ANNUAL REPORT
OF
PROGRAM ACTIVITIES

DIVISION OF RESEARCH GRANTS
DIVISION OF RESEARCH RESOURCES
DIVISION OF RESEARCH SERVICES

FISCAL YEAR 1973

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

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U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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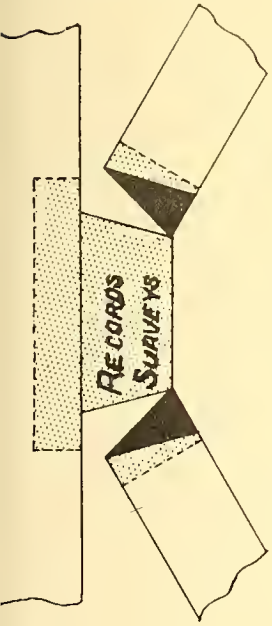

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HIGHLIGHTS

The Director and Deputy Director attended several national meetings to keep open the lines of communication between NIH and the biomedical research community.

The Office of Research Manpower was established as the successor to the Career Development Review Branch to provide central services pertinent to the phaseout of training programs.

A series of eight seminars has been held to keep staff abreast of key aspects of the extramural programs.

The campaign to recruit women and minorities to serve on the study sections continued throughout the year. As a result there are now 34 more women and nine more minority group members serving than at the end of May 1972.

The Division continued to be actively involved in the EEO program and the provisions of the NIH Affirmative Action Plan.

The new NIH exhibit of NIH support programs had its first showing in April at the FASEB meetings.

The conversion of the former PHS institutional general assurance system for the protection of human subjects instituted in 1966 to the broader institutional assurance system required by DHEW policy issued in 1971 has been substantially completed.

The NIH policy on proper care, use, and treatment of laboratory animals was redrafted by Division staff to conform with proposed Departmental requirements.

A total of 24,083 research grant applications were processed, of which 14,500 were assigned for technical merit review.

There was a slight increase in the number of training applications of all types received and processed during the period April 1972-March 1973, from 10,933 to 11,087. Fellowship applications increased from 4,019 to 4,354.

A report on the Special Session entitled, "The Project-Grant Application of the NIH," presented at the April 1972 meetings of FASEB has been published in the Federation Proceedings, Volume 32, No.5, May 1973.

During the year, 336 employees completed training courses of all types.

Six Grants Associates graduated from the Grants Associates Program. The Executive Secretary undertook a recruiting campaign for potential associates during the April meetings of FASEB and interviewed 67 scientists.

A study was undertaken to streamline the current method of monitoring scientific evaluation grants so that more meaningful data can be provided to meet Division needs.

A report on support of new principal investigators of NIH research projects has been accepted for publication in Science.

Twelve reports were prepared analyzing NIH support of various biomedical disciplines and special areas of research.

A MEDLINE terminal was established in the Division to provide capability for automated searches of biomedical literature for I/D staff in the Westwood Building.

Implementation of a microfiche program to replace cumbersome line item listings now in use in the Data Capture and Control Unit is expected to be fully operational in FY 1974.

OFFICE OF THE DIRECTOR

In a continuing effort to keep open the lines of communication between NIH and the scientific community, the Director attended a number of national meetings during the year under review.

Among the meetings in which he participated were the Workshop for New Graduate Deans, August 7-12, 1972, sponsored by the Council of Graduate Schools at Colorado State University, Fort Collins, Colorado; the Association of Independent Research Institutes Annual Session, September 13-15, 1972, Buffalo, New York, at which he presented current highlights from NIH; the Graduate School, University of Hawaii, Honolulu, Hawaii, January 29, 1973, at which he spoke on "Grantsmanship"; and at the Northeastern Regional Meeting of the Group on Business Affairs of the Association of American Medical Colleges, May 13-17, 1973, at Kiamesha Lake, New York, at which he spoke on what is happening at NIH as part of the "Washington scene."

