraction period, ejection time and rate-related ejection time indices and iso-

metric relaxation period will be calculated. It is hoped that by this means asymptomatic CHD can be diagnosed. The initial test applied would be to see if this method can detect from the sample those at high risk of CHD and having evidence by ECG of either left ventricular hypertrophy or intraventricular block and hence a high probability of asymptomatic coronary artery disease and possible asymptomatic myocardial involvement. The eventual test would be the demonstration of a high incidence of symptomatic CHD in those with such evidence of impaired function in comparison to cohort without abnormality.

The Cardiology Division of the Lemuel Shattuck Hospital would obtain the funds for instrumentation and personnel to conduct the tests and would agree to install these in Framingham for use on Saturdays and evenings.

This would be part of a continuing effort to find atraumatic methods for detecting the onset of asymptomatic CHD in high risk persons.

Laboratory Activities

The new laboratory set up on the first floor is functioning well with no major problems in the physical lay out. Complete re-wiring and the voltage stabilized circuit has done much to increase instrument stability. Space is still a major problem owing to the greater number and complexity of tests being run including beta quantification lipid analysis established by the Laboratory of Molecular Disease. This procedure is being carried out under the direction of and with the cooperation of Drs. Fredrickson, Levy and Kwiterovich.

Development work is being carried out in agarose electrophoresis. A much finer separation of lipoprotein than that allowed by paper is possible, and there is potential for quantification and assay of the individual lipids separated, making the expensive beta quantification procedure unnecessary. Owing to shortage of personnel and the increased work load, developmental work modifying procedures for application in an epidemiologic setting has gone slowly, and our biochemist has been forced to spend most of his time accomplishing only routine laboratory work.

On the 11th biennial examination a complete lipid profile is being obtained on all subjects in the fasting state. This entails having subjects who are examined in the evening return fasting in the a.m. These lipid studies include: total cholesterol and its partitioning in the various lipoprotein fractions, including alpha cholesterol, beta cholesterol and VLDL (pre-beta) cholesterol. Plasma electrophoresis is being carried out in the total plasma (EDTA), in the top fraction and bottom fraction of the preparatory ultracentrifuge run. This allows beta quantification and along

with triglyceride determination, allows lipoprotein typing by the method of Fredrickson, et. al.

To complete the lipid profile a light scattering intensity is determined on the whole plasma and plasma that has been filtered through a 0.1 micron millipore filter system on all subjects who present themselves fasting. This allows an assessment of chylomicronemia to add to the other lipid component assessed. The immediate yield will be information on the lipid profile distribution in the general population, in cases of CHD, stroke, peripheral vascular disease, versus the general population or matched controls. An ultimate yield, if surveillance for cardiovascular disease continues six or more years following completion of the 11th biennial examination, will be prospective data relating the entire lipid profile, according to modern concepts, to risk of atherosclerotic disease outcomes.

This endeavor requires that three cholesterol determinations be run on each subject as well as three lipoprotein electrophoresis strips. A preparative run on the ultracentrifuge is also required. Due to difficulty in obtaining sufficiently reproducible triglyceride values the Lederer-Kessler automated triglyceride procedure has been adopted.

To provide a more adequate assessment of impairment of carbohydrate tolerance than possible to date employing casual blood sugar values, a one hour glucose tolerance test following 50 grams of carbonated dextrose load is currently being done on all 11th examination subjects.

Laboratory quality control has been tightened and since 1962 the laboratory has cooperated with the CDC Cholesterol Standardization Program. Of all laboratories cooperating and using the Abel-Kendall technique, the Framingham laboratory had the lowest technical error (4.9 mg%). We have also joined in the glucose cooperative standardization program. In addition, the laboratory participates in an internal control program run by CDC for the National Heart Institute supervised field studies in Puerto Rico, Honolulu and Framingham, for the determination of cholesterol and triglyceride. Each laboratory is informed when its standard deviation exceeds 5% for cholesterol and 8% for triglyceride. Finally, commercial standards are routinely run with each batch of tests.

Frozen serum pool. A pool of frozen serum specimens has been accumulated since the second biennial examination. Beginning in 1953 excess serum from study participants blood samples have been frozen and stored. This was, and still is, intended for use should some serum component be discovered which shows promise as a contributor to atherogenesis. On the average, 3-4 ml. is available on each subject at each biennial examination with a range of from 1-10 ml. A recent appraisal of the status of the pool

was undertaken by Dr. William P. Castelli. In general, most of the tubes appeared to be in good condition with little evidence of desiccation by sublimation. There are 24 lockers with approximately 1,440 specimens in each, a total of about 34,000 specimens. Only about 9% of subjects in the sample had no frozen specimens.

In order to safeguard future specimens they will be sealed in 1 ml. glass ampules. Apparatus has been ordered to accomplish this. This will prevent desiccation and allow withdrawal of aliquots without repeated thawing and refreezing of specimens. It is estimated that to thaw and reseal in glass ampules all the stored frozen sera would require 2,000 man hours - the work of a full-time laboratory technician for one year. Such a person is not currently available for this work.

Work continues on the "Framingham Monograph" which compiles and displays in detail data accumulated at Framingham for 14 years of follow-up. This has provided a valuable source of information for answering questions which have arisen. A total of 23 sections have been produced, the last dealing with a discriminant analysis of cholesterol, blood pressure and Framingham relative weight as discriminators of potential cardiovascular disease. This compilation of data which displays in great detail the distributions of cardiovascular disease and of population attributes and their relation to each other will allow a more detailed analysis of the interrelations of interest. This will be made available for those interested.

Publications over the preceding year are listed below:

Gordon, T., and Kannel, W. B. (Eds.): The Framingham Study. An epidemiological investigation of cardiovascular disease. Monograph Sections 1-23, National Heart Institute, NIH, Bethesda, Md. 1968/1969.

Kannel, W. B., Castelli, W. P., and McNamara, P.M.: Epidemiology of acute myocardial infarction. The Framingham Study. Medicine Today Karachi, Pakistan, Vol. 2. Nos. 8,9,19, p.56, 1968.

Dawber, T. R., and Kannel, W. B.: The early diagnosis of CHD. Presymptomatic Detection and Early Diagnosis. Pitman Publishing Co. Ltd. London, W. 1. England. 1968.

Vander, J.B., Gaston, E.A., and Dawber, T.R.: The significance of nontoxic thyroid nodules; final report of a 15 year study of the incidence of thyroid malignancy. Ann. Intern. Med. 69:537-540, 1968.

Damon, A., Damon, S. T., Harpending, H. C., and Kannel, W. B.: Predicting coronary heart disease from body measurements of Framingham males. J. Chronic Dis. 21:781-802, 1969.

Kannel, W. B., Pearson, G., and McNamara, P. M.: Obesity as a force of morbidity and mortality. Adolescent Nutrition and Growth. New York, New York. Appleton-Century Crofts. In press.

Kannel, W. B., Castelli, W. P., Verter, Joel, and McNamara, P. M.: Relative importance of factors of risk in the pathogenesis of coronary heart disease. Advances in Coronary Heart Disease. Philadelphia, Pa. J. B. Lippincott Co. In press.

Kannel, W. B., Gordon, T., and Offutt, D.: Left ventricular hypertrophy and electrocardiogram: Prevalence incidence and mortality in the Framingham Study. Ann. Intern. Med. In press.

Kannel, W. B., Schwartz, M. J., and McNamara, P. M.: Blood pressure and risk of coronary heart disease. The Framingham Study. Diseases of the Chest. In press.

Kannel, W. B., Dawber, T. R., Feinleib, M., and McNamara, P. M.: The unrecognized myocardial infarction (14 year follow-up experience) The Framingham Study. Geriatrics. In press.

Kannel, W. B., Gordon, T., and Castelli, W. P.: Electrocardiographic left ventricular hypertrophy and risk of coronary heart disease. The Framingham Study. Circulation. In press.

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

Type	Cumulative FY 1968	Estimated total FY 1969
11 Personnel services	202,650.00	207,222.00
12 Related costs	21,950.00	26,000.00
21 Travel	8,000.00	6,000.00
22 Transportation of things	1,825.00	1,100.00
23 Rent, communications, utilities	28,750.00	31,000.00
24 Printing and binding	35.00	500.00
25 Other contractual services	25,000.00	28,000.00
26 Supplies and materials	23,000.00	20,000.00
31 Equipment	6,200.00	6,000.00
Total	317,410.00	325,822.00

Staff for the fiscal year is indicated below:

Commissioned Officers
William B. Kannel, Medical Director
William P. Castelli, Senior Surgeon
Georgiana Pearson, Dietitian
Mariano J. Garcia, Surgeon (R)

Physicians - Civil Service
Nicholas Revotskie, GS-12, Medical Officer (40% part-time)

WAE
John S. Banas, GS-11 Medical Officer
Philip A. Wolf, GS-12 Neurologist

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-5)
Judith Sabourin, Clerk-typist (GS-3)

Statistical
Patricia M. McNamara, Statistician (GS-11)
Dorothy Costelli, Statistical Assistant (GS-6)
Lorraine Girard, Statistical Clerk (GS-5)
Ruth Anderson, Statistical Clerk (GS-5)
E. Carol Anglin, Statistical Coding Clerk (GS-3)

Laboratory
Robert F. Moran, Chemist (GS-9)
Gertrude Metzger, Medical Technician (GS-6)
Frederick Uhrig, Medical Aid (GS-4)
Albina Mariano, Medical Technician (60% part-time GS-6)
Noemia Bravo, Medical Aid (Medical) (75% part-time GS-4)
Marianne Moran, Chemist (25% part-time GS-5)

Clinic Staff
Mrs. Lorna P. Lyell, Project Aid (GS-8)
Mrs. Irene L. 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)

Clinic operation

The 11th biennial examination is well on its way and is proceeding smoothly with the usual good response rate. The 10th examination is close to completion and will close out July 1970. Exam 9 data are being edited and punched and put on tape. The 11th examination emphasizes the clinical outcomes of peripheral vascular disease, stroke and congestive heart failure and the forms have been modified accordingly. The examinations are currently being carried out by three full-time Commissioned Officers who also serve as researchers, laboratory director, and study director. In addition, two part-time examiners are doing part-time evening examinations. We also have a neurological consultant who sees all cases suspected of stroke in the clinic and all hospitalized cases on the wards. Electrocardiograms, chest x-rays, pulmonary function studies, peripheral pulse wave recording, measurement of body fat and body build and dietary assessment are being obtained by nursing and technical personnel. We will be losing one secretary. Our laboratory assistant has had an extended sick leave and will be retiring presently. One part-time examiner will probably be lost to us during the next fiscal year. We have only one Commissioned Officer joining us July 1. We have not replaced the Associate Director and therefore, have no epidemiologist to help the Director supervise research activities.

Proposals for the future of Framingham

The Framingham Study has been visited in the past year by a number of "Advisory Committees" concerned with the nature and extent of Framingham's future activities. To date no definite policy decision has been made concerning this. It is fair to say that the study has not exhausted its potential for supplying new information not now available in the area of coronary heart disease, peripheral vascular disease, cerebrovascular disease, congestive heart failure and hypertensive cardiovascular disease. Studies of cancer, senility, obstructive lung disease can also be readily accomplished within the framework of the existing operation. The determinants of important risk factors in the general population have yet to be elucidated. Much can be learned from an analysis of already existing data in this regard, but a full exploration of familial factors (viz., lipid profile) would require a study of the families of the population sample. The National Heart Institute must determine if it desires to maintain a position of leadership and give direction to epidemiologic research in cardiovascular disease. If it does, Framingham would not be a bad choice for the place to investigate new hypotheses and to develop new methods. This approach to the elucidation of the causes of chronic disease has proven its worth, and merits continued, if not expanded, support.

Continued surveillance of this population at the same biennial intervals has much to recommend it. Any less intensive surveillance would have the considerable liability of gross underestimation of myocardial infarction (one in five go unrecognized), angina pectoris, approximately a fourth of the strokes, a good deal of the congestive failure and intermittent claudication. Studies of the natural history of these diseases would be distorted by lack of information on the unidentified and milder disease not detectable without continued biennial examination of the entire population sample.

Longitudinal prospective studies are tedious, slow to yield results and expensive to carry out. However, they provide planned observations which avoid many of the pitfalls of retrospective studies. Because of their magnitude and the difficulties entailed, they are a legitimate concern of the Institutes of Health since they are generally beyond the capability of non-government financed research. Few other research organizations can muster the necessary resources.

Until the currently available resources are curtailed, it is the intention of the Framingham Study group to continue the present level of surveillance of the original population cohort, instituting those studies which reflect on the natural history of established coronary heart disease, with emphasis on the identification of factors which precipitate attacks in vulnerable persons as well as those which herald the onset of asymptomatic disease and those which lead to recurrences and affect survival. Careful surveillance of the development of stroke, peripheral vascular disease and congestive heart failure will be continued to be studied in relation to prior traits and habits measured in the population. The hypotheses introduced after the inception of the study (already enumerated) will be pursued and evaluated with the additional follow-up data obtained. New objectives will be implemented as old objectives are phased out. We will continue to strive to obtain additional collaboration and support from the NIND and NIMH for studies of stroke and intellectual impairment in this aging, well-characterized population. This level of activity seems amply justified until 1972 when 20 years of follow-up will be completed. After that point various alternatives, which have been enumerated, (see last annual report) should be considered. Plans, however, to implement this later phase must be formulated soon since we must presently start considering the implementation of the 12th round of biennial examinations if an uninterrupted follow-up is to be maintained.

PHS-NIH
NATIONAL HEART INSTITUTE
July 1, 1968 through June 30, 1969
EPIDEMIOLOGY AND BIOMETRY

FIELD EPIDEMIOLOGICAL RESEARCH SECTION

Change was the hallmark of the Field Epidemiological Research Section during fiscal year 1969.

There were changes in the professional and supporting staff of the section, in its geographical location, in its specific projects, and in its program goals.

Dr. Ralph Paffenbarger retired from active duty in the Commissioned Corps of the U. S. Public Health Service and Dr. Manning Feinleib was appointed Chief of the Section on August 1, 1968. Concurrent with this change in leadership, the section was relocated from Framingham, Massachusetts to Bethesda, Maryland. The Section staff in Massachusetts resigned their appointments and new professional and supporting staff were assigned in Bethesda. The new appointments were Dr. Richard Havlik, a physician, Mr. Robert Garrison, a statistician, and Mrs. Margaret Price, secretary.

With this change in personnel and location the Field Epidemiological Research Section assumed a new role in pursuing epidemiological research. Dr. Paffenbarger's study of 50,000 former students at the University of Pennsylvania and Harvard College was terminated as an NHI program and was transferred to his personal direction. The section was directed to develop new studies which would take advantage of unusual population or environmental situations and to explore significant epidemiologic problems in cardiovascular disease with a minimum of cost and maximum utilization of available resources. In line with these objectives, three main areas of research activity were identified as appropriate activities for this section.

The first was the area of genetic studies. Although genetic factors are of great importance in the occurrence of cardiovascular diseases, relatively little has been done to substantiate these guesses. The section staff, therefore, has been engaged in designing genetic studies which will help to elucidate the relative importance of genetic factors in heart disease and stroke. A protocol was prepared to take advantage of the more than 8,000 pairs of twins that have been located by the National Academy of Science-National Research Council Twin Panel. A protocol was submitted to the NAS-NRC Follow-up Agency and was approved for access to the twins. In collaboration with the Epidemiology Branch of the National Eye Institute, under Drs. Theodore Schwartz and Frank Reuling, a trial period was organized for the twin study protocol. Drs. Manning Feinleib, Richard Havlik, and Peter Kwiterovich have examined approximately 40 sets of twins at the facilities in the Professional Building at the Washington Hospital Center. Information from this trial period was used to revise the study procedures and forms and these were then submitted for clearance by the Bureau of the Budget. We are now proceeding with the examination of approximately 300 pairs of twins available in the New England

area. These twins will be brought into the facilities of the Framingham Heart Study and will undergo the standard Framingham examination with supplementary questionnaires about diet and twin experience.

In combination with this twin study, other genetic studies are being conducted on available materials on the Framingham Heart Study. Three different approaches to this problem are being tackled. First is the relationship between siblings to see whether or not the concordance of risk factors in siblings is greater than what one would expect in the general population. A second approach is a study of the relationship between risk factors in parents and their offspring. Over one hundred parent-offspring sets are available from the Framingham Study and these are being subjected to analysis to determine to what extent the identified risk factors correlate in first degree relatives. The third of these genetic studies is being done in collaboration with Dr. David Sackett of MacMaster University and will consist of comparing the correlation of risk factors in spouse sets. More than 1,600 husband-wife pairs are available in the Framingham Study and these will be subjected to intensive analysis to find out whether duration of married life, which is an index of sharing of common environment, influences the levels of various risk factors such as blood pressure, cholesterol, weight and a variety of other physiological parameters.

The second area of investigation of the Section was in special epidemiological studies relating to heart disease. It was felt that the Field Epidemiological Research Section would be in a unique position to take advantage of special population or other resources to explore specific epidemiologic hypotheses in relation to cardiovascular diseases. Hypotheses which have been formulated involve the effects of hard water and trace metals on the frequency of CVD, the psycho-social factors contributing to CVD, and the role of hormonal factors in CVD. Unfortunately, due to the limitations of staff and other resources during the current fiscal year, no major efforts have been made to launch these ancillary studies. However, the personnel of the Field Epidemiological Research Section have been continuing their close liaison with the investigators of the Framingham Heart Study and the Biometrics Research Branch to undertake specific analyses of important epidemiological questions which can be answered with the Framingham data. Specific areas of interest include an analysis of the natural history of risk factors themselves - such as, what are the antecendent characteristics of persons who develop hypertension, obesity, or hypercholesterolemia. Twenty years of data available from Framingham provide a rich source of information to answer these questions. It has been found that the natural rise in blood pressure which occurs with age in most individuals seems to be fairly specific regardless of antecendent blood levels so that once a person is classified by his blood pressure at about age 30 he seems to follow a single track throughout the rest of his life. This finding, which was reported at the Second Annual Meeting of the Society for Epidemiological Research, points out the importance of studying risk factors such as blood pressure in younger individuals, possibly even children, and of the importance of studying genetic factors in relation to the determinants of blood pressure level.

Another area of research has been the natural history of cardiovascular disease. The first paper in this sequence was the natural history of unrecognized myocardial infarction which Dr. William Kannel presented at the 41st Scientific Session of the American Heart Association. It was found that more than 20% of all ECG documented infarctions are not recognized by a physician at the time of their occurrence. This does not include those patients who die suddenly, but refers to those individuals who either have no symptoms at the time of the initial infarction or whose symptoms are so atypical that they do not lead to suspicion of an MI by the patient or his physician. It was also found that the subsequent survival of patients with unrecognized myocardial infarctions did not differ significantly from those with recognized myocardial infarction, most of whom were hospitalized.

The section also took responsibility for a special follow-up study on behalf of the Framingham Heart Program. This study was aimed at locating the approximately 400 persons who are alive but who had not taken their latest Framingham Heart Examination and inviting them to receive an examination and an electrocardiogram from a local physician at the expense of the National Heart Institute. This effort under the direction of Dr. Richard Havlik has been tremendously successful. About 40 people have already been located and contacted and there has been an 80% recovery rate of those people who would not ordinarly come in for ascertainment of their morbidity status at the 20 year end point.

The third research area for the Field Epidemiological Research Section was a morbidity and mortality survey coinciding with the 1970 U. S. Census. The census of the United States provides a convenient and accurate base for various surveys designed to answer specific questions about the frequency and social cost of cardiovascular disease among defined population groups. It is also a useful base for evaluating the validity of epidemiologic data obtained from specialized population groups such as industrial or insurance groups or volunteers followed in longitudinal studies. It was felt that it would be feasible to do a morbidity and mortality survey in the town of Framingham, Massachusetts. Initial attempts at this study were frustrated by a feeling that this proposed study might endanger the follow-up procedures in the Framingham Heart Study. It was felt that the physicians in Framingham were already being imposed upon in cooperating with the Framingham Heart Study and that further infringement upon their time would not be well received. A modified program was therefore proposed - namely, to do a mortality and hospital surveillance of documented myocardial infarctions and stroke. To this end a protocol is being developed which will attempt to locate all deaths, from cardio-respiratory diseases and stroke as well as all admissions of Framingham residents to Framingham Union Hospital and nearby hospitals for myocardial infarction and stroke. These firm end points will then be used to compare the incidence and mortality rates obtained from the Framingham Heart Study to ascertain whether or not the rates from the longitudinal study are representative of what is going on in the general population.

Methodological problems have also been investigated by staff members. A joint effort with Dr. Marvin Zelen of the State University of New York at Buffalo resulted in the development of a mathematical model to estimate the

lead time gained by chronic disease screening programs. The implications of this model were presented at the 25th Annual Meeting of Teachers of Preventive Medicine by Dr. Feinleib.

Finally, in the area of education and training, Dr. Feinleib has organized an NIH Epidemiology Seminar which provides a forum for world reknowned authorities to present significant epidemiologic issues. The speakers to date and the subjects of their talks were:

Dr. A. L. Cochrane, Honorary Director, Medical Research Council, Epidemiological Research Unit, Cardiff, Wales: The meaning of normality - with particular reference to the haemoglobin distribution. November 15, 1968.

Mr. Jerome Cornfield, Research Professor of Biostatistics, University of Pittsburgh: Can we prevent coronary heart disease? February 27, 1969.

Dr. Ken Tsuchiya, Professor of Preventive Medicine and Public Health, Keio University, Tokyo: Special opportunities in Japan for epidemiological research. March 26, 1969.

Dr. Robert W. Miller, Chief, Epidemiology Branch, NCI: Rubella vaccination - implications of the U. S. program. April 28, 1969.

Publications

Feinleib, M., and Garrison, R.J.: Interpretation of the Vital Statistics of Breast Cancer. Cancer, in press, Sept. 1969.

Feinleib, M.: Book Review: Infectious Diseases. J.A.S.A., in press, June 1969.

Zelen, M., and Feinleib, M.: On the Theory of Screening for Chronic Disease. Biometrika, in press, 1969.

Kannel, W.B., Feinleib, M., Dawber, T.R., and McNamara, P.M.: The Unrecognized Myocardial Infarction (14-year follow-up experience). The Framingham Study. Geriatrics, in press, 1969.

Feinleib, M.: Breast Cancer and Artificial Menopause: A Cohort Study. J. National Cancer Institute 41:315-329, 1968.

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. Amer. J. Epidem. 88:25-32, July 1968.

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; a Comparison of Trends in Memphis and Baltimore. Amer. J. Epidem. 88:308-317, November, 1968.

Unpublished Papers and Talks

Feinleib, M., and Zelen, M.: Some Pitfalls in the Evaluation of Screening Programs. Presented at the 25th Annual Meeting of the Association of Teachers of Preventive Medicine. Detroit, Michigam, November 10, 1968.

Feinleib, M., Gordon, T., Garrison, R.J., Kannel, W.B., and Verter, J.I.: Blood Pressure and Age. The Framingham Study. Presented at the Second Annual Meeting of the Society for Epidemiological Research, Chapel Hill, North Carolina, May 3, 1969.

Feinleib, M., and Garrison, R.J.: Interpretation of the Vital Statistics of Breast Cancer. Presented at the National Conference on Breast Cancer, Washington, D.C., May 8, 1969.

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Participation in outside committees and organizations:

Manning Feinleib:

was elected a Fellow of the Epidemiology Council of the American Heart Association.

was elected a Member of the Council on Epidemiology and Prevention of the International Society of Cardiology.

served on the Panel of Advisors of the National Center for Health Statistics.

served on an ad hoc Technical Review Committee for the National Cancer Institute.

served on a Contract Review Committee for the National Institute of Child Health and Human Development.

served as a referee for the Journal of the American Statistical Association, Journal of the National Cancer Institute, and Public Health Reports.

Serial No. NHI-FERS-1
1. Epidemiology & Biometry, NHI
2. Field Epidemiological Research Section
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

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

Previous Serial Number: NHI-BRB-20

Principal Investigator: Manning Feinleib, M.D.

Other Investigators: Richard J. Havlik, M.D., Peter Kwiterovich, M.D. and Frank Reuling, M.D.

Cooperating Units: Laboratory of Molecular Diseases, NHI
Epidemiology Branch, NEI
Framingham Heart Study

Man Years

Total:	1.0
Professional:	0.8
Other:	0.2

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 400 pairs of male twins aged 40-50 will be examined 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.

Major Findings: None to date.

Significance to Bio-medical Research and the Program of the Institute: Despite a growing awareness of the importance of genetic factors in CVD there have been relatively few studies in this area. It is recognized that twin studies are potentially the most powerful method available for studying genetic factors in human disease. The present study takes advantage of the largest population of male twins yet assembled to study this important question in relation to cardiovascular diseases.

Serial No. NHI-FERS-1
1. Epidemiology & Biometry, NHI
2. Field Epidemiological Research Section
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Proposed Course of Project: The protocol for this study was approved by the NAS-NRC Follow-up Agency and we have been granted access to their Twin Panel which contains more than 8,000 pairs of male twins who are veterans of World War II or the Korean War. In cooperation with a twin study currently being conducted by the National Eye Institute we have undertaken a trial period with the protocol and have examined 40 pairs of twins this year. On the basis of this trial period, forms and procedures have been revised and the expanded study in the New England area is being launched. This latter phase will entail inviting approximately 300 pairs of veteran twins to undergo the standard examination at the Framingham Heart Program facilities during the forthcoming year. Analyses and reports will be prepared concurrently with the examinations.

Serial No. NHI-FERS-2
1. Epidemiology & Biometry, NHI
2. Field Epidemiological Research Section
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Analysis of Framingham Heart Study Data

Previous Serial Number: NHI-BRB-18
NHI-BRB-19
NHI-BRB-21

Principal Investigator: Manning Feinleib, M.D. (This refers to FERS service)

Other Investigators: William B. Kannel, M.D.
Tavia Gordon
Max Halperin, Ph.D.
Richard Havlik, M.D.
Robert Garrison, B.S.
David Sackett, M.D.

Cooperating Units: Framingham Heart Study, NHI
Biometrics Research Branch, NHI
Department of Epidemiology, MacMaster University

Man Years

Total:	1.1
Professional:	0.8
Other:	0.3

Project Description:

Objective: The Framingham Heart Study is a long-term prospective study to elucidate the role of various risk factors in the incidence and natural history of cardiovascular disease. During the past 20 years, a vast amount of data has been collected. In cooperation with the Framingham Heart Study and the Biometrics Research Branch of the NHI, the FERS is assisting in the analysis of certain portions of this data. The major areas that members of the FERS are concerned with are:

1) The natural history of risk factors including hypertension, obesity, and hypercholesterolemia.
2) The natural history of coronary heart disease including studies of subsequent morbidity and survival.
3) Autopsy correlation with selected risk factors.
4) Familial and spouse aggregation of CHD and associated risk factors.
5) Cancer and other disease end points.

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Individual Project Report
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6) Ascertainment of morbidity status of patients missing recent Framingham examinations.

Methods Employed: New techniques are being developed to analyze longitudinal data. These include application of the theory of stochastic processes and regression procedures. Genetic models are being applied to existing familial data. Physician visits are being arranged for patients who cannot return to Framingham.

Major Findings:

1) With regard to blood pressure, it has been found that the increase of systolic blood pressure with age which is seen in most individuals is relatively independent of initial blood pressure levels if these are ascertained after age 30. This strengthens the hypothesis that this risk factor is established early in life and may be resistant to alteration after middle age.

2) More than 20% of ECG documented myocardial infarction go unrecognized at the time of their occurrence. This is primarily due to the absence of symptoms or to atypical pain patterns. However, the subsequent survival of these MI's does not differ from hospitalized MI's.

Significance to Bio-medical Research and the Program of the Institute: All of the goals of these analyses are of vital importance to the understanding of the causes and course of heart disease. Many of these analyses have had to await the accumulation of adequate numbers of cases to provide meaningful rates and comparisons. It is anticipated that the results of these analyses will provide essential information for guiding further research and program planning.

Proposed Course of Project: These analyses and follow-up studies will continue to be pursued during the forthcoming year. Several manuscripts are in preparation for publication and presentation.

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

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

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.
Professor & Head, Department of Family Medicine
Tel-Aviv University

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

Cooperating Units: National Heart Institute
Hadassah Medical Organization
Ministry of Health, Government of Israel
Hebrew University-Hadassah Medical School

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.

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.

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

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 was 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.

Progress to June 1969: The past year was primarily devoted to completion of the third examination cycle and preparation of the examination data for punching, editing and for final tabulations relating incidence to previous baseline characteristics.

Examinations were completed on 97 per cent of living subjects and systematic follow-up data to establish cause of death have been collected for use in the final incidence tabulations. The greatest problem related to the reading of the 10,000 ECG's by independent readers and providing a further cardiologist review to resolve any disagreements on diagnostic classifications. These readings were finally completed in March 1969 and have now been punched, edited and placed on the data tapes for the planned tabulations.

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

Major Findings: No new findings based upon incidence data have yet been produced since they were dependent upon the completion of the diagnostic classification by cardiologist review. Programs have been established for multiple logistic risk function analyses as well as standard tabulations.

Proposed Course of Project: The study staff is being reduced to maintain only mortality surveillance in the three areas. Primary attention is being directed toward the preparation of clean tapes of data to allow extensive analysis of the findings related to the incidence measurements.

Mr. Harold Kahn could not be continued on assignment past June 1969 so that the direction of the data analysis will have to be conducted from Bethesda. This will impede the work and reduce the quality of supervision for this most important final phase of the project.

The unexpended funds within the P.L. 480 Agreement will be carried over to 1970 in order to complete as much of the computations as possible.

Publications:

Medalie, J.H., Neufeld, H.N., Riss, E., Groen, J.J., Kahn, H.A. and Bachrach, C.A.: Variations in prevalence of ischemic heart disease in defined segments of the male population of Israel. Israel J. Med. Sci. 4: 775-788, 1968.

Kahn, H.A., Medalie, J.H., Neufeld, H.N. and Riss, E.: The screening efficiency of two variable cross classifications compared to discriminant functions-The Israel Ischemic Heart Disease Study. Proc. Asian-Pacific Congress of Cardiology, Sept. 1968.

Vlodaver, Z., Kahn, H.A. and Neufeld, H.N.: The coronary arteries in early life in three different ethnic groups. Circ. 39: 541-550, 1969.

Kahn, H.A., Medalie, J.H., Groen, J.J., Balogh, M., Neufeld, H.N. and Riss, E.: Serum cholesterol: Its distribution and association with dietary and other variables in a survey of 10,000 men. The Israel Ischemic Heart Disease Project. J. Chr. Dis.

Herman, J.B., Kahn, H.A., Medalie, J.H., Neufeld, H.N., Groen, J.J., Riss, E., and Perlstein, T.: Diabetes Incidence, a two year follow-up of 10,000 men in a survey of ischemic heart disease in Israel. Israel J. Med. Sci.

Serial No.
1. Epidemiology & Biometry
2. Geographical Pathology
3. Honolulu, Hawaii

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Honolulu Heart Disease Epidemiology Study

Previous Serial Number:

Principal Investigator: Abraham Kagan, M.D.

Other Investigators:
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.
George G. Rhoads, M.D.
Tavia Gordon

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:	18
Professional:	5
Other:	13

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:

Parallel studies began in Honolulu and in Hiroshima-Nagasaki in January 1965, utilizing comparable self-administered questionnaires specifically devised for the purpose. The study cohort in Hawaii was identified expeditiously through Selective Service registration records, the addresses being updated by the 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 are therefore 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, was completed in late 1965. Of the total 12,417 questionnaires which were mailed out, 9,887 eventually were completed and returned. These 9,887 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 triglyceride. The first examination of the cohort was completed in November 1968, with the examination of some 8,000 subjects.

A program of re-examinations was initiated in October 1967, with the examination format altered by the omission of the 24-hour diet history but with the addition of a brief, structured 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. The oral glucose load has been eliminated, but

blood is drawn and the serum is 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. By the end of June 1969, more than 4,000 men will have been examined for the second time.

A substudy, 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 approximately 1,000 brothers who are not in the cohort of 9,887, it will provide valuable data for characterizing a sizeable sample of the men who were not identified through the Selective Service mechanism.

Serum samples and electrocardiograms are being interchanged with the Hiroshima investigators, and staff pathologists from both Hiroshima and Honolulu are independently grading the atherosclerotic lesions in necropsy material from both areas. In addition, electrocardiograms are being mounted on identical forms and Xerox copies of these cardiograms are being interpreted and coded by trained personnel in the laboratory of Dr. Henry Blackburn in Minneapolis.

The third phase of the study is the on-going system of surveillance of hospitalizations and deaths in these subjects, with particular emphasis on 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, pretested 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.

Major Findings:

A preliminary comparison of the data accumulated during the first examination of the 8,000 Honolulu men with an examination cycle of the Hiroshima cohort has revealed similarities in measurements which would be consistent with the hypothesis of genetic similarity of the two populations;

that is, they are similar in height, in various anthropometric measurements and in their blood types. On the other hand, differences have been found in measurements which may reflect differences in their environment or in their way of life, such as in weight, skin-fold thickness and serum cholesterol determinations. In each of these cases, the measurements have been higher in the Honolulu men than in their Hiroshima counterparts, and in the case of the cholesterol determination, the finding is intermediate between those noted in Hiroshima and those previously reported for mainland Caucasian populations.

These findings in turn are consistent with what would be expected according to the dietary hypothesis of the relationship of dietary components in terms of calories and various types of carbohydrates and lipids to weight, obesity, and serum lipid measurements. A recent analysis of dietary components in the Hiroshima and Honolulu populations has shown the following striking differences:

Mean Value for Nutrients; 24-Hour Recall Nutrition Study

Nutrient	Hiroshima	Hawaii
Calories	2186 cal	2411 cal
Total Protein	76 g	99 g
Total Fat	37 g	92 g
Total Carbohydrate	342 g	273 g
Alcohol	31 g	13 g
Cholesterol	474 mg	569 mg
Animal Protein	39 g	73 g
Vegetable Protein	37	26
Saturated Fat	17	61
Unsaturated Fat	20	31
Simple Carbohydrate	63	94
Complex Carbohydrate	279	179
% Calories from Protein	14	17
% Calories from Fat	15	34
% Calories from Carbohydrate	65	46
% Calories from Alcohol	6	4
% Animal Protein	51	72
% Vegetable Protein	49	28
% Saturated Fat	45	65
% Unsaturated Fat	55	35
% Simple Carbohydrate	18	34
% Complex Carbohydrate	82	66

Between 1965 and 1968, 493 Japanese men who had been born between 1900 and 1920 died. According to their death certificates, 125 or 25% died of coronary heart disease, while 13% died of cerebrovascular accident.

Significance to Biomedical Research and to the Program of the Institute:

This study represents an important component in the overall program of the Geographic Pathology Section of the National Heart Institute. It was conceived as one portion of a tripartite 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 backgrounds but with different ways of life.

Proposed Course:

With the completion of the first examination cycle, the data tapes are in the process of being edited to permit final tabulations of descriptive data on the population cohort.

With the end in the delay of the funding of the California study, meetings have been planned to ensure the smooth and orderly integration of the California phase of the study into the rest of the tripartite format with particular emphasis on the common examination, diagnosis, and interpretation of findings relative to cerebrovascular disease.

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 pretested extensively; and agreement has been reached to use the 8th Revision of the International Classification of Diseases and Causes of Death to assure comparability with the other studies.

Common methods of data processing, tabulation, and analysis have been developed and agreed upon; and the first formal use of this common format will be used for the upcoming report to the American Heart Association.

A substudy has been started and will continue through the coming year on a sample of men stratified according to serum cholesterol levels to determine more quantitatively

their dietary intake by means of a 7-day diet record. Volunteers among them will have a needle aspiration of adipose tissue for analysis of the fatty acid composition by gas chromatography.

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

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

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 & Biometry, NHI

Other Investigators: 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: Christine Cole, 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	3/4 Professional		3/4
			18¼

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

Progress to June 1969: The baseline examination cycle to establish the characteristics of the urban and rural men age 45-64 was completed successfully in December 1968. An over-all response rate of 80.5 per cent was attained from the census enumerated subjects in the defined areas. A total of 9,802 men were examined and provide the baseline cohort for the incidence measurements which have already started. More than 2,500 subjects have now completed their second examination approximately 2 years from their first baseline measurements.

Data from the completed baseline examination cycle are now being prepared for extensive internal tabulations and correlations of variables. The prevalence cases of coronary heart disease will be used for analysis of risk factor characteristics, with particular interest in the physical activity and dietary variables.

Major Findings: The analysis of data from the first baseline cycle has not been carried out pending clean editing of the data which is still in progress. The preliminary data from the population show internal differences between rual and urban men in a variety of characteristics. Some of these are illustrated below:

Puerto Rico Heart Study Exam I Data, Males Free of CHD Age 45-69

	Urban	Rural
Physical activity index	31.2	38.0
Systolic blood pressure	135.2	129.0
Diastolic blood pressure	83.7	80.4
Heart rate	73.9	68.7
Height (in.)	65.1	64.4
Weight (lb.)	156.5	138.0
Vital capacity	30.9	31.7
Metabolic equivalent	45.9	62.0
Anxiety index	1.1	1.0
Monthly income (Dollars)	462	167
Serum cholesterol (fasting)	205.2	195.6
Triglycerides (fasting)	159.9	128.2
Glucose (fasting)	97.9	92.9
Calories	2394	2338
Dietary cholesterol (mg.)	439	358
SFA (gm.)	36.3	33.0
P/S ratio	0.50	0.34
% calories from fat	36.6	32.3
% calories from CHO	46.0	51.2
% calories from SFA	13.5	12.6
% calories from PFA	5.9	3.9
Salt index	26.9	29.9

Serial No.
1. Epidemiology & Biometry, NHI
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Significance to Bio-medical Research and the Program of the Institute: This major epidemiological study is the only one involving a large U.S. population now documented to have a mortality and prevalence of coronary heart disease substantially lower than generally found throughout the U.S. The significance of the demonstration that low coronary disease mortality and morbidity is an attainable natural biological state in a general population within the U.S.A. lies in the potential for delineating natural determinants for relative coronary disease prevention.

Findings in the Puerto Rico study will have more direct relevance to other U.S. populations than is likely to be possible from populations in under-developed countries where the limitations of medical care and surveillance, lack of autopsies and complications of indigenous diseases make interpretation of the determinants of coronary disease more complicated.

Proposed Course of Project:
1. Further intensive analysis of the data from the completed prevalence cycle will be continued and a report of findings is scheduled for presentation at the November 1969 American Heart Association's Scientific Session. A series of publications will also be scheduled.
2. Completion of one re-examination cycle to obtain reliable incidence data is a high priority further objective. The firm establishment of low incidence and the correlations against the baseline measurements will provide the confirmation or refutation of key hypotheses relating to risk factors and relative protection against coronary heart disease. The re-examination cycle is targeted for completion by December 1970 to provide an interval of two years between baseline and incidence examinations.
3. Concurrent morbidity, mortality and autopsy follow-up is established and will be continued to provide reliable end-point disease measurements and indices of severity of atherosclerosis in this population. This confirmatory evidence of reduced CHD mortality and severity of atherosclerosis will be needed for definitive evidence of low incidence of atherosclerotic coronary artery disease. Mortality and autopsy follow-up should continue beyond the termination of the incidence cycle examination in December 1970.

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

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

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, Fed. Inst. Pub. Health, Belgrade

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

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.
1. Epidemiology & Biometry, NHI
2. Geographical Pathology
3. Zagreb, Yugoslavia and Bethesda, Maryland

Man Years:				
Yugoslavia	4 Professional	12 Other	16
NHI	1/6 Professional		1/6
			16 1/6

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 adapted 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. The health status of living non-respondents has been established to some degree so that some information on the complete cohort is available.

Progress to June 1969:

1. The period since the last annual report has been one of follow-up for mortality from all causes with particular interest in coronary heart disease. Morbidity surveillance at health clinics and hospitals in the two communes has also been maintained by a full time nurse in each area. All deaths have been followed-up with the physician in attendance or with the family of the deceased to obtain descriptive information for confirmation of the diagnosis.