The Director also attended the meetings of the American Council on Education, October 4-6, 1972, and the Association of American Medical Colleges, October 30-November 6, 1972, both at Miami Beach, Florida; the First Annual Session of Deans of Graduate Study in Medical Centers, November 29-30, 1972, in New Orleans, La.; the Council of Graduate Schools Annual Session, December 1, 1972, also in New Orleans; the Western Regional Group on Business Affairs of the Association of American Medical Colleges, January 23-February 1, 1973, in Honolulu, Hawaii; and the Western Association of Graduate Schools Annual Session, March 2-7, 1973, in San Diego, California.

The Deputy Director attended the annual meetings of the Association of American Medical Colleges, November 1-6, 1972, in Miami Beach, Florida. On November 20, 1972, he met with the faculty and graduate students of Meharry University, in Nashville, Tennessee; and on February 22-23, 1973, represented the NIH at meetings of the Midwest and Southern Regions of the Group on Business Affairs of the Association of American Medical Colleges in Washington, D.C. The Deputy Director also participated in a seminar at the University of Maryland School of Medicine, December 13, 1972, in Baltimore, Maryland; and in seminars for graduate students and faculty of Southern Illinois University, March 7, 1973, in Carbondale, Illinois, and of the University of Illinois, March 8, 1973, in Chicago, Illinois, and on May 25, 1973, at Southern Illinois University at Edwardsville, Illinois.

The Career Development Review Branch was abolished in May 1973, following the termination of new awards in the various NIH training programs. To administer the phaseout operation, to provide an information source on the programs, as well as to keep abreast of biomedical training needs, the Office of Research Manpower was established within the Office of the Director, DRG.

Several members of the staff continue to work with the Office of the Associate Director for Extramural Research and Training, NIH, in preparing materials for use in the grants programs; for example, revising instructions to adapt current application forms to new policies, NIH implementation of OMB Circular A-102, and procedures for complying with the Federal Advisory Committee Act.

The Deputy Director has served on the ECEA and its subcommittee on training; the Manpower Impact study group; the study group on the Protection of Human Subjects in Research; and the task force on Recommendation 2 of the NIH Program Mechanisms Committee.

Nine members of the Division staff participated in the first collaborative/Extramural Program Retreat held at Airlie House, Warrenton, Virginia, March 29-30, 1973. They represented the Division on five of the six workgroups organized to study major issues in depth. The Deputy Director attended the Retreat as an observer.

Eleven staff members participated in the second Retreat, May 30-June 1, 1973, in Fredericksburg. The Director attended as an observer.

Eight staff members will participate in the retreat to be held at Airlie House in June 1973.

The Director initiated a series of seminars, principally for executive secretaries and senior staff members, to keep them informed on key aspects of the extramural programs. Eight presentations have been given since November 1972: Dr. Leon Jacobs spoke in November on the NIH Collaborative Programs; Dr. Ernest M. Allen and some of his staff, in December on the functions of the DHEW Office of Grant Administration Policy; Dr. Milo D. Leavitt and others from FIC, in February on the programs of the Fogarty International Center and their relationship to the overall extramural programs of the NIH; Dr. William H. Goldwater reviewed the recommendations of the Cooper Committee on NIH program mechanisms with the group in March; Dr. J. Palmer Saunders, in April, described the programs of the National Cancer Institute. Two seminars were held during May. The first was a presentation by Dr. Richard Phillipson and Dr. Robert C. Petersen on the work of the Division of Narcotic Addiction and Drug Abuse, NIMH. The second was a discussion led by Dr. John Sherman on the future of the peer review process and the role of the consultants. In June, Dr. Charles McPherson spoke on Animal Resources: Their relationship to research quality and research funding.

The Director appointed a committee, including two members of his own staff, to study the use of Scientific Review and Evaluation grants to determine if more effective, efficient, and economical use can be made of the funds available.

A campaign to recruit women and minorities to serve on the DRG study sections was initiated mid-year by the Director. Over 600 letters were mailed out to study section members; and FASEB as well as Biomedical News ran a notice asking for all qualified readers to send in their own c.v.'s. Although it is too early to see the long-term results of the campaign, the number of women now serving on the study sections has increased since May 1972 from 26 to 60, and for all minorities from 12 to 21. Files of several hundred curriculum vitae are being maintained in the Division for future reference and two lists of available women scientists have had wide circulation.

As in past years, the Division experienced difficulties in the recruitment of lower grade personnel. A contributing cause is the location of the

Westwood Building and the lack of easily accessible public transportation. The lack of a full range of employee services in the Westwood Building also is a deterent.

In accordance with the provisions of the NIH Affirmative Action Plan, a program of regularly scheduled visits by representatives of the Guidance and Counseling Branch, Office of Personnel Management, was begun in the Westwood Building. Such visits by the representatives afforded DRG employees an opportunity to seek guidance and counseling about career opportunities and training in addition to that obtainable from supervisors and/or members of the DRG Personnel Office.

The Division's formal employee training program continued to grow at a steady pace, continuing the trend begun several years ago. At the present time, 24 employees are attending Federal City College under the Upward Mobility Program. During the year 773 requests for all types of training courses were initiated by employees of which 484 were approved, resulting in 336 completions. In addition to Federal City College, training was provided at the National Institutes of Health and through facilities provided by other interagency programs or non-Government organizations.

During the reporting period, nine members of the Office of the Director received cash awards for superior performance of duties.

The Opportunity Program Committee (TOP) conducted a survey of Division employees on the feasibility of establishing a liaison branch of the NIH Credit Union in the Westwood Building. Response to the survey was favorable and plans for the branch were formulated and negotiated with the NIH Credit Union Board. The Westwood Branch became operational in May 1973.

The Committee initiated dissemination of information through the DRG Personnel Items on the availability of personnel folders, both official and unofficial, for examination by the employee.

Efforts have continued with the Personnel Office staff to consider publication of a pamphlet, or alternatives, to describe the functions of the Personnel Office as they relate to employees and to management.

In December 1972, the Committee met with the Civil Service Commission's EEO survey team during their review of DRG's EEO program.

The Committee sponsored a film showing of "Uptight -- Black and White." It was well attended by DRG staff.

The DRG Equal Employment Opportunity Counselor was appointed for an additional 2-year term. To increase the Counselor's knowledge of EEO, three training courses were attended: Personnel Management for EEO, and two workshops on EEO counseling sponsored by the NIH/EEO Office.

Approximately 75 employees were counseled during the year. Not all of the problems were related to the five areas of EEO responsibility, neither were they all problems of DRG employees. NIH employees are free to consult any

NIH-EEO counselor.

A meeting open to all DRG employees was held by the Counselor to discuss the role of the EEO Counselor in the Division.

The Counselor continued to be active in the EEO Council during the period under review.

GRANTS ASSOCIATES PROGRAM

The Grants Associates Program graduated six associates during fiscal year 1973, all of whom remained with the National Institutes of Health. Six new associates were appointed bringing the number of associates assigned to the program during the year to twelve.

In April 1973 the Executive Secretary and two of the current associates attended the Federation of American Societies for Experimental Biology meetings in Atlantic City, N.J. For the Executive Secretary this was a recruiting trip for potential associates in FY 1975. Sixty-seven scientists were interviewed and 25 application kits were distributed. Approximately 200 job seekers asked to discuss possible employment.

Interest in the program is still at a very high level, much of it stimulated by the current economic situation resulting in reduced opportunities for scientists in industry and academia. As of April 30, 1973, the Grants Associates Office had processed 460 inquiries regarding the program, and 215 applications. Twenty-six applicants were considered by the Grants Associates Board. Five accepted an invitation to join the program.

The Grants Associates Office continues to be involved in the placement of applicants in direct hire positions. As in the past, emphasis has been on the referral of minorities and women.

INFORMATION SECTION

Pursuant to P.L. 92-463, the Information Section has been mailing on request summaries of closed study section meetings and rosters of committee members. Since the policy came into effect, 21 requests have been met for two rounds of study section meetings.