Serial No.
1. Epidemiology & Biometry, NHI
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2. All electrocardiograms from the Exam Cycle II showing definite or possible evidence of ischemic abnormalities have been re-read by the consultant cardiologist for uniform diagnostic interpretation. These final diagnoses will provide the basis for the comparative incidence measurements between the two populations.
3. All data from Exam Cycle II have been processed and edited with preparation of a clean tape for internal data analysis. The end-point diagnoses from the cardiologist readings of the ECG's are now being punched and entered on the tape for the analyses.

Major Findings: The further re-reading of electrocardiograms may change the incidence figures for new myocardial infarction to some degree, however, the overall incidence will still be extremely low-close to the level of 1 per 1,000 per year. Insufficient cases developed to allow comparison of characteristics for new cases of MI as contrasted with the population clinically free of CHD.

The high prevalence of impaired pulmonary function, 22 per cent vs 10 per cent for Framingham, provides a potential added area for investigation of chronic obstructive pulmonary disease.

Proposed Course of Project:
1. A report is being prepared for presentation at the Annual Scientific session of the American Heart Association in November 1969.
2. In view of the extremely low incidence of myocardial infarction found on Exam II, the final examination cycle is being deferred until the Fall of 1970. Further morbidity and mortality follow-up will be maintained during this period but no examination clinics will be established. An expanded effort in relation to the findings of high prevalence of chronic obstructive respiratory disease will be incorporated into the 1970 incidence examination cycle.

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.

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

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Nutritional Studies in Conjunction with Epidemiological Studies of CHD Conducted by the Branch.

Previous Serial Number: None

Principal Investigator: Jeanne Tillotson, Consultant Dietitian

Cooperating Units: Programa de Salud Del Corazon, University of Puerto Rico, San Juan, Puerto Rico.
Honolulu Heart Program, Honolulu, Hawaii.
Framingham Heart Program, Framingham, Massachusetts.
National Heart Institute Twin Study.

Man Years

Total:	1.5
Professional:	1.0
Other:	0.5

Project Description:

Objective: The nutritional studies in progress in the above areas are designed to assess the relationship of dietary habits to serum lipid levels, and to the prevalence and incidence of CHD. These particular geographic locations are of interest because dietary patterns common in Puerto Rico and Hawaii, (together with those being studied in the companion study in Hiroshima, Japan with the cooperation of the Atomic Bomb Casualty Commission) are sufficiently different from current mainland-USA dietary patterns to make possible an interesting natural experiment. Serum cholesterol levels also show different mean levels between Japan and Hawaii; differences also exist between rural and urban groups under study in Puerto Rico, and in general all levels are lower than those recorded in the Framingham Study. Principal differences between dietary intake levels in these areas versus mainland-USA lie in (1) generally lower levels of fat intake, (2) correspondingly lower intakes of saturated fat, (3) lower intakes of dietary cholesterol, (4) a larger proportion of the carbohydrate intake as starch, and (5) lower mean caloric intakes with generally higher levels of physical activity and correspondingly less obesity. These are all topics of current interest in this country; some of these were investigated furing the National Diet-Heart Study conducted in 1963-64 but no firm conclusions have yet been reached. Dietary patterns within Puerto Rico are changing with increasing urbanization and better economic conditions; the same is true of the Japanese who migrated to Hawaii. Dietary

patterns which prevail now are ideal for study; within a few years these dietary differences (and differences in mean serum lipid levels) may disappear.

The nutrition studies were initiated with the beginning of each study. Progress for the current year parallels the progress of each study as a whole. In addition, the Field Epidemiological Research Section has recently inaugurated the National Heart Institute Twin Study; a dietary interview has been developed for use in this area.

PHS-NIH
NATIONAL HEART INSTITUTE
July 1, 1968 through June 30, 1969
EPIDEMIOLOGY AND BIOMETRY

PUERTO RICO HEART PROGRAM

The first examination cycle ended at the close of the calendar year 1968. Tabulations of the dietary data for the entire first examination became available during the spring of 1969. The data was edited by computer using a program which listed subjects with dietary intake values above and below specified extreme limits. The data has subsequently been corrected on this basis. Tabulations have been outlined and formats described so that the dietary data can be correlated with other variables for inclusion in preliminary publications.

With the beginning of Exam II in July of 1968, a more intensive dietary interview form was set up for use on a population subsample. This modification of the Burke Dietary Interview technique is a method which is reputed to give more valid information on dietary intake of the individual. Forms and food composition tables were finalized and a pre-test was carried out early in fiscal 1969. Procedure books, coding rules and extreme values were set up for use in editing. The pre-test period closed September 30, 1968 and interviews conducted after October 1 were submitted for inclusion in the study.

Plans were drawn up to compare the calculated values included in the food composition table with those based on chemical analysis of locally consumed foods. Foods popularly used in Puerto Rico were listed and a protocol was drawn up for analysis of foods for total fat and fatty acid content. Samples were submitted late in 1968 and early in 1969.

The Exam I dietary data collected on 1490 fasting male subjects by Dr. Christian Gulbrandsen has undergone some preliminary analysis. This substudy included subjects undergoing their regular clinic examinations together with a more extensive lipoprotein electrophoretic workup (done only on men who were fasting). The preliminary analysis of this data was useful in looking at relationships of dietary intake patterns to serum lipid levels, particularly in preparation for setting up tabulations of the dietary data from the entire cohort.

HONOLULU HEART PROGRAM

The first examination cycle ended December 1, 1968. Processing of the dietary data is beginning with preliminary editing.

The second examination cycle began early in fiscal 1969. Procedures were drawn up for collection of written 7-day dietary records on a subsample of the subjects seen during Exam II. Procedures similar to those in use in Berkeley, California were adapted in order to achieve future comparability with the study to be carried out in San Francisco. One objective of collecting 7-day dietary records in Exam II was to "validate" the mean nutrient intake levels collected on all subjects by 24-hour recall in Exam I. The validation procedure was completed early in 1969; mean nutrient intake levels collected by 7-day records during Exam II were not significantly different from mean intake records of the same subjects collected during Exam I. Two small methodology studies were carried out--the 7-day records were calculated using two different methods of recipe calculation, and the usual use of table salt was ascertained on 50 subjects keeping 7-day dietary records.

The dietary protocol for the tripartite study (Hiroshima-Honolulu-San Francisco) was drawn up. Areas where strict comparability is possible as well as areas where comparability cannot be exact were spelled out.

A protocol for analyzing commonly used foods in Hawaii was drawn up. The actual analysis of food will not begin until fiscal 1970.

PHS-NIH
NATIONAL HEART INSTITUTE
July 1, 1968 through June 30, 1969
EPIDEMIOLOGY AND BIOMETRY

FRAMINGHAM HEART PROGRAM

The principal dietary study in the Framingham Heart Program was conducted a number of years ago. During the present fiscal year the male subjects age 46-64 were interviewed using a 24-hour dietary recall form designed to be very similar to those in use in Puerto Rico and Honolulu during the first examination cycles. The primary purpose for conducting the same type of interview in Framingham is to obtain up-to-date information on dietary intake patterns of mainland-USA men for comparison purposes.

THE NATIONAL HEART INSTITUTE TWIN STUDY

The study was initiated during the fall of 1968. The dietary interview consists of a 24-hour dietary recall together with a frequency-type dietary interview. Forms were drafted and pretested during the fall of 1968. They were finalized early in 1969 and clinic dietary interviewing procedures were finalized. Interviewing continues as subjects are brought in to a local clinic, and plans are under way for expansion of the procedure to the New England area.

Serial No.
1. Respiratory Disease
2. Epidemiology and Biometry
3. Bethesda, Maryland

Individual Project Report

July 1, 1968, through June 30, 1969

Project Title: Coordination of Cardio-Respiratory Research

Principal Investigator: Albert Roberts

Man Years:

Total:	1.0
Professional:	.9
Other:	.1

Objectives

To determine prevalence, incidence and causal factors in cardio-respiratory disease--with particular emphasis on chronic obstructive lung disease--through analysis of data collected by the collaborative studies of heart disease of the Epidemiology and Biometry Program.

Methods Employed

The ratio of the first second expiratory volume to the total Vital Capacity (FEV-1.0/FVC) was selected as principal screening tool for obstructive disease, setting values of 60% or less as criteria for positives. These are to be complemented with information on respiratory symptoms and other parameters after the standardized British questionnaire currently employed in every respiratory survey. Beginning with the Framingham study, where adequate data has been collected for at least the last ten years, a cross sectional study of the population at Examination V (1958-60) was done to identify a cohort of cases on which retro and prospective studies could later be made. Use of a common protocol based on the Framingham model was implemented in all the other studies (Honolulu, Puerto Rico, Yugoslavia, Israel), so that their data will be directly comparable thus permitting an identification of geographic and ethnic factors related to these diseases.

Major Findings

Analysis of Framingham V data yielded a prevalence profile of obstructive lung disease according to sex and age among 1350 males and 1612 females ages 35 to 70. Total prevalence among males was 10.2% (range 8.0% in the 35-39 years, and 21.5%/65-69 years) and for females 4.3% (range 3.4%/35-39 years and 7.7%/65-69 years.)

A preliminary analysis of data from Honolulu Heart Study on 1000 males gave a total prevalence of 15% (range 10.6%/45-49 years and 28.5%/65-69 years.)

Data collected in the first round of examinations of 2400 males at 2 different cities in Yugoslavia, one predominantly Christian, the other Moslem (PL-480 Project #178901) is undergoing thorough analysis. A total prevalence of 26.7% obstructive lung disease has so far been established for Remetinec, Croatia (Christian), against 18.9% for Tuzla, Bosnia (Moslem) and the reasons for the unexpectedly dissimilar urban/rural prevalences among these two cities (17.6%/31.2% at Remetinec; 26.1%/11.7% at Tuzla) are now being sought.

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

Investigations of chronic obstructive respiratory disease by epidemiological methods similar to those employed in studies of cardiovascular disease have been repeatedly urged by advisory groups in and outside the Government. Extension of the collaborative studies of heart disease conducted by the Epidemiology and Biometry Program into the area of respiratory diseases provides an economical and immediate way to gather knowledge that would be very costly and slow to obtain elsewhere.

Proposed Course

Analysis of Framingham V data will continue to explore the relationships of obstructive lung disease to every pertinent historical and social parameter and preparation of a report paper is planned within the next fiscal year. At the completion of current Examination X a comparative study of both surveys will be made to determine if incidence of these conditions is actually increasing as alleged by some. Retro and prospective studies will be attempted on identified cases in a search for clues to the causation of obstructive disease.

Exploration of Yugoslavia data will be continued in collaboration with Yugoslav investigators and this should produce an interesting report a few months hence. Plans are under discussion for a new PL-480 project to study environmental versus genetic factors influencing lung disease.

Collection of data by methods similar to those employed at Framingham is already underway at Puerto Rico, Japan, Honolulu and Israeli projects, in addition to Yugoslavia. This will permit future comparative study of geographic and ethnic differences in the frequency of obstructive lung diseases.

BLOOD PROGRAM

EXTRAMURAL PROGRAMS

ARTIFICIAL HEART

MYOCARDIAL INFARCTION

THE ARTIFICIAL HEART PROGRAM

of the

NATIONAL HEART INSTITUTE

ANNUAL REPORT

July 1, 1968 through June 30, 1969

THE ARTIFICIAL HEART PROGRAM
of the
NATIONAL HEART INSTITUTE

ANNUAL REPORT
July 1, 1968 through June 30, 1969

The Artificial Heart Program of the National Heart Institute has as its major goal the reduction of deaths and disability from all forms of heart disease through the development and use of a variety of therapeutically effective, safe and reliable circulatory assist devices, including total heart replacements. Work on the biological and physical problems involved is being done, at both the basic and applied levels and in both academic and industrial settings, by research and development groups under contract to the Artificial Heart Program. The primary monitoring of the scientific and technical aspects of these contracts is at a scientist-to-scientist level, with close contact between the Program Office scientific staff and the principal investigators of the various research groups.

The Artificial Heart Program is a systematic, goal-oriented research and development program. It outlines an overall plan based on the establishment of long-range and intermediate goals, identifies problems related to the achievement of those goals, and supports work designed to solve these problems in a timely, effective manner. In accordance with its program plan, which is subject to constant updating, the Program Office issues Requests for Proposals (RFPs) requesting work directed at the solution of specific problems related to the achievement of the program goals. Responses to such RFPs in the form of proposals are reviewed by three separate review committees and selections are made on the basis of their likelihood of contributing to the solution of the identified problems. Within the relatively broad scope of each RFP the Artificial Heart Program encourages prospective contractors to submit new and original ideas and techniques as well as improvements and modifications of existing concepts and devices. The Artificial Heart Program is a directed program and is, therefore, quite different from the research grant programs of the NIH, in which prospective grantees take the initiative in selecting research areas of interest to them.

Directed and goal-oriented research has been performed by investigators working under contract to the Program Office, in the following areas during the past year: the development and evaluation of materials compatible with blood, the physiologic effects of blood pumps in animals, the effects of additional endogenous heat, energy systems, the use of a biological fuel cell as a possible source of energy for circulatory assist devices, percutaneous leads, cardiac control parameters, new pump designs, blood flow studies, improved oxygenators, and instrumentation applicable to artificial heart development and utilization.

In addition, short-term contracts, of two- or three-months duration, have been awarded for the purpose of funding specific tasks identified by the Program Office. One task order was issued to secure animal models of arteriosclerotic heart disease in failure; two others were for an analysis of the emergency aspects of heart disease in order to enable the Program Office to make plans for programs.

It is the plan of the Program Office to make sure that all components, materials, and devices developed under the Artificial Heart Program are adequately and systematically tested before being considered for clinical use. A year ago contracts were awarded to 13 organizations for the preparation of plans for the establishment and operation by those organizations, of testing and evaluation facilities. These planning contracts were for six months; the reports and plans prepared during that phase were submitted and subsequently have been under extensive study and review. 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 and the ultimate utilization of the devices by the entire medical community would be inhibited.

During the past year, 28 contracts have been terminated; 5 new contracts have been awarded, and an additional 22 are currently under negotiation. It is expected that there will be a total of 106 active contracts under the Artificial Heart Program, as of June 30, 1969. Continued development in each of the above areas is planned for the next year. 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 PROGRAM, NHI
(Active during FY 1969)

STUDIES RELATIVE TO MATERIALS SUITABLE FOR USE IN CIRCULATORY ASSIST DEVICES

Recent technological advances in materials research and development have made available many new families of implant materials. Yet it is deficiencies in materials and a lack of knowledge about how they will work in the human body over a long period of time which are some of the key factors holding up the development of a totally implantable artificial heart. Research on materials and their effects on biological systems is therefore vitally important in ensuring the ultimate success of the total developmental effort of the Artificial Heart Program. Considerable progress in these areas has been made during the past year.

The commercial development of the majority of the earlier implant materials was of course not aimed at surgical applications. Rather, these materials were adopted in an empirical way because they seemed to possess the necessary compatibility and strength. The purpose of the present research projects is the planned development of materials suitable for cardiovascular use through the interdisciplinary collaboration between materials engineers, biologists, and the medical profession. The successful development of such prosthetic materials will to a great extent depend upon an increased understanding of the basic processes involved between different implant materials and the living tissue both at the cellular and at the molecular level, and some contractors are therefore exerting their primary efforts in these areas of research. Several hundred different materials have been formulated and tested in vitro and in vivo by Artificial Heart Program contractors. The materials are evaluated by subjecting each to a series of tests that become progressively more difficult. The most severe tests currently in routine use within the Program are the two-week in vivo implantation tests in dogs. Extremely encouraging results have been obtained with several of the recently developed materials.

An implanted device intended to become a permanent functional part of the human body may be considered a potentially hazardous bulk pharmaceutical. Reactions of cardiovascular materials to biological systems can be divided into two main categories: reactions with blood and reactions with tissues. Most immediate failures of cardiovascular prosthetic materials are related to problems in the first category. However, it is the long range performance under body conditions which ultimately limits the application of a particular prosthetic material or device.

The purpose of the current biological testing programs is to contribute to the development of reliable and meaningful biological specifications, ensuring the human safety of cardiovascular implant materials. The successful achievement of this goal will serve as a useful guide for future development of materials designed specifically for cardiovascular use.

The materials investigated during the previous year's contracts represented only one of three possible avenues for the development of improved cardiovascular tissue replacements. The materials developed and evaluated during this year's contracts, on the other hand, represent both of the two main approaches, namely: (i) The concept of a prosthesis (suggested designation:

"homoprosthesis"), composed entirely of a more or less homogeneous mass of foreign material, the surface of which is rendered smooth and antithrombogenic so as to be suitable for continuous, direct contact with flowing blood in humans. (ii) The concept of a prosthesis (suggested designation: "heteroprosthesis") composed of a mixture of foreign inert material and living tissue, existing in the body as a unit. In this case the material acts only as a porous or fibrous scaffold into which tissue cells can migrate in vitro or in vivo. The scaffold can be made flexible, semi-rigid, or rigid as the need may be. Once the surface of such a "heteroprosthesis" becomes completely covered with tissue cells, it has been found to possess antithrombogenic properties similar to those of normal endothelial-lined cardiovascular surfaces. Thus, almost any candidate material can be considered for "heteroprosthesis" use, as long as it is compatible with human body cells and cellular products. The "heteroprosthesis" has a third advantage in that it is self-renewing, allowing the natural life processes of cell death and cell division to proceed in response to the continuous high rate of wear and tear within the cardiovascular system. The third concept of a compound cardiovascular replacement (Wesolowski, 1959) consisting of both permanent and adsorbable components has not yet been investigated during these contracts. However, it would be the logical extension of the "heteroprosthesis" concept. Partially or completely resorbable "heteroprostheses" of different sizes and shapes might have great future potential, particularly in pediatric cardiovascular reconstructive surgery. It should become possible, in the future, to program the interlocking of, the gradual resorption of, and physiological excretion of the reinforcing foreign material scaffold in such a manner as to allow the continuous growth and increase in size of the "heteroprosthesis" to proceed in pace with the increasing age and size of the child.

Materials Development

During the past year significant advances in materials development have been made by Artificial Heart Program contractors. Seventeen contractors are contributing to these efforts. Specific current approaches include the development of techniques for improving the bonding of heparin to surfaces and devices; studies aimed at improving the fabrication and surgical handling properties of non-thrombogenic silicone elastomers; ways of improving the surface characteristics of silicone polymers in the body environment; studies of non-thrombogenic carbonaceous materials; the development of epoxy resins with excellent anticlotting activity; further evaluation of polyelectrolyte complexes as antithrombogenic materials; studies of thromboresistance of modified celluloses in relation to functional groups; investigation of synthetic hydrogels for non-thrombogenic properties; studies of the electrical effects of polymers on the initiation of thrombosis; the development of a mechanically useful peptide-like polymer; basic studies of the physicochemical factors involved in blood compatibility; the preparation of segmented copolymers with potential for use in contact with blood; development of a solid-walled vascular prosthesis which contains an inner, blood-contact layer of covalently bonded cholesterol and sialic acid; the reconstruction of differentiated tissue layers from dissociated cells; and the development of textile structures for preparing composite materials with a surface of

micro-cellular anchoring devices. Below are summaries of the contract work which has been done during the past year on materials development.

Amicon Corporation, Lexington, Massachusetts

POLYELECTROLYTE COMPLEXES AS ANTITHROMBOGENIC MATERIALS. H.J. Bixler, R. A. Cross, and D. W. Marshall.

This contract is concerned with the evaluation of polyelectrolyte complexes (Ioplex) as antithrombogenic materials. During an earlier contract it was demonstrated by in vivo tests that a slightly anionic form of Ioplex was antithrombogenic. During the past year efforts have been directed toward the further characterization of these materials. Sufficient tests have been completed to indicate a possible correlation between the polyanionic density and the thrombo-resistant characteristics. Reinforcement of the polyelectrolyte complexes has been accomplished by the use of polyester or special glass fabrics so that a range of strengths and stiffness can be made available. Attempts to improve the basic structure have resulted in new materials which also exhibit antithrombogenic properties and may offer certain advantages over current systems.

Contract Amount: $134,020 Contract Number: PH43-66-1129

Battelle Memorial Institute, Columbus, Ohio

DEVELOPMENT OF HEPARINIZED MATERIALS FOR USE IN CIRCULATORY ASSIST DEVICES. G. A. Grode, R. D. Falb, and S. J. Anderson.

The objectives of this research program are: modification of materials to produce non-thrombogenic surfaces and studies of the basic interactions occurring at the blood/foreign surface interface. Techniques were developed for both ionic and covalent bonding of heparin to a wide variety of polymers including all of those currently used for prosthetic devices. A method for ionic bonding of heparin using water-insoluble quaternary ammonium salts was developed and results show good in vitro and in vivo performance. Studies of the blood/foreign surface interface were carried out. The basic interactions of blood components such as lipids, lipoproteins, proteins, coagulation factors and formed elements with heparinized and control surfaces were investigated. Heparinized surfaces prepared by means of water-insoluble quaternary salts were found to interact strongly with lipid and lipoprotein components upon initial contact.

Contract Amount: $197,611 Contract Numer: PH43-68-649

University of California, San Diego, California

RECONSTRUCTION OF DIFFERENTIATED TISSUE LAYERS FROM DISSOCIATED CELLS: USE OF TISSUE CULTURE TECHNIQUES TO DEVELOP NONTHROMBOGENIC AUTOLOGOUS CELL SURFACES FOR USE AS CARDIAC LININGS. Leonard Schutz, M.D., Clifford Grobstein, Ph.D., Ruth Grobstein, Ph.D., Brian S. Bull, M.D., and Nina S. Braunwald, M.D.

This program is concerned with tissue culture studies aimed at accelerating the growth of cells within microfiber materials. The rationale behind these studies is that it has been found that the lining of exposed portions

of a prosthesis with a porous fabric results in the deposition of an autologous tissue lining which in turn appears to be highly resistant to thrombosis. However, this development takes over a month to be completed in experimental animals and is certain to take longer in humans. The current studies are aimed at accelerating the process of cellular infiltration by allowing the materials to be in contact with growing cells prior to implantation in vivo, so that the tissue covering will be complete either at the time of implantation or shortly thereafter. In order to achieve this goal, fabric lattices are being seeded with cells from autologous endocardium, endothelium, circulating leukocytes, bone marrow, skin, or blood vessel adventitia, and then grown in tissue culture prior to reimplantation in the body.
Contract Amount: $60,000 Contract Number: PH43-68-1378

Carnegie-Mellon University, Pittsburgh, Pennsylvania

THE HEPARINIZATION OF SILICONE RUBBER USING AMINOORGANOSILANE COUPLING AGENTS. Robert L. Merker, Liberty J. Elyash, Susan H. Mayhew, and Jean Y. C. Wang.

The major goal of this research program is to improve the surface characteristics of silicone polymers in the body environment with particular emphasis on achieving a higher degree of nonthrombogenicity. In the first phase of this investigation, finely divided silicas were successfully heparinized utilizing aminoorganosilanes as coupling agents. The incorporation of these heparinized silicas as fillers into polymeric systems such as room temperature vulcanizable silicone rubbers and polystyrene led to only modest improvement in surface characteristics based on Lee-White blood clotting times. The second phase of the research concerned the heparinization of vulcanized silicone rubber already containing finely divided silica as a reinforcing agent. Utilizing this approach, surfaces possessing greatly enhanced non-thrombogenic character were reproducibly obtained.
Contract Amount: $105,000 Contract Number: PH43-66-977

Denver Research Institute, Denver, Colorado

DEVELOPMENT OF COAGULATION RESISTANT COATINGS BY BONDING KNOWN INHIBITORS OF BLOOD COAGULATION FACTORS TO THE SURFACE OF PROSTHETIC MATERIALS. H. Yen, R. Predecki and J. D. Andrade

This contractor has attempted to develop blood compatible surfaces produced by bonding known inhibitors of blood coagulation factors to the surface of prosthetic materials or incorporating such inhibitors within the structure of the material. The rationale behind this contract is to develop materials which prevent the coagulation process at its beginning, contact activation, rather than relying on an anticoagulant which stops coagulation after it has already been initiated. One of the promising materials developed during this contract is polystyrene which has been chloromethylated and then reacted with bovine albumin. Acute in vivo studies conducted at Johns Hopkins on albuminated polystyrene vena caval rings look quite encouraging. This is the first surface evaluated in vivo during the Artificial Heart Program which does not depend upon either heparin or heparin-like negatively charged radicals, and yet shows good thromboresistance. This program was terminated on April 30, 1969.
Contract Amount: No additional funds Contract Number: PH43-67-1407

Dow Corning Corporation, Midland, Michigan

DEVELOPMENT OF BLOOD COMPATIBLE SILICONE ELASTOMERS. Martin C. Musolf, Verne D. Hulce, and Virgil L. Metevia.

This study is aimed at improving the fabrication and surgical handling properties of potentially non-thrombogenic silicone elastomers. Thermoplastic silicone elastomers were prepared and evaluated. Three promising trifluoropropylmethylpolysiloxane containing elastomers were implanted for chronic two-week periods. The results continue to indicate that these elastomers can possess non-thrombogenic characteristics. The high durometer elastomer, RB-1622, containing fluoroalkyl functionality was shown to be thrombotic. One thermoplastic elastomer containing a 50/50 mole ratio of tetramethylsilphenylene/dimethylsiloxane was found to be quite non-thrombogenic while another with a 75/25 mole ratio was very thrombotic. Parts molded from two promising silicone elastomers were submitted to four NHI sponsored contractors for testing.

Contract Amount: $60,251 Contract Number: PH43-66-979

The Epoxylite Corporation, South El Monte, California

DEVELOPMENT OF MATERIALS FOR ARTIFICIAL HEARTS AND BLOOD OXYGENATORS. Henry Lee, Donald G. Stoffey, and Frank Abroson.

The purpose of this research is to develop a solid-walled vascular prosthesis which contains an inner, blood-contact layer of covalently bonded cholesterol and sialic acid, that may simulate the environment of the natural intima, and a soft outer layer of a flexible plastic for tissue compatibility. Polyvinyl alcohol films and test tubes were lightly and heavily esterified by steric acid, by the adipic acid monocholesterol ester (AAME), and by a combination of AAME and dodecanedioic acid monosialic acid ester (DAMSE). PVA, stearated PVA, and PVA lightly esterified with AAME had clotting times in the range of most other plastic surfaces. Two materials, Lycra T-126 and Roylar A-850 seemed to offer the most promise. Tensile bars of these two materials were made and tested. Also tensile bars were implanted in dogs for long term compatibility studies. The synthesis of more soluble spandex materials has been started.

Contract Amount: $59,313 Contract Number: PH43-68-1379

Gulf General Atomic, San Diego, California

COMPATIBILITY OF CARBON AND BLOOD. L.D. LaGrange and J.C. Bokros

The objective of this program is to determine the relationships between the crystal structure, surface topography and surface chemistry of a variety of different carbonaceous materials and their compatibility with blood. Past work has shown that certain outgassed and smooth surfaces of isotropic carbons deposited at low temperature (LTI carbons) have significant thromboresistant properties which are independent of the usual pretreatments with benzalkonium chloride and heparin. One aspect of the current work has involved developing methods to firmly bond heparin covalently to these surfaces and thus provide added active suppression of coagulation initiated at the blood-carbon interface. In vivo results from tests at the Johns Hopkins Hospital during the current contract year have shown that porous carbon Gott rings are quite thrombogenic if they are implanted without pretreatment but

are significantly thromboresistant if pretreated in such a way that the benzalkonium-heparin complex is formed and held within the accessible porosity. In vivo tests also show as-deposited outgassed coatings with a preponderance of layer faces at the blood-carbon interface are more thromboresistant than isotropic coatings.
Contract Amount: $41,980 Contract Number: PH43-67-1411

Harris Research Laboratories, Rockville, Maryland

INTERACTIONS OF HEPARINIZED AND NON-HEPARINIZED SURFACES WITH BLOOD. Vera R. Usdin and Lyman Fourt

Work carried out during the contract year was divided into two areas: investigations of the properties of ionically bound heparin, and attempts to prepare non-heparinized, anticoagulant surfaces. The investigations with heparinized surfaces included the development of a non-destructive, colorimetric procedure for measuring heparin-loading of opaque and treatment materials, the preparation of surfaces evenly coated with varying amounts of heparin, and studies of the desorption of heparin from surfaces. Attempts were made to prepare anticoagulant surfaces by brief treatment of polycarbonate (Lexan) with sulfonating agents. Under the particular experimental conditions employed, the use of sulfonating agents did not lead to satisfactory materials. This program was terminated on October 28, 1968.
Contract Amount: No additional funds Contract Number: PH43-68-38

Melpar, Incorporated, Falls Church, Virginia

ANIONIC CELLULOSE: A POTENTIAL BLOOD COMPATIBLE MATERIAL. Robert G. Nemchin.

In earlier studies by this contractor it was demonstrated that chemically modified celluloses were thromboresistant in vitro and showed promise in vivo. The degree of thromboresistance depended on the type and distribution of the modifying functional group; anionic celluloses (phosphate, sulfonate, carboxymethyl) were essentially blood compatible, while cationic celluloses (diethylaminoethyl, quarternary ammonium) were not. If the degree of cellulose functional group substitution was greater than 0.10 (i.e. one group per 10 glucose residues) significant thromboresistance was observed. The weakly acidic carboxymethyl group was the most effective. Recent structure-function studies with carboxymethyl cellulose (CMC) and structurally related derivatives (oxy-, α-propionate-, esterfied CMC) show a direct relationship between D.S. and in vitro thromboresistance and solubility. This relationship holds for both the oxycelluloses and the CMC, but not for the other derivatives.
Contract Amount: $97,100 Contract Number: PH43-67-1413

Monsanto Research Corporation, Dayton, Ohio

FURTHER STUDIES OF EPOXY RESINS. I.O. Salyer and W.E. Weesner.

Epoxy resins with heparin uniformly distributed throughout were studied in vivo and found to possess excellent anticlotting activity. Compositions 3 and 7 parts of heparin/100 parts of resin (phr) have passed the chronic 2-week in vivo test. Strength and toughness of these products have been improved by curing with "Ajicure", a cyclic ether amine. Samples of heparin-containing epoxy polymers are being prepared for evaluation by nine other

contractors. A study of polymers that do not contain heparin was also continued. Epoxy resins containing Santomerse SX (an alkylbenzene sulfonate), Fluronic F-68 (a non-ionic detergent), EN-1661L (from Endo Laboratories), and vinylpyridine/ethyl acrylate copolymer showed no anticlotting activity in in vitro tests. The first three samples were tested in vivo and the products with EN-1661L and Pluronic F-68 had moderate anticlotting activity in the acute, 2-hour test.
Contract Amount: $75,000 Contract Number: PH43-66-975

Monsanto Company, Everett, Massachusetts

THE DEVELOPMENT OF TEXTILE SURFACES COMPATIBLE WITH BLOOD. E.S. Nuwayser

The objective of this program is to develop textile structures for preparing composite materials with a surface of micro-cellular anchoring devices (micro CAD) having a "pile" height of 15-30 microns. The devices will be used to anchor fibroblastic and endothelial cells to form a "living" surface similar to that present on the intimal wall of the adult normal artery. The approaches which have been investigated for preparing the textile structures include nonwoven fabrics, flocked surfaces, knitted and woven fabrics, textured surfaces, polyblend fibers, and core wrap yarns. Sheets and tubes were fabricated from these structures and submitted for animal evaluation. They were made from nylon, polyester, carbon, and silicone rubber, and were prepared in "pile" heights ranging from 15-400 microns. Methods for determining the entrapment of fetal calf fibroblasts by the surface are being studied.
Contract Amount: $134,300 Contract Number: PH43-67-1417

Polysciences, Incorporated, Warrington, Pennsylvania

HYDROGELS AS NON-CLOTTING SURFACES. B. David Halpern, Hsiung Cheng, Shen-yeh Kuo and Herman Greenberg.

A number of synthetic hydrogels which approximate some of the physical characteristics of tissue were investigated for non-thrombogenic properties. Parameters which were studied in relation to clotting behavior included the nature of the polymer backbone, gel solids, % cross-linker, gel osmolality, heparin in gel, pH, and various ionic and non-ionic functional groups pendant on the polymer backbone. At 20% of polacrylamide solids, significant anti-thrombogenic character was found. For non-purified acrylamide, Lee White times of approximately 45 min. were found, whereas greater than 24 hrs. resulted for purified acrylamide. Basic or acidic comonomers in low mole percent resulted in very significant improvement in clotting time. Dimethylaminoethylmethacrylate with unpurified acrylamide was the best of a number of weak base monomers studied, showing clotting times greater than 24 hrs. Strongly cationic comonomers were not effective.
Contract Amount: $55,365 Contract Number: PH43-66-1124

Shell Development Company, Emeryville, California

BLOCK COPOLYMERS FOR USE IN BLOOD PUMPS AND OXYGENATORS: PREPARATION AND CHARACTERIZATION. Eugene T. Bishop and William P. O'Neill.

The objective of the present program is to prepare segmented copolymers with potential for use in contact with blood. The techniques of block

copolymerization and chemical derivatization were employed to synthesize new elastomeric substances which might be useful in cardiovascular assist devices. Two general types of block copolymers have been prepared: 1) hydrophobic, saturated hydrocarbon materials, and 2) materials containing polar groups in order to make them hydrophilic and anionic. By performing various derivatization reactions on the block copolymer polystyrene-polyisoprene-polystyrene, materials with useful concentrations of hydroxyl, carboxylate, sulfate and sulfonate groups in continuous phases were prepared and characterized. Evaluation and comparison of this homologous series in contact with blood is under way.

Contract Amount: $99,995 Contract Number: PH43-68-1299

Stanford Research Institute, Menlo Park, California

THE EFFECT OF CHEMICAL STRUCTURE AND SURFACE PROPERTIES OF SYNTHETIC POLYMERS ON THE COAGULATION OF BLOOD. Donald J. Lyman, John L. Brash, and Karen G. Klein.

This contractor has continued to develop information on the physico-chemical factors involved in blood compatibility. Studies were performed on the interaction between platelets in flow systems rather than static systems. It was shown that platelet adsorption decreases with decreasing critical surface tension of the polymer surface. The lower energy surfaces, and thereby the surfaces with lower platelet adsorption, are the less thrombogenic. Polymer surfaces that have been precoated with a plasma protein monolayer - a layer in which the protein is in its native globular state - showed marked reduction in platelet adsorption. These data indicate that platelet-polymer interaction is the initiating step in in vivo clotting on neutral, hydrophobic polymer surfaces. A variety of new segmented urethane elastomers were also prepared as potential candidates for intra-aortic balloons. These materials show low platelet adsorption and can be prepared with a variety of mechanical properties.

Contract Amount: $37,743 Contract Number: PH43-64-84

Thermo Electron Corporation, Waltham, Massachusetts

STUDIES ON THE ROLE OF ELECTRICAL EFFECTS AT POLYMER SURFACES ON THE INITIATION OF THROMBOSIS. P. Murphy, A. Lacroix, and S. Merchant

The objective of this program is to examine the role of electrical effects at polymer surfaces on the initiation of thrombosis, and to improve the thrombus resistance of selected polymers by means of persistent electrical polarization. Parallel efforts have been carried out on the characterization of surface properties related to the electret state in polymers, on the stability of the electret state under simulated blood pumping conditions, and on in vitro and in vivo blood compatibility experiments. In all cases, negatively polarized samples showed improved blood compatibility in vivo. No significant difference in clotting time in vitro was observed for polarized samples. However, the materials with negative charge did adsorb fewer platelets.

Contract Amount: $24,000 Contract Number: PH43-66-1126

Union Carbide Corporation, Bound Brook, New Jersey

THE DEVELOPMENT OF PEPTIDE-LIKE POLYMERS FOR CIRCULATORY ASSIST DEVICES. Joseph S. Byck, Sui-Wu Chow, Leonhard J. Gonsior, Walter A. Miller, William P. Mulvaney, Lloyd M. Robeson, and Mark A. Spivack.

This program is concerned with the development of a mechanically useful peptide-like polymer by block copolymerization of poly (amino acids) with polysiloxanes. Recent experiments have shown that difunctional hydroxyl terminated poly (α-benzyl L-glutamate) oligomers can be prepared and then coupled with suitably terminated silicones to produce promising block copolymers. In a second phase of the program, the factors influencing polyelectrolyte blood compatibility are being studied by systematic synthesis of several families of carboxylic and sulfonic acid substituted copolymers. Attention has also been given to the problem of developing a polymeric material which can be rendered compatible by growth and anchoring of a thin nondegenerating neointima. The fabrication of such an experimental material has been accomplished. These gossamer networks can be reinforced and bonded to a nonporous support by vapor deposition of a several thousand angstrom conformal coating of a Parylene polymer.

Contract Amount: $189,727 Contract Number: PH43-68-1388

Materials Testing

The materials testing activities of the Artificial Heart Program are designed to permit timely evaluation of materials in order that they are not prematurely used or inadvertently rejected because of a lack of knowledge concerning their in vitro or in vivo performance. The long life and high reliability requirements of the final intra-thoracic prosthesis require extensive physical, mechanical, and biological evaluations to eliminate harmful iatrogenic effects on blood and tissues. During the past year, seven contractors have directed their efforts toward biological evaluations of the output of the various materials and device developers, while two contractors have been primarily concerned with studies of the physical and mechanical properties of materials and finished devices.

The decision as to which materials to select for extensive biological evaluation is made on the basis of physical, chemical, and preliminary blood compatibility studies conducted by each individual contractor while developing the material. The selected material is then produced in quantities sufficient to permit repeat evaluations by several contractors designated by the Program Office to perform biological evaluations on other contractors' materials. These projects insure the use of uniform testing conditions, permit effective comparison between existing and new materials, and aid in the continuous development and updating of methodology. Close collaboration between the materials developers and the materials testers is encouraged in order to promote rapid communication of new findings, of importance to the planning of future material modifications.

Each material is carefully investigated to insure its safety for ultimate use in humans. It is screened by a series of tests to determine that it

does not exhibit undesirable properties on contact with blood or tissues, e.g., toxicity, inflammatory responses, allergic effects, carcinogenicity, or other identifiable adverse actions on cells or body constituents. The blood compatibility of each material is given a comparative numerical rating based upon results obtained with various in vitro and ex vivo systems. Electrochemical and biophysical studies are pursued in an effort to develop criteria for the selection of materials compatible with blood. The effect of materials on plasma proteins is investigated. Special microscopic techniques are employed to study the interface between the materials and blood or tissue cells. Tissue culture carcinogenesis studies of the materials have been initiated. The possible immunogenicity of autologous plasma proteins being adsorbed on the candidate materials is investigated. Two approaches are being utilized in an attempt to develop tissue indicators of embolic and thrombotic episodes occurring at the surface of intravascular implants. The effect of blood pumps on the physiology and structure of leukocytes is being studied. Materials showing reproducibly satisfactory results in the in vitro evaluation systems are subjected to increasingly severe in vivo evaluations in dogs. When the materials have passed these in vivo evaluation tests they are finally considered for incorporation into cardiovascular devices and subjected to further biological testing in animals under actual operational conditions.

The fabricated devices are also extensively tested with respect to their physical and mechanical characteristics in order to insure their efficacy, safety, reliability, applied quality control and other pertinent characteristics.

Battelle Memorial Institute, Columbus, Ohio

FURTHER STUDIES OF THE INTERACTION OF BLOOD AND TISSUE CELLS WITH ARTIFICIAL HEART IMPLANT CANDIDATE MATERIALS IN VITRO. R. J. Hegyeli, R. Gallagher, and C. Pennington.

The objectives of this study are cell culture studies with prosthetic materials, further development of a dynamic test system, investigation of other contractors materials, and scanning electron microscopy studies. Thirteen materials contractors are providing materials for study. Several new observations which may be of practical importance to the development of and evaluation of prosthetic materials were made, i.e., (1) Human cells were found to react differently to certain materials than did animal cells. (2) The treatment necessary to render a material nonthrombogenic sometimes results in a surface which is highly toxic to tissue cells. Studies recently initiated will concentrate on the evaluation of microfiber materials.
Contract Amount: $76,045 Contract Number: PH43-67-1404

Cordis Corporation, Miami, Florida

STUDIES OF THE EFFECTS OF IMPLANT MATERIALS ON PLASMA PROTEINS. Seymour P. Halbert, Milton Anken, and Alexis E. Ushakoff.