A new self-contained exhibit of NIH support programs had its first showing in April at the Federation of American Societies for Experimental Biology in Atlantic City, N.J. The plan for phaseout of NIH research training programs, and increased interest in contract support, generated numerous inquiries at the Exhibit, which was visited by approximately 3,000 persons who requested more than 2,000 pieces of literature during the 5-day meeting.

Questions posed by approximately 90 institution representatives who visited the Information Section during the year centered on policy. Their questions related to the ethics of submitting the same proposal as a grant and a contract, and whether such practice might be detrimental to approval through either mechanism. Concern was expressed over reduced funding after schools had made their programs out for the year--a situation worsened on some campuses by union enforcement of salary increases for laboratory technicians. The possibility of new applicants enhancing their chances of approval through affiliation with their peers on a program-project was also among the many issues raised.

Students have been actively inquiring about alternative sources of financial assistance for their studies now that fellowship and training grant funds are no longer available. The most the staff has been able to do is refer them to the Dean's office of their school to inquire whether the school participates in any student loan or scholarship programs or has funds available to provide financial aid to needy students.

The Section undertook a number of manual searches, in addition to those referred to the Research Documentation Section for computer runs, on support of research in specific States and institutions, and for research projects of individual investigators. Requests for data on categorical areas of research and specific disease entities were numerous. There has been an increased interest in support of research on the use of computers in diagnosis, amyotrophic lateral sclerosis, abortion, and use of the fetus in research.

Demand for the brochure, Guide to Grant and Award Programs - National Institutes of Health, has continued high. A revision is being prepared to take into account the elimination of training programs, the transfer of the Bureau of Health Manpower Education and its programs to the new Health Resources Administration, and NIMH's re-entry into the NIH family.

ADMINISTRATIVE BRANCH

A study was undertaken to streamline the current method of monitoring the scientific evaluation grants, so that meaningful data can be provided to meet Division needs. Based on this study, a new system is expected to become operational on July 1, 1973.

The Reference Room Committee, established initially to advise the DRG Director, now advises the Administrative Branch Chief on requirements for reference materials. An inventory of major items available in the Reference Room and proposed acquisitions was circulated by the Committee to the DRG staff for comment. On the basis of the responses, changes have been introduced to increase and maintain the usefulness of the Reference Room for NIH staff in the Westwood Building.

The DRG Mail Room received and processed approximately 25,000 research grant applications; 292 NLM grant applications; and 11 construction grant applications; and a large volume of supporting documents, letters, and publications.

The Office Services Section compiled and handled an average of 9,000 grant application kits of all types and mailed 9,500 miscellaneous packages a month during the period under review. The Section also provided planning and assistance in accomplishing several major moves within the Division; acquired and maintained equipment, furniture and supplies, and provided printing services for Division personnel.

The Special Services Section continued to provide typing and repetitive typing assistance for DRG and NIH institute/division staff. Repetitive typing assistance (automatic) decreased slightly to approximately 4,000 jobs. Typing assignments included approximately 250 summary statements, 200 statistical tables, and 170 assurance letters, as well as the preparation of several booklets and papers for publication. Section personnel have assisted in the Upward Mobility Program by giving individual typing instruction to several Division personnel. This program will continue.

CAREER DEVELOPMENT REVIEW BRANCH

As a result of the phaseout of the NIH research training programs, the Career Development Review Branch (CDRB) was abolished, effective May 8, 1973. All CDRB employees were transferred to appropriate existing vacancies within the Division of Research Grants. At the same time, the Office of Research Manpower was established in the Office of the Director, DRG, to administer the training program phaseout operation and to serve as the key informational source on NIH research training programs. The following is a report of the activities of the Career Development Review Branch before its abolition.

Receipt and processing of all types of applications during the 12-month period, April 1972 through March 1973, increased slightly from 10,933 to 11,087, an increase of less than 1 percent. The competing applications during this period increased 10 percent from 5,162 to 5,791. The noncompeting applications decreased 8 percent from 5,760 to 5,296. The fellowship program experienced the greatest growth in numbers of applications--8 percent from 4,019 applications to 4,354 despite a decline of 22 percent in predoctoral applications from 953 to 742. Of the total applications received in CDRB, 33 percent (3,630) were directed to the Health Services and Mental Health Administration.

During the year, the Branch streamlined its processing and data capture procedures. Greater reliance was placed upon SAB printouts.

Research Career Program

As of March 31, 1973, the NIH Research Career Program had 1,131 awardees on duty. This is an increase of 14 awardees over March 31, 1972. The greatest change within the awardee group occurred in the original research career development program (K3), where there was a drop of 57 percent (409 to 175 awardees). This program stopped making new awards in 1967. The number of awardees in the different award categories as of March 31, 1973 is as follows:

Research Career Award (K-6)	128
Research Career Development Award (K-3)	175
Modified Research Career Development Award (K-4)	794
Academic Career Development Award (K-7)	23
Clinical Investigator Award (K-8)	11

A revision of the policy brochure for the modified Research Career Development Award (K-4) was initiated.

Training Grants

The Deputy Branch Chief chaired a drafting committee to revise the training grants policy statement last issued July 1, 1967. The new policy

brochure dated December 1, 1972, was immediately disseminated to all institutions, training grant program directors, and others.

Computer assistance in the actual processing of Type 5 training grant applications is underway. This involves preparation by the computer of listings and mailing labels for Type 5 mailouts. The Coordination Section has continued to acquire fiscal data from Training Grant Award Statements. This data relating to the categories of costs appearing on the award is not captured by SAB; therefore, CDRB is the only source for NIH-wide data. The section now has comparable data from 5 fiscal years available for inquiry and analysis.

Fellowships

The Fellowships Coordination Section audited approximately 613 Predoctoral Report of Expenditure forms for NIH and NIMH resulting in a saving of $8,346 that otherwise would not have been returned to DHEW.

The Reference Data Book on NIH Research Fellowships FY 1972 was revised for this fiscal year's operations. This book contains 36 various statistical reports comprising 54 pages. The booklet, Research Fellowship Awards for Study Abroad was compiled and issued as of September 30, 1972. This booklet is distributed to U.S. Embassies, the State Department, and other Government agencies. As a result of the phaseout of the fellowship programs and the resulting decrease in the number of awardees going abroad, this document will no longer be prepared.

Phaseout

The Branch served as the focal point within NIH for the phaseout of the training programs. Sample letters were developed and approved by ADERT for use in notifying awardees and applicants about the phaseout. All participating institutions in the training programs received a bulletin addressed to the coordinating official notifying them of the termination of the programs and furnishing additional administrative details of continuation of committed grants/awards.

INSTITUTIONAL RELATIONS BRANCH

The prime endeavor of the Branch at this time is administration of the Department of Health, Education, and Welfare policy on protection of human subjects. Other obligations include establishment of eligibility to serve as a grantee; establishment of eligibility for waiver of equipment accountability under PL 85-934; negotiation of successor in interest agreements, liaison with OS-DHEW with regard to responsibilities under Title VI of the Civil Rights Act; and central administration of the NIH policy on animal welfare. In addition, IRB is conducting a pilot study in institutional distribution of renewal applications. The Branch also continues to publish the Notice of NIH Conferences and the NIH/DRG Newsletter.

Protection of Human Subjects

IRB has substantially completed conversion of the former PHS institutional general assurance system instituted in 1966 to the broader institutional assurance system required by DHEW policy issued in 1971. This required renegotiation of some 650 surviving general assurances submitted by major grantees, while simultaneously reviewing a steady stream of single-project special assurances received from grantees and contractors with only a few active projects involving human subjects.

The Branch has rewritten the present policy for issuance in the Federal Register and ultimate promulgation as part of the Code of Federal Regulations. Simultaneously IRB is developing a draft Federal Policy at the request of the Assistant Secretary for Health. Discussions have taken place with several Federal agencies at the operational level and other agencies will be contacted as the policy is developed. Efforts of the Branch have been directed towards coordinating the implementation of the policy by all DHEW agencies and of informing DHEW grantees and contractors of decisions made by the Director, NIH, on behalf of the Office of the Secretary, HEW. IRB's primary function in this regard is to provide assistance, as requested, to all agencies of the Department in developing implementation and enforcement guidelines for the policy.