The effects of various implantable materials on plasma proteins have been further investigated in a specially devised experimental system, using a

large number of specific parameters for evidence of denaturation. A carbon surface, polycarbonate, several acrylamide surfaces, and silicone rubber proved relatively inert toward plasma proteins. Silicone rubber and polyurethane heparinized by means of quarternary ammonium salts produce profound turbidity of plasma due to denaturation of lipoproteins. This effect was found to be due to the quarternary ammonium salt rather than the heparin. Heparinization by a different technique via an amino-organesilane covalently bonded cause no similar effect.
Contract Amount: $173,250 Contract Number: PH43-66-980

The Holter Company, Bridgeport, Pennsylvania

THE FABRICATION AND EVALUATION OF IN VIVO TEST UNITS AND BLOOD PUMPS FOR IN VITRO TESTING. John L. Hausner, Robert E. Pickup

This project is concerned with the fabrication and evaluation of test devices, designated by the Artificial Heart Program, from materials selected by the Artificial Heart Program. The fabricated devices are evaluated with respect to their physical and mechanical characteristics in order to insure their efficacy, safety, reliability, applied quality control, and other pertinent characteristics. All fabrication, quality control, and specific testing procedures are defined by the Artificial Heart Program Office, and the materials supplied for fabrication purposes are not analyzed or utilized for any purpose other than fabrication of devices.
Contract Amoutn: $112,925 Contract Number: PH43-68-1402

Johns Hopkins University School of Medicine, Baltimore, Maryland

THE IN VIVO SCREENING OF POTENTIAL THROMBORESISTANT MATERIALS. Vincent L. Gott, Manuel D. Ramos, Faysal B. Najjar, James L. Allen and Karl E. Becker.

The primary purpose of this study has been to screen potentially thromboresistant materials which have been developed by research groups supported by the Artificial Heart Program. After considerable experience with several in vivo test techniques this contractor has found that the inferior vena caval rings provide the most consistent information with regard to material thromboresistance. Materials from twelve different materials contractors have been evaluated with extremely encouraging results. Effects were also directed towards the development of standardized, more severe screening tests.
Contract Amount: $35,200 Contract Number: PH43-68-84

University of North Carolina, Chapel Hill, North Carolina

IN VITRO AND EX VIVO BLOOD COMPATIBILITY STUDIES OF IMPLANT MATERIALS. R. G. Mason, D. E. Scarborough, H.G. Clark, L. D. Ikenberry, and J. J. Kearney.

Blood compatibility studies have been conducted in one in vitro and two different ex vivo test systems of fifteen polymeric and three nonpolymeric materials. Based upon these studies the following materials were listed in order of decreasing compatibility with blood: collagen, L-1624 (3M Co.), poly(dicholoro para xylylene), carbon-graphite, poly(methyl acrylate) isotactic, balata rubber, poly(methyl methacrylate), poly (hydroxypropyl methacrylate), hevea rubber, and poly(exymethylene). The type and number of surface reactive groups were found to correlate poorly with observed blood compatibility.
Contract Amount: $100,000 Contract Number: PH43-67-1416

State University of New York, Brooklyn, New York

ELECTROCHEMICAL AND BIOPHYSICAL STUDIES OF IMPLANT MATERIALS. P.N. Sawyer and S. Srinivasan.

Electrochemical and biophysical studies are being made aimed at the selection of materials compatible with blood. Studies on a number of materials show that (i) with conducting materials, all those which establish negative rest potentials in blood tend to be antithrombogenic while those registering positive potentials are always thrombogenic; (ii) with insulator materials, the homogenously negatively charged surfaces tend to be non-thrombogenic; (iii) conducting materials, even if they are normally thrombogenic at their spontaneous potentials (such as is the case of copper), when cathodically polarized to negative potentials, are non-thrombogenic. Powders of various materials were mixed with blood to determine their blood destructive and anti-thrombotic characteristics. These studies show that chemically treated (sulfonated, carboxylated) insulator materials cause minimum destruction of blood components and prolong blood clotting times. The antithrombogenic characteristics of homogeneously negatively charged clean surfaces and the thrombogenic characteristics of both positively charged and unevenly charged surfaces was demonstrated.

Contract Amount: $89,934 Contract Number: PH43-68-75

Travenol Laboratories, Inc., Morton Grove, Illinois

IMMUNOGENIC EFFECTS OF MATERIALS ON PLASMA PROTEINS. Ivan J. Stern, Andreas A. Kapsalis, and Barbara L. Neil.

A possible characteristic of materials which may have long term toxic potential is the promotion of immunogenicity in absorbed autologous plasma proteins. Implants of materials promoting immunogenicity in autologous proteins would present constant antigenic stimuli to the recipient which might predispose towards autoimmune phenomena or neoplastic plasma cell transformations. Tests for immunogenicity are beginning to be performed with materials samples of smooth surface and high surface-area-to-volume ratios.

Contract Amount: $89,483 Contract Number: PH43-68-1411

University of Vermont, Burlington, Vermont

DEVELOPMENT OF TISSUE INDICATORS OF EMBOLIC AND THROMBOTIC RESPONSES TO IMPLANT MATERIALS. B. Kusserow, R. Larrow and J. Nichols.

Two approaches have been utilized in an attempt to develop sensitive tissue indicators of embolic and thrombotic episodes occurring at the surface of prosthetic intravascular implants. One technique involves supplementation of the currently used caval ring implant system (in dogs) by experimental alteration of the pulmonary circulation in such a fashion that the lung becomes susceptible to infarction subsequent to the lodgment of embolic particles in the pulmonary arterial bed. A second method utilizes the renal vascular bed and parenchyma in a similar fashion. The resulting infarcts serve as permanent tissue markers of embolic events. A third technique measures the effects of material tubing and prolonged blood pumping on leukocytes. Effects observed were: changes in physiology, alterations in morphology, and a decrease in number.

Contract Amount: $29,913 Contract Number: PH43-68-1427

Western Gear Corporation, South Gate, California

DEVELOPMENT OF FABRICATION TECHNOLOGY FOR CIRCULATORY ASSIST DEVICES. John Sprung.

This project is concerned with the development of techniques to produce pre-production quantities of an intra-aortic balloon/catheter emergency assist type device and the fabrication of prototype devices such as blood pump components for left heart assist devices. Several major problem areas have been identified and improved quality control instituted. These improvements in fabrication technology have resulted in a reduction of the high percentage of rejects experienced with previous production techniques.

Contract Amount: $39,199 Contract Number: PH43-68-1426

CIRCULATORY ASSIST DEVICES

The goal of the Artificial Heart Program is the development of mechanical assist and total heart replacement devices having maximum assurance of safety and clinical effectiveness. During the past year, work on emergency, temporary and permanent circulatory assist devices and a total heart replacement device has been supported. In recognition of the fact that large numbers of patients die, either en route to a medical center or shortly after admission, increased attention has been paid to devices for emergency application. In addition, advances during the past year in the area of energy transmission and conversion have prompted increased attention to the laboratory evaluation of the left ventricle-to-aorta bypass pump. Since the development of drive control units for individual assist devices is an important part of most of these contracts, a great deal of effort has been put forth by Program Office personnel to insure that these units have maximum triggering accuracy and reliability.

Fluidonics Research Laboratory, Salt Lake City, Utah

ALL FLUID CONTROL SYSTEM TO COUPLE A STIRLING ENGINE GAS COMPRESSOR TO A LEFT VENTRICULAR ASSIST DEVICE. G. H. Peterson, A. G. Kessler and G. H. Thorne.

A fluid control system has been under development to couple a Stirling engine gas compressor to a left ventricular assist device via a piston-type pump actuator. The pump actuator is powered by the compressed gas and delivers liquid to the assist pump for actuation. The control system components developed control the actuator motion to result in variable stroke volume and variable pulse rate operation of the assist pump in response to natural heart requirements. The pump actuator is powered both during assist pump systole and diastole and therefore is an active filling system. The control system is designed to limit the minimum assist pump pressure during filling. Control components are employed in both the gas and liquid areas of the system. The present control concept developed from a study of the possible use of fluidic (no moving parts) components for both control and power delivery to the assist pump. The study was designed to identify the best fluidic components, their size, and efficiency for use in the implantable assist application. The results of this initial study demonstrated that, while fluidic devices could be used in non-implantable systems, inherent inefficiencies in all fluidic components negated their potential use in implantable assist systems. The fluidic work in which the Program has been involved will not be continued because of the information which was developed on efficiency and on the applicability of all fluidic devices. The work involving fluid logic circuits and mechanical valving techniques will be continued in order to establish a system that utilizes the optimum characteristics of each. The combined system will be used in control of assist devices.
Contract Amount: $59,850 Contract Number: PH43-68-1446

Hamilton Standard Division, Farmington, Connecticut

DEVELOPMENT AND INITIAL PHYSIOLOGICAL EVALUATION OF THE CO-PULSATION TECHNIQUE FOR CIRCULATORY ASSIST. B. L. Hochman, T. Sato (Yale University), and W. L. Sugg (Southwestern Medical School, University of Texas).

An electrohydraulic servo system and blood pump was constructed to evaluate the efficacy of a circulatory assist technique which amplifies the systolic pressure pulse. Preliminary in vivo data have been obtained with the co-pulsation system. The hemodynamic changes induced by co-pulsation were as follows: (1) pressure ratio of mean descending aortic pressure to mean ascending aortic pressure increased up to 2.6:1; (2) left ventricular systolic pressure and tension-time-index decreased by approximately 30 percent and 40 percent respectively; (3) left ventricular stroke volume increased by approximately 10 percent; (4) left ventricular external work decreased by approximately 30 percent; (5) left ventricular end-diastolic pressure decreased slightly (3-4 mm Hg); (6) left ventricular ejection fraction slightly increased (about 5 percent), and left ventricular end-systolic volume decreased by approximately 10 percent. Co-pulsation has proved effective in decreasing left ventricular work as measured and defined by these parameters. The proposed plan for the next contract year is for continuing modification, refitting and reconditioning the co-pulsation device, and for providing and training the necessary personnel to maintain and service the device.

Contract Amount: $148,366 Contract Number: PH43-67-1113

Hamilton Standard Division, Farmington, Connecticut

SEQUENCED EXTERNAL PULSATION IN THE THERAPY OF CARDIOGENIC SHOCK. D. C. Porterfield and L. S. Cohen, J. H. Mitchell and C. B. Mullins (Southwestern Medical School, University of Texas).

Many ventricular assist devices have been used in the therapy of cardiogenic shock, but cannulation of one or more major vessels is usually necessary. Although external pulsation is not a new concept, the sequenced application of external pressure is anticipated to provide increased diastolic augmentation due to increased diastolic return of blood to the central circulation. A series of bladder cuffs placed on the arms and legs is inflated and deflated rapidly by a pneumatic pressure system utilizing solenoid valves phased with the electrocardiographic signal. The cuff bladders are inflated during early diastole in a sequential manner starting distally on each extremity. Arterial blood from the extremities is returned to the central circulation causing an augmentation to central aortic pressure and possibly in coronary arterial filling. At the onset of each ventricular systole, the cuffs are rapidly deflated so that resistance in the periphery is lessened, thereby decreasing the afterload against which the left ventricle must pump. The animal phase of the program utilizes baboons as the anatomy of these primates resembles that of man. During right and left heart catheterization, intracardiac pressure, cardiac output, coronary flow and cineangiographic ventricular volumes are measured in a controlled state and with sequenced pulsation. In 4 baboon experiments to date, sequenced pulsation has led to diastolic augmentation in 2 animals. The next laboratory phase of the program will be with animals in cardiogenic shock. During the coming year, the sequenced pulsation apparatus will be further tested in normal baboons and in

baboons with myocardial infarction induced via coronary artery ligation and microsphere injection. If warranted, clinical studies may be performed in normal human volunteers and in patients undergoing routine cardiac catheterization.
Contract Amount: $149,680 Contract Number: PH43-68-1448

Johns Hopkins University School of Medicine, Baltimore, Maryland

NEW MODIFICATIONS FOR MECHANICAL VENTRICULAR ASSISTANCE (MVA). D.B. Skinner, M. Dutka, A. Raciti, P. Schiff and G.L. Anstadt

The purpose of this contract was to evaluate Silastic coated rigid assister cups for chronic implantation, fabricate and evaluate flexible assisters, develop synchronization for MVA, and study the effects of synchronized MVA in dogs. When implanted around the heart, inactivated rigid assister cups coated with Silastic caused decreased cardiac action and compression of the base of the heart. The longest survivor with an implanted cup lived 10 days. Coronary artery flow during MVA given to the fibrillating heart by rigid cups was studied by cineangiography, flow meters, and radioisotope washout. Flows comparable to control levels were demonstrated. Flexible assisters were fabricated to the investigator's specifications by the Dow Corning Corporation. Using flexible cups to assist the fibrillating heart, hemodynamics and metabolism during 3-5 hours of assistance were comparable or better than results achieved using rigid cups. Cardiac damage was significantly less, and flexible cups were better tolerated during chronic implantation. An electronic programmer to synchronize MVA to the QRS was developed and proved to be extremely accurate in following arrhythmias. The delay time between the QRS until pressure was applied to empty the ventricles averaged 40 msec so that mechanical systole occurred before the myocardium contracted actively. Hemodynamics and metabolism during synchronized MVA were well maintained. Measurement of heart work by oxygen consumption and coronary flow during synchronized MVA demonstrated that both were decreased, so that there was not a net increase in coronary flow relative to heart work as seen when MVA was given to the fibrillating heart. The potential value of synchronized ventricular assistance employing flexible cups has been assessed. During the coming year, the use of synchronized mechanical ventricular assistance will be evaluated, the assister cups themselves will be modified and standardized, and cups fabricated of various materials will be tested, and a portable hand-operated pumping device will be designed, developed and fabricated.
Contract Amount: $51,239 Contract Number: PH43-68-1434

Massachusetts Institute of Technology, Cambridge, Massachusetts

FLUID MECHANICS OF INTRA-AORTIC BALLOON COUNTER PULSATION. A.H. Shapiro, M.Y. Jaffrin, C. Clark, V.S. Murthy, and T.A. McMahon

The technique of intra-aortic balloon pumping, which consists of counterpulsing a balloon positioned in the descending aorta, has been studied both theoretically and by means of an experiment in which the cardiovascular system is modelled by a lumped hydraulic circuit. An attempt has been made to explain the local fluid mechanics around different types of intra-aortic balloons. A general theory for counterpulsation devices has

been developed for the arterial system represented as a network of tapered elastic tubes. An analytical model of the arterial system was developed, based on the reported physiological measurements of input impedance, and on approximate physical dimensions available for man and for dogs. Experimental observations and theoretical understanding of the operational modes of the balloon have led to criteria for design of constrained balloons. Also presented is a comparison between the analytical results, which consider the balloon as a loss-free volume source, and measurements made with the experimental model. Although this group has done excellent theoretical research concerning the hydrodynamics of the intra-aortic balloon, it was decided that more in vivo data should be obtained in this area before proceeding further with this contract. It is expected that, as more of this data is obtained, a renewal of these theoretical approaches will become necessary.
Contract Amount: $50,000 Contract Number: PH43-67-1114

University of Mississippi Medical Center, Jackson, Mississippi

TOTAL HEART REPLACEMENT DEVICE AND ITS CONTROL AND DRIVING SYSTEM.
T. Akutsu, H. Takagi, H. Takano and C.A. Farish.

A pair of air-driven total prosthetic hearts for use in sheep have been designed and constructed to be implanted inside the pericardial sac. Each side of the heart has been made of a single piece of Silastic including two valves. The outlet valve is bicuspid with an S-shaped closure line. One such valve functioned in a test circulatory system 24 hours a day for six months. The inlet valve, an oval mono-membrane type, has a large cross-sectional area and is built completely inside the ventricle. An automatic control and driving system presently under construction will regulate the cardiac output through a servo-control mechanism using atrial pressures as reference. The systole-diastole ratio will also be controlled. Thirteen experiments were performed in sheep weighing about 67 kg. The control and driving machine used was a simple manual system which has two main dials indicating the duration of systole and diastole in milliseconds. The pulse rate and systole-diastole ratio was easily determined from a nomogram. Average time of extracorporeal circulation was 69 min. Average time required for connection of artificial hearts was 41 min. Two sheep were lost by irreparable tear of each aorta and pulmonary artery. Severe hypoxia due to improper extracorporeal circulation killed two others. Four sheep which were pumped from one to three hours died from bleeding at the atrial edges. Three died from air emboli resulting from insufficient removal of residual air in one and from suction of air through the left atrial monitoring tubing in two. They were pumped each for 7, 12, and 8 hours. One sheep died after 8 hours of pumping from thrombo-emboli originating from side monitoring tubes that had improper antithrombogenic treatment. Two major causes of death, bleeding and air-emboli, have been eliminated each by application of double pursestring sutures and by low pressure-vacuum gauges. Further work in this area will include additional development of the drive control system and longer perfusions with the total artificial heart with complete hemodynamic and metabolic monitoring of the experimental animals.
Contract Amount: $60,000 Contract Number: PH43-68-1439

University of Mississippi Medical Center, Jackson, Mississippi

LEFT HEART ASSIST DEVICES. T. Akutsu, H. Takagi, H. Takano and C.A. Farish

Both series-type and bypass-type air-driven left heart assist devices have been constructed. The V-shaped implantable series-type device has an air-driven outlet valve. The volume of two sizes of this device is 65 and 95 ml respectively. The bypass-type device has 6 chambers arranged in a hexagonal shape and functions in a peristaltic fashion. The 6 pumping chambers are formed by a one-piece tube divided into 6 sections with 6 rigid outer housings. The device fills as it pumps. The control system for the series-type device has a rate compensation circuit which can automatically change the systole-diastole ratio with changes in pulse rate. The control system for the bypass-type device allows pumping once every 2nd to 8th trigger, and can adjust the number of functioning chambers from 6 to 3. Twenty-eight acute experiments with the series-type device were performed in calves. Extracorporeal circulation was used during implantation. With Model 1 (65 cc), the decrease in LV systolic pressure area was 25 to 30%. With Model 2 and the calf normotensive, the decrease was 52.4% with the valve off and 61.5% when on. With the calf hypotensive (80/50 mm Hg) at a cardiac output of 3.5 l/min., the decrease was 76.3% with the valve off and 82.5% when on. Two acute experiments using the bypass-type device were done in calves. When the pulse rate was 120 in 1:1 trigger using all chambers, alternative peak LV output decreased about 80%, with an average decrease of LV systolic pressure area of 11.6%. Using 2:1 trigger, every other LV output decreased about 90%. Decrease of LV work load varied from 38.5 to 49%. In 3:1 trigger, the average area of 3 consecutive LV pressure curves was almost the same as control. When the number of chambers used was decreased to two and one in 2:1 trigger, aortic peak flows decreased markedly during pumping, and those in between showed 40 to 25% increase. Decrease in LV work load ranged from 25 to 15%. During the coming year, it is proposed that the work will be continued and that the studies which to date have been confined to dogs will be extended to calves with the expectation of developing a unit to meet human clinical requirements.

Contract Amount: $84,900 Contract Number: PH43-67-1118

New England Medical Center Hospitals, Boston, Massachusetts

THE IN-SERIES SUBCUTANEOUS EXTERIORIZED PUMPING VENTRICLE WITH POSITIVE ACTING VALVE. F. Giron, W.C. Birtwell and H.S. Soroff

A pneumatically operated, tubular, prosthetic ventricle designed for subcutaneous implantation has been produced. The molded silicone rubber ventricle, lined with Dacron velour, has been implanted in 12 dogs to study the long-term physiologic effects of non-actuated prostheses. Two animals survived for one month, and 4 for one week or more without the use of anticoagulants. The linings which formed on the velour surface were of irregular thickness, often ridged in areas of curvature, and rough. The poor survival rate experienced in this series and the activity and excitability of the healthy survivors lead to the choice of the calf as the experimental animal for chronic studies of the effects of continuous actuation of the prosthesis. Of the first 6 calves in which the prosthesis was implanted for patency studies without actuation 1 survived for more than 3 months, 3

survived for 3 weeks to 1 month, and 2 died 3 days after the procedure as a result of technical errors. Pulmonary infection was the cause of death in all animals except the 3-month survivor which succumbed to an uncontrollable infection at the site of the prosthesis. The use of anti-coagulants has resulted in the development of smooth, thin, glistening linings well adherent to the Dacron velour. In acute studies, 3 models of distal valve operation have been studied: passive-open to provide counterpulsation, pressure-loaded to provide a controllable differential between the proximal and distal pressure, and active-pressure operation for normal valving. The pressure-loaded mode permits the elevation of coronary perfusion pressure to a selected level above the distal aortic pressure. The hemodynamic effects of the in-series pumping ventricle have been documented previously in acute studies. Continuation of this program is not planned.
Contract Amount: $70,000 Contract Number: PH43-67-1117

New England Medical Center Hospitals, Boston, Massachusetts

COMBINED PERIPHERAL AND THORACIC MODALITIES OF SYNCHRONOUS EXTERNAL PRESSURE ASSIST. W.C. Birtwell, F. Giron and H.S. Soroff

External pressure actuators have been produced for the hindquarters and thorax of the dog to provide pressure pulses with a peak value from 50-200 mm Hg synchronous with cardiac activity. Hydraulic operation results in minimal system delay (30-50 milliseconds) and sharp pressure pulses. In normal animals the diastolic peak pressure in the root of the aorta has been raised by 30-60 mm Hg and the systolic pressure reduced by 20-40 mm Hg. Retrograde flow pulses from 6-10 cc. have been recorded in the descending aorta with similar increases in the antegrade flow. The thoracic venous pressure remains at control level while the venous bed in the actuated portion of the body reflects the applied external pressure. In 10 animals with experimentally produced acute left heart failure by serial ligation of branches of the left coronary arteries, external assist reduced the end-diastolic pressure in the left ventricle from 20 mm Hg to 3 mm Hg and decreased peak ventricular pressure by 25-40 mm Hg. Initial experiments in normal dogs with the thoracic unit functioning every other heart beat indicated that the driving pressure in the aorta was increased by 25 mm Hg and the peak flow in the carotid artery was increased by 100% with an intrathoracic pulse pressure of 40 mm Hg. In these experiments, the diaphragm coupling between the thorax and abdomen has been greater than the coupling which was experienced with the peripheral modality. During the coming year, studies will be performed to determine the effects of combined external assist in dogs with electrically induced ventricular fibrillation and in dogs subjected to microsphere coronary occlusion. In addition, technical modifications and improvements to the existing combined system will be made.
Contract Amount: $60,000 Contract Number: PH43-68-1438

University of Pennsylvania, Philadelphia, Pennsylvania

EVALUATION OF THE ANSTADT VENTRICULAR ASSIST DEVICE IN ACUTE AND CHRONIC STUDIES. E.T. Tragus, H.W. Wallace, J. Marchesini, M. Bendon, P. Jennings and W.S. Blakemore

Evaluation of the Anstadt mechanical ventricular assist module was performed with chronic and acute studies. Chronic implantation experiments evaluated assister cup design and materials. Silastic and polyurethane were used. Initially, the original design cup was implanted in dogs that were not assisted and allowed to survive. Failure to survive for more than 48 hours led to design modifications consisting of changes in housing form, position of sidearms, intratubal pressure, presence or absence of the atrioventricular flange and its corrugation, fibrillation and defibrillation and type of incision. Conclusions are that a Silastic coated glass housing with a Silastic liner, electrode implanted into liner, corrugated flange, right angle sidearms and left thoracotomy permitted longest survival. One animal survived for two weeks and at that time was fibrillated and assisted without thoracotomy for three hours, maintaining good urine output and blood pressure. In acute studies animals were assisted for 1, 3, 6 and 9 hours. No significant differences were observed between Silastic lined or polyurethane lined cups, nor the presence or absence of flange corrugation, with regard to hemodynamic and enzyme measurements. An additional group was assisted for four hours and renal function was measured. Renal plasma flow, tubular function and glomerular filtration rate were adequate during this time. In another group of animals, assist was synchronized with the EKG and compared to non-synchronous assist. Synchronization produced better cardiac output, blood pressure, and flow of thoracic duct lymph. Synchronized assist also permitted a reduction in the sustained negative pressure necessary to hold the cup on the heart. Continuation of this program is not planned.
Contract Amount: $57,478 Contract Number: PH43-68-1503

Thermo Electron Corporation, Waltham, Massachusetts

DEVELOPMENT AND EVALUATION OF A LEFT VENTRICULAR-AORTIC ASSIST DEVICE
W.F. Bernhard, C.G. LaFarge (Surgical Research Laboratory, Children's Hospital, Boston) and S.S. Kitrilakis, T.C. Robinson (Thermo Electron Corporation)

A totally implanted assist device capable of complete functional replacement of the left ventricle is being developed and evaluated in animal experiments. Improved blood interface configuration, hydrodynamic characteristics and valve function, decreased pressure drops, and increased life and reliability have been incorporated in the series of pump models designed, developed, fabricated, and tested to date. Thirty studies of 7 to 120 days duration have been performed in healthy calves, with 1500-3000 ml/min. assisted circulation provided continuously by the blood pump. In some experiments, the flocked Dacron pump matrix was seeded with bovine fetal fibroblasts to accelerate pseudoendothelial development. In 20 animals, sacrificed after 30 to 120 days by bypass, histologic study of the lining revealed masses of viable fibroblasts and collagen attached to the Dacron matrix. Identification of fetal cells was accomplished with liquid scintillation using C^{14}-thymidine. Blood trauma was minimal and consisted of

15% hematocrit reduction, temporary (14 day) increase in incubated osmotic fragility, and a 24-hour increase in mechanical fragility. Erythrocyte survival (D.F.P.^{32}) was reduced approximately ten percent (24 day half-life). Red cell mass (Cr^{51}) was also less, with a reciprocal rise in plasma volume. Plasma hemoglobin, haptoglobins, reticulocyte count, platelets, and intracellular cations were unchanged. Reduction of left ventricular pressure to atmospheric levels has been demonstrated in acute studies in calves. The maintenance of the normal hemodynamic state during acute left ventricular failure (induced in chronic pump implantations) has also been demonstrated. During the next year, studies will attempt to clarify the efficacy of the assist device in animals with chronic left ventricular failure, and to further describe the development of the autologous interface produced with fetal fibroblasts.

Contract Amount: $198,867 Contract Number: PH43-67-1116

Westinghouse Electric Corporation, Pittsburgh, Pennsylvania

DEVELOPMENT OF AN INTRA-AORTIC BALLOON ASSIST DEVICE. B.G. Brown (Johns Hopkins University) and J.M. Evans (Westinghouse Electric Corporation)

During the past year, this contractor continued physiological evaluation of the intra-aortic balloon, made improvements in the total system, and provided assistance to the Artificial Heart Program. Studies of renal function, chronic implantation, coronary collateral flow, and the effects of a triple balloon were conducted. Ten chronic experiments were done to determine the effect of diastolic augmentation on renal artery pressure and blood flow, urinary output, creatinine clearance, and sodium and potassium excretion. In allcases, augmentation with the balloon positioned in the thoracic aorta did not alter the above indices of renal function. Chronic implantation studies showed that balloons prepared with a variation of the TDMAC process yield excellent results for up to four days. Experiments in the mechanisms of coronary collateral flow indicate that retrograde flow collected from the cannulated distal coronary artery occurs essentially during diastole, and is proportional to the diastolic trans-collateral pressure difference. This result indicates that systolic contraction may mechanically occlude these collateral channels. Based on the results of the coronary collateral flow studies, a triple balloon has been designed which will selectively increase aortic root mean diastolic pressure without compromising the rest of the circulation. With reference to system improvements, the minimum time to failure of balloons subjected to cyclic testing has been increased by 30%. Development of the assist device has included improved gas porting in the actuator, redesigned and improved ECG amplifier and 60 Hz filter, improved automatic gain control circuit, and simplified trigger setup. Two assist device consoles, plus intra-aortic balloons, have been provided for independent evaluation. The proposed plan for the upcoming contract year includes the following tasks: (1) evaluation of the latest assist device control circuitry and actuation system; (2) basic studies; (3) hemodynamic studies of balloon diastolic augmentation; and (4) provision of assistance to the Artificial Heart Program.

Contract Amount: $106,006 Contract Number: PH43-67-1139

The contribution of the five physiologic effects contractors to the Artificial Heart Program has been physiologic and engineering evaluation of circulatory assist devices (CADs) and related components which have been fabricated by other contractors within the Program for the purpose of design modification rather than ultimate clinical use. During the past year, these five groups have evaluated the Baylor Left Ventricular By-pass pump and an intra-aortic balloon. Data concerning the safety and efficacy of these devices is contained in the following summaries of contract work. Many additional CADs and drive systems have been developed during the past year and will soon need evaluation. During the subsequent contract year, these physiologic effects groups will perform the necessary evaluation of these new CADs and related components, and also perform screening evaluation in order to expedite evaluation through the test and evaluation facilities which will be established by the Artificial Heart Program.

Case Western Reserve University, Cleveland, Ohio

ASSISTED CIRCULATION: EXPERIMENTAL INTRA-AORTIC BALLOON PUMPING (IABP).
Mario Feola, Nils A. Norman, Otto Haiderer, John H. Kennedy.

I. Hemodynamic Observations in Experimental Acute Left Ventricular Failure: An acute left ventricular failure (LVF) preparation was developed in 60 dogs pretreated with reserpine, by ligation of coronary artery branches and by propranolol-chlorpromazine infusion. In 15 dogs with LVF_1, characterized by 15-25% reduced cardiac output and mean aortic pressure, IABP reestablished normal hemodynamics. In 15 dogs with LVF_2, characterized by further reduction in previous parameters, plus elevated left ventricular end diastolic and mean left atrial pressures and central venous blood desaturation, IABP improved all parameters within three hours. In these two groups of dogs, IABP decreased tension-time-index and minute work; increased stroke volume, mean aortic pressure, coronary flow, myocardial contractility (dp/dt) and oxygen utilization. In 12 LVF_3 dogs characterized by above 40% decreased cardiac output, mean aortic pressure, coronary and systemic flows, IABP had insignificant hemodynamic effects, compared to a group of eight untreated dogs, and did not prevent progression of failure or prolong survival.
II. Aortic Baroreceptor Output: In anesthetized dogs, the nerve impulses were recorded from the left vagus nerve and by analog-computational techniques separated from activity in other fiber groups. The results demonstrate that balloon "pumping" increases and drastically alters the output pattern in aortic baroreceptor nerve fibers. Operation of the balloon reduces the baroreceptor output ("BRO") during systole, a reduction which, however, is outweighted by the increase caused during diastole. Thus, total "BRO" (integrated over 10 second periods -- "N_{10}") increased. The temporal relationship between heart action and "pump" timing appears as a more critical parameter than the direct interpretation of the pressure tracings would indicate. This group will continue their physiologic evaluation of the intra-aortic balloon until the necessary data on this device has been obtained.
Contract Amount: $199,000 Contract Number: PH43-67-1424

Melpar, Inc., Falls Church, Virginia

PHYSIOLOGICAL EFFECTS OF BLOOD PUMPS IN ANIMALS. William E. Palich, Benjamin Dennison.

Melpar Laboratories has been evaluating a totally implanted cardiac assist device system in experimental animals. Specifically, their work has involved developing surgical techniques for implanting various components of the entire system, with a view toward defining certain anatomic constraints. Melpar has implanted a left ventricle-to-aorta cardiac assist device together with drive system and energy source, thus determining the physiologic effects of the components and of the total system, utilizing the integrated developments of many contractors. Melpar has also worked with a developer in the development of a reproducible, easily implanted blood pump to use in the evaluation of promising materials. During the subsequent contract year Melpar will perform implantation and evaluation of circulatory assist device total systems, including CAD, drive system and energy system.

Contract Amount: $245,300 Contract Number: PH43-67-1418

University of Minnesota, Minneapolis, Minnesota

EVALUATION OF THE BAYLOR LEFT VENTRICULAR BYPASS DEVICE IN NORMAL CALVES, AND IN CALVES WITH INDUCED MITRAL INSUFFICIENCY. Eugene F. Bernstein and Michael A. Shea.

The Statham-Baylor Left Ventricular Bypass Device (BLVB) was initially evaluated in vitro to determine its performance characteristics, most efficient operating parameters, and hemolysis rates. Acute hemodynamic studies in normal calves revealed minimal pressure and flow changes, with the BLVB generally replacing 5 to 25% of the control cardiac output, but never exceeding 2.5 L/min. Variations in pump control parameters produced similar responses to those seen in the previous in vitro studies. BLVB implantation in calves for up to 12 days of continuous pumping demonstrated problems with pump and connector thrombosis, pump diaphragm leaks, development of a moderate anemia, transient leukocytosis, increasing plasma volume, transient tissue enzyme elevations, and frequent pulmonary complications. Extensions of these studies include the development of a reproducible model of acute mitral insufficiency. Measurements of left ventricular function, including LV dp/dt, aortic flow acceleration, LV stroke work, and LV power, are rapidly and strikingly decreased. Following BLVB insertion, pumping of 2-3 L/min is possible since left atrial pressure is high. Left ventricular function changes little, however, and calf survival is prolonged only briefly. In a parallel effort, an optimal BLVB pump controller has been designed, following hybrid computer simulation of a cardiovascular system and pump. Predicted measurements of benefit are comparable to measured experimental values. A sensitivity analysis based on the reduction of flow work resulted in defining optimum delay and duration settings for extensive ranges of heart rate and peripheral resistance. This group will complete their physiologic evaluation of the Baylor Left Ventricular Bypass in animals with induced myocardial failure, on an extension of the present contract.

Contract Amount: $78,140 Contract Number: PH43-66-974

Thermo Electron Corporation, Waltham, Massachusetts

A PHYSIOLOGIC EVALUATION OF THE BAYLOR LEFT VENTRICULAR BYPASS. C. G. LaFarge, W. F. Bernhard, (Children's Hospital Medical Center, Boston) and T.C. Robinson.

An engineering and physiological evaluation of the Baylor left atrium-to-aorta assist device has been completed. Circulatory analog studies have been performed to analyze the hydrodynamic, mechanical, and electronic functions of the blood pump and its control system. The hemodynamic, hematologic, and pathologic effects of pump function in healthy calves has been studied in short- and long-term experiments. A total of 9 animal experiments have demonstrated that the device is capable of assisting the systemic circulation by a maximum of 2.5 liters/minute for periods up to 45 days, with an average of 20 days. Blood trauma was significant early in each study, but the hematocrit increased, and osmotic and mechanical fragilities decreased during the experiments. Effective pump function was terminated in these experiments by the development of a thick non-uniform fibrin layer on all the Dacron velour surfaces of the pump, preventing adequate pump filling and proper valve and diaphragm action. This contract was terminated in January, 1969.

Contract Amount: $100,508 Contract Number: PH43-66-1123

Travenol Laboratories, Inc., Morton Grove, Illinois

PHYSIOLOGIC EFFECTS AND ENGINEERING EVALUATION OF INTRA-AORTIC BALLOONS AND CONTROL CONSOLES. F. T. Galysh, A. S. Patel and C. Y. Lin.

Westinghouse balloons and control console, Western Gear balloons, and the Avco Model 5 console were evaluated. Observed balloon defects were: balloon pinholes, catheter wall breakdown and subsequent kinking, and slip joint dislodgement. Catheter kinking was found in the mock circulatory system (MCS) to be mechanistically associated with longitudinal balloon-catheter movements. Inflation-deflation characteristics of the ends vs. the central portion of single segment balloons were studied in the MCS using an electrical technique. ECG triggering evaluation studies were performed on the Avco and Westinghouse controllers over a variety of clinical arrhythmias. Pressure triggering circuits of both consoles could not discriminate the animal's pulse pressure from the aortic pressure rise elicited by balloon inflation. Surgical installation of ~22 mm diameter, 40-50 ml, 14 Fr catheter balloons in calves (C) and ~15 mm, ~25 ml, 14 Fr catheter balloons in dogs (D) was a simple procedure, but was attended with thrombosis of the femoral artery insertion site and circulatory insufficiency (weakness) of the extremity in calves. Hemodynamic studies were carried out in the MCS and in calves and dogs with normal cardiac status. Mean diastolic pressure ($\bar{P}_d$) in the aortic root was ↑ (increased) 48% in D and 12% in C; aortic root mean pressure was ↑ 13% in D and unchanged in C; abdominal aortic $\bar{P}$ was ↓ 19% in D and 11% in C; $\bar{P}_{LV}$ was ↓ 8% in D and 7% in C; cardiac output as pulmonary artery blood flow (QPA) was ↓ 4% in D and 2% in C; Qcor. art. was unchanged in dogs and ↓ 4% in calves; Qrenal art. was ↓ 19% in D and 8% in C. Differences in responses of $\bar{P}_d$ between these species are attributable to lower aortic compliance in dogs and pigs as compared to calves and sheep. Renal clearances (GFR and ERPF) in calves were not altered by one week of

continuous pumping. Four techniques to achieve the clinical counterpart of chronic cardiac failure in calves and dogs failed. During the subsequent contract year this group will continue physiologic and engineering evaluation of the intra-aortic balloon and drive systems, in addition to evaluating other CADs and related components.

Contract Amount: $247,620 Contract Number: PH43-67-1425

At present, much effort is expended in testing designs of materials and configurations of surfaces in contact with blood. The empirical approach of iterative testing and modification is necessary because theoretical predictions are not accurate enough to provide more than broad guidelines. The objective of this work is to provide support for the development of more reliable theoretical guidelines, both to improve the efficiency of laboratory testing and, also, to be sure that current theoretical assumptions as to optimal characteristics and avoidable faults are correct. To this end, work is being supported on both theoretical analysis and experimental documentation. Studies include the effects of gross geometry, surface effects, and interactions of cells and cells with other surfaces.

Avco Everett Research Laboratory, Everett, Massachusetts

THROMBUS FORMATION ON ARTIFICIAL SURFACES. H. E. Petschek and P. N. Madras.

A number of chambers have been developed which allow the observation of thrombus formation on artificial surfaces while varying the rate of blood flow. Using this chamber, a sequence of reactions in thrombus formation has been observed on polyurethane and on a wide variety of other materials supplied for evaluation. Platelets are always the first formed element to attach to a surface, but do not necessarily lead to thrombus formation. In all regions where thrombi form, leukocytes also become attached to the surface. In an area occupied by leukocytes, platelets draw together but do not necessarily form aggregates. In contrast to platelets, however, the tendency for leukocytes to stick to the surface appears to be both flow and chemistry dependent and may represent an important link between blood flow and thrombus formation. In all observations on different materials, the above sequence could be determined in thrombus formation. However, significant differences in the rate at which these events occurred were found. These differences permit a comparison of materials regarding their tendency for platelets to adhere, for leukocytes to adhere and for thrombus formation. It appears at present that those surfaces which show least tendency for leukocytes to adhere may be the most nonthrombogenic. This contract has accomplished its goal and will be terminated at the end of the contract year.

Contract Amount: $89,014 Contract Number: PH43-67-1120

General Electric Company, Philadelphia, Pennsylvania

STUDIES OF BLOOD FLOW IN AND ADJACENT TO BLOOD PUMPS. S. M. Scala, N. R. Kuchar, M. P. Sherman and L. U. Lilleleht (University of Virginia).

The objective of this study is the investigation of the hydrodynamic aspects of hemolysis and clotting in and adjacent to artificial blood pumps and other blood processing devices. The study is focused on the determination of the permissible ranges of the various flow parameters such that they may be held within desired physiological limits while minimizing hemolysis and thrombus formation. The equations of motion in which blood is treated as a non-Newtonian fluid consisting of a mixture of red cells, rouleaux and plasma are presented. The boundary conditions utilized allow

for finite length, variable cross sectional area and blood vessel distensibility. Numerical results are presented for the streamline patterns and the pressure and velocity distributions for a number of geometries of physiological interest. A phenomenological model for blood based on experimental data expressing the rheological properties in terms of hematocrit and fibrinogen concentration has also been derived and solutions of the non-Newtonian equations of motion, giving details of the velocity profiles and pressure and shear stress distributions, have been found for steady and unsteady flows in circular tubes. A new model is presented for the self-collisions of erythrocytes and red cell collisions with surfaces. The model includes the electrical double layer, London-van der Waals forces and the low Reynolds number hydrodynamic forces. The model has a small potential well at about 100 Å from the cell wall corresponding to rouleaux formation, and a potential barrier at about 15 Å which prevents agglutination except for those energetic collisions which overcome the repulsive forces and lead to hemolysis. In vitro experiments with "pseudo-blood" were conducted in distensible tubing for a range of geometries including uniform tubing, constrictions (stenoses) and bifurcations. Comparisons between the theory and the experiments are made. The model described in the original part of the program plan requires three year minimum support at the current level of effort. Progress has been according to schedule, and it is currently planned to continue the work for a third year to obtain the completed model.
Contract Amount: $73,935 Contract Number: PH43-67-1121

University of Minnesota, Minneapolis, Minnesota

RED CELL BEHAVIOR NEAR WALLS. P. L. Blackshear, Jr., K. H. Keller, R. J. Goldstein, F. D. Dorman and M. Rosenberg.

Several groups at the University of Minnesota are studying the flow of blood near walls. Each focuses on a region limited by the technique. These regions overlap. Starting nearest the wall, the studies are: "Distance 0-1000Å. Resolution 1Å." Ellipsometric studies of deposits on chrome-plated slides following exposure to cells show that red cells stick to surfaces not first exposed to protein and leave behind a 30Å thick deposit of material. Cells did not stick to surfaces that have been first exposed to plasma until lysolecithin was added. "(D) 0-1000Å, (R) 10Å." The surface contact microscope shows that red cells in plasma rarely settle closer than 0.1μ from the wall and that there is evidence of microscopic reversibility of cell motion near walls. "(D) 0-1000μ, (R) 2μ." The 3-D microscope shows red cells in ghost suspensions display velocity vectors with marked lateral components. "(D) 0-1000μ, (R) 1-10μ." The uptake of radioactivity of a plasma free suspension of red cells in a radioactive cholesterol coated tube increases sharply at wall shear rates of $\approx 1000\ sec^{-1}$. No such jump occurs when cells are absent. "(D) 0-1cm, (R) 0.01cm." The Laser Doppler technique is used to measure velocity components of pigmented cells in ghost suspensions. These research efforts combine to give the means for studying the relevant particle behavior in flowing blood in those regions where wall induced lysis and mass transport near walls are important. All of this work will be continued during the coming year. The projects described are all ongoing, and require further documentation.
Contract Amount: $41,920 Contract Number: PH43-67-1122

CARDIAC CONTROL PARAMETERS

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. 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 Medical Center, Stanford, California

CARDIAC CONTROL: HEART RATE OPEN LOOP RESPONSE. E. Dong, H. Glaze, E. Stinson, C. Weaver.

Last year it was reported that cardiac autotransplantation results in the absence of sinus arrhythmia, increased blood and plasma volume, decreased diuresis to acute volume load, absence of infusion tachycardia, and diminished cardiac output response to infusion. That these alterations existed in a preparation which conforms to "Starling's law", suggested that rate and frequency would be important although not absolutely necessary for optimal control of an artificial heart.

These studies are the first in which we document the open loop response of heart rate and peripheral resistance to alterations of ventricular rate and filling. Method: during cardiac autotransplantation the heart is removed and sutured by transection of atrium. Thus, a rim of atrium (containing the sinoatrial node) is still responsive to the central nervous system. The ventricle and attached atria are now termed "donor heart". Under anesthesia the animal was studied by driving the donor atria with a voltage controlled pacemaker in sine and square wave configurations and in a stop-beat mode. A bipolar intracavitary (atrial) lead, respiration, ECG, and arterial pressure were recorded. Mathematical work for the development of the transfer function between blood pressure and heart rate has not been completed but the initial data support the assumptions made. Opening the loop at the atrial level is important for studying the control of the cardiovascular system. The remnant atrial rate (now called the P'-P' interval) can be measured so that the system response is identified: (arterial pressure, baroceptors, central nervous system, motor nerve and pacemaker tissue).

Results: Static - RR 800 700 600 500 400 300
P'-P' 320 338 343 380 383 453
AP 125 130 130 132 130 143

Stop-beat - P'-P' control 450 milliseconds, on the 5th beat the P'-P' is 420 and it reaches its minimum (300 milliseconds) 30 beats post "R arrest". Work during the coming year will be primarily concerned with the development of a model of the preparation, with emphasis on results translatable to developing hardware elsewhere in the program. Particular emphasis will be placed on the consequences of 'rate' versus "stroke volume" control, and the effects of varying ejection time.

Contract Amount: $103,300 Contract Number: PH43-67-1109

STUDY OF THE EFFECTS OF ADDITIONAL ENDOGENOUS HEAT

The objective of this work has been to define the levels of endogenous heat production which can be satisfactorily tolerated. Basic acute experiments were conducted in the first two years. During the past year, further data on chronic preparations were obtained.

Battelle Memorial Institute, Pacific Northwest Laboratories, Richland, Washington

STUDIES ON THE EFFECTS OF ADDED ENDOGENOUS HEAT AND ON HEAT EXCHANGER DESIGNS. M. F. Gillis and P. C. Walkup.

In order to define limits on tolerance of added endogenous heat from an internal source, using blood as a coolant, electrically energized heaters were surgically implanted in the descending thoracic aorta of miniature swine and power levels of 0 to 60 watts (0-4.7 watts/cm^2 flux, 0-1.1 watts/kgm body weight) applied for periods up to and exceeding twelve months. High ambient temperatures (over 80-85°F) or pyrexic states produce severe hyperthermia at the higher power levels, necessitating discontinuance of power to prevent death. Otherwise, no alteration of physiologic function has been observed. There are no gross or microscopic lesions unequivocally attributable to added endogenous heat, and hematologic/serum biochemical changes are minimal to absent in both heated and control (0 watt) animals. Gamma irradiation of implants (0.3 megaroentgens, cobalt-60) and nylon velour coating of percutaneous lead bundles has essentially eliminated problems of infection. A specially designed leather swine harness continues to be highly successful in extending percutaneous lead life and eliminating skin trauma. Extended area heaters having longitudinally finned lumens of carbon (antithrombogenic coating by Gulf Atomic Corporation) appear to be compatible with hemic and hemodynamic requirements as well as increasing heat transfer per unit length over straight tubular designs. Preliminary results with Dacron-flocked exchange surfaces in vivo indicate higher thermal resistances than previously predicted, creating serious concern regarding their applicability to artificial heart systems using heat cycle engines. During the coming year, it is planned to continue the chronic studies. Work will also be done to investigate the effects of heat on the stability of surfaces coated with living cells. Thermal resistance will be measured, and maximum values for heat transfer obtained.

Contract Amount: $91,150 Contract Number: PH43-66-1130

John B. Pierce Foundation Laboratory, New Haven, Connecticut

STUDIES OF THE EFFECTS OF ADDITIONAL ENDOGENOUS HEAT. R. O. Rawson.

Three general areas of study have been investigated relative to the effects of additional endogenous heat: 1) effects on the thermoregulatory responses of dogs and sheep; 2) histological changes at the blood or tissue interface in dogs and sheep; and 3) effects on body temperature cycles in dogs. In short term experiments in which respiratory frequency, respiratory evaporative heat loss, and certain body temperatures were measured in dogs, it was confirmed that no significant thermoregulatory responses could be elicited in 25 kg dogs subjected to additional endogenous heat loads of

0.6 - 0.7 watts/kg in a neutral or warm environment. In 50 - 60 kg sheep, a 0.5 - 0.6 watts/kg heat input was immediately followed by a significant increase in panting in the absence of a rise in temperature of skin or brain thermoreceptors. This was interpreted as evidence of the operation of unknown deep body temperature receptors. Histological studies in sheep have confirmed previous findings of marked vascularization of fibrous encapsulation tissue around implanted prostheses which have a tissue interface temperature maintained at 43-45°C, and that potential heat exchange to adjacent tissue regresses with time if encapsulation continues in the absence of high temperature at the interface. In dogs, histological examination of ingrowth in the aortic heat exchanger lumen lined with flocked Dacron revealed some indication of an epithelioid movement along the blood-lumen interface. The original work described in the contract was completed. No further effort at this laboratory is contemplated at the present time.
Contract Amount: $2,325 Contract Number: PH43-66-978

Thermo Electron Corporation, Waltham, Massachusetts

EFFECTS OF INTRACORPOREAL HEAT AND RADIATION ON DOGS. F. Huffman and J. Norman, C. Pegg, G. Sandberg and R. Lee (Sears Surgical Research Labs.).

The body must be capable of dissipating the reject heat from the power source which drives the blood pump(s) of an implantable circulatory support system. If the energy source is a radioisotope, the body must also tolerate nuclear radiation exposure. The objective of these studies is to characterize the effects of additional heat and nuclear radiation on dogs by implanting blood-cooled heat exchangers in the thoracic cavity, using Pu-238 (plutonium-238) capsules as well as RES (radiation equivalent sources) capsules, which simulate the Pu-238 neutron and gamma radiation environment. Implantation entails excision of a segment of the descending thoracic aorta and replacement with a titanium tube heat exchanger. Within the observation periods (16 watt Pu-238, 18 mos.; 24 watt Pu-238, 10 mos.; RES, 10, 10, and 8 mos.), all radioisotope dogs are in apparent good condition except for chromosomal changes in their lymphocytes cultured in vitro after phytohemmaglutinin stimulation, similar to those found in patients after radiation therapy. Serial hematologic, endocrine, hepatic and renal function tests are within normal limits. These continuing studies indicate that the temperature regulation mechanisms of mongrel dogs adjust to dissipate additional endogenous heat loads up to 0.8 watt/kg (corresponding to a heat flux of 1 watt/cm^2 and a maximum blood temperature rise of 4°C within the exchanger) and that the anticipated reject heat and dose rate levels from an implantable circulatory support system may be permissible. It is planned to continue the same effort during the coming year. Animals will be carried as long as possible. In the event that an animal is lost, the source will be reimplanted.
Contract Amount: $24,950 Contract Number: PH43-66-982

At this stage of development, tubes and wires passing through the skin are required. Even when implantable energy systems are perfected, wires may be more useful for certain experimental situations. For this reason, work has been supported during the past two years on developing a satisfactory long term method of bringing leads through the skin.

Amicon Corporation, Lexington, Massachusetts

BIOLOGICALLY COMPATIBLE POLYELECTROLYTE COMPLEX HYDROGELS FOR USE AS TISSUE/LEAD ADHESIVES FOR LONG TERM PERCUTANEOUS LEADS. E. Friedman, L. Nelsen and H. J. Bixler.

Bacterial infection along the tract of a percutaneous lead can be reduced or avoided if the adhesive binding the lead to the tissue has the following properties: bacterial impermeation and inertia, good bonding to tissue and lead, adequate tensile and elastic properties, suitable cure times (0.1-24 hrs.), and body compatibility and stability. The utility of polyelectrolyte complexes as such adhesives is under investigation. Preformed complexes of this type have demonstrated good body compatibility and adequate strength. Adhesion is brought about by the free radical in situ polymerization of one ionic monomer in the presence of the counterpolyion. The major problems thus far encountered are rapid gelation times, inadequate strength, and toxicity of one of the better adhesive systems. The adhesive systems studied contained sodium polystyrene sulfonate (NaPSS), polysodium acrylate (NaPAA) or styrene/maleic acid copolymer (SMA) as the polyanion in conjunction with 2-hydroxy-3-methacrylyloxypropyl trimethylammonium chloride (Q-1) as the cationic monomer. The (in vitro) tensile strengths of the hydrogels thus prepared are: NaPSS/Q-1, 111 psi with 25% elongation; SMA/Q-1, 20 psi, NaPAA/Q-1, 110-265 psi. Cure times were controlled by precooling the reactants. Current research is centering on extensive evaluation of the compatibility of these systems in vivo and on testing of the tensile strength and bacteria permeability of the gel systems. The Ioplex concept has not proven to be useful for application to percutaneous leads. Gels with adequate mechanical properties have been irritating to tissue, or required excessive time for in vivo stabilization. It is not planned to continue this work.

Contract Amount: $69,725 Contract Number: PH43-67-1107

Epoxylite Corporation, South El Monte, California

DEVELOPMENT OF SATISFACTORY LONG-TERM PERCUTANEOUS LEADS. H. Lee, D. E. Ocumpaugh, G. W. Culp and A. L. Cupples.

The lead which has been developed features a central percutaneous, cylindrical conduit which has an exterior flange and a subcutaneous fenestrated skirt. The central conduit passes the cannulae or electrical wires needed for artificial heart or assist device operation. The flange prevents overgrowth of the conduit, while the skirt provides immobilization when connective tissue invades the fenestrations. Animal experiments, including 88 leads in 23 dogs, 2 leads in 2 monkeys, and 10 leads in 4 pigs, were performed using 12 different materials of construction and 28 variations of

configuration. Satisfactory lead performance is characterized by absence of serous weeping despite induced trauma by the free-ranging animal, continuous exposure to ubiquitous vivarium organisms, and externally applied broths of virulent bacteria. The apparently necessary histological precursor to satisfactory performance is epithelial encapsulation of all subcutaneous surfaces. The absence of epithelial encapsulation has, without exception, been associated with edematons adjacent to tissue with chronic serous or seropurulent weeping at the emergence site, and in some instances, peripheral exposure of the subcutaneous skirt. Subcutaneous implantation revealed no tissue toxicity due to any materials used in the leads: no lead construction materials, per se, could be implicated in unsatisfactory performance. Minor variations of the configuration of the leads have not had statistically significant effects on lead performance. Docile animals, i.e., those that appear to ignore the emergence sites, have a higher incidence of satisfactory lead performance. We therefore conclude that animal-induced trauma, preventing the epithelial encapsulation in the first few weeks postoperative, is one cause of unsatisfactory performance. The data suggest that geometry is the most important determinant of satisfactory lead performance, not material. This design of percutaneous lead shows some promise but since it does not require further development at this time, the research and development contract will not be continued next year. Instead, percutaneous leads of this design will be obtained as needed on a purchase order basis.

Contract Amount: $73,077 Contract Number: PH43-67-1108

As a part of the goal of developing ventricular assist devices the Artificial Heart Program is considering the use of a blood oxygenator as part of a system for long-term perfusion to assist the failing heart. An important limitation to use of the presently available blood oxygenators is the harm they cause to blood due to denaturation of proteins and lipoproteins and destruction of cellular and non-cellular elements. There is evidence that the presence of a direct blood-gas interface is a major problem in the long-term use of these oxygenators. Several investigators have had some success in using blood diluents and chemical means to improve the potential for long-term use of these oxygenators. Other investigators have approached the problem by attempting to design oxygenators without a blood-gas interface; these include both membrane and liquid interface devices. However, most of these oxygenators have limitations due to poor gas transport, poor hemodynamics, high cost, and difficult assembly. The poor gas transport, due primarily to poor and varying blood flow patterns, results in the necessity for a large surface area and high priming volume. The problems of high cost and difficult assembly limit the use of these oxygenators on a large scale. An additional problem with these oxygenators is that the efficiency tends to decrease when scaling up from a small test cell to a high capacity unit. This is due to poor blood manifolding, shunting, and varying flow resistance in the individual oxygenating subunits. Some of the oxygenator concepts which have been supported during the past year by the Artificial Heart Program are briefly described below.

Five of the oxygenator programs have been for the further development of previously existing flat membrane oxygenators: These were: (1) the Institute of Medical Sciences for further development of the Bramson oxygenator; (2) the General Electric Company for further development of the Peirce oxygenator; (3) Cornell University for further development of the Lande Oxygenator; (4) Litton Industries for further development of the Kolobow oxygenator; and (5) Columbia University for adapting the Leonard tidal flow dialyzer to function as an oxygenator. Three other programs are concerned with the development of capillary membrane oxygenators. One of these, Abcor, Inc. (6), would have blood flowing through many parallel capillaries and gas flowing over the surface of the capillaries. The second, Medical College of Virginia (7), would have gas flowing through the capillaries and blood flowing over the surface. A major problem with these concepts is the unavailability of small diameter hollow permeable tubes at a low cost. The third program, Dow Chemical Company (8), is presently concentrated on developing techniques for producing hollow fibers of permeable materials at a reasonable cost. Two programs are concerned with modified techniques for forming capillaries. One of these concepts, Monsanto Research Corporation (9), involves forming grooves in a porous hydrophobic substrate. This grooved substrate and a similar, but ungrooved, substrate are coated with a membrane and are then pressed together to form parallel capillaries for blood flow. The gas flows through the porous substrate itself and blood flows in the capillaries. The major problems with this concept have been in forming suitable grooves, coating the substrate, and maintaining performance in larger capacity units probably due to local shunting. The second concept, Hauser Research & Eng. Co.(10),

is the formation of an interconnecting network of hollow tubes by coating a porous metal onto an open cell foam and then removing the foam material. The resulting material is then coated with a membrane and manifolded so that the gas flows through the tubes, and the blood flows over the surface. Another program, University of Minnesota (11), is to study the feasibility of an oxygenator based on couette flow to increase the effective diffusion of oxygen and CO_2. The major problem with this concept has been the construction of a prototype with closely controlled dimensions so that the concept could be adequately tested. Another program, Abcor, Inc. (12), is to study the feasibility of a liquid-blood interface oxygenator utilizing a liquid with high oxygen and carbon dioxide solubility instead of a membrane. Following are summaries of the work of contractors in this area:

Abcor, Inc., Cambridge, Massachusetts

DEVELOPMENT OF A CAPILLARY MEMBRANE BLOOD OXYGENATOR. Richard P. deFilippi, Frederick C. Tompkins, James H. Porter, and Grady W. Harris.

Both experimental and theoretical work has been carried out in parallel during the current contract year. In vitro and in vivo evaluation of small oxygenators containing 100 silicone rubber capillaries was continued to establish a firm basis for scale-up to larger sizes. Oxygen exchange rates were in the range of 40 to 100 cc/min-m^2 depending on blood flow rate. In larger capillary bundles having a blood flow capacity of about 500 cc/min, the exchange rate was lower (30-50 cc/min-m^2), and the reason for this decrease with scale-up is presently being sought. In vivo hemolysis rates are low (HI≈0.16g hemoglobin/100ℓ blood flow) compared to bubble and disc oxygenators (HI>1.8), and platelet removal is minimal. A bundle of ten helically coiled capillaries was tested in vitro to evaluate the effect of secondary flow. Oxygen transfer rates were increased to as high as 120 cc/min-m^2. The latest literature data on oxygen and carbon dioxide transport in whole blood has been assimilated and incorporated into an existing computer program for predicting theoretical performance. Further in vitro and in vivo tests on 500 cc/min oxygenators is in progress in preparation for the design and construction of oxygenators of sizes up to those large enough for total bypass. Oxygenators with varied blood flow capacities will be delivered for independent evaluation. Lower production costs will be investigated.

Contract Amount: $107,500 Contract Number: PH43-67-1405

Abcor, Inc., Cambridge, Massachusetts

DEVELOPMENT OF A LIQUID-LIQUID BLOOD OXYGENATOR. Richard P. deFilippi, Richard M. Anderson, James H. Porter, and Grady W. Harris. Yukihiko Nose, (Cleveland Clinic).

An experimental blood oxygenator has been tested wherein a falling fluorocarbon (FC-43^R) film inside a vertical Teflon^R tube contacts a rising column of blood. Oxygen and carbon dioxide transfer occurs across the moving interface between two immiscible liquids, thus eliminating the need for membranes or blood-gas contacting. The liquid-liquid contacting device is

operable over a wide range of blood and fluorocarbon flow rates without the formation of fluorocarbon emboli. No detectable blood components are removed and no foreign substances are introduced. In vivo hemolysis rates with the falling fluorocarbon film are an order of magnitude less than with disc or bubble oxygenators. Intravenous injections of fluorocarbon slugs have shown that there is no apparent chemical toxicity and that the fluorocarbon can be removed from the body at rates up to 0.2 cc/kg body weight/day, apparently by exhalation. Because of the high interfacial velocities in the counter-current liquid-liquid contactor, high mass transfer rates are possible. Oxygen and carbon dioxide flux rates of 30-80 cc/min-m^2 and 40-150 cc/min-m^2, respectively, have been measured in vitro and in vivo. Based on these measurements, several different devices based on multiple cylinders or parallel plates have been designed having blood flow capacities of five liters per minute. Future work will concentrate on demonstrating a practical design for larger scale oxygenators.
Contract Amount: $80,100 Contract Number: PH43-68-1393

Columbia University, New York, New York

DEVELOPMENT OF A TIDAL-FLOW OXYGENATOR. Edward F. Leonard and Robert M. Koffsky.

A membrane oxygenator based on the tidal-flow concept has been designed, constructed, and tested. This concept was developed earlier as a hemodialyzer. The tidal-flow oxygenator in addition to its gas exchange capability is able to accept blood at venous pressure and deliver it at arterial pressure levels with no auxiliary or serial blood pump in the system. The basic construction of the exchange device of the system includes a continuous strip of membrane (presently silicone base material folded transversly to a convenient size, supported by frames die-cut from a suitable material (i.e., latex, silicone rubber). The frames are sandwiched between two end plates, enclosing a defined volume and completing a unit. The membrane divides the enclosed volume into blood and gas spaces. These spaces reciprocate in size from zero to the completely enclosed volume as the incoming and egressing flows cause the membrane to move over its excursion of one frame thickness. Six such units are packaged into one cartridge with two sets of three units operating serially and in complementary fashion. A mechanical system has been constructed to control cartridge function. This operator controls flow and has a rudimentary CO_2 bleed control as well. Initial tests with sodium sulfite in place of blood indicate oxygen uptake rates of 100 ml/min at an oxygen pressure of 15 psig and a "blood" flow rate of 540 ml/min through a membrane area of 0.95 M^2. A redesign of the mechanical operator will be performed to reduce complexity. Oxygenators will be delivered for independent evaluation.
Contract Amount: $20,000 Contract Number: PH43-68-1383

Dow Chemical Company, Walnut Creek, California

HOLLOW FIBERS FOR USE IN MEMBRANE OXYGENATORS. B. J. Lipps, W. E. Skiens, E. A. McLain, P. D. Oja.

The object of this study was to produce and evaluate hollow fiber capillaries prepared from a variety of synthetic polymer materials for potential use as membrane oxygenators in artificial heart devices. Commercially available gas permeable capillaries are unsuitable for inclusion in an operable membrane oxygenator because of their: 1) low percent open cross-section area, 2) large internal diameter, and 3) prohibitive cost. The gas permeabilities and predicted ease of hollow fiber spinning of the selected materials were initially evaluated in flat membrane form. The polymers studies include polycisisoprene, poly-4-methylpentent-1, polybutadiene, poly (propylene co-ethylent), poly (butadiene co-styrene) polyisobutylene, poly (ethylene co-octent) and an experimental silicone rubber. The most promising of those materials were selected for conversion into hollow fiber form. Hollow fibers ranging in size from 30 to 300 I.D. with 40-65 percent open cross-sectional area have been successfully prepared from: 1) poly-4-methylpentene-1, 2) modified poly-4-methylpentene-1 and 3) the experimental silicone rubber. Gas permeability measurements indicate that these fibers have respectively 1/20, 1/4, and 2/3 the oxygen and carbon dioxide permeability of Silastic Membranes. Good in vitro blood compatibility has been reported for the modified poly 4-methylpentene-1. This contract will shift from a materials study to device design and fabrication using materials developed in the current program.

Contract Amount: $51,644 Contract Number: PH43-68-1387

General Electric Company, Schenectady, New York

DESIGN AND FABRICATION OF BLOOD OXYGENATOR FOR CIRCULATORY ASSIST DEVICES. W. F. Mathewson, Jr. E. Converse Peirce 11 (Emory Univ. School of Medicine, Atlanta, Ga.)

The evaluation of General Electric silicone copolymer, with regard to gas exchange capability and blood trauma studies, continued. Both oxygen and carbon dioxide transfer have been studied as a function of membrane support technique, membrane thickness, blood film thickness and flow rate, and shim pressure in the Peirce oxygenator. To further evaluate the usefulness of this membrane material, it has been compared with Teflon and the disc oxygenator in paired in vitro experiments to distinguish the difference in blood trauma. Comparable circuits were primed with 500 ml fresh heparinized blood simultaneously drawn from the same dog. One used a six inch Esmond oxygenator with 13 convoluted discs run at either 75 or 100 rpm. Another used a Peirce lung with 0.5M^2 of Teflon or copolymer membrane. Six-hour tests were run at 500 ml/minute flow and 37°C. Each experiment represented 360 circulations of the entire blood volume. Supplied gas was 3% CO_2 in air. Blood held at 37°C or 25°C was used for control. Tests included: Plasma hemoglobin (PHb), cell counts, O_2 saturation, glucose, lactic dehydrogenase (LDH), viscosity, prothrombin time (PT), partial thromboplastin time (PTT), euglobulin clot lysis (ECL), fibrinogen, pH, pCO_2, and culture. Trauma could not be assessed by cell counts, changes in viscosity, PT, PTT, ECL, or

fibrinogen. LDH values correlated with time but only in individual experiments. PHb levels provided a satisfactory measure of trauma. Copolymer membranes with intrinsic point support caused little more trauma than the circuit alone, while the inclusion of polyvinyl coated fiber glass screen between the copolymer membrane resulted in severe trauma. The disc, run at 75 rpm, was comparable to the Teflon membrane lung but was much more traumatic at 100 rpm. Oxygenators with varied blood capacities will be delivered for independent evaluation. If continued past that point, further work will concentrate on reducing production cost.
Contract Amount: $74,245 Contract Number: PH43-67-1458

Hauser Research and Engineering Company, Boulder, Colorado.

DEVELOPMENT OF CAPILLARY NETWORK MEMBRANE OXYGENATORS. Ray L. Hauser, David H. Thompson. John A. Jacobey, (Denver, Colorado).

A unique geometry was studied in this contract, consisting of an interconnecting capillary network. The capillaries were made of porous nickel coated with silicone rubber, or of just silicone rubber. The network was manifolded for oxygen flow within capillaries. Oxygenator elements were made with 2.5 square meter diffusional area within 0.7 liter priming volume. Blood flow pressure drop was low and mixing was excellent. As of this writing, reliable leak-free elements have not yet been made with sufficient diffusion for complete blood oxygenation. Future work will concentrate on resolving the production problems. If these are solved, oxygenators will be fabricated for independent evaluation.
Contract Amount: $25,000 Contract Number: PH43-68-1404

Institute of Medical Sciences, San Francisco, California.

DEVELOPMENTS TO IMPROVE THE BRAMSON MEMBRANE OXYGENATOR. Robert C. Eberhart, Myer L. Coval.

Photometric and photographic techniques were developed which allowed mapping of O_2 saturation and blood streamlines throughout the individual gas exchange cell. A numerical technique, based on Hele-Shaw flow, was also developed to calculate the local velocity vector. Local oxygen flux, pO_2 drop across the blood layer and local oxygen mass transfer coefficients were calculated from these data. A mass transfer correlation parameter was modified to resolve variations of pH, temperature, hemoglobin and inlet saturation between experiments. Simple modifications of the Bramson machine, based on these analyses, have increased the oxygen exchange efficiency by 40%, with 60% increase in blood pressure drop. In clinical blood samples obtained during heart lung bypass, consistent changes have been observed in the plasma protein pattern obtained with the procedure of analytical acrylamide gel electropheresis. The technique was modified to allow routine separation of more than 40% human plasma proteins. A quantitation procedure was developed to measure the protein content of individual bands in the gel. The concentrations of several proteins were found to change as a function of the length of the bypass. Some of these proteins were identified as haptoglobins. Other studies of blood trauma included erythrocyte osmotic fragility and screen

filtration pressure. This contract has terminated. The Bramson oxygenator studied under this contract will undergo independent evaluation in another program to furnish baseline information.
Contract Amount: $91,310 Contract Number: PH43-68-67

Litton Industries, Minneapolis, Minnesota.

SPIRAL COIL BLOOD OXYGENATOR. Kenneth Abel.

An oxygenator of the Kolobow spiral coil configuration capable of providing adequate respiratory gas exchange for blood flows up to 5 liters per minute is under development. A highly specialized membrane design is required for the configuration in order to achieve maximum gas exchange with minimum oxygenator size. A cooperative task of membrane development and testing between Litton-Rhone Polenc (Paris) and Litton-Fuji Polymer (Tokyo) has been completed. This part of the program has resulted in the establishment of high volume sources of suitable high quality membrane for use in both spiral coil and conventional membrane oxygenators. The incorporation of these membranes into the spiral coil oxygenator and testing of the oxygenator is now in progress. Oxygenators will be delivered for independent evaluation.
Contract Amount: $40,787 Contract Number: PH43-69-48

Medical College of Virginia, Richmond, Virginia.

A HOLLOW FILAMENT FABRIC BLOOD OXYGENATOR. T. Leigh Williams, Teruhisa Nakamura, Lewis H. Bosher.

During the first contract year, two models of the hollow filament fabric blood oxygenator were constructed and evaluated. These demonstrated the expected mechanical and flow properties and the ability to oxygenate up to 1500 cc of canine blood per minute. Their capacity was severely limited by the low gas permeability of the only available hollow filaments (medium density polyethylene). Since then emphasis has been on obtaining more permeable hollow filaments. The criterion of relative permeability has been the ability to transmit CO_2 from within the filaments to the surroundings at a PCO_2 in the range 710 to 810 mmHg. This criterion was chosen because the venting of CO_2 is the really critical characteristic of any membrane oxygenator. An apparatus for measuring the permeation of CO_2 under those conditions has been developed. Hollow filaments from two types of polymers having much higher permeability than polyethylene were obtained. The first type, a methyl pentene, appears to have a permeability about six to eight times as great as polyethylene. Twelve samples based on this polymer, varying in inside diameter from 25 to 100 microns have been evaluated, and an optimum inside diameter of 60 microns selected. Such filaments are now being woven to fabric for evaluation in the oxygenators. The single sample of filaments made from a silicone copolymer appears to be about 25 times as permeable as the polyethylene. Work on improved spinning is underway. Further studies on cleaning and sterilizing procedures, and on blood trauma in the oxygenator are encouraging. An arteriovenous shunt with the small polyethylene oxygenator interposed was operated at flow rates of 1000-1400 cc per minute on dogs for four hours. Flow rate and pressure gradient were stable, plasma-hemoglobin remained very low (not over 5 mg%), other parameters showed no remarkable changes, saline washings of the oxygenator before each procedure were negative, blood cultures

were sterile, the dogs survived. Future work will concentrate on cost reduction by use of new basic materials. Oxygenators will be delivered for independent evaluation.
Contract Amount: $39,641 Contract Number: PH43-67-1426

Monsanto Research Corporation, Everett, Mass.

BLOOD OXYGENATOR WITH PREFORMED, MEMBRANE-LINED, CAPILLARY CHANNELS. Philip Dantowitz & Alex Borsanyi.

Arterialization of blood in parallel capillaries about 200 microns effective diameter requires a thin membrane barrier (<60u) if full advantage is to be taken from this geometry for both oxygen and CO_2 transfer. This contract deals with the design, construction and evaluation of a membrane oxygenator which will utilize thin film (5-10u) coated capillary channels. The basic functional element of the device consists of two 23.1 x 11.6 cm substrate sheets, one of which is flat and the other preformed with 580 parallel grooves 11.6 cm long and about 200u x 200u cross section. When pressed together the two sheets delineate a flat layer of parallel capillaries with rated blood flow of 60 ml/min and pressure drops of 80 mmHg. The substrate material is a highly porous, hydrophobic mix rolled onto a stainless steel screen support. Elements can be stacked to form larger capacity units. In the first year of the program feasibility was demonstrated by in vivo testing in which oxygen uptake was close to the original goal of 80 ml/min/m^2. In the second year improvements were made in the geometry of the blood side to reduce shunts and maldistribution. Progress was also made in applying the thin coating of silicone rubber to the grooved and flat substrates. Dog perfusions have been carried out for up to 6 hours. Occasionally red cell aggregation has caused a sharp rise in the head of pressure necessary to maintain the rated flow. This phenomenon, which is fully reversible upon washing the oxygenator with saline, is not completely understood. Gas exchange data from in vivo testing show considerable scatter, only a portion of which can be explained. Oxygenators with varied blood flow capacities will be delivered for independent evaluation. In addition, improvements in gas transport and reductions in manufacturing cost will be investigated.
Contract Amount: $101,000 Contract Number: PH43-67-1420

University of Minnesota - Cornell University, New York, N.Y.

PROGRESS IN THE TESTING AND DEVELOPMENT OF PRACTICAL FLAT PLATE MEMBRANE OXYGENATORS FOR CARDIO-PULMONARY ASSIST. A.J. Landé, R.N. Tiedeman, V.A. Subramanian, S.J. Fillmore, C.W. Lillehei.

In order to test our disposable membrane oxygenators, we inserted vena-caval and arterial catheters through the external jugular and carotid of anesthetized dogs. While still anesthetized, the dogs were subjected to partial veno-arterial bypass and breathed with 8%O_2 & 92%N_2. Although some useful information on oxygenation and CO_2 removal was obtained, this was an unstable preparation and the dogs soon died. Partial perfusions of awake dogs that had had catheters inserted 24 hours previously under anesthesia were then undertaken. Perfusions of 10 dogs for 24 hours yielded 5 long term survivors. Perfusions of 5 dogs for 48 hours yielded 2 long term

survivors. Mortality could be traced to technical mishaps and pneumonia. Although a variety of parameters were studied, morbidity was limited to a temporary reduction in platelets. A decrease in Hgb. was noted; however plasma Hgb. only reached the range of 50 mgm.% and no priming or replacement blood was required. Oxygenators with varied blood flow capacities will be delivered for independent evaluation. Continuation past that point is not planned.
Contract Amount: No additional funds Contract Number: PH43-67-1446

University of Minnesota, Minneapolis, Minn.

DEVELOPMENT OF A COUETTE OXYGENATOR. Kenneth H. Keller.

The purpose of this project is to develop a membrane oxygenator in which the blood flow field induces rotation of the RBC's thus promoting plasma mixing and reducing the resistance of the plasma to oxygen transport. A concentric cylinder device has been built and tested which induces a Couette flow field and a blood shear rate of up to 2000/sec. In the initial design using a G.E. XD polymer membrane, a blood throughput rate of 850 cc/min, and a blood layer thickness of 1 mm, uptake rates were about 25 ml(STP) /(sq.m) (min) without rotation and 160 ml(STP)/(sq.m.)(min)with rotation (shear rate of 1500 inverse sec), representing an improvement of a factor of 6 due to flow-induce RBC rotation. A modified design with reduced dead space and improved bearing and seal construction is presently being tested. Continuation of this contract is not planned.
Contract Amount: No additional funds Contract Number: PH43-67-1419

Two technological problems are recognized in the area of instrumentation. The first problem is to improve quantitatively the performance of devices which are currently available. This usually involves refinement of existing techniques, rather than substantial changes in the state-of-the-art. The second technological problem is that of identifying new concepts and techniques for data aquisition and manipulation which will improve our knowledge of device performance and physiologic state. Currently available techniques are rarely equal to the anticipated demands, as other program areas progress. Consequently, some support is provided for concepts which have indications of possible success and which would have substantial benefits if developed as initial estimates suggest. A number of new contracts are being negotiated to: study non-destructive testing of implanted devices, using sound analysis; study the use of lipid bilayers in automated analytic techniques; employ disc gel electrophoresis to increase resolution of the general technique; study the feasibility of a new type of blood flowmeter; investigate long term stability of pressure transducers and provide improved types for program use; study the development of a new type of disposable pressure transducer; attempt to reduce to practice a new method for production of capacitance ECG electrodes; and study the magnetic fields produced by the heart, using a cryogenic magnetometer.

Case Western Reserve University, Cleveland, Ohio

IMPLANTABLE IMPERMEABLE ENCAPSULANTS FOR ARTIFICIAL ORGANS. C. C. Enger and F. W. Rhinelander.

This project aims to develop a membrane impermeable to body fluids for use as an encapsulant of implantable devices. Sheets of unvulcanized Silastic have been impregnated with various waxes -- beeswax, spermaceti and carnauba, to date. The resulting membranes are being tested for ion permeability and water-vapor transmission; samples have been implanted into rabbits to test tissue compatibility. Ultraviolet microscopy studies, to determine the eveness of wax penetration, are being carried out. The ion-permeability tests and the tissue compatibility tests are as yet incomplete. The water-vapor transmission tests indicate that 60-mil Silastic impregnated with spermaceti is superior to beeswax and carnauba-impregnated membranes, and to a control membrane of unimpregnated Silastic. Waxes additional to those mentioned above are being sought for impregnation into Silastic membranes. The original work plan will be complete by the end of the year. A renewal is not planned, but considerable interest in the technique has been noted by other contractors, and further implementation is almost certain.
Contract Amount: $16,214 Contract Number: PH43-66-1397

Corbin-Farnsworth, Smith Kline Instruments, Inc., Palo Alto, California

A MINIATURE CATHETER TIP CAPACITANCE PRESSURE TRANSDUCER. M. Klenits, T. S. Finnegan and F. Sutter.

This program has been directed to the development of manufacturing ultra miniature capacitance transducers ... ing a high frequency response, for travascular pressure measurements. The transducers were first developed by

NASA, Ames Research Labs, who built them in small quantities for test in dogs. This program has had two principal goals: 1) to produce catheter-tip mounted transducers in sizeable quantities and with high yield, and 2) to design and test prototype implantable transducers. Under the first phase of the program, 50 catheter-tip mounted transducers will be produced and delivered. The transducer sensing diaphragm is located at the end of a 40" long triaxial cable having a central airway. The cable outside diameter is only .043", allowing it to be inserted through a #17 needle. When in place, the transducer measures changes in blood pressure by measuring the tiny deflections of the diaphragm at the end of the cable. Capacity changes on the order of .02PF are measured. The central airway in the cable allows the transducer to be referenced at atmospheric pressure even when in place. Techniques for manufacturing transducers with high yield have been developed, as well as the techniques for building the .043 triaxial cable, triaxial connector with airway, and the assembling of them into working units. These catheters can be reused several times. In phase two of the program, a pair of implantable pressure sensors are being developed to be mounted in a single implantable package. One transducer is mounted in the blood stream at the measurement point; the other measures pressure of body fluids outside the cardiovascular system, such as in the interpleural space. The electronics for measuring the differential change in capacitance between the two transducers is a hybrid integrated circuit mounted in a hermetically sealed can. The implantable transducers are made of titanium, while the catheter mounted transducers are nickel steel. Because of the loss of a number of key personnel in the past few months, this program has fallen behind schedule. A six-month, no-cost extension is being negotiated to complete the original workscope.

Contract Amount: $65,000 Contract Number: PH43-68-666

Epoxylite Corporation, South El Monte, California

DEVELOPMENT OF IMPROVED ENCAPSULATION MATERIALS FOR IMPLANTATION. H. Lee, A. L. Cupples, K. Neville and G. W. Culp.

This program is intended to: (a) develop encapsulating resins suitable for long-term implantation in the body to serve as insulants for high impedance circuits used in artificial heart power sources and control devices, (b) develop methods for mounting artificial adnexa within the body, and (c) provide fast-response encapsulation and mounting fixture fabrication services. Epoxy-resin encapsulation systems have been developed with low water vapor permeability, low water absorption, and improved electrical properties. Concurrent with the encapsulation development, impermeable films of vacuum-deposited parylene have been investigated for use in sandwich constructions for some encapsulation applications. Results indicate the best systems so far developed preserve stable electrical properties in in vitro testing in moist and fluid environments and are superior to those systems presently employed for pacemaker encapsulation. Three types of polyurethanes, segmented, polyester-based, and unsaturated, have been characterized for use as flexible, tissue-compatible overcoats for encapsulated artificial adnexa and for potential use in the fabrication of flexible stress-relief cones to prevent lead breakage on electrical units. Biodegradation studies in dogs have been initiated to confirm the suitability of the encapsulation materials and the polyurethane overcoats for use in biological environments. Scanning

electron microscopy was used to determine histology and degree of surface attack on the implanted polymers. With regard to internal prosthopexy, an arrangement which distributes the weight of heavy artificial adnexa partly on bone and partly on soft tissue appears required. No directly applicable literature was found in a detailed Index Medicus search. From 200 articles reviewed in detail, however, location adjacent to a section of stabilized rib cage is recommended, with weight being distributed to soft tissue by means of fabric tabs and to bone through the rib stabilization device. These devices are now being evaluated in cooperation with other contractors. The contract will be extended for another year, with primary emphasis on support for other contractors in supplying appropriate materials and encapsulation service.