Plans are underway to meet with a number of grantee institutions throughout the country to survey the systems employed for compliance with and implementation of the policy.

Care and Treatment of Laboratory Animals

As required by Under Secretary Veneman's directive of February 23, 1972, the Branch has collaborated with other DHEW elements in the development of a DHEW issuance, which shortly will become official policy of the Department. Simultaneously,the Branch has revised the existing NIH policy to make it conform with Departmental requirements. Coverage is extended to all warm-blooded species, and awarding components will not be permitted to provide support for protocols that include the improper use of animal subjects. Institutions or individuals that persist in the performance of unacceptable procedures may be declared ineligible to receive further DHEW support for research on animals.

Currently the Branch has received acceptable assurances of compliance with present NIH policy from 608 institutions. These represent essentially all of the institutions that use animals in NIH-supported activities. The revised policy requirements will require only minor modifications in existing assurances. They will be applicable to activities supported by DHEW elements other than NIH.

Pilot Study to Improve the Speed of Handling Renewal and Continuation Applications

The study to examine the feasibility of routing renewal and continuation application kits through one control point was started in October 1970. Three institutions participated in the original study. At present there are 36 major institutions participating in the program and another 10 have indicated interest and are developing internal procedures for early participation.

Plans are being developed for a follow-up study to determine the specific benefits derived from the "pilot study," and to consider the recommendation that applications be routed through a central point in all grantee institution

Equipment Accountability

The provisions of PL 85-934 were fully implemented during 1972. A listing consisting of approximately 1200 grantee institutions that are NOT eligible for Waiver of Equipment Accountability under the Public Law, was published and distributed to the institutes and divisions whose programs were included under PL 85-934.

Eight major grantee institutions classified as NOT eligible for Waiver of Equipment Accountability have submitted detailed documentation as requested in an effort to establish eligibility as a nonprofit organization whose primary purpose is the conduct of scientific research. After a careful review of this documentation, four of the institutions clearly established their eligibility under PL 85-934 for Waiver of Equipment Accountability.

NIH/DRG Newsletter

The Newsletter represents a communication media directed to NIH grantees and contractors. It elaborates on policy requirements, transmits information about NIH-sponsored programs, and makes known personnel, location, and organizational changes. It also provides general information necessary to institutions in performance of functions relating to NIH.

The Division now has the responsibility for maintaining a mailing list for distribution of the NIH Guide for Grants and Contracts. The mailing lists for the Newsletter and the Guide have recently been combined.

Safety

IRB's function regarding laboratory safety is essentially that of providing assistance as requested where an application appears to involve ethical problems or hazardous procedures that require some resolution prior to award.

RESEARCH ANALYSIS AND EVALUATION BRANCH

During 1973 the Research Analysis and Evaluation Branch emphasized studies analyzing the support of new principal investigators (P.I.'s) of NIH research projects. A report on this subject, begun in the previous year, has been accepted for publication in Science. Data from the study showing the rate of entry of new P.I.'s over the last 7 fiscal years and other indicators of flux in the research project grant system were used in briefings for NIH-OD. Growing out of this report several studies relating to principal investigators were begun:

- Survival rates of grants and investigators from the FY 1966 cohort of new P.I.'s.
- Linkage of FY 1972 cohort of new P.I.'s with prior research training support.
- Degrees held by principal investigators and by subproject leaders.

The FY 1973 and 1974 research grant budgets were analyzed in relation to competing and noncompeting funds. Ratios of noncompeting to competing awards have tended to fluctuate within a tolerable range, but during years of abrupt changes, up or down, in the research grant budgets, aberrations may occur which cause problems in the administration of extramural research programs. The sets of ratios may serve as indices to indicate troubled areas and to spot possible inappropriate budget projections for the future.