Contract Amount: $59,344 Contract Number: PH43-68-1409

Hydrospace Research Corporation, Rockville, Maryland

ENCAPSULATION PROCEDURE TO ISOLATE COMPONENTS FROM BODY FLUIDS. C. R. Nichols.

The technical objective of this program was to prepare and evaluate encapsulating materials that achieve reduced permeability by introducing high concentrations and/or selective distributions of impermeable inclusions to the base encapsulation. Reduced permeability is achieved by effectively increasing the diffusion path for body fluids. A mathematical model of the diffusion process has been developed that includes the effects of spherical and flake-type impermeable inclusions in the base material. The model indicated that hundredfold reductions of permeability should be theoretically possible for spherical inclusions and thousandfold reductions for flake-type inclusions. The present mathematical model does not include other mechanisms of permeation. Tests were conducted using Dow Corning RTB-382 as the base material and glass microspheres as the inclusion material. A volume fraction 0.70 inclusion was selected as a representative sample and permeation tests were conducted. Test results indicated that significant improvement in permeability reductions were obtained (1.6 fold compared to the theoretical sixfold improvement). The test results indicated what mechanisms of fluid transport are present. It is postulated that another mechanism involves "short channeling" of the diffusing material in the immediate vicinity of the interface between impermeable inclusions and the base material. Surface treatment of the spherical inclusions to reduce "short channeling" will be required to approach the theoretical improvement possible. The contract will expire at the end of this year. Because the investigation shows that only modest improvements are possible, no further effort is planned.

Contract Amount: $17,834 Contract Number: PH43-68-1410

Monsanto Research Corporation, Everett, Massachusetts

INSTRUMENTATION APPLICABLE TO ARTIFICIAL HEART DEVELOPMENT: ANALYSIS OF BLOOD LACTATE AND PYRUVATE. D. L. Williams and A. R. Doig.

Electrochemical monitoring of the LDH (cytochrome b_2) reaction of lactate with $K_3Fe(CN)_6$ is being investigated for the measurement of blood lactate. A thin enzyme layer is maintained between a platinum electrode and a dialysis membrane. Lactate diffusion into this layer produces pyruvate and $Fe(CN)_6^{-4}$. A potential is maintained at the platinum electrode such that

$Fe(CN)_6^{-4}$ is oxidized back to $Fe(CN)_6^{-3}$. The resulting current is thus a measure of lactate. Whole blood can be used, but must be diluted with a buffer - $K_3Fe(CN)_6$ solution. Oxygen does not interface in this method. However, a background current in plasma and blood must be measured and subtracted. This can be accomplished electronically, using a second similar electrode system, but without enzyme. A similar approach is being attempted with a $Fe(CN)_6^{-3}$ acceptor, pyruvate dehydrogenase, for the measurement of pyruvate in blood. It is planned to continue this work during the coming year, with sustained emphasis on reduction to practice.
Contract Amount: $55,335 Contract Number: PH43-68-1405

Statham Instruments, Inc., Oxnard, California

CHRONICALLY IMPLANTABLE PRESSURE TRANSDUCERS. J. Chambers.

This program undertook the development of chronically implantable pressure transducers with blood interface capability and capability to maintain constant output. A series of differential pressure transducers have been developed with a sensitivity increase of nine times over the transducers available at the beginning of the program. These transducers utilize the deposited film approach that is known to provide long term stability. The developed transducers have active diameters of 1/2, 3/8, and 1/4 inch with ranges of 60, 125, and 350 millimeters respectively. Preliminary in vitro and in vivo tests have been made on the use of an interface membrane in front of the transducer diaphragm. A serum-filled chamber has been used between this membrane and the pressure sensing member of the transducer. The primary goal of this contract has been realized -- the construction of a pressure transducer of suitable size and estimated range. The contract is not being renewed at this time; future work will depend on assessment of the delivered transducers by other testing groups sponsored by this program.
Contract Amount: $93,845 Contract Number: PH43-68-1418

Texas Instruments, Houston, Texas

IMPROVED DIAGNOSTIC ACCURACY IN ACUTE MYOCARDIAL INFARCTION WITH MULTICHANNEL ELECTROCARDIOGRAPHIC DATA ACQUISITION AND ANALYSIS. J. H. Cyprus and C. G. Blomqvist, A. B. C. Dowdy, S. Lightfoot and R. S. Putnam (Southwestern Medical School).

A study designed to correlate electrocardiographic, serum enzyme, and pathology data in cases of known or suspected myocardial infarction was begun. For each patient, the following measurements are made during the course of observation and treatment: (1) repeated simultaneous collection of 30 channels of electrocardiographic data from thoracic surface leads for a period of 10 seconds, and (2) repeated serum enzyme analysis. In those patients who succumb and are autopsied, detailed pathological examination is performed. The electrocardiographic data is analyzed as follows: A suitable portion of the signal, spanning one cardiac cycle, is selected. The interval is then subdivided into ten time frames for further analysis. The data is subjected to a transformation which extracts a set of statistically independent ECG signals having maximal energy over each time frame. The number and energy distribution of these signals is being examined for correlation with the serum enzyme data and (when available) with pathology data. In addition, the ensemble of derived signals is being correlated with the original data to try

to construct the geometry of conduction and hence to construct a map of viable and non-viable myocardium. Work under the current plan will continue for the second year. The equipment has been delivered to Texas Southwestern and this effort will primarily involve data acquisition and analysis techniques.
Contract Amount: $231,853 Contract Number: PH43-68-645

Thermo Electron Corporation, Waltham, Massachusetts

ELECTRODELESS ELECTROMAGNETIC FLOWMETER. S. Kitrilakis and F. N. Huffman.

This contract was for the further development of an electrodeless electromagnetic flowmeter and for a study of the feasibility of using it for chronic implantations. This flowmeter represented a promising new approach. Power requirements were to be investigated. In vitro experiments with this flowmeter, using the principles of induction magnetohydrodynamics, have failed to produce a practical device. Although the basic concept is sound, the relatively low electrical conductivity, permeability and velocity of the blood result in such a small ratio of signal-to-quadrature voltage that the technique holds limited promise of development into a clinical tool. This contract was terminated January 31, 1969.
Contract Amount: $28,500 Contract Number: PH43-68-1413

Westinghouse Electric Corporation, Pittsburgh, Pennsylvania

DEVELOPMENT OF A CONTINUOUS BLOOD pO_2 MEASURING SYSTEM. P. Reichner and Y. Tamari.

The objective of this program is to develop a continuous, in vivo, blood pO_2 measuring system. Continuous in vivo and in vitro analysis of blood pO_2 and pCO_2 is important for the monitoring and control of artificial heart devices and for the evaluation and control of blood oxygenators. The oxygen measuring device now under development uses solid electrolyte oxygen sensors with a circulating carrier gas in a null-balance system. The carrier gas composition is automatically adjusted to equilibrate the partial pressure of oxygen across the sensing membrane. This results in a measuring system with high accuracy that is essentially independent of the mass transfer characteristics of the membrane/blood interface, disposability for all elements that contact the body, freedom from calibration requirements, and no electrical potential within the patient. The oxygen in an N_2/O_2 gas mixture has been readily measured with the null-balance system to within 1 mmHg of a direct sample measurement. Membrane transfer of gases other than oxygen was found to cause significant errors in the O_2 measurement. These secondary gas transfer errors were eliminated by using a slightly more complex dual-null system which allows oxygen measurement of an $N_2/O_2/CO_2$ gas mixture with a deviation of less than 1 mmHg from the direct sample measurement. Feasibility has also been shown for the objective of developing a miniature catheter-tip device. Work will be continued, with the next step represented by development of a clinically functioning system.
Contract Amount: $49,431 Contract Number: PH43-68-661

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. Current investigations among six contractors have ranged from development of specific electrocatalysts for oxygen reduction and blood carbohydrate oxidation (particularly glucose) through studies of reaction mechanisms and kinetics to development and testing of complete biological fuel cells. Electrodes and cells have been tested in vitro in blood and in other solutions to evaluate their performance. Advances in catalyst activity and specificity over those of conventional catalysts such as platinum have been realized. Continuing work will be directed at further improvements in catalyst activity, specificity, stability, reproducibility, and restorability; in understanding reaction mechanisms and mass transfer limitations; in design of improved electrodes; and in performance testing of components and complete biological fuel cells in animals. Following are summaries of the work of contractors in this area.

Esso Research and Engineering Company, Linden, New Jersey

FEASIBILITY STUDIES - IMPLANTABLE BIOLOGICAL FUEL CELLS. J. S. Batzold and M. Beltzer.

In theory, implantable biological fuel cells are attractive power sources for artificial heart devices. In practice, several difficult problems must be solved to provide a viable system. These problems stem from the attempt to operate the fuel cell in vivo, with a body fluid electrolyte, blood plasma, near normal body temperature. Blood plasma is seriously deficient in a critical property of any fuel cell electrolyte, the ability to resist pH changes caused by the production and consumption of hydrogen ions during anodic and cathodic electrochemical reactions respectively. This problem is further complicated by the low reactant concentrations present in blood plasma. Experimental measurements of the magnitude of these mass transfer limitations suggest that conventional fuel cells show little promise for this application and novel concepts are needed. A second problem, the electrochemical oxidation of glucose, has also been studied and two promising electrocatalysts based on platinum and ruthenium have been found. Two approaches to the solution of the major problem of mass transfer have shown promise. One approach involves the rapid flow of electrolyte through a porous electrode, whereby the diffusion layer thickness can be minimized. As a consequence, the limitations of pH changes and low glucose concentration are dramatically reduced, and acceptable performance for an anode operating on glucose in electrolytes similar to blood plasma appears to be within reach. Parasitic power requirements must be evaluated in this approach. A second approach involves the development of a solid state mediator cell, whereby the anodic and cathodic reactions are mediated through an impervious thin film of redox polymer. This system would eliminate the need for a body fluid electrolyte and thus avoid the electrolyte buffer limitations entirely. Experimental evidence for the operability of such a system has been obtained. Acceptable reaction mediation rates must now be demonstrated. Work will continue on

the evaluation of improved catalysts and electrodes with emphasis on the flowing electrolyte concept. Redox polymers will be synthesized for the solid state mediator fuel cell, and mediator electrodes will be fabricated and tested in half cells.
Contract Amount: $71,000 Contract Number: PH43-68-1390

Leesona Moos Laboratories, Great Neck, New York

OXYGEN REDUCTION ON GOLD-PALLADIUM ALLOYS IN NEUTRAL MEDIA. J. H. Fishman and J. F. Henry.

The need to find active electrocatalysts for the selective reduction of oxygen in human body fluids motivated the study of Au-Pd alloys, to relate catalytic selectivity to the electronic configuration within the alloy series. In the pH range 6.8-7.6, at 37°C, Pt, Pd, Au and Au-Pd alloys, in bulk and metal black form, displayed reproducible prime and steady state cathode activities. Prime activity and its rate of transition to the substantially lower steady state activity, depend on the open circuit potential, which, in turn, depends on the prior polarization history, i.e., potential, degree of approach to the steady state and time on open circuit. The open circuit potential tends spontaneously but slowly to the stable rest potential. Potentiostatically dorced return to the stable value is associated with transient anodic currents. It is thought that the described polarization phenomena could reflect the adsorption and removal of hydrogen peroxide from the catalyst surface. Maximum activity for O_2 reduction at the steady state was found at about 35% and 65% (atomic Au content for alloy blacks and at 30%, 40% and 75% for Bulk alloys. Alloy blacks exceed Pt black activity by a factor of about 2-3. In the combined presence of 0.1 M NaCl, 1 mg/ml dextrose, 0.25 mg/ml lactic acid and 0.3 mg/ml urea, the cathode activity of 35% and 65% Au-Pd blacks is suppressed by about 20% and 30% respectively, while that of Pt black by 70%.

Thus, some Au-Pd alloys are not only more active than Pt black for oxygen reduction in nautral media, but they are also more selective for this process.

Fabrication and evaluation of oxygen electrodes based on gold-palladium alloys will continue as well as studies of electrode regeneration processes and peroxide concentration effects.
Contract Amount: $59,995 Contract Number: PH43-68-1380

Monsanto Research Corporation, Boston Laboratory

IMPLANTABLE FUEL CELL FOR AN ARTIFICIAL HEART. R. F. Drake

Research and analysis has required a substantial modification of the original neutral electrolyte cell concept that involved free solution exchange at flat, planar electrodes. Problems with mass transfer of reactants and products, electrode kinetics at neutral pH, and non-selective catalysts have lead to the design and evaluation of an "acid" electrolyte cell (pH = 1.4) that requires phase separation of gaseous O_2 at the cathode and

hydrogen from dextrose at the anode through a Pd foil. Prototype cells have been designed that have performed in vitro at 0.6 volt/cell at 50 ua/cm^2 with flat electrode structures. Design studies are underway to extend this performance by providing larger exchange surface areas in the electrode structures. An in vitro and in vivo evaluation of these prototype cells is planned as well as for a "second generation" prototype in which the results of a component optimization study are included. Improved dialysis membranes, separators, anodes, and cathodes will be incorporated in complete biological fuel cells, which will be subjected to extensive in vivo tests in animals.
Contract Amount: $150,940 Contract Number: PH43-66-976

Pennsylvania Research Associates, Philadelphia, Pennsylvania

ON THE DESIGN OF CATALYSTS FOR BIOLOGICAL FUEL CELLS. Carlo V. Bocciarelli and Halina Wroblova.

A new theory of metallic catalysis has been developed which is based on the electron density of a metal under the further requirement that the catalyst show nearly complete immunity to chemical attack. Catalysts designed on the basis of this theory have been produced and tested. These differ from previous practice as they are crystalline powders (mounted in Teflon), not blacks. As specific oxygen electrodes in neutral or alkaline solutions, they outperform existing catalysts such as platinum black by a very wide margin. For example, the gold-copper alloy catalyst at a potential range of 0.85 to 0.75 volt in 5N KOH yields current densities from 300 to 1000 ma/cm^2, whereas platinum black prepared and operated under identical conditions gives current densities from 100 to 300 ma/cm^2. Studies on the design of glucose electrodes have also been carried out. Further development work will be carried out on gold-copper alloy electrodes for oxygen reduction, on crystalline platinum alloy electrodes for oxidation of blood carbohydrates, and on testing of these materials in half-cells and fullcells. The catalytic theory will be extended to the carbon-carbon bond.
Contract Amount: $47,682 Contract Number: PH43-68-1417

Tyco Laboratories, Incorporated, Waltham, Massachusetts

ANODIC OXIDATION OF GLUCOSE. Jose Giner and Paul Malachesky.

An implantable fuel cell is an ideal power source for artificial heart systems. With the objective of developing such a fuel cell working on oxygen and carbohydrates readily available in the blood, we have studied the mechanism of the anodic oxidation of glucose on smooth platinum electrodes in neutral solutions using transient electrochemical techniques. It has been found that glucose can be oxidized at potentials very close to the reversible hydrogen electrode to produce a chemisorbed product which can be irreversibly oxidized at higher potentials. This chemisorbed product has been tentatively identified as "reduced CO_2", an adsorbed species common to the oxidation of most organic fuels. It has been demonstrated that gluconic acid itself is oxidized at potentials where glucose is oxidized and therefore should not be the sole oxidation product. Determination of the rate of formation of the oxidation intermediate indicates that the electro-oxidation of glucose

occurs via the open-chain or aldehyde form. In continuing studies of mechanisms in the anodic oxidation of glucose, smooth electrodes of Ir, Rh, and Ru and of Pt alloys with these metals will be used as electrocatalysts, and electrodes of these materials will be tested as blood carbohydrate anodes in glucose half-cells.
Contract Amount: $60,000 Contract Number: NIH-69-32

Union Carbide Corporation, Cleveland, Ohio

SPECIFIC CATALYSTS FOR ELECTROCHEMICAL OXYGEN REDUCTION IN NEUTRAL NaCl SOLUTION. A. Kozawa, V. E. Zilionis, R. J. Brodd, and R. A. Powers.

An implantable fuel cell which will drive an artificial heart requires a specific catalyst for oxygen reduction at the cathode. The specific catalyst applied on the cathode use in a blood stream should not catalyze a direct chemical reaction between molecular oxygen and glucose coexisting in the blood. In a search for such a catalyst, various carbons, graphites, metals, carbides, borides, blood components, and other catalytically active materials were tested in an isotonic saline solution (0.15 M NaCl + 0.1M phosphate buffer, pH 7.22), with and without 10 percent human blood added. These materials were first screened using linear sweep voltammetry techniques in quiescent solutions. More definitive measurements were carried out with a rotating disk electrode technique. It was found that ferric phthalocyanine deposited on graphite was the best catalyst among the materials tested. Ferric phthalocyanine was deposited on the electrode surface by dilution of sulfuric acid solution or by evaporation of a pyridine solution of phthalocyanine. The phthalocyanine catalyzed graphite (P. C.-Gr) electrode exhibited an open circuit voltage of +0.3 to +0.4 volt vs. S.C.E. in the O_2-saturated saline solution and the current capability as well as the current-potential curve taken at this electrode was approximately the same as that taken at a smooth platinum electrode. This P.C.-Gr electrode operated in whole blood and did not react with isotonic saline solutions containing glucose and gluconate. The importance of substrate material should be noted. It was found that ferric phthalocyanine was an excellent catalyst only when deposited on graphite and carbon. Ferric phthalocyanine deposited on Ti, Zr, and porous nickel electrodes was not active.

Improved electrocatalysts and flow-through electrode structures will be developed and tested for oxygen reduction performance in half-cells in isotonic solutions and in blood. A mathematical model and computer program will be developed to aid in predicting and explaining electrode and cell behavior and in understanding reaction mechanisms, kinetics, and mass transport.
Contract Amount: $87,754 Contract Number: PH43-68-1391

Energy to power circulatory assist devices or total replacement artificial hearts must be derived from sources within the body or from external sources by transmission of power through the skin. Two energy systems which are considered potentially practicable as totally implanted sources of energy for the fullest rehabilitation of the patient are (1) those which derive their energy from an implanted radioisotope, and (2) those which derive their energy biochemically from the body, e.g., biological fuel cells (discussed elsewhere in this report). Until totally implanted energy systems are perfected, early artificial heart systems will depend on transmission of power from external sources. All these systems require implanted means for efficient energy conversion and storage. In addition, they require control subsystems for effective utilization of energy in response to physiological demand. During the past year, research and development has been carried out under 15 contracts on energy transmission, conversion, and storage. Three distinctive skin transformer systems have been subjected to extensive in vivo tests in animals and all have proven capable of transmitting in excess of 30 watts into the body through intact skin; one, with modification, has transmitted over 100 watts. Two implantable energy systems based on dc brushless motors coupled to linear and rotary hydraulic pumps have demonstrated their ability to actuate blood pumps with suitable hydraulic flows. Three different piezoelectric converter concepts have been investigated and developed; one of these has provided an average hydraulic pumping flow of several liters/minute at physiological pressures and rates. Three thermal engine designs under development are approaching performance characteristics which would make them attractive energy converters for coupling to a heat source energized by a radioisotope or by electrical energy. Implantable energy storage has been under development in the form of thermal energy storage, rechargeable electric batteries, and regenerative fuel cells. Goals for the immediate future include development of greater energy capacity and energy density for implantable electrical energy storage, continued performance testing of energy subsystems in integrated systems with improved control, and continued development of new and existing systems to improve efficiencies, performance, implantability, and reliability.

Aerojet-General Corporation, San Ramon, California

DEVELOPMENT OF A MODIFIED STIRLING CYCLE HEART ENGINE. K. E. Buck.

This contract was for the development of a completely implantable Stirling cycle power conversion system. The system being developed is capable of converting thermal power to hydraulic power. The thermal power is received from a thermal storage unit which is periodically recharged using electric power transmitted through intact skin. The hydraulic power output is used directly to drive a circulatory assist or artificial heart device. The engine being developed is novel in two respects. Engine output is in the form of pressurized gas. This pressurized gas is used in a piston and bellows arrangement (pump actuator) to produce the required pressure pulses in the hydraulic fluid which drives the artificial heart. Only linear motion is used in the engine to convert heat to hydraulic power. Crank mechanisms, which result in high bearing loads and lateral loads on

sliding surfaces, are avoided. Bearing loads are low enough to permit unlubricated operation for very long periods of time. An engine which resembles, as closely as possible, the final implantable configuration is now under test. The test engine requires only the addition of instrumentation, elimination of the thermal storage unit, and substitution of more convenient though less effective thermal insulation. Test results to date largely confirm the anticipated engine operating characteristics. Test model and implantable pump actuators are also being built and tested. This Stirling cycle engine converter program will be continued to further define the in vitro operating techniques of the engine when coupled with other major subsystems. The specific in vitro evaluations will include operation with an automatic control subsystem and a thermal storage subsystem that will provide the basic energy for driving the unit. It is also planned that in vivo evaluations will be performed with the unit. These efforts are to quantify operational techniques, efficiencies and weight and volume constraints on the system.
Contract Amount: $44,411 Contract Number: PH43-68-1435

ERG, Inc., Oakland, California

PIEZOELECTRIC IMPLANTABLE ENERGY CONVERTERS. G. M. Benson and J. W. Christie
Work under this contract was on piezoelectric (PZ) electromechanical energy converters. The operating principles and performance levels of PZ materials are reviewed and compared with more conventional electromechanical energy converters. This comparison suggests that efficiency, reliability and compactness can be maximized by exciting the PZ material at an ac voltage frequency determined by the mechanical resonant frequency of a mass-loaded, spring-biased oscillator. A reduction in the oscillator mass is achieved by the use of a mechanical transformer which effectively couples the high-force, low-displacement output of the PZ material to the low-force, high-displacement of the oscillator. This transformer employs differential area, mercury-filled, metal bellows of advanced design which drive a double-acting positive displacement pump whose variable displacement output is determined by the ac voltage applied to the PZ module. Experimental results for preliminary designs are presented and compared with theory. Designs are described that operate at either cardiac frequency or at high frequency with mechanical frequency transformation. Endurance tests on advanced PZ modules were conducted to over several billion cycles under high electric field and mechanical strain conditions without measureable degradation. Electromechanical conversion efficiencies for PZ modules were determined to be in the ninety percent range for practical operating conditions. Mechanical output energy densities of over 0.1 J per cycle per cc of PZ material were reproducibly obtained. Flow rates of over 40/min. against a pressure head of 150 mmHg were produced by the hydraulic pump at frequencies up to 200 Hz. As a result, resonant, high-frequency PZ driven double-acting, positive displacement pumps appear promising for hydraulically driven systems. This program was terminated in December, 1968.
Contract Amount: $52,100 Contract Number: PH43-67-1409

ERG, Inc., Oakland, California

ELECTROMAGNETIC IMPLANTABLE ENERGY CONVERSION SYSTEMS. G. M. Benson and J. W. Christie.

This contract was for research and development to determine the performance of advanced electromagnetic energy converters that may be employed to power blood pumps in implantable artificial heart systems. Theoretical and experimental results for electromagnetic machines indicate that a high frequency parametric oscillator operating on the variable reluctance principle and directly coupled to a positive displacement double acting fluid pump offers promise in terms of reliability, efficiency, compactness and controllability over the complete operating range required. The basic design of this electromagnetic-hydraulic (EMH) converter is based on a 2-pole magnetic oscillator consisting of a core and coil assembly for each pole and a laminated iron disc armature. Under operation the armature is pulled toward one re-entrant magnet structure (pole) on one half-cycle and then pulled the opposite way by an identical magnet structure on the alternate half-cycle. By commutating the two field coils an efficient energy transfer between coils is achieved which increases the power factor at the terminals. The mechanical forces, efficiently produced by the alternating magnetic fields, are sufficient to directly drive a hydraulic plunger, which may be the armature. By this action, electric power synchronously pumps an isotonic fluid at a rate and pressure sufficient to directly displace blood from a bladder-type blood pump. Performance trade-offs and operating characteristics of these converters have been determined for both valved and valveless (peristaltic) pumps. System integration approaches incorporating these non-rotating, bearingless, vibration-balanced, statically sealed converters are potentially promising systems. Work is continuing on design modifications to improve efficiency.

Contract Amount: $130,175 Contract Number: PH43-68-1441

General Electric Company, King of Prussia, Pennsylvania

ELECTRICAL ENERGY STORAGE SYSTEM. R. A. Miller and E. J. Glanfield.

An Electrical Energy Storage System (EESS) for use with a circulatory assist device is being designed, developed and tested. The operational concept is based upon the reversible fuel cell reactions. Cells employing a Solid Polymer Electrolyte (SPE) in the form of an Ion-Exchange Membrane (IEM) and platinum black electrodes operate alternately as electrolysis cells (charge mode) and fuel cells (discharge mode). In the charge mode, water contained in wicks in each cell is electrolyzed to form hydrogen and oxygen gas which are stored in separate sections of a pressure tight housing enclosing the unit. During discharge, these gases are recombined to produce electrical power and form water which is again retained by the wicks. Cells are alternately charged (at 1.95 volts and 1.5 amperes) and discharged (at 0.65 volt and 1.5 amperes) for periods of 2 hours each. The present design calls for a system having nine cells, a volume of approximately 25 in^3, and a weight of approximately one pound. Energy storage capability is 18 watt hours with a continuous power output capability of approximately nine watts or one watt per cell. Overall system energy conversion efficiency is approximately 28%. Subsequent work will emphasize improvement in reliability and operation in an enclosed, pressurized vessel at eighty atmospheres.

Contract Amount: $11,350 Contract Number: PH43-67-1410

General Electric Company, Schenectady, New York

INTERNAL ENERGY STORAGE FOR CIRCULATORY ASSIST DEVICES. R. P. Hamlen, E. G. Siwek, G. Rampel and L. D. Wechsler.

Nickel-cadmium batteries offer the capability for sealed isolated operation for prolonged periods. However, at elevated temperatures, such as body temperature, their charge acceptance is reduced, decreasing electrical efficiency and increasing cell pressures. Since rapid recharge is desirable, auxiliary electrodes, along with appropriate charge control circuitry, are employed to sense internal cell pressure. Various plate and electrolyte modifications have been made in cells with auxiliary electrodes in attempting to improve high temperature charge acceptance. The necessary circuitry is being developed to prevent malfunction on overcharge or overdischarge. These cells are being tested at about the two-hour charge rate and the half-hour discharge rate. Three-cell batteries of two-terminal four amp-hour cells have also been cycled at body temperature at the 8-hour charge rate and the 1-hour discharge rate to observe changes in capacity and in charging efficiency. This contract will be continued to develop, test, and deliver nickel-cadmium batteries having improved charge acceptance and charge control characteristics and to carry out development of a rechargeable cadmium-air battery.

Contract Amount: $49,416 Contract Number: PH43-68-1445

Hamilton Standard, Farmington, Connecticut

HIGH FREQUENCY PIEZOELECTRIC MOTOR PUMP FOR IMPLANTED ENERGY CONVERSION. L. A. Heimlich, P. D. Knerr, B. Hanson, R. Colville and H. Chalifoux.

The high frequency piezoelectric energy conversion unit provides a unique approach to converting electrical energy into hydraulic energy suitable for use with implantable bladder-type heart assist devices. The unit derives its hydraulic output from a single piezoelectric bender which is coupled with high frequency electroviscous valves. Flow is provided by the continuous summation of the incremental volume displacements of the piezoelectric bender through "check-valve" operation. The driving element of the energy conversion unit is a single piezoelectric bender which oscillates at frequencies of 100 to 200 Hz. When an AC voltage is applied to the bender, the bender flexes, producing small spherical volume displacements. The high frequency check-valve function utilizes the electroviscous valves and fluid. Electroviscous effects can be defined as reversible changes in the apparent viscosity of a fluid when it is subjected to an externally applied electric field. The fluid is basically a dispersion of silicon dioxide in a mineral oil base. The valves are plate grid structures which are placed perpendicular to the direction of flow. Upon the application of an electrical field, the fluid gels, and a "no flow" fluid condition is obtained. The development of the pump is presently being pursued at Hamilton Standard, and it is being evaluated for use as an implantable unit. The energy conversion unit will be used in conjunction with other subsystems designed to transfer electrical energy across intact skin as a total energy system. Continued emphasis will be placed on improving pumping performance and performance of high frequency hydraulic valves, as well as on reducing the size of the converter.

Contract Amount: $29,838 Contract Number: PH43-67-1412

Hamilton Standard, Farmington, Connecticut

ENERGY TRANSMISSION THROUGH THE INTACT SKIN. L. A. Heimlich and F. H. Christiansen, and T. Sato (Yale University).

A system has been developed to transmit 40 watts of regulated electrical power across the intact human skin. The transmitted power may be utilized to supply energy to artificial heart assist devices. Radio frequency transport of electrical power is accomplished by inductive coupling between external and internal coils. Transport via inductive coupling has been shown to be very efficient, provided the coils are not too small and the separation between the coils is not too great in relation to their diameter. The system consists of an external power and regulation control unit, transmitting coil and implanted energy receiver unit. The control unit contains the fundamental RF source and power amplifier as well as the control signal conditioning circuitry. The implanted energy receiver unit, in addition to supplying power to an implanted load, contains power sensing and control circuitry that generates a control signal frequency proportional to the received power. The 530 KHz RF signal is generated by a crystal-controlled oscillator. Class S amplification and solid state switching regulation are utilized for high efficiency. The demodulated control signal is used to control the switching regulator which, in turn, controls the RF power delivered to the load. Demonstration of a closed loop for power regulation indicates possible solutions for power control over variable physiological conditions. In particular, the system has the capability to transmit power across the intact skin with the feedback control signal transmitted back via the same power transmission coils. Use of state-of-the-art technique and components has resulted in minimal size and weight units. In vitro and in vivo evaluations of the system are being conducted at present. Large semi-restrained pigs and sheep are used for the in vivo tests. Further work will emphasize improvements in fabrication to improve reliability and in circuit design to provide adjustable or variable level regulated operation as determined by control response in continuous in vivo operating tests.
Contract Amount: $24,770 Contract Number: PH43-67-1406

Indiana University Medical Center, Indianapolis, Indiana

DEVELOPMENT OF ELECTRO-HYDRAULIC ENERGY SOURCES TO POWER AND CONTROL CIRCULATORY ASSIST DEVICES. N. J. Griffith and W. H. Burns.

Recently developed circulatory assist and total cardiac replacement blood pumps require hydraulic or pneumatic energy transfer mechanisms to pump blood. An implantable electrohydraulic energy source, consisting of a high-speed rotary pump, a brushless DC motor and the attending control system has been developed. This configuration, drawing power from implantable batteries or a transthoracic energy transmission system, delivers 10 watts of hydraulic power (3 psi at 7.6 gal/min) to the circulatory assist device. A 1:1 volumetric correspondence is maintained to ease control problems and minimize blood trauma. Operating at high speed (15000 RPM) to achieve high efficiency and power output/volume indexes, the motor and pump are coupled through either a 3:1 magnetic gear reducer or a 1:1 magnetic coupler. Since the pump-motor system is completely immersed, this configuration isolates the motor interior and rotating parts from the corrosive, isotonic solution and permits flexibility in matching the pump and motor.

Pumps with specific speeds of 2260 and 6350, which have marked differences in zero-flow power drain and pressure-flow characteristics, were fabricated to evaluate their pulsatile flow-generating capabilities and their effect on selecting the control logic. Hydrodynamic bearing designs for the pump and motor were considered in the interest of reliability. The electro-hydraulic energy source is being integrated to a circulatory assist device for evaluation. Control logic for the system is based on monitoring the hydraulic fluid energy state in the blood pump, thus reflecting the output condition of the natural heart. The electrical energy system developed will be continued to further define the in vitro operating techniques of the engine when coupled with other major subsystems. The specific in vitro evaluations will include operation with an automatic control subsystem and an electrical storage subsystem that will provide the basic energy for driving the unit. It is also planned that chronic in vivo evaluations will be performed with the unit. These efforts are to quantify operational techniques, efficiencies and weight and volume constraints on the system.
Contract Amount: $130,000 Contract Number: PH43-68-1443

Kollsman Instrument Corporation, Syosset, New York

TRANSMISSION OF ENERGY THROUGH INTACT SKIN BY ULTRASONIC POWER. J. Kritz and W. M. Nelson.

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. In vitro and in vivo tests were carried out. Problems of coupling ultrasonic energy into biological tissue were identified. Various measures were tried to improve coupling efficiency. Since ultrasonic energy transmission was found to be less effective and less reliable than electromagnetic energy transmission methods, the work of this program was terminated in September 1968.
Contract Amount: No Additional Funds Contract Number: PH43-67-1415

McDonnell Douglas Corporation, Richland, Washington

DEVELOPMENT OF THE THERMOCOMPRESSOR AS THE POWER SOURCE FOR AN ARTIFICIAL HEART. W. R. Martini.

The power source under development employs a thermocompressor, a heat engine to compress gas. Compressed gas under automatic control operates a pump actuator to pump blood through an intermediate drive liquid. The heat engine now being developed is a type of Stirling engine because it employs a moving thermal regenerator oscillating in a hollow cylinder between a heated and a cooled end. This regenerator serves to increase and decrease the average gas temperature almost reversibly resulting in pressure and/or volume surges. Inlet and outlet check valves in the cooled end harness these surges and compress the working gas - hence the name thermocompressor. An analysis was made of thermocompressor properties and of devices for oscillating the regenerator by the use of the engine output. A method of engine design based upon a periodic integral energy balance was developed. Three test engines have been built with a cylinder volume of ~33 cubic inches. The best measured overall efficiency for this size engine has been 14% for an externally driven regenerator and 6% for a self driven test. The newer implantable engine cylinder size (2 $in.^3$) is under test. In the pump actua-

tor, the pneumatic power is stored in surge tanks, is controlled by a three-way valve, is applied to a small, bellows sealed, double acting drive piston. This small piston pumps the blood by moving a large piston which displaces the drive liquid around the blood pump bladder. The pump actuator is being tested with a blood pump acting as an assist pump to a simulated vascular system. Compressed gas under automatic control is applied to the actuator as required to maintain proper pressures and adequate synchronization with the heart. The components of the system are to be packaged for implantation inside of experimental animals. Total size of 600 to 800 ml, including blood pump, is planned. This Stirling cycle engine converter program will be continued to further define the in vitro operating techniques of the engine when coupled with other major subsystems. The specific in vitro evaluations will include operation with an automatic control subsystem and a thermal storage subsystem that will provide the basic energy for driving the unit. It is also planned that in vivo evaluations will be performed with the unit. These efforts are to quantify operational techniques, efficiencies and weight and volume constraints on the system.
Contract Amount: $46,000 Contract Number: PH43-67-1408

New York University, New York, New York

A TRANSCUTANEOUS POWER TRANSFORMER FOR MECHANICAL HEARTS. A. I. Thumin, G. E. Reed, F. J. Lupo and G. H. Myers.

A power transformer which is capable of transmitting over 30 watts of power through intact skin has been constructed and tested in animals. Modified models of the transformer which have an efficiency of 80 to 90% can also be used at higher power levels to charge implanted power storage devices. With proper cooling of the primary, power in excess of 100 watts has been transferred. The device which works at audio frequency range of 3 to 30 k_c is double tuned and air gap variations between 8 to 15 mm and lateral motion of $\pm$ 1 cm can be tolerated with little reduction in power transfer. The device consists of two circular "cup cores" 6 cm in diameter, weighing 300 g each; one is placed subcutaneously and one externally. The internal unit is stabilized by a Teflon "skirt" sutured to the fascia, and by a molded cup on the external unit. The electronics consists of a multivibrator followed by a transistorized power switching stage. Acute and chronic tests in five dogs and three sheep indicate no deleterious effects. The measured temperature rise is less than 3°C inside the encapsulation and 1°C at a point 3 cm distal to the unit. The new feature is a method of permitting large variations in air gap, accomplished by tuning the transformer so that it becomes "double tuned", and then making the coupling coefficient greater than the critical value for the nominal skin thickness. Thus, as the air gap is increased, the coupling coefficient approaches the critical value and the power transferred increases slightly and then decreases. The study confirms that the power transformer can transmit adequate power for energizing an artificial heart and, with some modification, can be adapted to transmit higher levels of power for charging implanted storage devices. In accordance with expectations, implanted units that have been removed after long-term implantation show good ingrowth of fibrous tissue through the Teflon skirt which fixed the unit firmly in its position. This contract was terminated in December 1968.
Contract Amount: No Additional Funds Contract Number: PH43-67-1414

Stanford Research Institute, Menlo Park, California

A TRANSCUTANEOUS POWER TRANSMISSION SYSTEM AND POWER CONDITIONING COMPONENTS. P. M. Newgard and G. J. Eilers.

Acute tolerance of animals to transcutaneous power transfer of from 20 to 120 W by the intact-skin transformer technique has been demonstrated. During this past year, prolonged experiments have been conducted to establish the longevity of the implants and to explore the increase in heat dissipation capability of the implant with the expected increase in local vascularity. Heat flux at the coil tissue interface was increased from the two hundred-three hundred W/m^2 range used in acute experiments to nine hundred W/m^2 over a three-month interval without excessive tissue temperatures. With each incremental increase in heat dissipation, the local tissue temperature immediately increased. This was followed generally within a few days by a decrease to near normal temperature. This response continued with increases in heat dissipation up to the nine hundred W/m^2 level. An energy transmission system was designed employing the SRI skin transformer to supply power to a piezoelectric pump/storage battery combination. It was discovered that low-voltage rectifiers are especially difficult to drive efficiently from the skin transformer. Harmonic currents, which are required for rapid switching and high efficiency, cannot be obtained from the skin-transformer secondary, owing to the presence of leakage reactance. A hydraulic control and reservoir unit was designed and built to adapt to an existing blood pump for hydraulic actuation. The device presents a low hydraulic impedance for hydraulic fluid displaced during systole. Further work will be carried out to select an optimum operating frequency for this configuration with weight, size, and transmission efficiency as design criteria. Chronic in vivo tests in animals will be continued, as well as system integration with energy conversion subsystems.

Contract Amount: $10,031 Contract Number: PH43-67-1422

Statham Instruments, Inc., Oxnard, California

IMPLANTABLE ENERGY SYSTEM FOR A CARDIAC ASSIST DEVICE. J. Chambers.

The purpose of this program was to develop an energy system to power a circulatory assist device. The project includes integration of components and testing of the system. The basic energy converter is a small DC torque motor coupled to a ball and screw actuator to convert rotary motion to linear motion. The linear output is directly coupled to a bellows which uses hydraulic fluid to drive the blood pump. The energy converter allows passive filling of the blood pump; in addition, a bias towards filling of the blood pump may be provided if indicated. The system is developed to synchronize with the end of biologic systole and can provide varying blood output volumes. The primary control for this response is flow into the blood pump from the left ventricle. The energy converter is driven by a transcutaneous energy transmitter and may be driven temporarily by an implanted battery. Power conditioning components have been designed to drive the converter from either of these two energy sources. The electrical energy system developed by Statham will be continued to further define the in vitro operating techniques of the engine when coupled with other major subsystems. The specific in vitro evaluations will include operation with an automatic control subsystem and an electrical storage subsystem that will provide the basic energy

for driving the unit. It is also planned that chronic in vivo evaluations will be performed with the unit. These efforts are to quantify operational techniques, efficiencies and weight and volume constraints on the system.
Contract Amount: $143,845 Contract Number: PH43-68-1502

Thermo Electron Corporation, Waltham, Massachusetts

DEVELOPMENT STATUS OF AN IMPLANTABLE RANKINE CYCLE CIRCULATORY SUPPORT SYSTEM. F. N. Huffman, T. C. Robinson and S. S. Kitrilakis.

The objective of this effort was to develop and evaluate a thermally rechargeable circulatory support system using a miniature steam engine. Electrical energy coupled across the skin is stored in the latent heat of fusion of the eutectic composition of LiF/LiCl. The stored heat produces steam which is expanded in a single cylinder, flywheel return engine to pump up a hydraulic accumulator. The accumulator is coupled to a left ventricle-to-aorta assist pump (which also functions as a blood-cooled heat exchanger and physiologic sensor) via a counterpulse, hydraulic control system which responds to changes in both heart rate and stroke volume. Transcutaneous power transmission levels of 150 watts into a 16 ohm load across a gap of 1 cm have been demonstrated using Ferroxcube cores with Litz windings. Engines of 1.2 ml displacement, miniaturized for integration into an implantable source, with both internal and external exhaust valves have been tested and an engine output of 8 watts has been measured. Extensive testing of a hydraulically actuated Model VI CHMC-TECO assist blood pump has lead to an improved model with an 80% increase in effective stroke volume. Control system function has been demonstrated on a mock circulation loop. Initial in vivo tests of power transmission, component suspension, heat dissipation and diaphragm penetration have been favorable. The Rankine cycle engine converter program will be continued to further define the in vitro operating techniques of the engine when coupled with other major subsystems. The specific in vitro evaluations will include operation with an automatic control subsystem and a thermal storage subsystem that will provide the basic energy for driving the unit. It is also planned that in vivo evaluations will be performed with the unit. These efforts are to quantify operational techniques, efficiencies and weight and volume constraints on the system.
Contract Amount: $84,940 Contract Number: PH43-68-1455

Physics International Company, San Leandro, California

DEVELOPMENT OF A PIEZOELECTRIC DRIVER FOR AN ARTIFICAL LEFT VENTRICLE. P. C. Smiley, C. G. O'Neill, W. W. Olander and J. C. Creighton.

This contract was for development work on a piezoelectric driver for an artificial left ventricle. The objective was to convert the high force, low-displacement output of a piezoelectric device into a low pressure, large displacement pulsatile hydraulic output that could be accurately and rapidly controlled and synchronized with the natural heart. Initial efforts were directed at the design of equipment to demonstrate feasibility. Later design work was aimed at reducing the size, weight, and power consumption of the piezoelectric driver and at the solution of problems in electrical insulation and reliability. Inadequate data on the performance of piezoelectric ceramic materials at high electric fields necessitated a program of piezo-

electric properties measurement. Piezoelectric strain was measured at 180 volts/mil. Improvement of assembly techniques and insulation methods gave reliable operation up to 124 million operating cycles at 85 volts/mil. The energy available from a stack of piezoelectric disks (or the work done by a piezoelectric driver) increases as the square of the applied electric field. Several bench model experimental drivers were built and tested. The most successful was a hydraulically amplified model that produced a stroke volume of 58 cc against a discharge pressure of 130 mmHg with a systolic duration of 200 msec with check valves from a blood pump currently under development by another contractor. This is equivalent to an output of 7 liters/min at 120 strokes/min. This program will continue with the objective of fabricating an implantable piezoelectric driver and testing it as part of a complete energy system including transmission, conversion, and storage subsystems.

Contract Amount: No Additional Funds Contract Number: PH43-67-1115

STUDY OF THE VASCULATURE OF SHEEP

Sheep are one of the more readily available animals comparable to human size for the study of the chronic effects of circulatory assist devices. There has been a minimum study of the vascular anatomy of these animals to date. A contract was awarded to remedy that situation and fill a need of Artificial Heart Program contractors and others who may be planning to use sheep for cardiovascular research.

University of Minnesota, Minneapolis, Minnesota

A STUDY OF THE OVINE THORAX AND ASSOCIATED STRUCTURES. W.D. Anderson

The objective of this study was to describe and illustrate the gross morphology of the thoracic wall and intrathoracic anatomy of the sheep and relate these findings to comparable structures in man. The thorax of adult mature sheep of mixed breeds was illustrated while directly viewing the dissected cadavers. Plastic cast preparations were made of the arterial and venous systems using Tensol cement (manufactured by the Imperial Chemical Industries, Ltd., Great Britain). When directional terminology for the quadruped differed from that of man, the human term has been included in parenthesis. The shape of the ovine bony thorax and the character of the endothoracic fascia differed from that of man while the pleural cavities were similar. The ventral (anterior) mediastinum and in situ position of the lungs, pericardial sac, its attachments and pericardial sinuses resembled that in man. The surfaces of the ovine heart were similar to the human; however, the distribution of the coronary arteries corresponds to one of the common variations seen in man. Pulmonary, aortic and atrioventricular valves of sheep and man were similar morphologically in number and position of valvules and cusps. In 50 ovine aortic arches studied, the aorta was characterized as giving origin to a single branch, the brachiocephalic trunk. The bronchoesophageal artery arose from the aorta at the level of the hilus of each lung and coursed to the esophagus and lung. The terminations of vagal and sympathetic fibers have been traced and photographed with the use of the Zeiss operating microscope. The azygos venous system in sheep was found to be poorly developed while the hemiazygos vein on the left was the predominant venous drainage of the thoracic wall. The general quality of the work was excellent and much of what was reported was not well documented previously. The objectives of the program were accomplished. It is anticipated that this report will be received with interest in many areas outside those directly related to the Artificial Heart Program.

Contract Amount: $19,852 Contract Number: PH43-68-1377

BASIC AGREEMENTS AND TASK ORDERS

For some time, the Artificial Heart Program Office has felt the need for a number of relatively small tasks to be performed in a fairly short time. Such tasks would include fabrication of materials or components according to specifications, modification or assembly of components supplied by the Program Office, paper or analytic studies of concepts or designs resulting from program contracts, feasibility or preliminary studies of program areas not yet ready for the full scale RFP approach, and report analysis or literature survey as a preliminary to deciding what R&D is necessary. A number of Government agencies make use of a contract approach called "quick reaction" contracts for such purposes. Using this approach, the Program Office advertised its needs and interests in such contracts in the "Sources Sought" section of the Commerce Business Daily, and invited organizations to submit information on their capabilities in a number of areas. After review and evaluation of the responses, the Program Office awarded basic agreements to 22 organizations which have agreed to accept inquiries on specific tasks and to submit specific cost and time estimates on such tasks. Following is a list of the organizations which were awarded basic agreements:

Autonetics Division
North American Rockwell Corporation
Anaheim, California

Avco Corporation
Lowell, Massachusetts

Battelle Memorial Institute
Columbus, Ohio

Bendix Research Laboratories
Southfield, Michigan

Booz, Allen & Hamilton, Inc.
Washington, D. C.

Cornell Aeronautical Lab, Inc.
Buffalo, New York

Electrochimica Corporation
Menlo Park, California

Geomet, Inc.
Rockville, Maryland

Geoscience Ltd.
Solana Beach, California

Gulton Industries, Inc.
Metuchen, New Jersey

Hittman Associates, Inc.
Columbia, Maryland

IIT Research Institute
Chicago, Illinois

Information Systems Corporation
Washington, D. C.

Mechanical Technology Inc.
Latham, New York

Medical Systems, Inc.
Rolling Hills, California

Midwest Research Institute
Kansas City, Missouri

Monsanto Research Corporation
Dayton, Ohio

MPR Associates, Inc.
Washington, D. C.

National Bureau of Standards
Product Evaluation Division
Washington, D. C.

Southwest Research Institute
San Antonio, Texas

Stanford Research Institute
Menlo Park, California

URS Systems Corporation
Burlingame, California

Vitro Laboratories
Silver Spring, Maryland

When performance of a specific task is needed, a task description can be sent to several of the organizations best suited for that task. Since basic agreements have been negotiated, the actual issuance of a task order, or short-term contract, can be done quickly. During the past year, short-term contracts, of two- or three-months duration, have been awarded for the

purpose of funding specific tasks identified by the Program Office. One task order was issued (to Hittman Associates, Inc., for $32,727) to secure animal models of arteriosclerotic heart disease in failure. Two others were issued (to Medical Systems, Inc., for $24,350 and to Geomet, Inc., for $25,000) for analyses of the emergency aspects of heart disease in order to enable the Program Office to make plans for programs. Reports on work resulting from these task orders are being received and evaluated.

PLANNING FOR TEST AND EVALUATION FACILITIES

The Program Office plans to develop Test and Evaluation Facilities in which circulatory assist devices, components and other prostheses under development by the Artificial Heart Program 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 for cardiac patients. These Test and Evaluation Facilities will provide testing and evaluation, under controlled conditions, by competent and objective groups that have had no part in the development of the devices being tested. A year ago contracts were awarded to the following 13 organizations for the preparation of plans for the establishment and operation of testing and evaluation facilities:

	Contractor	Location
1.	Arthur D. Little, Inc. Massachusetts General Hospital Boston University	Boston, Massachusetts
2.	Brown University	Providence, Rhode Island
3.	Case Western Reserve University	Cleveland, Ohio
4.	Cox Coronary Heart Institute	Dayton, Ohio
5.	EG&G, Inc. Peter Bent Brigham Hospital	Boston, Massachusetts
6.	Fluidonics Research Laboratory University of Utah	Salt Lake City, Utah
7.	IIT Research Institute University of Chicago	Chicago, Illinois
8.	Mechanical Technology, Inc. Albany Medical Center	Albany, New York
9.	Midwest Research Institute	Kansas City, Missouri
10.	National Inst. of Scientific Research	Los Angeles, California
11.	St. Louis University	St. Louis, Missouri
12.	University City Science Center	Philadelphia, Pennsylvania
13.	University of Nebraska	Omaha, Nebraska

These planning contracts were for six months. The reports and plans prepared during that phase were submitted and subsequently have been under extensive study and review. It is planned that one or two Test and Evaluation Facility contracts will be awarded for the coming year.

BRANCH SUMMARY

The Myocardial Infarction Branch has the responsibility for the design and administration of a national research program leading to the reduction of death and disability from heart attack. The Program is fostering the development of new knowledge and the translation of results into methods which will have wide clinical application.

To achieve these goals, the Program has sought to focus the attention of the scientific community upon heart attack, and it has attracted new people and new disciplines to work upon the problem. Broad multi-disciplinary research programs have been established, as well as projects of limited scope and short-term goals. Special resources to facilitate research upon heart attack are being developed. Cooperation and communication have been fostered among participants. Effective techniques for targeting and structuring research are evolving.

To study the acute illness in the hospitalized patient, nine Myocardial Infarction Research Units are now active, four having become operational within the past year. Each has a multi-disciplinary program emphasizing clinical investigation, supported by more fundamental studies. They are designed to answer specific questions about the disease process and its therapy; at the same time, they are to nurture creative research upon the problem of heart attack. The basic measurements and historical information which characterize the patients coming into the studies and during the investigations have been standardized; however, the specific research projects of each MIRU are varied since they are designed to capitalize upon the unique resources and interests at each institution and thus provide a broad and balanced total program.

Sudden death within minutes of the onset of symptoms accounts for a very substantial fraction of the deaths from heart attack; indeed, more than half of the deaths occur before hospitalization. A program of research on this topic and upon the intimately associated questions regarding the onset of myocardial infarction is being developed. It is designed to elucidate the apparent precipitating factors for myocardial infarction and sudden cardiac death, and the physiological and environmental settings in which they occur; it is to clarify the physiological events leading to and immediately following the onset of the acute event as well as the pathology associated with sudden death; it is to identify risk factors sensitive for sudden cardiac death and to identify premonitory symptoms of impending heart attack which have heretofore been unrecognized; it is to begin the development of prophylactic measures and methods of early therapy. Forty-six proposals received in response to a request for proposals have been reviewed; several are currently under scientific negotiations, and it is anticipated that this program will become operational by October 1969.

Laboratory investigations of myocardial infarction could be substantially strengthened by the availability of more satisfactory animal models of the

acute illness. Accordingly, six contracts are now active for the development of non-atherosclerotic models of myocardial infarction which are predictable in their hemodynamic and anatomic consequences and their time of occurrence. These techniques, which represent important resources for future research, are progressing satisfactorily and in large measure will be completed by March 31, 1970.

Clinical research on myocardial infarction requires the development of more satisfactory instrumentation methods and data management techniques. At several of the MIRU's, computer data management systems have been implemented which are suited to their unique resources and needs; each is different. Since important advantages can be realized by having identical computer data management systems at several institutions, such plans have been developed by the Computer Systems Laboratory, DCRT, in conjunction with the MIRU's; the system is likely to be made operational. Instrumentation and methodology developments are taking place at several MIRU's. The Biomedical Engineering and Instrumentation Branch, DRS, is collaborating in this area. In addition, a contract is active for the development of a promising method for the repeated and continuous measurement of cardiac output suitable for use in patients with acute myocardial infarction; the proposal had been 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. One study is completed; the second will be completed by June 30, 1969.

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 heart attacks, a Symposium on Research on Acute Myocardial Infarction was supported, with the American Heart Association as prime contractor. The Symposium proceedings are to be published as a supplement to a widely circulated journal.

The sudden development of cardiac arrhythmias, particularly ventricular fibrillation, has been suspected as a frequent cause of sudden and unexpected death. The electrocardiographic records of the Framingham Heart Disease Epidemiology Section, OADEM, NHI, have been examined by Program staff to assess the importance of premature ventricular contractions and left ventricular hypertrophy singly and in combination as risk factors for sudden death.

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 very 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 the projects - within the bounds of Program structure and priorities - and of the need for sound administrative and fiscal practices. The cooperation of the Research Contract Branch, ODA, in contractual matters and the cooperation of the Biomedical Engineering and Instrumentation Branch, DRS, and of the Computer Systems Laboratory, DCRT, in technical matters is 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 the additional study of the proposals by Program staff and in the context of Program needs; Program Office recommendations are further considered by reviewers advisory to the Director, NHI, before contact is made with potential contractors. Scientific discussions between Program staff and potential contractors precede formal contract negotiations.

In the coming year, the Myocardial Infarction Program will continue along the directions previously outlined. The Myocardial Infarction Research Units represent a long-term investment; they have made important contributions to date, but their full contributions will be achieved in the coming years. The program for the development of non-atherosclerotic models of myocardial infarction will be essentially completed by March 31, 1970. In the coming austere year, only those new activities will be implemented which are most critical to Program needs and also most favorable in a cost/benefit sense. Thus, it is planned to implement the program on research on sudden death from heart attack and the closely related problems of the precipitating factors, pathophysiology and pathology of myocardial infarction.

MYOCARDIAL INFARCTION RESEARCH UNITS

A network of nine Myocardial Infarction Research Units (MIRU's) is now active; five were established in June 1967, four in June 1968. The central effort of each MIRU is the comprehensive study of the heart attack patient. This clinical research is strengthened by related studies in the biochemistry, pathology, and animal laboratories and by the support of instrumentation, data management, and biostatistics groups.

The MIRU's are to improve our understanding of myocardial infarction - its onset, the precise course of the illness, and the response of the body with the complex interaction of its organ systems. The MIRU's are to develop more effective management for the basic illness and for the prevention and therapy of complications; they are to seek methods of minimizing the extent of myocardial damage and of reducing subsequent disability and recurrence. The MIRU's are to develop methods of measurement which have wide utility in the evaluation of myocardial infarction - measurements which require minimum penetration of the body, which are most specific for following the course of the illness and the effects of therapy, and which serve as reliable prognostic factors for identifying incipient complications.

In each MIRU, clinical investigation is conducted in specially designed facilities which combine many of the features of the cardiac catheterization laboratory and the coronary care unit. This provides optimal patient care and observation; it permits such apparatus as the radiographic image intensifier, radioisotope scanning equipment, and mechanical circulatory assist devices to be used with the patient in his bed; it incorporates special instrumentation and data management systems. The course of the patient's illness is characterized by a series of direct and indirect hemodynamic measurements, by constant electrophysiological observations, and by regular determinations of blood and urine chemistries in addition to the standard hospital care routinely administered. Further studies may include pulmonary, renal, metabolic, endocrine, hematological, and behavioral factors.

The MIRU's are studying the etiology, manifestations, and therapy of the derangements produced by heart attack upon the heart itself and upon other organ systems. The degree of hemodynamic impairment, the derangements of rhythm, the site and extent of infarction, and the effects upon coronary flow and the coronary sinus effluent are under study. Direct hemodynamic measurements from the right and left heart, cardiac output determinations and indirect measurements of cardiac performance are utilized for studying the disease process and the effects of therapeutic interventions. The electrophysiology of the heart is being examined by surface and intra-atrial electrocardiography and by surface mapping techniques. The alterations of pulmonary perfusion and ventilation and blood gases are under investigation. Studies are being directed at the derangements in metabolic equilibrium, the substrates and products of metabolism, renal function, the endocrine systems (insulin, growth hormone, anti-diuretic hormone, aldosterone, and catecholamines) and the vaso-active polypeptides (bradykinin, angiotensin, and renin). The alterations in the thrombotic and fibrinolytic systems and in platelet function are being studied. The autonomic nervous control of the circulation and the role of behavioral factors are under investigation. Clinical observations in the MIRU are

correlated with subsequent follow-up data, including postmortem findings.

The development of more satisfactory therapy for myocardial infarction is being made possible by a better understanding of the natural disease process and by observing in detail the effects of therapy in patients whose illness is precisely characterized. The effects of presently used regimens and drugs are being recognized in greater detail, including the effects of graded oxygen inhalation, digitalis, specific diets, positions in bed, and levels of activity. Prophylactic measures against dysrhythmias utilizing procaine amide, quinidine, lidocaine, and other agents are being developed with the aid of metabolic studies and blood levels of these drugs. The roles and effects of pacing techniques are being examined for the treatment of profound bradycardia, and for the management of dysrhythmias and tachycardias unresponsive to other therapy. The therapy of cardiogenic shock is being investigated with the systematic use of sympathomimetic amines (with and without alpha blockers), dopamine, glucagon, control of blood volume and venous return for optimal ventricular filling, pacing to restore optimal atrial ventricular synchrony, and pacing to enhance the inotropic state of the myocardium; laboratory experience makes imminent the clinical study of mechanical circulatory assistance utilizing bypass and balloon diastolic augmentation techniques.

Measurement methods are being developed and tested which are necessary for clinical investigation of acute myocardial infarction - indirect measures of ventricular performance utilizing pre-ejection and ejection periods, and size and silhouette tracking by radiographic and ultrasonic techniques; methods of quantifying flow by pressure contour analysis, thermal indicator and ultrasonic techniques; regional flow mapping in the lungs, heart and kidney utilizing radioisotopes; rhythm monitoring utilizing intra-cardiac electrodes; and surface mapping electrocardiographic techniques. Several of these methods are potentially widely applicable in the coronary care setting.

The instrumentation and data management needs of the research program have been substantial. Carefully integrated systems have been developed to include transducers, signal modifiers, display devices, recorders, on-line computers, and data storage and retrieval methods. While at several MIRU's different computer data management systems have been implemented to suit unique resources and needs, a system to fulfill the needs of several institutions has been designed and is expected to accelerate the usefulness of the computer and to achieve financial and manpower savings.

Laboratory research is designed to augment the clinical effort in each MIRU. Studies are in progress on the effects of hypoxia upon myocardial metabolism, protein and RNA synthesis, and electrophysiology. The formation of collagen and the development of coronary collaterals are being studied. Pharmacological methods of minimizing the work load upon the acutely ischemic heart are being developed. Fundamental methods for quantifying blood levels of digoxin and vaso-active polypeptides are being developed; methods of measuring blood levels of other cardioactive drugs and hormones are being refined and applied. The therapy of cardiogenic shock is under investigation in animal models of myocardial infarction utilizing drugs, electrical pacing techniques, and mechanical assist devices. The hemodynamic and electrophysiologic measure-

ments being developed and evaluated in the clinical setting have had prior development in the animal laboratories.

Since they are designed to capitalize upon the unique resources and interests at each institute, the specific research projects of each MIRU are varied, thus providing a broad and balanced total program. In certain areas, the MIRU's share common goals and many basic techniques. The basic measurements and historical records of each patient entering are according to standardized protocols common to all MIRU's; subsequent observations also include standardized data as well as the data for specific research projects. These standardized inter-MIRU measurements constitute a common core protocol and core data which serve to enlarge the data base and to constitute a common frame of reference. Inter-MIRU protocols for additional specific studies beyond the core measurements are being developed by sub-groups of MIRU's. The MIRU Directors meet regularly, and most MIRU investigators have participated in one of the full-day MIRU meetings held in conjunction with national cardiovascular scientific meetings.

In the coming year, the major directions of the MIRU's will continue. The clinical investigation will become increasingly productive with the availability of the renovated clinical facilities and the suitable instrumentation and data management systems. The MIRU program has been undertaken as a five-year endeavor. Each MIRU and the specific projects therein are reviewed regularly. Some projects have been completed or terminated; a limited number of promising, high priority projects have been added.

Myocardial Infarction Research Unit

University of Alabama Medical Center
Contract Number: PH-43-67-1441
Contract Amount: $1,416,455 (6/29/68 - 6/28/69)
Principal Investigator: Harold T. Dodge, M.D.

During the past year, this unit has continued to concentrate on collecting hemodynamic, biochemical, and gas exchange data from patients with acute myocardial infarctions. An important objective of these studies is to derive a reliable prognostic index from a composite of the measured variables. Complete information on a series of 72 patients has been entered onto specially designed forms and analyzed in detail. Although the results from this limited series shows a wide scatter of variables, the continued use of this basic form should provide adequate information for the development of a reliable index.

Other clinical research projects designed to better understand and treat the patient with acute myocardial infarction have been in progress. The goals of these projects include: (1) the relationship of atraumatic techniques to more direct measurements of left ventricular characteristics which includes simultaneous recordings of the phonocardiogram, apexcardiogram, and carotid pulse compared with pressures recorded directly from a left ventricular catheter, and also the determination of left ventricular volume by comparing the ultrasonic echocardiogram with contrast angiocardiography of the left ventricle, (2) assessment of left ventricular performance by observing the response to variations in filling pressure, (3) the value of metanephrine excretion rates as an index of clinical severity, (4) effects of posture and meals on hemodynamics, (5) a study of the diurnal variability of accepted biochemical and hemodynamic measurements, (6) determination of the optimal blood level to therapeutic effectiveness of procainamide, xylocaine and atropine, (7) the usefulness of integrated blood enzyme values to quantitate the amount of infarcted tissue as opposed to the commonly measured peak values which are not a reliable index of severity.

Special thermistor catheters have been developed in the electronic laboratory and extensively tested in animals. These catheters are designed to measure cardiac output and blood velocity profiles. Other animal studies have concentrated on the perfection of venoarterial bypass circulatory assist with a membrane oxygenator for the patient in cardiogenic shock.

In the pathology laboratory, the heart and vessels of each non-surviving patient are examined in detail. To better understand the mechanisms of death, special studies of the blood supply to the His bundle and a careful investigation of the nerves involved in the von Bezold-Jarisch reflex are in progress.

An important advancement at this unit has been the development of the prognostic index protocol mentioned above which includes historical, clinical, hemodynamic, and biochemical information. Other results from individual projects have been of significant clinical and research interest. A controlled study of heparin dosage in the acute phase of infarction showed no increased requirement as had been previously suspected. The postulated hypercoagulable state therefore does not directly influence heparin requirements. A similarly

designed study of oxygen inhalation therapy in the uncomplicated infarct patient showed no significant hemodynamic effect. An evaluation of atropine effects in patients with normal heart rates showed a significant decrease in cardiac output without a change in heart rate or clinical status. In the area of non-invasive techniques, in patients with heart failure, although the total electromechanical systolic interval (QS2) remained normal, the pre-ejection period was prolonged and ejection time proportionally shortened. In addition, reports of ultrasound echocardiography compared with clinical angiocardiographic measurements of left ventricular volume showed a good correlation between the two methods. The results suggest that further refinements of these non-invasive techniques will significantly aid in the clinical assessment of the acute myocardial infarction patient. The thermistor catheters and venoarterial bypass, which are now ready for clinical trials will offer significant diagnostic and therapeutic benefits.

Most of the projects listed above are to be continued in the coming year. Certain projects such as urinary enzymes have not been technically feasible or have proven to be of limited research value and have been discontinued. A computer has recently been installed and a definitive study area will be completed by June 30, 1969. Both facilities will greatly aid the number and scope of projected studies. In addition, new studies are planned on antibody formation, platelet aggregation and post-infarction thrombosis in patients with acute myocardial infarction.

Myocardial Infarction Research Unit

University of California, San Diego
Contract No. PH-43-68-1332
Contract Amount: $710,000 (6/28/68 - 6/27/69)
Principal Investigator: John Ross, Jr., M.D.

During the past year, efforts have been directed toward preparing the resources necessary for clinical evaluation of patients with acute myocardial infarction. These preparations are now completed and clinical investigation has recently commenced. Studies in the biochemical and animal laboratories have been actively underway for some time and are lending complimentary research support to these clinical projects.

The forthcoming clinical studies have the following specific objectives: the characterizations of hemodynamic, clinical, and biochemical changes in complicated and uncomplicated myocardial infarction; a systematic evaluation of various therapies in the treatment of cardiogenic shock including drugs and the positive-negative pressure box; the characterization of regional pulmonary ventilation-perfusion relationships during the illness using Xe^{133} and scintillation mapping techniques; an evaluation of the relative usefulness of surface and intra-atrial electrocardiography in the diagnosis of arrhythmias and the role of coupled ventricular pacing techniques in its therapy; the non-traumatic assessment of left ventricular function by the quantification of cardiac motion and size using automatic edge-tracking and ultrasound techniques, and by the measurement of peripheral flow and pressures using the Doppler flow probe.

In the pathology laboratory, a protocol for the detailed examination of infarcted hearts was developed and is operational. Numerous animal studies are actively underway; these include studies on serum enzyme changes in acute myocardial infarction and pulmonary embolism, changes in the collateral circulation during myocardial infarction and drug intervention, and the effects of experimental drug and mechanical therapy on myocardial mechanics and respiration during myocardial infarction.

The major task of preparation and testing obviously required to implement the above clinical projects has been completed, the MIRU facility is now operational, and active studies on patients with myocardial infarction have recently begun. The positive-negative pressure box has been constructed and proven effective in altering cardiovascular dynamics in a predictable fashion in man. Preliminary clinical experience with "radarkymography"--a technique which tracks and measures the pulsating heart border as reproduced on videotape--has indicated that it is a useful and sensitive device for monitoring alterations in heart size, and that the measurements correlate well with those of the more traumatic technique of cineangiography for determining cardiac diameter. The Doppler flow probe has been found to be an accurate non-traumatic method for continuous measurement of peripheral blood pressure, and holds promise as a superior method for monitoring this important parameter in myocardial infarction patients; its use for the non-traumatic measurement of central pressures and flow rates is being investigated.

In the animal laboratory, studies of serum enzymes have revealed a heretofore unappreciated rise in creatine phosphokinase levels with pulmonary infarction which may modify the notion of the value of this enzyme in the diagnosis of myocardial infarction. Other animal studies have shown a previously unrecognized alteration in myocardial lactate dehydrogenase isoenzyme patterns which seem to reflect the degree of cardiac hypertrophy.

For the coming year, all the projects listed above will be continued with some minor modifications. The autopsy studies will extend their examination to include an evaluation of both the intra and extra-cardiac coronary collateral circulation. The animal studies on coronary collaterals will broaden their investigations to include cardiac hypertrophy and failure states. The anticipated full operation of all these clinical and laboratory projects during the coming year will further facilitate the attempt to better understand and treat myocardial infarction in man.

Myocardial Infarction Research Unit

Cedars-Sinai Medical Center
Contract Number: PH-43-68-1333
Contract Amount: $633,000 (6/28/68 - 6/28/69)
Principal Investigator: H. J. C. Swan, M.D.

A detailed evaluation of the cause and therapy of acute myocardial infarction in hospitalized patients is the primary focus of this MIRU. During the past year, considerable progress has been made toward completing the extensive preparations required to begin these studies and some clinical investigation has already begun.

The patient with acute myocardial infarction will be studied from several aspects by this group. Because many patients with heart attack are seen at this institution, a large number of patients with shock and other complications are encountered. Thus, a major emphasis will be placed on the characterization of the hemodynamic and biochemical changes in cardiogenic shock and a systematic assessment of its therapy, although the detailed evaluation of noncomplicated myocardial infarction patients will also be done, including a systematic characterization of pulmonary function. The renal status of both complicated and uncomplicated patients with acute myocardial infarction will receive special scrutiny, including detailed frequent measurements of renal function, renal hemodynamics, acid-base metabolism, water and electrolyte balance, and the related hormonal status including antidiuretic hormone. Because of their particular experience with thermodilution techniques, the measurement of cardiac output and coronary sinus flow will be assessed using this method in patients. Other research projects on the acutely ill patients include a detailed clinical assessment of new antiarrhythmic drugs, an analysis of coronary sinus metabolic products, and an evaluation of the use of high fidelity inscription electrocardiography in the clinical diagnosis of acute myocardial infarction. In the animal laboratory, valuable experience in the use of circulatory assist devices is being gained for future clinical evaluation.

Many of the above studies have actively begun on the patients with myocardial infarction; preparations for the remaining projects are approaching completion. This has been accomplished despite the fact that a separate MIRU facility has not yet been constructed. On the basis of this early experience, major advances toward the formulation of a final protocol in the shock and renal studies have been made. Pilot studies on the evaluation of lidocaine have provided preliminary experience for the forthcoming assessment of new antiarrhythmic drugs. Tracings of high fidelity inscription electrocardiograms are being accumulated in normal and myocardial infarction patients to provide a background for future assessment. Results already obtained in the respiratory studies suggest that oxygen administration in mildly hypoxemic myocardial infarction patients does not significantly alter oxygen transport and that mild hypoxemia is not the primary cause for the dyspnea and hyperventilation that is often seen in these patients. Studies related to the renal project have shown that membrane transport of sodium and potassium in the red blood cell of patients with myocardial infarction is abnormal.

In the coming year, the projects listed above will continue and will achieve full operational status. Major advances in the understanding and treatment of myocardial infarction are anticipated.

Myocardial Infarction Research Unit

University of Chicago
Contract Number: PH-43-68-1334
Contract Amount: $550,000 (6/28/68 - 6/27/69)
Principal Investigator: Leon Resnekov, M.D.

The basic approach of the Myocardial Infarction Research Unit is to study and correlate the clinical and electrocardiographic manifestations of acute myocardial infarction with the hemodynamic, electrophysiological, and biochemical abnormalities occurring in patients with acute myocardial infarction. Concurrent studies of certain basic aspects of these phenomena in the laboratory are closely related to the observations on the clinical unit. The goal of these investigations is to be better able to predict individual prognosis and to improve overall survival rate.

The objectives of the research on patients with acute myocardial infarction include: classification and description of the hemodynamic, biochemical, and electrophysiological status of the patient with acute myocardial infarction; determination of the indications for pacemaking in the suppression and treatment of dysrhythmias; evaluation of the treatment of cardiac pump failure with digitalis, blood volume expansion, vasodilators, and mechanical assistance; evaluation of various clinical and experimental surgical procedures in the treatment of acute myocardial infarction; relationship of rapid eye movement phases of sleep to arrhythmias; long term study of ECG changes associated with environmental factors during care of acute myocardial infarction; investigation of dynamic radioisotope scanning as an aid in the evaluation of myocardial metabolism and the size and locus of myocardial infarction; and study of the biochemistry of coronary sinus effluent. In the pathology laboratory, the postmortem examination of hearts from MIRU patients is performed according to a specific protocol. A digital computer system has been developed in the instrumentation laboratory for the real-time handling and analysis of monitored physiologic data.

In the animal laboratory, studies include the circulatory effects of paired, coupled, and triple stimulation of the heart in the presence of acute myocardial infarction; left ventricular function studies following experimental myocardial infarction with emphasis on rhythm disturbances; evaluation of low energy defibrillation of the heart. Studies of electrophysiologic changes under investigation involve ischemic or infarcted myocardium and the influence of hypoxia on vagal tone. In the biochemistry and biophysics laboratory, studies include: effects of oxygen supply on the uptake and exchange of cardiac ions; mechanisms of mitochondrial replication in normal and hypertrophied hearts; and a study of RNA and protein synthesis in normal, hypertrophied, and hypoxic hearts.

Considerable preliminary planning has taken place in the development of logistics of patient handling, care, and records as well as organization of the patient monitoring system. Actual investigations have been delayed due to the construction and equipping of a discrete clinical patient area. A series of statistical summary programs are being developed in the long term study project of ECG changes associated with environmental factors during

care of acute myocardial infarction. The pathology investigators have developed a technique of perfusion of fresh unfixed postmortem hearts with nitro-blue-tetrazolium for detection of dehydrogenase. This maintains intracardiac relationships and increase the value and efficacy of detecting recent and healed infarction. The electrophysiologic behavior of the rabbit Langendorff perfused heart has been reported under conditions of hypoxia and ischemia. These initial studies determined baseline values for detailed investigation into the time course of the development of A-V conduction disturbance and the influence of the vagal component. The effect of anterior wall infarction will be compared to that of posterior wall infarction. Studies on ischemic or infarcted myocardium indicate that a considerable conduction delay is imposed on impulses entering the ischemic zone. At the same time, its excitability is retained for a considerable time. Further studies are seeking to define temporally when the ischemic zone is excluded from normal myocardial units and how this correlates with Q wave development in the ECG.

In order to further evaluate the efficacy of infarctectomy, the surgical laboratory has made studies on an animal model of acute myocardial infarction. In the biochemistry laboratory, the intracellular concentrations of cardiac ions have been measured in the rat heart both in control and hypoxic conditions, the effects of severe hypoxia on mitochondrial turnover have been elucidated, and the specific activities of nucleolar and nuclear DNA have been recorded.

In the coming year, present projects will continue. The clinical phase of the MIRU will become active and will be the major thrust of the investigation.

Myocardial Infarction Research Unit

Cornell Medical Center
Contract No. PH-43-67-1439
Contract Amount: $1,403,242 (6/26/67 - 6/25/69)
Principal Investigator: Thomas Killip, M.D.

Studies on the hospitalized patient with acute myocardial infarction remain the central occupation of this MIRU, and activity in this regard has been brisk during the past year. Support for these studies has continued in the pathology, biochemical, and the animal laboratories.

Patients with acute myocardial infarction are being evaluated by the following specific studies: the characterization of hemodynamic and biochemical changes in cardiogenic shock and a systematic assessment of its therapy; serial measurement of blood gases in acute myocardial infarction and cardiorespiratory arrest; a retrospective analysis of prodromal symptoms in myocardial infarction; non-traumatic assessment of left ventricular function with simultaneous recordings of the phonocardiograms and apical and carotid pulses; the determination of the optimal blood levels of the antiarrhythmic agent lidocaine in relation to therapeutic effectiveness; an assessment of the role of the renin-angiotensin system; and an evaluation of psychiatric phenomena on the course of the disease.

In the biochemical laboratory, the carbohydrate and lipid metabolism of ischemic myocardium has been studied. Methodology for the clinical determination of digitalis and its metabolites has been investigated. In the pathology laboratory, a protocol for the detailed examination of MIRU hearts has been developed. Animal studies have concentrated on the development of a technique for delineating myocardial infarct size in dogs using Xe^{133}, and on seeking to confirm a model for cardiogenic shock in dogs using intra-coronary injection of mercury.

Although the construction of a separate MIRU facility was just recently completed, all the projects listed above are in progress and initial reports of major findings have already appeared during the past year. In the retrospective studies of hospitalized patients with acute myocardial infarction, it was shown that approximately two-thirds of these patients have prodromal symptoms, and that these symptoms are usually associated with anterior rather than diaphragmatic infarction. Studies on non-traumatic assessments of left ventricular function have suggested that pre-ejection and ejection times are useful in indicating the presence and extent of myocardial infarction, and in assessing prognosis with regard to mortality. The serial measurement of blood gases in acute myocardial infarction has proved useful in categorizing the class of congestive heart failure, and results suggest that these determinations may have early prognostic value. Equally important, the portable chest x-ray was not found to be of value for categorizing the degree of congestive heart failure or assessing prognosis for mortality. Biochemical laboratory studies have further elucidated our understanding of the metabolic fates of glucose and fat in the myocardium during anoxia; it was learned that fatty acids ceased to be a major source of energy to the anoxic myocardial cell, and instead are utilized primarily for the snythesis of neutral fats.

Preliminary studies of myocardial metabolism in patients have demonstrated the feasibility of this approach and will serve as the critical complementary pursuit to the above laboratory studies. In the animal laboratory, extensive attempts to utilize the mercury model for cardiogenic shock proved unsuccessful, thereby adding important information to the animal model problem. All these findings in the laboratory animal are further steps toward a better understanding and management of acute myocardial infarction in man.

For the coming year, the digitalis assay studies are being terminated. The methods were laborious and expensive; the recently developed radioimmunoassay for digoxin is a much more practical study. The psychiatric project is being terminated. For the coming year, the remaining projects listed above are to be continued with some modification. Hemodynamic and biochemical tests will be initiated in patients with uncomplicated acute myocardial infarction and in patients with prodromata of myocardial infarction and will be continued in the patients with shock. Detailed studies of platelet function on patients with acute myocardial infarction will be initiated. Blood levels and therapeutic effectiveness for antiarrhythmic drugs besides lidocaine will be tested. Finally a new laboratory study will be initiated to further develop a promising new method of assessing human arterial damage through the measurement of blood levels of arterial intimal protein.

Myocardial Infarction Research Unit

Duke University
Contract No. PH-43-67-1440
Contract Amount: $1,519,481 (6/28/67 - 6/27/69)
Principal Investigator: Andrew G. Wallace, M.D.

A major objective at this unit is to characterize as completely as possible all suspected and proven acute myocardial infarction patients admitted to the coronary care unit. Each patient on admission has direct recordings of right heart and systemic arterial pressures, cardiac output, blood gases, and biochemical determinations. Depending on severity of the attack, the measurements are repeated at variable intervals during coronary care unit stay. Computerized history, physical, and laboratory records are maintained for efficient and rapid data analysis. To assess the responses of various endocrine systems, many of the patients also have glucose tolerance tests, growth hormone responses, insulin clearances, plasma renin levels, and catecholamine excretion rates. In addition, psychologic evaluations are obtained on admission, throughout hospitalization, and during the post-hospital recovery period. In selected cases, anatomic, physiologic, and metabolic evaluation of the coronary circulation is studied after hospitalization during the late recovery phase. On each non-surviving patient, in addition to a complete anatomic post-mortem examination, special attention is directed toward the major coronary arteries, pattern of microvascular supply, all gross and microscopic evidences of infarction, quantitative analysis of the infarction areas, and a careful search and investigation of lesions in the conducting system of the heart.

Coincident efforts in the laboratory are directed towards technological advances which will directly benefit the clinical studies. The intracavitary right atrial and ventricular electrograms for the computerized on-line analysis of cardiac rhythms, and computer analysis of intra-arterial pulse contours for assessment of changes in cardiac output, are now ready for clinical trial. Surface mapping of the electrocardiogram from 50 simultaneous points on the chest wall continues under development.

Corollary studies to better understand the course and nature of acute myocardial infarctions are also in progress. Surgical patients at high risk for sustaining a myocardial infarction are monitored before, during, and after surgery to determine what factors signal or influence the onset of myocardial infarction. In another study, direct recordings of myocardial electrical potentials in normal, peri-infarcted, and infarcted heart tissues are obtained at open-chest surgery with plunge electrodes. In the animal laboratory, the effects of induced changes of carbohydrate metabolism on the course of experimental myocardial infarctions in the minipig is under investigation. In dogs, dating of vascular thrombi with radioactive I-125 labeled fibrinogen has been used successfully to determine the exact time of vascular occlusions.

Most of the studies mentioned above are still in progress and planned to be continued into the coming year. Since they are, in general, long-term projects, findings of major interest at present are still preliminary. The computer analysis of the various factors measured on admission appear to give a better indication of eventual prognosis than has previously been possible.

Definite abnormalities of glucose metabolism and growth hormone responses have been noted in different types of infarct patients. In the high risk surgical patient, a decrease in blood pressure is frequently a sign of impending myocardial infarction. Finally, in post-mortem studies, a positive correlation has been found between the syndrome of "power failure" and occlusion of coronary arteries.