Reports analyzing the NIH support of various biomedical disciplines as well as reports estimating support of special areas of research during FY 1972 were:

- FY 72 Awards to Schools of Pharmacy
- Estimate of NIH Research Grant Support for Chemistry
- Grants and Contracts in Bioengineering
- NIH Support of Research in Departments of Chemical Engineering
- Estimate of NIH Support of Research in Immunology - R, P and N Programs
- Health Care Technology
- Emergency Medical Services
- Biomechanics Research
- NIH Support of Phage Studies and the Origins of Molecular Biology
- Nuclear Medicine Research

- Marine Research

- NIH Support of Research in Hematology

The "phage group" study was initiated in response to a suggestion by the Associate Director for Program Planning and Evaluation. The report entailed the amount of NIH funding for early phage investigators and for investigators during the development of a new scientific discipline, molecular biology (1938-65). It was found that 60 investigators conducting research on bacteriophage and biological self-reproduction were supported by NIH grants. The data show that the NIH system of selection of research project awards accommodated the emergence of a new scientific specialty by supporting the kinds of research and novel ideas proposed by scientists in the field. The amount of support provided to phage investigators grew steadily and at a rate averaging higher than the rate of increase for other recipients of NIH research grants.

A study on the NIH Support of Research in Immunology included data on research grants, program projects and contracts. The report delineated seven divisions of research interest in immunology and described the research activities of each. NIH awarded approximately $70 million for immunology research in FY 1971. Nearly $14 million each went for contracts and program projects, while research grants received $41 million.

As a service to scientist administrators and BID staff in the Westwood Building, a MEDLINE terminal was established in RAEB which provides capability for automated searches of the biomedical literature based upon NLM's Medical Subject Headings. Searches can also be made by authors, journals, and specified periods of time.

The Research Analysis and Evaluation Branch continues to code all research contracts according to the Central Scientific Classification System. Staff members have begun to write new purpose codes for contracts to reflect current usage of this instrument of support. An operational definition of development will be devised to differentiate between research and development in the contract program. Beneficiaries of the Branch effort in CSCS coding are the IMPAC system, CASE reports, and Federal Fields of Science annual reports.

Two employees are attending Upward Mobility College and one Project Stride trainee is assigned to the Branch. Several members of the RAEB staff took advantage of training courses at DCRT and other offerings by NIH training programs.

RESEARCH GRANTS REVIEW BRANCH

The Research Grants Review Branch received, referred, and reviewed a larger number of applications than in the previous fiscal year. Competing and non-competing applications processed by the Branch during the year totaled 24,083. Of the total, about 14,500 were assigned for technical merit review. Of these competing applications, about 77 percent were assigned to the NIH. The Branch provided the initial scientific review for approximately 88 percent of the NIH competing applications.

A table showing the distribution of applications processed in fiscal year 1973 is appended to this report.

In the current fiscal year, one new study section, Visual Sciences B, was added to share with Visual Sciences A Study Section responsibility for reviewing the large number of applications in the visual sciences field. Another change in the study sections was the renaming of Pharmacology B Study Section to Experimental Therapeutics Study Section to indicate more accurately the scientific subject matter of applications reviewed by this study section.

The Special Study Section reviewed new types of applications received as a result of the initiation by various institutes of the following programs: genetic disease centers, diabetes-endocrinology centers, peptic ulcer centers, and acupuncture.

A published report of the special session entitled, "The project-grant application of the National Institutes of Health", presented at the April 1972 meeting of the Federation of American Societies for Experimental Biology, appears in the Federation Proceedings Vol. 32, No. 5, May 1973. The introduction, and one of the papers, "The grant application: an exercise in scientific writing," were written by Dr. George N. Eaves, a member of this Branch until April 1973. A second paper, "Preparation of the project-grant application: assistance from the administrator in charge of a study section," was presented by Dr. Helen Hofer Gee, who was a member of the Branch staff until July 1972.

The Branch revised two of its publications this year. The Handbook for Executive Secretaries, Third Edition, came out in February 1973, and the current Orientation Handbook for New Members of Study Sections in April 1973.