Johns Hopkins Hospital
Contract No. PH-43-67-1444
Contract Amount: $1,148,000 (6/29/67 - 6/29/69)
Principal Investigator: Gottlieb Friesinger, M.D.

Multiple studies to systematically characterize the patient with acute myocardial infarction have been done on a regular basis during the past year. In addition, supportive investigations have actively continued in the pathology and animal laboratories.

As originally planned, specific clinical studies in patients with acute myocardial infarction this year have included: the characterization of hemodynamic, clinical, and biochemical changes in complicated and uncomplicated myocardial infarction; an assessment of the clinical, biochemical, and hemodynamic effects of prophylactic digitalization, oxygen, lidocaine, diet, morphine, and diurnal activity during the course of the illness; a systematic evaluation of various therapies in the treatment of cardiogenic shock; nontraumatic assessment of left ventricular function with simultaneous recordings of the phonocardiogram, apical, and carotid pulses; and an evaluation of the histogram and contourogram as methods for display and analysis of electrocardiographic data.

In the pathology laboratory, hearts are examined in detail according to a systematic protocol. Also pathological studies on the role of elastogenesis in the post-infarction tissue repair process are being conducted using autopsy material. In the animal laboratory, experience has been gained in circulatory assist techniques utilizing diastolic augmentation, in preparation for future clinical evaluation. Also in the animal laboratory, the relative distribution of coronary blood flow in endocardium and epicardium, and its changes with vasoactive drugs during acute myocardial infarction are being studied using radioactive microsphere techniques. Finally, the development of a reproducible model for myocardial infarction was investigated in dogs using balloon inflation in branches of the left coronary artery.

Although all of the projects listed above are in progress, initial reports of major findings have appeared during the past year. The feasibility of safe, bedside, direct catheterization of the left ventricle has been demonstrated, and left ventricular pressure measurements are now a standard and important characterization in their MIRU patients. Detailed protocols for the evaluation of prophylactic digitalization and the therapy of cardiogenic shock are operational. Very preliminary results so far have indicated no consistently beneficial effect from prophylactic digitalization. In contrast to findings at two other MIRUs, this group has not found the preejection and ejection times to be of prognostic or diagnostic value in myocardial infarction, thus generating productive debate on the value of this technique. Further refinements in the production of the contourograms have enhanced the value of this technique for analyzing large amounts of electrocardiographic recordings.

In the pathology laboratory, the role and process of elastogenesis in the repair of myocardial infarction has been further defined. Preliminary results suggest that the degree of elastic tissue repair is related to the mural tension on the infarcted myocardial wall. Early results of the regional myocardial blood flow studies suggest a relative underperfusion of the dog endocardium during chronic myocardial ischemia produced by ameroid constrictors. Preliminary data further suggests that this ischemia is relieved by propranolol but not by nitroglycerin. Extensive efforts to produce a standardized reproducible model of myocardial infarction in dogs was unsuccessful, thereby adding further definition to the animal model problem. All these findings in the experimental animal are further fundamental steps toward a better understanding and management of acute myocardial infarction in man.

In the coming year, the above projects will be continued with minor modifications. Several important new projects will be initiated in patients with myocardial infarction: a systematic characterization of pulmonary gas exchange in ventilatory function; a quantitative assessment of cardiac motion and size utilizing fluoroscopy and automatic edge tracking techniques, and statistical studies of all clinical data utilizing multiple regression analysis to identify those factors which influence and correlate with the course of the illness. In the animal laboratory, the research effort will shift toward including a study of the effect of shock and its therapy upon the distribution of blood flow in the differing layers of the heart, and a project will be initiated to assess the hemodynamic effects of hyperlipidemia in the animal before and after experimental myocardial infarction.

Myocardial Infarction Research Unit

Massachusetts General Hospital
Contract No. PH-43-67-1443
Contract Amount: $1,419,000 (6/29/67 - 6/28-69)
Principal Investigator: Charles A. Sanders, M.D.

During the past year, major emphasis has been directed toward the clinical evaluation of patients with acute myocardial infarction. In addition, research support for the clinical projects has continued in the pathology, biochemical, and animal laboratories.

The objectives of specific clinical studies in patients with acute myocardial infarctions have included: the characterization of hemodynamic and biochemical changes in shock, comparative effectiveness of ventricular and atrio-ventricular pacing, atraumatic assessment of left ventricular function with the simultaneous recordings of the phonocardiogram and apical and carotid pulses, altered distribution of pulmonary blood flow measured with Xenon 133, determination of the optimal blood levels of the antiarrhythmic agent procainamide in relation to therapeutic effectiveness, relationship of digoxin blood levels to clinical effect, required length of hospital stay, and psychiatric influences on the course of the disease.

In the pathology laboratory, the relationship of infarct size to clinical course, myocardial tissue levels of epinephrine and norepinephrine, degree of small vessel sclerosis, and types of infarct healing are being investigated. In biochemistry, methodology is being refined for the determinations of blood levels of renin, angiotensin I and II and bradykinin. Also, a radioimmunoassay technique for digoxin and digoxin specific antibodies in blood is ready for clinical trial. Animal studies have concentrated on the development of a suitable model of cardiogenic shock in the dog. In the shock model, hemodynamic and biochemical changes before and after various cardiac drugs and different forms of mechanical circulatory assist are being evaluated.

Although all of the projects listed above are in progress, initial reports of major findings have appeared during the past year. In patients with acute myocardial infarctions, the added hemodynamic advantage of atrio-ventricular pacing over ventricular pacing has been clearly demonstrated. Studies with procainamide have shown that for optimum effect the drug should be given every three hours as opposed to the usual every six hour dosage schedule previously recommended. Studies of pulmonary distribution of blood flow with Xenon 133 have shown a redistribution of the pulmonary blood flow even in patients with apparently uncomplicated myocardial infarctions which strongly suggest an element of left ventricular failure even in these uncomplicated patients.

A major advance from the laboratory is the development of an adequate and reliable radioimmunoassay to determine digoxin blood levels. This is the first time a clinically feasible method to determine levels of this important cardioactive agent have been available. In addition, in the animal laboratory in the past year a suitable model for the study of cardiogenic shock has been developed with the use of the multiple ligation technique of the coronary arteries

in the dog. All of these findings in the laboratory are further steps towards a better understanding and management of acute myocardial infarctions in man.

For the coming year the majority of projects listed above are to be continued with some minor modifications. The surgical effort will shift from the animal laboratories to the study of the effect of diastolic augmentation with an intra-aortic counterpulsed balloon device in patients with cardiogenic shock unresponsive to maximum drug therapy. In the uncomplicated patient, hemodynamic and biochemical tests will be performed similar to the studies now limited to shock patients. Blood levels and therapeutic effectiveness of antiarrhythmic agents besides procainamide will be tested. Pulmonary capillary blood volume and ventilatory function will be added to the pulmonary flow studies.

Myocardial Infarction Research Unit

University of Rochester
Contract No. PH-43-68-1331
Contract Amount: $635,000 (6/28/68 - 6/27/69)
Principal Investigator: Paul N. Yu, M.D.

Since award of this contract one year ago, the major objective has been to characterize the syndrome of acute myocardial infarction by intensive clinical, physiological, biochemical, psychological and related investigation in the acute phase of the disease. In addition to extensive in-hospital studies, the clinical research has also focused on the earliest phase of the acute attack prior to hospitalization. Support for the clinical studies has been undertaken in the pathology and animal laboratories.

Specific objectives of individual in-hospital projects during the past year have been to determine in patients with acute myocardial infarction: 1) the validity of non-invasive diagnostic techniques for the measurement of ventricular volumes and cardiac output with the ultrasonic echocardiogram and for the evaluation of ventricular function by calculating the pre-ejection period from simultaneous recordings of the phonocardiogram, electrocardiogram and carotid artery pulsation, 2) alterations of pulmonary extravascular volume determined with double radioisotope techniques, 3) the relationship of psychological and behavioral characteristics of patients to the onset and prognosis of their acute illness, and 4) significance of changes in catecholamine excretion rates. To aid in these and other studies, a two-bed clinical research unit has been designed and is under construction.

In the prehospital program, major goals have been the evaluation of possible precipitating factors and the description of the earliest hemodynamic and biochemical events of the acute attack. To obtain this information, arrangments have been made for employees at a large industrial firm in the Rochester area to be seen immediately after the onset of suspicious symptoms. Early diagnosis is made and optimum therapy administered early in the course of the attack. In addition, continuous clinical and hemodynamic information is obtained according to a specially designed research protocol up to the time of hospitalization. The information obtained from the prehospital as well as in-hospital studies is recorded in a form suitable for rapid computer analysis and storage.

In the department of pathology, non-surviving subjects have a detailed examination of the heart and vascular system in addition to a complete routine autopsy. Special attention has been directed toward abnormalities of the cardiac valves and conduction system in relationship to the clinical course.

Supporting studies in animal models of myocardial infarction are directed at clarifying 1) the relationship of myocardial tissue to blood and urine catecholamines, 2) the role of exogenous and endogenous catecholamines in the production of arrhythmias, and 3) the changes in catecholamine and ATP content in myocardial muscle granules from normal and ischemic tissue.

Although the absolute number of studies at this time is limited, findings of significant clinical interest have recently become available. In the prehospital phase of the illness, an increased prevelance of bradyarrhythmias has been noted. Correlation of these cardiac arrhythmias with blood and urine hormonal levels are not yet available. In the in-hospital studies, increased catecholamine excretion rates have correlated with clinical complications but not with the extent of infarcted myocardial tissue. The increased epinephrine excretion ratios suggest that the adrenals and not the heart are the major source of the excess circulating catecholamines. In addition, a report on contrast media echocardiography which utilizes saline or indocyanine green as the contrast media suggests that this recent modification in the use of ultrasonics is a reliable and safe technique for the determination of heart chamber and great vessel size in the patient with acute myocardial infarction. Also, from the in-hospital studies the relationship of the pre-ejection period to directly measured characteristic of ventricular function suggests that this method is another useful diagnostic indicator of cardiac function in patients with acute infarction.

For the coming year, the projects listed above are to be continued. With the availability of the new clinical research area, the present ongoing in-hospital studies can be expanded and new research projects undertaken. New projects planned for the coming year include controlled studies of the efficacy of exogenous catecholamine administration, the value of prophylactic digitalization, and pulmonary-ventilation perfusion abnormalities in relation to altered blood gas tensions. In the prehospital studies, in addition to increasing the number of patients, a selected group of these same subjects will be re-evaluated after they leave the hospital. These follow-up studies, which include continuous ECG monitoring, will attempt to determine other factors which may influence the high incidence of recurrent morbidity and mortality from their disease.

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; but for other investigations, a previously operated-upon animal may be satisfactory. For some applications, a single infarction may be satisfactory; for others, myocardial infarction 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 comittee. The existing models were deemed sufficiently unsatisfactory or sufficiently incompletely perfected to warrant further refinement before they could 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 on this topic have now been in effect for 15 months. Each is developing 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 and a slowly expanding balloon. 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 and by heat production at a catheter tip. 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 has been under study. Each has required preliminary development and refinement. It is now 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 are being 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.

All tasks will be completed; and it is expected that all contracts will be terminated by March 31, 1970 with the exception of one, which will require further renewal for 6 to 12 months.

Mallory Institute of Pathology
Contract Number: PH-43-68-687
Contract Amount: $113,700 (2/29/68 - 3/31/70)
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.

The initial proposal to use casein-ameroid devices for large vessel narrowing was modified when in vitro and in vivo tests demonstrated wide variability in rate and extent of ameroid expansion and consequently artery narrowing. However, the investigators subsequently have developed an open chest model of reduced right coronary artery flow using a wire band.

After the methodology of adenosine diphosphate preparation and administration was developed in vitro, infusion of the substance into the right coronary artery of closed chest pigs resulted in severe electrocardiographic abnormalities and a moribund animal. Posterior infarcts developed in 70% of the pigs, but the remaining 30% failed to demonstrate myocardial lesions or platelet aggregates at autopsy (1-4 days post-infusion).

The methodology of the preparation and administration of the collagen extract was studied in the rabbit. It has been injected into a small number of pigs who have developed infarcts. Data is too preliminary to draw conclusions.

These studies as well as the microsphere and endothelial injury techniques will continue in the coming year. It is anticipated that an additional 6-12 months will be necessary to complete the studies.

Oregon Regional Primate Center
Contract Number: PH-43-68-686
Contract Amount: $47,000 (2/27/68 - 7/31/69)
Principal Investigator: M. R. Malinow, M.D.

The technique under development is the radio-controlled gradual tightening of a snare positioned about a coronary artery at prior thoracotomy; rhesus monkeys are being studied.

After 3-5 days recovery, the monkey is restrained in a chair and baseline ECG and hemodynamics are recorded. The snare is then tightened until an injury current appears. An extensive anterolateral septal infarct is seen after ligation of the upper 1/3 of the left anterior descending coronary

artery. Electrocardiographic evidence of ischemia appears immediately after occlusion and within ten minutes aortic flow and blood pressure drop. These parameters return toward normal within 24 hours. Severe impairment, interpreted as cardiogenic shock, frequently develops.

The investigators will complete these studies during the next four months by investigating and quantitating the reproducibility of this method.

Cox Coronary Heart Institute
Contract Number: PH-43-68-688
Contract Amount: $64,809 (3/1/68 - 3/31/70)
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. Insertion of the device in a selected artery results in acute myocardial infarction distal to the gradual, 24 hours, occlusion. Serial ECGs show ischemic changes; decreases occur in blood pressure and cardiac output; enzymes are elevated, and heart rate increases. With left anterior descending coronary artery occlusion, approximately 25% of the ventricle is involved. Some recovery of the hemodynamic, electrophysiologic, and biochemical parameters occurs within 3-4 days. In the coming year, these studies will be completed by two wire placement, both at simultaneous and at separate times, in different sites in the coronary vasculature. In addition, small vessel occlusion will be studied.

Harvard University (Boston City Hospital)
Contract Number: PH-43-68-684
Contract Amount: $59,106 (3/25/68 - 3/24/69)
Principal Investigators: John Norman, M.D. and William Hood, Jr., M.D.

At thoracotomy, a balloon occlusive device is implanted around the left anterior descending coronary artery at its origin. After two weeks recovery, acute myocardial infarction is produced by gradual inflation of the balloon over 2 hours with a microflow pump. Results with dogs indicate successful implantation and infarction in the majority of animals. Anterior wall infarcts are seen at sacrifice that range from 22-37% of the ventricular weight. Electrocardiographic evidence of acute ischemia appears within one-half hour after occlusion and at this time cardiac output is decreased, left ventricular pressure is decreased, pulmonary artery pressure is slightly increased, and aortic pressure is increased. Enzyme levels increase at one day after occlusion. Recovery of these variables occurs within one week.

New York University Medical Center
Contract Number: PH-43-68-685
Contract Amount: $45,305
Principal Investigator: Jacob Hirsch, M.D.

An electrical current between a catheter positioned in the coronary artery and an external electrode is used to provoke thrombosis. When the catheter is placed into the left anterior descending coronary artery 2-4 cm. from the ostium, an occlusion greater than 90% can be produced with low intensity, long duration DC current. The catheter is left in place for 2 1/2

hours to allow a stable occluding thrombus to form. These are short term experiments, lasting only about three hours. Hemodynamic studies indicate no consistent changes. However, serum enzymes, SGOT, and CPK rise.

In the next six months, these investigators will complete the study by evaluating hemodynamics and infarct size in animals maintained for several days after the acute experiment.

University of Wisconsin Medical Center
Contract Number: PH-43-68-689
Contract Amount: $69,390 (3/14/68 - 3/31/70)
Principal Investigator: James A. Will, D.V.M., Ph.D.

Three techniques, which do not require thoracotomy, are under study in dogs and calves. These are thermal burn, infusion of vasotoxic substances, and catheter placement of intraluminal metal rings.

With the thermal burn technique, endothelial damage is produced by heating the nichrome coil tip of a catheter. In calves, using only local anesthesia, the catheter is passed down through the carotid artery into a coronary artery. Within 30 minutes of the thermal impulse, ischemia appears on the ECG and within 4 hours, ECG evidence of myocardial infarction appears. The cardiac index falls to 50% of its pre-infarction level and serum enzymes increase. In the next year, this method will be further quantitated by studies of various catheter tip locations and extent of infarction. In addition, intracoronary thermal burns will be evaluated in dogs.

In the second method, the intracoronary infusion of vasotoxic substances, a chronic, indwelling catheter was developed. The catheter is made of radiopaque teflon and its tip is guided to the ostium of a coronary artery through a #9 G-L catheter. When the coronary ostium is entered, the smaller teflon catheter is advanced under fluoroscopic control into the desired position in the coronary artery and flushed periodically with heparin. It can be maintained for periods up to nine days. To produce infarction, allylamine, a vasotoxic substance, is infused through the catheter. In the coming year, dose-time combination for optimum results will be determined and the effects of this substance as well as others will be evaluated.

In the last method, graphite-benzalkonium-chloride-heparin coated brass rings have replaced the originally proposed intraluminal casein-ameroid devices which were too rough when exposed to moisture. Four hours after catheter placement of the ring in the coronary artery, ECG evidence of infarction appears, enzymes are elevated, and hemodynamic measurements show a decreased cardiac output and increased left ventricular end diastolic pressure. In the coming year, the studies will be completed by standardization of the ring size and evaluation of the reproducibility of the technique.

Indicator Dilution Measurement of Cardiac Output with Dissolved Hydrogen

Research Foundation of the State University of New York at Buffalo
Contract No.: PH-43-69-28
Contract Amount: $39,951 (7/1/68 - 6/30-69)
Principal Investigator: Francis J. Klocke, M.D.

Among the increasing number of instruments and methods available for clinical investigation which are 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 withdrawal of blood. A promising indicator dilution technique is being developed which utilizes certain unique characteristics of hydrogen: It is poorly soluble in blood, but its concentration can be determined precisely in small quantities of blood by gas chromotography techniques, its relative concentration can be determined in vivo by electrochemical techniques using a platinum-tipped catheter, and it is almost completely eliminated from the blood during one passage through the lungs. The goal of this contract has been the further development of the technique, the definition of its accuracy and its limitations, the development of simpler, smaller, and more reliable gas chromotography apparatus and more stable platinum electrodes, and making the techniques available to other investigators in the Myocardial Infarction Program and the total scientific community. Major strides have been made toward each of these goals. In addition, in studying the sources of potential error by the hydrogen technique, important limitations of the widely used indocyanine green indicator dilution technique became recognized, including the inability of the standard logarithmic extrapolation to reliably exclude recirculation, the importance of a minimum time for achieving optical stability after indocyanine green is introduced into the blood, and certain problems associated with the flow and mixing through multi-compartmental paths. Prior to its use in a coronary care unit setting, the technique developed is now being used regularly in the clinical catheterization lab. In individual patients it has permitted 20 or more rapidly repeated determinations of cardiac output. In addition, the technique is being introduced into one of the MIRU's.

In the coming year, further developments in the methodology will take place, and the technique will be utilized regularly in patients with acute myocardial infarction. It will make possible investigations of the hemodynamic effects of electrophysiological events and interventions by these investigators, and it is expected to have wide applicability for frequent, reliable cardiac output determinations.

Electrocardiography and Electrophysiology in Relation to Myocardial Infarction

Research Foundation of the State University of New York at Syracuse, Buffalo
Contract No.: PH-43-67-680
Contract Amount: $36,620 (3/3/67 - 2/28/69)
Principal Investigator: J. A. Abildskov, M.D./Francis J. Klocke, 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. An extensive report is in preparation and will be completed by June 30, 1969. 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 electrophysiology 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 being identified. Pilot clinical electrophysiological studies are being conducted. The report will be completed imminently, and the clinical studies will be completed in the coming year.

Symposium on Research on Acute Myocardial Infarction

American Heart Association
Contract No.: PH-43-68-1015
Contract Amount: $57,000 (6/18/68 - 6/17/70)
Principal Investigator: Richard Hurley, M.D./Stuart Bondurant, M.D.

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 heart attack, a Symposium on Research on Acute Myocardial Infarction was supported. The American Heart Association established a planning committee responsible for the organization of the scientific program and for the editing and scientific analysis of the Symposium proceedings. The major topics of the Symposium were the etiology and pathogenesis of acute myocardial infarction, a critical appraisal of what has been learned about myocardial infarction from studies on prevention, potential improvements and means of evaluation of acute myocardial infarction, and research on the treatment of acute myocardial infarction. Eighty-three scientists participated in the three-day conference. Recent advances and potential developments in many areas were presented and discussed. The proceedings of the conference are edited and will soon be published as a supplement to a widely circulated scientific journal. The analysis of the meeting by the planning committee has been reported to the Heart Institute. The project will be completed in the coming year with publication of the proceedings.

Serial No. _____
1. Myocardial Infarction Branch
2. Collaborative Studies Program, NHI
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968, through June 30, 1969

Project Title: Electrocardiographic Warnings of Sudden Cardiac Death

Previous Serial Number: None

Principal Investigators: Alan N. Weiss, M.D.
Charles L. Jobe, M.D.
Tavia Gordon
Paul H. Lange, M.D.
Peter L. Frommer, M.D.

Cooperating Units: Biometrics Research Branch, OADEM, NHI
Framingham Heart Study, OADEB, NHI

Man Years

Total: .2
Professional: .1
Others: .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 arteriosclerotic 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 (PVC) in the development of arrhythmias following acute myocardial infarction, we have postulated that PVC 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.

ECG warnings of sudden cardiac death (SCD) were sought in the records of 2336 men aged 29 to 62 examined biannually up to 14 years in the Framingham Study. SCD (within 1 hour) occurred in 69 men at age 58 $\pm$ 5.7 (S.D.), 7.8 $\pm$ 3.7 years after initial exam. Both PVC and LVH in the initial ECG were significantly ($p<0.05$) related with eventual SCD, even after age correction: SCD occurred in 11% (8/72) of those with and 2.7% of those without PVC, and in 26% (12/46) of those with and 2.5% of those without LVH. The importance of PVC in those free of symptoms of ECG evidence of arteriosclerotic heart disease (ASHD) or LVH was examined: 7.3% (4/55) with PVC and 1.9% (40/2134) without PVC eventually developed SCD, but age disparity of groups and small numbers

negate significance. Of the 69 with eventual SCD, 25 already had ASHD or LVH on initial exam. On their last pre-SCD exam, 43 had ASHD or LVH, and 10 of the 43 also had PVC; only one of the 69 had PVC in the absence of LVH or ASHD.

Thus, the data suggest that (a) LVH substantially increases the risk of SCD, (b) PVC has prognostic implications for SCD, but (c) in the absence of ASHD or LVH, SCD in the near future is rarely heralded by PVC in the 42 second routine ECG. The analysis of this aspect of the Framingham data is near completion and a manuscript will be prepared for publication. On the basis of these data and the results of other investigators, it is likely that the importance of arrhythmias as prognostic factors and as mechanisms for sudden cardiac death must be pursued by more extensive recordings on subjects, at rest and during activity. These studies will probably be conducted as a part of the program of contracts on sudden cardiac death which will probably be operational by October, 1969.

Honors and Awards: None

Publications: None

BLOOD PROGRAM

EXTRAMURAL PROGRAMS

PHS-NIH
NATIONAL HEART INSTITUTE
July 1, 1968 through June 30, 1969

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 1.715 million dollars, a part of which went to provide for continued support of the twelve original projects. Because many of the original goals were accomplished in FY 1969, only a small part of the Blood Program budget of 2.792 for that year went to continue the efforts in the blood preservation and fractionation field:

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 Support: $36,000, June 29, 1968 - June 28, 1969
   FY 1969 Contract Terminated: June 28, 1969

ACCOMPLISHMENTS: 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 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 Support: $17,710, June 27, 1968 - January 26, 1969
FY 1969 Support: $39,978, January 27, 1969 - January 26, 1970

ACCOMPLISHMENTS TO DATE: Under this contract Dr. Gibson has attempted to evaluate the effect of adenine on the viability of human red cells preserved in the frozen state. To this end he used glycerol as a protective additive to red blood cells prior to freezing and processed these cells in a bio-mechanical device designed by the Institute. Evaluation of the effects of adenine on the viability of human red cells has been based on in vitro tests of dimensional, osmotic and chemical deviations of red cells from normal, and by post-transfusion survival studies using a radio-chromium tagging technique in normal human volunteers. All transfusions were autologous. Survival data calculated from results of tests using 20 ACD-adenine transfusions and 20 CPD-adenine transfusions show that the 24 hour post-transfusion survival was 79-93% for ACD-adenine and 77-96% for CPD-adenine. These values do not differ significantly from the corresponding control bloods which were not fortified with adenine. ACD and CPD bloods fortified with adenine were also stored for 24 hours after thawing before being transfused. About ten ACD-adenine and ten CPD-adenine bloods stored in this manner were infused into normal controls. The 24 hour post-transfusion survival for ACD-adenine bloods stored in this manner was 73-93% and for CPD-adenine bloods 79-87%. These also do not differ significantly from controls.

Dr. Gibson has determined the percent recovery of red cells from the mechanical processing technique and has determined that the loss in processing is due primarily to osmotic and mechanical trauma. The overall recovery of cells was about 90% regardless of the anticoagulant used as a preservative. Biochemical parameters were also measured in blood stored in ACD-adenine and CPD-adenine. ATP, glucose, pH and hemoglobin levels after 24 hours of refrigeration of post-thawed bloods resuspended in ACD-adenine or CPD-adenine were not statistically different.

The principal investigator has scientific evidence to assume that his system for glycerolization, freezing, storage, thawing, deglycerolization, and resuspension of red cells for transfusion has, in his laboratory, reached a stage which allows further clinical trials. We feel this has been a significant contribution to the adenine program and to blood-banking in general in that these findings indicate that bloods frozen by the technique described by Dr. Gibson may be integrated with the normal procedures in current blood bank practice.

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 Action: Extension without additional funds through June 27, 1969
FY 1969 Action: Extension without additional funds through June 27, 1970

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 were 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 clinical 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.

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 Support: $16,000, June 22, 1968 - December 31, 1968
FY 1969 Contract Expired: December 31, 1968

ACCOMPLISHMENTS: 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 was 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 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 Support: $29,400, June 21, 1968 - June 20, 1969
FY 1969 Action: Extension without additional funds through December 20, 1969

ACCOMPLISHMENTS: 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 Support: $65,135, June 20, 1968 - June 19, 1969
FY 1969 Contract Expired: June 19, 1969

ACCOMPLISHMENTS: 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 Support: $100,000, June 12, 1968 - January 15, 1969
FY 1969 Support: $ 69,300, January 16, 1969 - January 15, 1970

ACCOMPLISHMENTS TO DATE: This contract has had five integrated subdivisions, all designed to determine the *in vitro* effect of adenine supplementation on stored whole blood. These studies may be summarized as follows:

A. Studies of quantitative hemagglutination assays to determine the suitability for serological studies of red cells stored as whole blood at 4° C, performed under the direction of Dr. Rosenfield, have indicated that both ACD blood and ACD-adenine blood display little loss in specific hemagglutinability for at least three weeks. Beyond four weeks for ACD blood, and beyond six weeks for adenine-fortified blood, decay and specific agglutinability becomes marked. These studies suggest that loss of specific agglutinability when red cells are stored resembles, and perhaps is related to, the loss in post-transfusion viability. These measurements were determined by instrumented assays utilizing autoanalyzers.

B. Studies of physical-chemical changes in stored red cells and plasma proteins, under the direction of Dr. S. Kochwa, have revealed no significant differences between ACD and ACD-adenine in viscosity of blood stored at about 70% hematocrit, and no significant changes in red cell electrophoretic mobility over an eight-week storage period. The results of viscosity studies on stored plasma, and immunologic and ultracentrifugal studies of separated plasma proteins, are currently in progress and data has not been made available to us for analysis of the results.

C. Functional integrity of red cells, under the direction of Dr. R. Zalusky, was measured by evaluating mean corpuscular volume, osmotic fragility, red cell sodium and potassium content, ATP content, and free plasma hemoglobin. Of these measurements, better maintenance of red cell ATP levels was the only measure which distinguished blood stored in ACD-adenine from control studies in ACD. The presence of adenine in ACD protects the ATP levels, even when the red cells are stored in a packed state, with a hematocrit above 70%.

D. The activity of stored plasma clotting factors was studied under the direction of Dr. J. Niemetz. No appreciable differences between plasma collected in ACD and ACD-adenine were detected.

E. Studies comparing the effects of platelet function in blood collected in ACD and ACD-adenine were conducted under the direction of Dr. L. Aledort. Adenine had no deleterious effect on plasma volume; membrane permeability measured as changes in intracellular sodium, potassium, calcium or magnesium; platelet aggregation and platelet dependent clot retraction. There was no singificant difference in either platelet ATP content or in ATPase activity. Dialysis of ACD or ACD-adenine platelet-rich plasma restores clot retraction to normal. Additional studies comparing platelet function were carried out under the direction of Dr. H. Weiss. These studies dealt with platelet aggregation, release of platelet-ADP, and platelet factor III activity. Platelet aggregation was less in ACD-adenine blood than in ACD blood. The differences disappeared after dialysis against platelet-poor plasma.

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 Support: $37,000, June 27, 1968 - June 26, 1969
FY 1969 Contract expired June 26, 1969

ACCOMPLISHMENTS: 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
   FY 1969 Contract Expired June 14, 1969

ACCOMPLISHMENTS: The objective of this project was to study the clinical effectiveness and safety of ACD-adenine preserved blood in human transfusions. Dr. Strumia measured 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.

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 June 27, 1969
    FY 1969 Action - Extended without additional funds through June 27, 1970

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.

Few 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 - June 30, 1969
FY 1969 Support: $30,800
FY 1970 Recommended Support: $36,000 July 1, 1969 - June 30, 1970

ACCOMPLISHMENTS TO DATE: Dr. Huisman outlined in his proposal three years of study aimed at elucidating the effect on heterogeneity and physiology of hemoglobin of various additives including adenine. His first two years 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.

12. American National Red Cross
Washington, D.C. PH-43-67-1364
Project Director: Tibor J. Greenwalt, 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 Action: Extension without additional funds to February 28, 1969
FY 1969 Support: $260,240, March 1, 1969 - February 28, 1970

ACCOMPLISHMENTS TO DATE: The original Red Cross contract was intended to develop and demonstrate the operability of an integrated system for fractionating large quantities of blood to produce maximum yields of all cellular and protein fractions. Being a voluntary agency, the Red Cross would dedicate improvements to the public interest and make them freely available to all blood handling agencies.

During the contract period the American National Red Cross acquired a building with 21,000 square feet of floor space, located at 9312 Old Georgetown Road, Bethesda, Maryland, and remodeled, staffed and equipped this building to undertake the work performed under the contract. Important additions to the senior research staff of the American Red Cross were made as a direct result of having acquired and equipped these research facilities.

The production of a high potency antihemophilic factor (AHF) has been achieved. During the contract period, 3100 vials of high potency AHF were produced containing 300-400 AHF units/vial. An equal number of vials containing 100-250 AHF units/vial of the intermediate potency AHF were also produced. Dr. Alan Johnson's method for the production of AHF from fresh frozen plasma has now been widely publicized and has been scaled to meet production requirements by many different laboratories. Participating production units now include Squibb Laboratories and the Michigan State Department of Public Health. The American Red Cross has also developed pilot production methods for processing a factor IX complex containing factors II, VII, IX and X. The factor IX complex can be produced either from Cohn fraction III or from fresh frozen plasma. The Red Cross is hopeful that it can develop improvements and refinements of methods designed to further process the factor IX complex.

Procedures have also been developed by the American Red Cross for isolating albumin from outdated plasma. They have also prepared standard protein solutions for use by DBS and WHO.

The Red Cross has developed an active rare donor file which functions effectively in the Washington area and has resulted in guidelines applicable to other Red Cross regions. A protocol for testing a candidate plastic container for potential use in the frozen blood and routine blood-banking practices has also been carried out under the contract. Toxicity and developmental studies have been done under the auspices of Dr. Julian Autian. Improved methods for freezing platelets by using 7.5% DMSO and dextrose has resulted in the capability of a 50% recovery of platelets having 50% efficiency in vivo. New observations on the short-term storage of platelets have alao resulted in the finding that platelet recovery is best when stored at 22^{o} for periods up to 72 hours in the form of a platelet concentrate.

Data has been obtained which suggests that a lymphocyte culture technique being evaluated by Dr. Barbara Mella, in the Red Cross laboratories, is capable of detecting carriers of serum hepatitis.

At present the American National Red Cross is undertaking a program designed to investigate new methods for the production of intermediate and high potency AHF concentrates from frozen cryoprecipitates and outdated plasma. They are also adapting the methods which have been developed for concentrating AHF from fresh frozen plasma to the purification of AHF from frozen cryoprecipitates in Cohn fraction I, derived from outdated plasma. The Red Cross is also developing a procedure for production of factor IX concentrates utilizing fresh plasma either in diluted form or with anticoagulants other than ACD. It is hoped that the pilot plant phase for the production of a prothrombin and factor IX complex concentrate can be scaled to production levels within a 12-month period. The Red Cross will also undertake a project to prepare IgA and IgM concentrates from Cohn fraction III. The preliminary phase will include physical-chemical studies, preparatory methods and serologic studies conducted in cooperation with the Communicable Disease Center for detecting the presence of specific antimicrobial antibodies.

The investigators at the Red Cross are investigating newer methods of separating platelets in order to establish the quantitative efficiency of recovery and to study the in vitro qualities of platelets obtained by these new methods as well as to perform in vivo studies of their efficiency and viability. They are performing short-term and long-term preservation investigations in order to improve the limited supply of platelets which now exists in the United States.

In addition, they are attempting to improve the methods for processing frozen red blood cells. They will formulate an ideal glycerolizing medium for red blood cells and determine what factors influence glycerolization techniques. Pre-freeze apparatus, storage racks and deglycerolization procedures will also be outlined. Finally, they will determine an ideal, clinically acceptable resuspension medium for thawed and washed red blood cells.

The Red Cross also is undertaking a detailed comparative evaluation of plastic containers fabricated from polycarbonate, polyethylene and teflon-FEP. They intend to determine the toxicity, physical-chemical analysis and long and short-term storage properties of these containers.

AUTOMATED DONOR BLOOD INVENTORY AND DONOR-RECIPIENT INFORMATION SYSTEM

A new direction was taken in FY 1968 when 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 Branch 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 were awarded to the following organizations in FY 1968 with supplemental support in FY 1969.

1. Community Blood Council of Greater New York
   New York City, New York PH-43-68-1403
   Project Director: Robert L. Hirsch, M.D.
   Project Title: A Computerized Blood Inventory System in the Service of the Community, the Blood Donor and the Patient Recipient
   FY 1968 Support: $357,386, June 25, 1968 - June 24, 1969
   FY 1969 Recommended Support: $330,000, June 25, 1969 - June 24, 1970

ACCOMPLISHMENTS TO DATE: At the onset of this study, key non-medical personnel visited several hospital blood banks in the Greater New York area in order to acquaint themselves in general terms with the activities of a blood bank and to insure that all future ideas in proposals be consonant with the realities of the situation. A data base was then created by investigating the units of blood and components delivered to the hospital and the number of units utilized each day as well as the individual requests for the crossmatching of blood each day, including patient's sex, age, blood type, etc. These data filed into a computer are admirably suited to serve as a base from which to carry out a large number of investigations designed to identify and study blood bank management practices and to learn about the actual blood inventory requirements of a hospital. Studies of the human factors involved in the operation of a blood bank were initiated early in the contract period by a group of psychologists with experience in complex systems that utilize computers. They began investigations of several areas of concern, namely, the impact of similarities and differences in the size, configuration, working conditions, etc., of blood banks on the efficiency

of their operations; the clerical methods employed and how automation could improve them; and the existing constraints and prejudices that will modify the types of automated equipment.

Six separate programs have been written and tested to extract various kinds of information from the data base described in the preceding paragraphs. Thus, analysis of the data base and the programs that have resulted have been designed to analyze the source of blood received by the hospital, the hospital's daily inventory report, and the hospital's crossmatch policies. Determinations of the fluctuation in blood inventory from day to day, week to week, month to month and season to seasonhave been established. Derivation of the rate of change of the inventory for some appropriate unit of time has also been determined. The test to determine whether or not the average number of "days to go" of blood in each ABO-Rh group has been done in order to create useful indices of optimal stock rotation practices. This study has also identified the factors needed to determine how much blood a hospital should order each day taking into account seasonal variation, vacations, conventions, and the like.

Simulation models of hospital blood banks, a community blood distribution center, and a computerized network linking them together, have also been constructed. This is only in the planning phase, but it is the intent in the next contract year to construct these models of the various aspects of the proposed computerized regional network information system in order to test its feasibility and to investigate specific ideas derived from the data base.

2. Milwaukee Blood Center, Inc.
Milwaukee, Wisconsin PH-43-68-1425
Project Director: S. P. Masouredis, M.D., Ph.D.
Project Title: Automated Blood Bank Information System
FY 1968 Support: $184,000, June 26, 1968 - June 25, 1969
FY 1969 Recommended Support: $251,024, June 26, 1969 - June 25, 1970

ACCOMPLISHMENTS TO DATE: The Milwaukee Blood Center and its subcontractor, the International Computing Company (ICC), have exchanged ideas regarding blood bank requirements and possible data processing solutions. Detailed studies have been made of the present Milwaukee Blood Center operations, including observations of the movement of blood in the system, observation of the data flow, collection and analysis of the forms used, and observation of the personnel and their work habits.

Based on these observations and discussions, formal system specifications were drawn up by the ICC and the MBC. An active automated blood inventory system of any importance should meet the following requirements: 1) it should be capable of being operated by personnel, unskilled in data processing; 2) it should process the day-to-day transactions reliably, assume active control of the inventory to reduce dependence on a few personnel, accept transactions as they occur to minimize multiple recording and provide immediate error detection and simple error correction procedures; 3) it should support experiments in blood resource management and in data processing; 4) it should provide research data in the form of permanent medical

historical records of the blood and the blood center's operation; 5) it should permit the testing and confirmation of results of the design process and develop those characteristics important to a blood center management in order to permit the design of an efficient production system.

Having fulfilled these fundamental specifications, ICC and the MBC selected the scientific data systems Sigma 2 computer in order to fulfill the hardware, software and system availability for use in its program development.

The computer program design proceeded simultaneously with the selection of the scientific data systems Sigma 2 computer. The computer program has been developed from the functional specifications and includes the use of a machine-independent language and a machine-independent program design. For this task Fortran language was selected. In addition the machine design and its computer program have been developed so that they will deliver dependable, flexible and simple systems capable of use by blood bank personnel unskilled in data processing. The program has been designed with Fortran chosen as the primary programming language on the basis of its almost universal support by computer manufacturers. It includes a user interface, query programs, query processors, a file handler, information output support, and a scheduler. This hierarchical design minimizes the specialized knowledge required for implementation of each module, allows simultaneous development of module, localizes the effects of design changes, and provides the overall flexibility desired for this project.

In terms of the overall project of ICC and MBC its status is as follows: the planning, development and installation of the automated blood bank information system has been completed in its planning and procurement of hardware phases. The programming and development of software is approximately 50 to 75% completed in terms of effort expanded/estimated total effort required. The preparation of the MBC data base has been expanded to include a number of auxillary files as well as the blood inventory data base. A brief orientation of the objectives of the automated blood bank information-inventory system was given early in the contract year in order to train Milwaukee Blood Center's staff. A more detailed orientation is being planned and manuals for the terminal users of the system are being written. By the end of the first contract year, the Milwaukee Blood Center integrated the hardware, software and personnel in order to produce a reliable operation of the computer equipment. They will also begin to operate the system without remote terminals initially in order to generate some operating reports concerning inventory and collect current donor data in a machine-readable form. They also intend to collect current recipient data in a machine-readable form and to create, maintain and expand a blood inventory data base.

3. Research Foundation of State University of New York
   Buffalo, New York PH-43-68-1281
   Project Director: Edward L. Wallace, Ph.D.
   Project Title: Analysis and Design of a Model Regional Blood Management System
   FY 1968 Support: $177,860, June 28, 1968 - June 27, 1969
   FY 1969 Recommended Support: $209,000, June 28, 1969 - June 27, 1970

ACCOMPLISHMENTS TO DATE: During the first contract year, the State University of New York at Buffalo concentrated its efforts in four key areas: 1) planning the organization and conduct of the total study; 2) planning and launching the studies of donor characteristics, donor involvement processes, and donor organization and management; 3) planning studies of the short-term management of collections and distribution planning processes; and 4) designing the supportive information system.

Short-term planning of blood collections and distribution is the crucial element being studied in this blood management system. During the contract period the following important decisions were made: 1) final adjustments in future collections schedules; 2) forecasts of future short-term collections by week; 3) forecasts of future short-term blood requests by week; 4) forecasts of future short-term center inventories by weeks; and 5) decisions on how present and future center inventories will be distributed within the region. In developing a revised system of short-term blood planning, the proposed management system consists of six separate planning functions and a supportive computerized information system. Each of the six planning functions will be performed by an analytic or Heuristic decision model or a computer-assisted individual decision process. Models for performance of most of these planning functions have been developed during the contract year. Considerable work in the project year has been done in modifying and adapting a short-term out-flow forecast model to the peculiarities of blood usage. Particular attention has been given to the problems of seasonality of demand and unusual fluctuations of demand, occasioned by such considerations as the day of the week on which a holiday falls.

Work which has been performed on the design of the supportive information system has concentrated largely on the design of files for four of the major parts of the system, and development of the inventory data subsystem. Files for the inventory data subsystem are largely complete and a major portion of design work for the initial system has also been completed. Donor files and the donor information subsystem are still under development. The donor group files and donor group information subsystem are intended to provide the regional system and the donor group chairman with management information required to contact potential donors and assure their presence at a collection.

The computer hardware study only reached the exploratory stage during the first year, since the information system has to be reasonably well defined before various computer hardware configurations could be considered.

For the second year's effort there will be four key areas of development: 1) blood collections; 2) blood distribution; 3) hospital operations, organization and administration; and 4) supportive information system. Subtasks under blood collection include investigation and expansion of data on donor characteristics, donor involvement, donor group organization and management, and assurance replacement and replacement guarantee processes. Additional studies on collections and planning processes are intended to develop a procedure for smoothing collection of blood over the long term and to develop a technique for forecasting long range demands and respective needs for required collections. The investigators will also develop a method and technique for providing an accurate daily collections forecast over the near-term.

4. Michael Reese Research Foundation and Blood Center
Chicago, Illinois NIH 69-57
Project Director: Aaron Josephson, M.D.
Project Title: Automated Blood Inventory Feasibility Study
FY 1969 Support: $319,000, September 3, 1968 - September 2, 1969

ACCOMPLISHMENTS TO DATE: Michael Reese and its subcontractor, IBM Corporation are actively working on the design and development of an inventory control system which will be applicable for any size blood bank, large or small.

The objective of inventory control is to to track each unit of blood from the time it is introduced into the system until it is transfused, outdated, lost or fractionated. Tracking would include packed cells and could be expanded to other blood products. In addition, all the information necessary for generating management and operational reports will be maintained. Blood allocation and distribution within the blood center and its associated hospitals has as its objective to move blood from the blood center to the hospitals and between hospitals in such a way as to minimize outdating and transportation costs. The inputs to this model are the blood center policy and the dynamic inventory level as determined by the supply/demand forecasting models and the blood inventory. Such a forecasting model is being designed by IBM for the Michael Reese Blood Center. Supply/demand forecasting for the short term is just what the name implies--how much blood will come into the blood center and how much blood will be used, lost or outdated during 21 days. Supply and/or demand varies with season, location of the hospital or blood center and the economic health of the area. Each of the eight group types must be treated separately. The potential supply of blood will be based on the past history of walk-in donors and the predicted response to the bloodmobile based upon group analysis. Demand can be based upon past history as modified by information on surgery, physicians' practices, specific illness, patient blood group/type, etc.

During the last four months, IBM has collected data representing a two-year experience at the Michael Reese Blood Center. These data have been pooled and utilized as a data base on which to construct many of the inventory models. Flow charting of the major facilities at Michael Reese has also been accomplished. IBM has conducted site visits to most of the participating hospitals in the Michael Reese Blood Center and has started analysis of the site visit reports. Flow charts of each of the individual hospital's function have also been prepared. An analysis and formulation of file data and forms to be used by the Blood Center has also begun. IBM has made a study of the active inventory control systems in the United States and has found that none of them are comparable to a blood inventory control system. Most of the presently operating systems are status tracking systems much like the Lockheed Spacecrafts' prototype model.

Progress by this contractor towards the contract goals has been rapid and it is expected that they will have a functioning prototype system by the end of the second contract year.

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 is a controlled study of over 200 patients with pulmonary embolism by various participating institutions 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. In March 1965 the Heart Council recommended the use of $350,000 of grant funds to purchase an additional 1.614 million units of urokinase.

The current protocol calls 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).

The development of a Manual of Operations for the trial was begun 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 begin the study in June 1968, contracts were awarded to the following institutions to participate in this controlled clinical trial. The 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. Biometric control of the experiment is being provided by the NHI Biometry staff.

Boston City Hospital, Boston, Massachusetts
Principal Investigator: Joseph V. Messer, M.D.
FY 1968 Support: $60,000, June 27, 1968 - June 26, 1969
FY 1969 Action: Extension without additional funds, June 27, 1969 - December 31, 1969

University of Cincinnati, Cincinnati, Ohio
Principal Investigator: Noble O. Fowler, M.D.
FY 1968 Support: $45,000, June 27, 1968 - June 26, 1969
FY 1969 Action: Extension without additional funds, June 27, 1969 - December 31, 1969

University of Colorado Medical Center, Denver, Colorado
Principal Investigator: Edward Genton, M.D.
FY 1968 Support: $52,704, June 25, 1968 - June 24, 1969
FY 1969 Action: Extension without additional funds, June 25, 1969 - March 31, 1970

Duke University Medical Center, Durham, North Carolina
Principal Investigator: Donald Silver, M.D.
FY 1968 Support: $59,340, June 27, 1968 - June 26, 1969
FY 1969 Action: Extension without additional funds, June 27, 1969 - March 31, 1970

Hektoen Institute for Medical Research, Cook County Hospital
Chicago, Illinois
Principal Investigator: Robert M. Stanzler, M.D.
FY 1968 Support: $54,000, June 21, 1968 - June 20, 1969
FY 1969 Action: Extension without additional funds, June 21, 1969 - March 31, 1970

Johns Hopkins University, Baltimore, Maryland
Principal Investigator: Henry N. Wagner, Jr., M.D.
FY 1968 Support: $76,400, June 28, 1968 - June 27, 1969
FY 1969 Action: Extension without additional funds, June 28, 1969 - December 31, 1969

Marshfield Clinic Foundation for Medical Research and Education
Marshfield, Wisconsin
Principal Investigator: Richard D. Sautter, M.D.
FY 1968 Support: $59,600, June 27, 1968 - June 26, 1969
FY 1969 Action: Extension without additional funds, June 27, 1969 - March 31, 1970

University of Pennsylvania Graduate Hospital, Philadelphia, Pennsylvania
Principal Investigator: Moreye I. Nusbaum, M.D.
FY 1968 Support: $48,000, June 19, 1968 - June 18, 1969
FY 1969 Action: Contract expired June 18, 1969

Peter Bent Brigham Hospital, Boston, Massachusetts
Principal Investigators: Lewis Dexter, M.D. and James E. Dalen, M.D.
FY 1968 Support: $41,155, June 27, 1968 - June 26, 1969
FY 1969 Action: Extension without additional funds, June 27, 1969 - June 26, 1970

Veterans Administration Hospital, West Roxbury, Massachusetts
Principal Investigator: Arthur A. Sasahara, M.D.
FY 1969 Support: $37,500, July 1, 1968 - June 30, 1969
FY 1970 Action: $37,000 new funds, July 1, 1969 - June 30, 1970

University of Washington, Seattle, Washington
Principal Investigator: J. R. Blackmon, M.D.
FY 1968 Support: $65,000, June 28, 1968 - June 27, 1969
FY 1969 Action: $88,000 new funds, June 28, 1969 - June 27, 1970

Although many institutions and individuals estimated they would be capable of studying 25 or more patients annually, it was felt by others that a more realistic estimate might be closer to 10 patients studied per institution per year because of the protocol's rather strict eligibility criteria. After an initial "tooling up" period, the "shakedown phase" of the trial began in August 1968 and the trial was officially begun on October 16, 1968. In general, the efficiency of the participating institutions increased along with their patient accession rate. Progress to date has been satisfactory and over 70 patients were studied in the first year.

However, in order to reach the required scientific conclusions about urokinase with the greatest efficiency and in the minimum feasible time, the National Heart Institute decided to increase the number of participating institutions. In response to a Request for Proposals, a number of institutions submitted proposals for participation in the trial. The proposals were reviewed and the following eight institutions were selected as having the greatest potential to fulfill the goals of the trial in the most effective and efficient manner within the prescribed time frame:

University of Alabama Medical Center
Principal Investigator: William J. Hammack, M.D.
Recommended FY 1969 Funding: $67,478

Albert Einstein College of Medicine
Principal Investigator: William A. Cook, M.D.
Recommended FY 1969 Funding: $67,554

University of Chicago
Principal Investigator: C. Frederick Kittle, M.D.
Recommended FY 1969 Funding: $51,091

Emory University School of Medicine
Principal Investigator: Nanette K. Wenger, M.D.
Recommended FY 1969 Funding: $75,000

University of Michigan Medical Center
Principal Investigator: Park W. Willis, III, M.D.
Recommended FY 1969 Funding: $75,000

Mt. Sinai Hospital of Greater Miami
Principal Investigator: Frank J.Hildner, M.D.
Recommended FY 1969 Funding: $50,000

St. Elizabeth's Hospital, Boston
Principal Investigator: Thomas J. Ryan, M.D.
Recommended FY 1969 Funding: $55,270

University of Texas Medical Branch
Principal Investigator: Robert N. Cooley, M.D.
Recommended FY 1969 Funding: $61,654

EXTRAMURAL PROGRAMS

The Extramural Programs of the National Heart Institute is responsible for the administration of cardiovascular research and training grant programs of great scope and diversity. Research projects supported 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, however, 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.

The largest percentage of National Heart Institute funds, approximately $125 million in FY 1969, is devoted to this effort. The grants and awards support cardiovascular research and training activities in colleges, universities, medical schools, public and private hospitals, public and private research foundations and by individuals engaged in biomedical research. More than 1,700 research grants will be supported at a level of almost $100 million this year. These can be individual projects, large multidepartmental or multidisciplinary program projects, or parts of large scale cooperative studies and clinical trials. Approximately $25 million is devoted to training activities; $18 million to support almost 400 graduate and undergraduate training grants; and $7.6 million to support 400 research fellows and career development awardees.

PROGRAM REPORTS

The discussion of 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 also encompass broadly based fundamental and applied studies.

(2) Special Research Programs in which research and planning to reach highly focused objectives is being carried out with the commitment of specific resources on a large-scale, and for relatively long periods of time.

(3) Training including graduate research and clinical training and undergraduate training grants, postdoctoral and special fellowships, and career development awards.

RESEARCH

Arteriosclerosis is the most significant cardiovascular disease in America. It is responsible for more than half a million deaths from heart disease each year, many of them below the age of 65 years. About 3% of the adult population have manifest arteriosclerotic heart disease. Arteriosclerosis is also a major contributor to the death from stroke of about two hundred thousand people.

Epidemiological and geographic research has shown that many parts of the world have a lesser burden of arteriosclerotic disease. The implication is that a considerable amount of arteriosclerotic disease in America should be preventable. The magnitude of the problem is such as to emphasize the practical need for prophylaxis.

The support of research in arteriosclerosis continues to be the major orientation of the National Heart Institute. In fiscal year 1969 the Institute allocated almost $17.0 million to this research effort. About 80% of this work is related to fundamental or applied research that is directed to understanding the nature and development of arteriosclerosis and to applying this knowledge to its prevention. The remainder of the work is research in diagnosis and in therapy.

Arteriosclerosis and arteriosclerosis-dependent diseases are commonly considered to have multiple causes and multiple paths of development. Among these, processes related to fat and cholesterol metabolism and to blood coagulation dominate the current research thrust. Together they account for almost two-thirds of the research in arteriosclerosis. The major areas of activity are biochemistry, nutrition and pathology. An important component of this research has been the initiation of a long-term field trial of the potential usefulness of certain drugs to prevent second heart attacks in arteriosclerotic heart disease. (See Special Programs.)

Other areas of research interest in relation to the development and prevention of arteriosclerosis include the metabolic activity of the blood vessel wall, the nature of the vessel's reaction to injury, its ability to repair itself, and its responses to the flow and pressure of the blood.

In the area of clinical disease, research to improve diagnosis and therapy has been supported. Investigations related to angiography, flow meters, biochemical technology and vascular surgery comprise a major part of this work.

Coronary Heart Disease. Atherosclerotic coronary artery disease is one of the most deadly and debilitating manifestations of arteriosclerosis. As such, it requires special emphasis from the Institute. The research grant program complements the efforts to extend and improve clinical applications of existing knowledge that are supported by contract under the Myocardial Infarction Program. The grants program supports basic and clinical research endeavors designed to explore the multiple factors related to this condition and supports efforts to develop better therapeutic procedures for handling such patients. A significant portion of this latter effort is detailed elsewhere as the "Cooperative Study of Drugs and Coronary Heart Disease". Additional research is being conducted on other pathophysiological conditions involving the blood supply to the heart muscle.

Some promising drugs have been developed and are in various stages of being tested. These range from some widely publicized agents that affect blood lipid levels (such as clofibrate and cholestyramine) to some that have been more recently discovered and are less well known or understood, such as Hepatic catalase-peroxidase. Some drugs appear to have some promise of being valuable to the practicing physician, but the evidence concerning therapeutic or preventive efficacy is not yet complete. Many drugs have not yet been sufficiently tested to predict how valuable they may be. Until more satisfactory drugs are found, we must continue to support efforts to search for and test promising chemicals.

Other problems of the heart rather directly related to its blood supply are also being pursued in this program. Metabolic changes in heart muscle that cause lessening of functional capacity must be clarified and some promising leads have developed recently. Possible surgical approaches to the diversion of blood flow from neighboring structures to the heart (when its own blood supply has become deficient) are being actively studied and evaluated. Several of these are now being utilized in clinical practice.

The Institute has expended approximately $8.0 million in research grant support in this area.

Cerebrovascular Diseases are the third most important cause of death in the United States accounting for approximately 11% of all deaths. In the year 1967 over 203,000 deaths were reported as due to vascular lesions of the brain.

Occlusive cerebrovascular disease is responsible for most strokes. The lesions in this category include cerebral hemorrhage, cerebral embolism, and thrombosis; also included are such conditions as subarachnoid hemorrhage and a miscellaneous group usually reported as cerebral arteriosclerosis, apoplexy, stroke, and cerebrovascular accident. In most cases these lesions are part of a generalized arteriosclerotic process and are often associated with arteriosclerotic or hypertensive heart disease.

Deaths from cerebrovascular diseases increase substantially with advancing age. Death rates from cerebrovascular diseases are markedly higher for non-whites than for whites, and the greater prevalence of hypertension among non-whites is believed to be the principal factor responsible for this difference.

Research studies have indicated a striking association between hypertension and cerebrovascular diseases. Furthermore, age-adjusted death rates from cerebrovascular diseases have shown a distinct downward trend during the past decade; although some of this decrease may be due to changes in classification, it is believed that a significant portion is attributable to increasingly effective drug therapy of hypertension.

In FY 1969 the Heart Institute supported approximately 40 cerebrovascular research projects totaling some $1.5 million. Most of these projects involved human patients afflicted with these diseases; most of these studies were concerned with developing or evaluating therapeutic procedures. A large-scale cooperative trial designed to evaluate surgical therapy for certain types of neck vessel obstruction is nearing completion.

Jointly with the National Institute of Neurological Diseases and Stroke, the Heart Institute is focusing on several research opportunities that appear to be developing: autoregulation of the cerebral circulation; hydraulic influences on distribution of blood flow in the Circle of Willis; measurement of regional blood flows; the control of the cerebral micro-circulation; and the study of diving mammals (the influence of oxygen tension on cerebral flow).

At some time in the future it may be feasible to consider clinical investigations of thrombolytic agents in patients with acute manifestations of cerebrovascular diseases.

Peripheral Vascular Disease is not a specific or single disease but includes a number of unrelated conditions; some represent arteriosclerotic effects, such as aneurysms and others may be infectious or allergic in origin, still others are related to basic functional problems of blood vessels. Several advances have now been made in the replacement of diseased vessels with new, finely knit prosthetic units. They are now being used with greater success than the older molded variety. Although this is not a primary target area for research effort, it is important to the Institute's total program and is showing steady progress.

Approximately $1.5 million in research grant support is devoted to this effort.

Respiratory Diseases. The incidence of respiratory illness, especially chronic obstructive diseases such as emphysema and bronchitis, is increasing in the national population. These diseases are complex and intimately involved with other circulatory and organ systems. Patients usually become

chronically sick and debilitated. Specific etiology is controversial in many cases, although environment, heredity, smoking habits, allergy, infection and metabolic factors are variously involved. Research efforts have been and are often diverse and multidisciplinary. The Heart Institute is presently the largest single provider of support for such research.

The Institute's respiratory disease research program has several foci: chronic obstructive disease, pulmonary vascular disease, lung mechanics and pulmonary physiology. Nearly half of these sponsored studies are aimed at better understanding of causation and fewer than half toward better diagnostic techniques.

These diseases are considered a vital program area requiring increased national attention and greater research and training support. The Heart Institute has asked a Cardio-Pulmonary Advisory Committee composed of senior medical scientists from across the nation to study the present effort and future needs related to these diseases. The Institute now supports some 120 research grants (approximately $4.0 million) and 30 training programs responsible for approximately 140 trainees per year. New methodologies and research approaches are being pursued. Particularly promising are: new techniques of studying ventilation-perfusion phenomena, kinetics of lung fluid compartmentalization, improvement of alveolar exchange during exercise of patients with emphysema, and regional patterns of lung perfusion and ventilation by isotopic indicators. Also, support is being given to long-range prospective studies of chronic lung disease patients to clarify the natural history of these diseases.

Future emphasis is expected in experimental lung transplantation, ex situ preservation preparatory to transplantation, and the development of mechanical devices for certain pulmonary diseases.

Acceleration of new knowledge about respiratory disease is considered a high priority program by the National Heart Institute.

Hypertension and Kidney Diseases. High blood pressure is the most commonly diagnosed form of cardiovascular disease in the United States. Approximately 17 million adult Americans have hypertension and about 10 million have heart disease as a result of this underlying condition. Although hypertension per se is not a major cause of mortality, it is of great public health concern because it accelerates the development of atherosclerosis, stroke, heart failure, and kidney diseases.

Great advances in the diagnosis and therapy of hypertension have been made during the past two decades. A wide variety of effective drugs are now being utilized in every-day clinical practice. Drug therapy for hypertensive medical emergencies (i.e., the hypertensive crisis) has improved remarkably.

In FY 1969 the Heart Institute's research grant program supported over 250 projects in the area of hypertension and renal diseases. These projects amounted to approximately $11.5 million and were devoted to searches for new therapeutic agents, the role of endocrine disturbances in hypertension,

more precise chemical and immunologic techniques for the diagnosis of certain types of hypertension, and better understanding of neural factors in the control of blood pressure. Significant strides have been made in unraveling the association between hypertension and renal parenchymal disease. Renin-angiotensin mechanisms are under intensive study as are fluid and electrolyte aspects.

The clearer delineation of several types of hypertension offers a prospect for prevention and for more rational therapeutic approaches. It is now possible to identify those patients who will derive the most benefit from dialysis programs and those who are most suitable candidates for corrective surgery. Out understanding of the pathogenetic mechanisms of renoprival hypertension has improved considerably.

Adequate treatment of moderately severe hypertension has been shown to be of striking benefit both in terms of mortality and morbidity. It is not known, however, whether the treatment of mild hypertension will result in similar benefits. Currently, this is a matter of some controversy; no data are available from prospective studies. Hypertension is known to be a graded risk factor for coronary disease, stroke, etc. Long-term therapy for mild hypertension is feasible but it is not free of risk; the potential advantages are striking, however.

Thrombosis and Hemorrhagic Diseases. To develop an adequate base of information, the National Heart Institute has encouraged the vigorous pursuit of basic research studies in addition to those directed at specific blood diseases. Research projects are being supported on all of the formed elements of the blood, lymphatic, bone marrow and other blood-forming tissues. Other studies are being conducted on hemoglobin, coagulation components and the subcellular elements of plasma which relate to blood coagulation or lysis. Also supported are projects dealing with the spleen and other lymphoid tissues as they involve phagocytosis and other functions of the reticuloendothelial system.

Molecular, biophysical, biochemical, histochemical, genetic, immunologic, and structural and functional approaches are among those being used. As the result of such a broad attack, investigators are taking the basic information gained from these projects and applying it to specific blood disease problems (e.g., uncontrollable hemorraghing to idiopathic intravascular thrombosis). New schema of blood clotting are being presented which fill in important, previously unknown enzymatic steps. Such studies are leading to the discovery of different ways of inhibiting or augmenting the clotting process and hence to the identification of certain specific mechanisms and treatment of some of the hemorrhagic and thrombo-embolic diseases.

Significant advances have been made in elaborating the mode of inheritance, mechanism, and treatment of Hemophilia A and B. The development and wide availability of highly potent plasma fractions for both hemophilia A and B is especially notable. Although cryoprecipitate and intermediate potency hemophilia A concentrates (Factor VIII concentrates) were available two years

ago, the new high potency concentrate became available within the past year. No concentrates for hemophilia B were available until the last few months. Research is continuing in an effort to find even more effective AHF concentrates in sources other than from human plasma.

Another significant advance is the clinical recognition of a wide variety of disorders that have a thrombotic and/or hemorrhagic disorder as a complication. This is usually called "diffuse intravascular coagulation" or "consumption coagulopathy." It has been found that heparin and long-acting anticoagulants are beneficial in reversing the syndrome.

While no specific drug has yet been identified as suitable for clinical trials, there has been considerable progress in the search for better anticoagulants and drugs which interfere with platelet aggregation. A number are being widely tested in vitro and in vivo.

Sickle Cell Disease, an hereditary abnormality of the hemoglobin in red cells, is present in approximately 8% of the Negroes in this country. It is being attacked on a broad clinical and research basis. The establishment of a Sickle Cell Center at the University of Tennessee provides a resource that focuses on the problems of sickle cell patients and probably has the largest sickle cell clinical study in existence. The natural history of the disease is being studied by observing a large number of patients from birth until death. Particular emphasis is being placed on the treatment of the sickle cell crisis. In addition to the basic research performed and the better care and treatment of patients, the Center contains a comprehensive accumulation of information on sickle cell disease.

In fiscal year 1969 NHI research grant support in this area amounted to approximately $10.6 million.

Congenital and Rheumatic Heart Diseases remain important problems, despite a steady decline of the latter as a cause of death and disability. Rheumatic disease continues to occur in significant numbers; in 1967 some 15,000 deaths were directly attributed to rheumatic fever and rheumatic heart disease. Congenital cardiovascular defects remain a principal cause of death in 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. For survivors, congenital heart disease is one of the costliest of all diseases from the point of view of medical care, the cost of treating an individual patient frequently exceeding $2,000. More than 500 diagnostic centers and over 300 surgical teams in the United States are now specially equipped and trained for these purposes, at an annual cost of many millions of dollars. The Heart Institute's intra - and extramural research programs have placed heavy emphasis on improvement of methods for the diagnosis and evaluation of congenital heart defects, and on the perfection of surgical methods for correcting them.

Despite many technical advances, surgical treatment in infants less than six months old is still so hazardous that palliative procedures are employed whenever possible; definitive surgery is commonly postponed until after the age of two.

A group of investigators is now evaluating the short - and long-term outcome of surgical therapy for an assortment of well-defined cardiac lesions. One-third of the twenty-three hundred patients admitted to this study were referred for surgical treatment because of congenital defects, the other two-thirds were suffering from acquired, usually rheumatic, heart lesions. The value of the surgical correction of certain lesions is now unquestioned. In some instances, however, it is difficult to assess the precise value of surgical therapy. A group of pediatric cardiologists is, therefore, currently evaluating the natural history and the clinical prognosis in patients with certain congenital cardiac defects.

While rheumatic heart disease is associated with certain types of hemolytic streptococcal infection, pathogenesis remains obscure. Much has been accomplished with antibiotics in the area of prevention. Chemoprophylaxis depends for its success on a high degree of public awareness and cooperation in a segment of the population that is often difficult to reach; it would be extremely valuable to have a method for identifying the small fraction of susceptible individuals. Substantial further progress awaits further basic research, especially in (a) immunology; (b) reliable means for detecting incipient cardiac involvement in rheumatic fever victims; and (c) techniques for preventing or reducing the severity of damage when the heart has been attached. Opportunities for such research are limited in this country but could be developed in certain foreign countries where the incidence of rheumatic fever is still high. Meanwhile, advances continue to be made in the surgical replacement of damaged valves, usually in adults who experience late effects of damage from rheumatic fever in earlier years.

The Institute's research grant support in this area amounts to approximately $7.0 million per year.

Heart Failure and Shock. The problems of congestive heart failure and shock are of major clinical importance to the medical community. These are not discrete disease entities but rather symptom-complexes that are the products of severe underlying cardiovascular disease of several etiologies.

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. The Heart Institute is presently supporting a cooperative study of the effectiveness of anti-arrhythmic agents in patients with acute myocardial infarction. Lidocaine has recently been added to procainamide and quinidine as a life-saving drug for treatment of arrhythmias; powerful new diuretic drugs are now available for combating the associated fluid retention; and drugs which block sympathetic receptors have become useful in clinical practice.

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 in this area and the national importance of these disease problems, the Institute will continue to support the most promising research. Multidisciplinary approaches to the problem must be strongly encouraged.

In fiscal year 1969 the Institute allocated approximately $11.1 million to extramural research activities in this important area.

Circulatory Regulation. We must continue to develop a more complete understanding of the normal state of the cardiovascular system as background for research on the causes of the various diseases which affect its function. Except where such studies of the normal state pertain to one of the specific diseases that debilitate the system, they are placed in this category.

Knowledge concerning the electromagnetic currents created by the action of the heart is continually expanding. This provides insight into how certain aberrations may be used to interpret or diagnose dysfunctions of this vital organ. The details of the heart's metabolic requirements have been expanded considerably by recent studies of the changes in enzyme content of heart muscle under numerous conditions of stress and drug influence.

The ultimate mechanisms that result in the contraction of heart muscle fibers are not yet known; but many facets, such as the role of actomyosin, have been added to our knowledge.

Studies on capillary circulation, fluid exchange, and the regulation of these functions are still incompletely understood. Some fairly recent studies implied that there was negative (relative to atmospheric) pressure in tissues which facilitated the movement of solutions from the capillaries. More recent evidence tends to refute the possibility of such negative pressures and suggests instead a concept of constant pressure gradients moving materials (water, salts, metabolic substances) from one compartment of the body to another.

Cardiovascular dynamic studies are still plagued by our inability to develop adequate instrumentation to measure functional variables in an absolute sense. For example, it has been shown that one can obtain several different patterns of blood flow in one single vessel, depending on the dimensional characteristics of the measuring device. New approaches to transducing such energies to a recordable form must be tried in order to achieve absolute measurements.

Special Programs (Artificial Heart and Organ Transplantation). Currently active grants support a large gamut of research related both to cardiac transplantation and artificial replacement and assist devices. Open heart surgery for the repair of defects and the placement of artificial or homograft valves is now widely practiced throughout medical centers in this country. Total heart and/or large vessel replacement by synthetic or homograft means is done in very few places, and virtually all of these have a substantial scientific-supporting staff in immunology and other basic medical sciences.

Work on a total artificial heart, with the possibility of long-term implantation, is being supported at several medical centers. In these centers one finds close collaboration among basic scientists, clinicians, and bio-medical engineers. Development of a total apparatus at this time is largely an empirical process because a multitude of basic physiologic questions remain to be answered before a feasible device can be contemplated. Among the important subunits that are being researched are: (1) a reliable, long-term energy source; (2) sophisticated, versatile control mechanism; (3) the pump itself; (4) materials compatible with body tissues and fluids; and (5) basic mathematical-engineering problems in membrane development, electrical circuitry, and miniaturization.

A number of active grants support research on mechanisms of nervous and chemical control of heart function. Although a number of materials such as plastics and certain metals have been developed as replacement parts, none of them show consistent or sustained compatibility with the tissues of the body. The blood-material interface problem is one of great concern. Investigators are seeking materials which will form a compatible substrate upon which body tissues will grow in their normal state. For example, presently available materials tend to cause blood to clot and available pumps destroy red blood cells at a high rate. A recent report by one scientist, who is working with a team of clinicians and engineers on some of these implantation problems, is most intriguing. He has suggestive

evidence that young organ cells may regenerate themselves more readily on a given artificial material if the physical "architecture" is altered to provide pores and valleys as a matrix. Although much more research will have to be completed before this can be accepted, such a breakthrough would have remarkable consequences. The stage would be set for "growing" normal body linings (such as blood vessel linings) within the artificial materials and the impact of possible partial or whole organ regeneration would be dramatic indeed. (The example is illustrative of how basic scientific findings in one field could hold sweeping consequences for many other important undertakings.)

In view of the complex of problems that will have to be solved before any prosthesis or transplant procedure becomes feasible, the Heart Institute will continue to fund a few highly selected comprehensive programs and a variety of carefully planned smaller projects.

SPECIAL RESEARCH PROGRAMS

Cardiovascular Research and Training Centers. No Cardiovascular Research and Training Centers have yet been activated. However, planning activities in 14 institutions were continued in 1969. Four of these institutions have been engaged in planning for more than three years, six for two years, and four for approximately one year.

The independent thinking, evaluation, and planning at these 14 academic settings has resulted in a variety of concepts and ideas. However, there are certain emphases that are common to all. Taken as a whole these emphases illuminate those elements of a "Center" that are felt to be most significant by the academic community:

1. High caliber research under strong leadership is felt not only to provide the background for future prevention of heart disease, but it also provides the setting within which future researchers may prepare for their careers. Furthermore, a quality research program has very beneficial effects on the recruitment of faculty and students.

2. The need for collaboration among a wide variety of scientific disciplines is widely accepted. The development of traditional departmental and discipline lines is recognized generally as a deterrent to the kind of cooperation needed to comprehend and resolve the very complex problems of heart disease. To encourage development of well-functioning scientific "groups," most of the academic institutions are planning to organize themselves along programmatic lines.

3. All the institutions engaged in planning seem to agree that a clear administrative structure is necessary. However, as is typical for academic institutions, much of the decision-making would be decentralized and great use would be made of group processes rather than centralized authority. Naturally, there is hope that the

programmatic elements will engage in free communication and that departmental parochialism will be reduced. Included in all plans then is the objective of deliberate and local scientific evaluation. In this vein most of the planning programs give considerable attention to the possible functions of an outside board of visitors which would periodically evaluate the Center program.

4. There is considerable uncertainty about the relationship of a possible Cardiovascular Research and Training Center to other Federally-supported programs such as the Regional Medical Programs. Provisions for the continuing education of practioners are also prominent goals of these institutions. However, because there is uncertainty as to which Federal programs may be in a position to fund these diverse activities, the question of how they may be included in the Center program remains unresolved.

5. It is recognized that the leadership of the Cardiovascular Research and Training Center must be outstanding and the program must have the absolute commitment of the local academic community. These are critical elements for any Center.

6. There must be long-term and stable support. This, clearly, is crucial. Academic institutions will be reluctant to allocate the necessary resources without such assurances.

7. Most programs could not get underway without extensive renovation of existing space or considerable new construction of research and patient care facilities.

There is much to recommend the early activation of a highly-selected number of strong Centers.

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. Furthermore, 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 entering its fifth year of operation, with 53 participating clinics, including large medical centers, small private clinics, private and community hospitals, and V.A. and PHS hospitals. Approximately 6,700 patients have been entered into the study to date. While recruitment was slow in the early stages, the investigators have taken steps to overcome this by a widespread publicity campaign, and it is hoped that close to the full complement of 8,400 patients will be recruited by June 1969.

Study leaders and Heart Institute staff are actively involved in the review and evaluation of the performance of all participating clinics, and the continuing surveillance of trends in the clinical and laboratory data. This well-designed study continues to progress and should have an important impact on clinical care.

Other Cooperative Studies

The Cooperative Study of Extracranial Arterial Occlusion has been evaluating the effects of surgical versus non-surgical treatment on length and quality of survival in patients with operable occlusive lesions in extracranial arteries supplying the brain. The study now includes 11 clinical units and the final accrual of patients should be completed in June 1969. Totally, over 7,500 patients have been studied; about 1,300 have been randomized to date. A close clinical association of stroke with hypertension, diabetes, and heart disease is increasingly evident. Transient ischemic attacks portend future stroke. Surgery entails a high risk if performed within twenty-four hours of angiography or within ten days of a catastrophic episode. The investigators plan to follow their patients for two years following the accrual of full patient complements, and some of the early data from the study are now being published in appropriate journals.

The Cooperative Study of Renovascular Hypertension has been in full operation since 1963, in fifteen clinical units plus four laboratories for central evaluation of data. New patients were admitted to the study through August 1967, and the eleven remaining clinics will complete follow-up activities in August 1969. Support for the Coordinating Center has been recommended through August 1971, to complete analysis of results. Of twenty-four hundred patients with hypertension suspected to be of renovascular origin, only one-quarter have clear evidence of renal arterial obstruction. Of these, about 500 have had definitive surgery. Within a hard-core of 330 patients with renovascular lesions confirmed by surgery, complete physiological records, and at least one year of follow-up, the ratio of cures of hypertension to failures has been 2:1.

The Cooperative Study of Results of Cardiac Surgery was begun in 1966, and has support recommended through May 1970. Six groups of surgeons and their associates in cardiology, radiology, and pediatrics, have studied over 2,000 patients in 30 months, with extensive physiological and anatomical studies to obtain data pre-operatively and periodically after discharge. Surgical mortality for all lesions and in all units has been appreciably higher than that previously reported by these and other investigators. Post-operative morbidity and late mortality are under scrutiny.

A Cooperative Study of Renal Disease and Hypertension is attempting to determine the efficacy of long-term suppressive antibacterial therapy in chronic pyelonephritis; to characterize the pathogenesis and natural history of this disease; and to delineate more precisely the relationships between pyelonephritis and hypertension. Studies involving about 250

patients suggest that one primary objective of this study has been met. The data indicate that antibiotic therapy is effective in eliminating bacteriuria in patients with chronic urinary tract infection, and that subsequent control of bacteriuria can be achieved with acidifying regimens and nitrofurantoin. Also, it seems that renal function is significantly improved in those patients who do respond bacteriologically to chronic therapy. Renewed support recommended this past year will allow the investigators to accumulate additional information concerning relationships between bacteriuria, renal function, and hypertension.

A Cooperative Study of the Natural History of Congenital Heart Disease is now well into its fourth year. The investigators hope to characterize the clinical outlook for patients with either of three common forms of cardiac anomalies. The study involves five pediatric cardiology groups and a statistical coordinating center. Diagnostic cardiac catheterization data have been obtained on eight hundred patients between July 1958 and June 1965 and now annual follow-up, with re-catheterization at an eight-year interval, will provide information on anatomical and physiological changes in these patients over time. Seven hundred new patients, diagnosed and admitted prospectively since July 1966, are also being studied and followed in the same way. The investigators have recently instituted a system for telephonic transmission of vectrocardiographic patterns direct from each clinical unit to a central facility at the Mayo Clinic.

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 third year of full operation and has succeeded in entering over 3,000 patients, with over 90 percent retention of subjects after six months of follow-up. The incidence of symptomatic hepatitis is now under 5 percent. The results of this clinical trial are under careful and continuous scrutiny, with comparisons now being made between results from use of batches of Red Cross globulin, a commercial preparation presumably higher in hepatitis antibody titer, and a third batch of hyperimmune globulin being tested in one large medical center.

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, pulmonary, and renal scientists, teachers, and clinicians.

Undergraduate training grants are awarded to Schools of Medicine and Schools of Osteopathy to improve teaching in the cardiovascular, pulmonary, and renal disciplines. The Institute now supports 94 of these programs in Medical Schools, 5 in Schools of Osteopathy, and 13 in Schools of Public Health. The National Advisory Heart Council has recommended, however, that the program in the Schools of Public Health not be continued

beyond the present commitment and that these Schools be urged to utilize graduate training grants for their needs.

Two types of graduate training programs are supported by the Institute. One is the Research Training Program designed to prepare scientists for a career in investigation. The second, a Clinical Training Program, is designed to train physicians for patient care. Grants to support these programs are made to medical schools, universities, and other research-educational organizations. These grants assist the institution in providing high quality educational and training opportunities. Their goal is to satisfy the need for investigators, and also the demands of the community for utilization of the product of the research laboratory in the care of patients with cardiovascular, pulmonary, and renal diseases.

The Institute currently supports 198 research training grants and 79 clinical training grants. There are currently funds for 1,190 trainees in the research program, and 297 trainee positions in the clinical program.

Fellowships and Career Development Awards. The two primary objectives of the fellowship 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 and related fields. 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.

The Career Development Award Program is designed to provide stable career opportunities for scientists with outstanding potential and competence in cardiovascular, pulmonary, and renal 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.

The maximum salary permitted to be paid from the Career Development Award is $25,000. Due to the fact that academic salaries have risen sharply since this program was initiated, however, policy was recently changed so that institutions may now supplement the Career Development Award salary from non-Federal sources.

During FY 1969 the maintenance of a well-balanced cardiovascular research and training effort has been accomplished despite serious difficulties. Budgetary and personnel restrictions have imposed serious hardships.

To avoid arbitrary, across-the-board reductions in research grant awards, the professional staff negotiated budgets with prinicpal investigators and their grantee institutions on an individual basis. These negotiations, based upon need, scientific program content, research opportunity, and administrative considerations served to distribute the impact of the financial curtailment while the national research effort made optimal use of the resources available. During the latter portion of the fiscal year, the Institute staff, once again on an individual grant basis, was able to restore funds to many of these grants.

The number of research grant applications continued to decrease while applications to non-Federal agencies increased at a remarkable rate (e.g., the American Heart Association experienced a 70% increase in research grant applications). Furthermore, it has become apparent that the duration of NHI grant awards (the length of the project period) has decreased significantly. In 1964, 82% of new research grant awards had a project period of three years or less while the remaining 18% were for more than three years. In FY 1969, however, 92.4% of new awards had a project period of three years or less and only 7.6% were for more than three years. This will, in the long run, add a heavy burden to the NIH review system.

During the past year the Institute launched an intensive analysis of the research grant program on a more categorical basis. Thus, the National Advisory Heart Council has received additional information concerning research activities in several cardiovascular disease areas and grant applications are now presented to the Council in terms of eleven disease areas. This is part of a continuing activity on the part of staff and Council. As part of this overall effort, a number of particular activities are underway: special meetings of the Council to discuss program content and directions; special staff reports; the establishment of several advisory committees, panels, and task forces to examine certain areas or problems and to make recommendations. In the past year special emphasis has been given to pulmonary diseases, coronary artery disease, diet and heart disease, and cerebrovascular disease.

With regard to the development of Cardiovascular Research and Training Centers, this program has been hampered by the lack of additional funds; grant-supported activities have been limited to analysis and planning. The Institute staff and its advisory groups have taken advantage of this delay to re-examine the concepts and guidelines of the Center Program.

In the area of training, there are urgent, large, unmet needs for well-trained cardiovascular clinicians. The Heart Institute's Clinical Training Program has not been able to proceed beyond its initial phase--the training of clinical teachers and academicians. The necessary

second phase will be the training of highly-qualified physicians who have received specialized training in cardiovascular diseases and who intend to practice in the community.

An analysis of the Institute's Undergraduate Training Program is underway. In addition, a study of Institute-supported research trainees is now nearing completion.

Due recognition must be given to the staff of the Extramural Programs who have, in very adverse circumstances, continued to provide a remarkable degree of insight, efficiency, and service to the public and scientific community.

DATE DUE