Within tight budget and personnel limitations, the study sections sponsored and conducted a reduced number of workshops and conferences to survey the status of research in their areas, enhance reviewer competence, and stimulate research in neglected areas. Two workshops were held in the fall of 1972.

The first of these, "Human and Zoonotic Filariasis: Current Concepts and Directions of Future Studies", was held in New Orleans, Louisiana, on September 13, 1972. It was sponsored by the Tropical Medicine and Parasitology Study Section, the Geographic Medicine Branch, NIAID, and the Tulane University School of Public Health and Tropical Medicine. Thirty-eight conferees, members of the study section and of the U.S. Japan Panel on Parasitic Diseases as well as faculty members and graduate students of Tulane University and Louisiana State University met to consider current concepts, research directions and knowledge of human and zoonotic filariases. As a result of the in-depth review provided by the several presentations and discussion periods, certain problems in this field were highlighted for clarification with identification of topics that require immediate intensive study. The workshop explored the status of research on four aspects of these medical problems: (1) the disease in man and animal caused by human or zoonotic species of filariae and the pathology associated with these parasites; (2) animal models available or needed for study of infections with Brugia spp. or other filariae; (3) immunology and drug responses in infections with filariae; and (4) newer concepts of vector-parasite-host relationships.

The second fall conference, "Use of Accelerated Particles in Radiation Therapy", took place October 2-3, 1972, in Los Alamos, New Mexico, under sponsorship of the Radiation Study Section, the NCI, the National Science Foundation, and the Atomic Energy Commission. About 200 participants met to define the state of the art of the uses of accelerated particles in medicine; to determine the gap areas in which there is need for progress; and to attempt to develop programs and solutions for the understanding and implementation of the potentials for improved medical care by the use of such particles. A report of the conference is being prepared for publication in the Journal of Radiology.

The meeting was divided into five half-day sessions on the following subjects: (1) biomedical problems--nature of cancer, modern low LET radiation therapy, biological basis of success and failure, clinical trials of radiation therapy; (2) particles--possibilities and peculiarities, physical characteristics of particle beams, biological characteristics, therapy features, review of particle projects; (3) what physics researches are needed--theoretical dosimetry, charged particle delivery, neutron delivery, practical dosimetry; (4) what biological researches are needed--OER and cell cycle; repair, recovery, fractionation; biology of beam with mixed LET; early and late tissue effects; (5) where do we go from here--patient treatment with fast neutrons, NCI program in radiation therapy, and panel discussion.

Five of the workshops were associated with the regular January meetings of study sections. Neurology B Study Section's "Workshop on Experimental Models for Studying Neural Behavior" met January 11, 1973, in La Jolla, California. Approximately 56 scientists engaged in a comprehensive and critical overview of the usefulness and limitations of in vitro systems and the so-called simple nervous system in neurologic research. Presentations and discussion covered the following topics: (1) the leech CNS as a relatively simple preparation for studying general principles of neural organization; (2) acetyl choline metabolism in single identifiable Aplysia neurons; (3) the identification of 5-hydroxytryptamine in single nerve cells

in the simple nervous system of the leech; (4) some behavioral mutants of a nematode; (5) synapse formation in neuron and muscle cell cultures; (6) characterization and interaction of clonal nerve and nerve and muscle cell lines.

"Drugs and the Sea", a workshop sponsored by the Medicinal Chemistry A and B Study Sections, was convened January 11-12, 1973, in La Jolla, California. The primary purpose was to assess the state-of-the art and hence improve the Study Sections' ability to evaluate the relative novelty, originality and scientific merit of the increasing number of research grant applications they are called upon to review in this interdisciplinary area.

The widespread occurrence of symbiosis, toxic chemical defense mechanisms and pheromone communication among marine organisms is being recognized; they have provided powerful stimuli to basic studies, as has the discovery of prostaglandins comprising 2 percent of the dry weight of the coral Plexaura homomalla. Concern was expressed by the workshop about the environmental impact of the blossoming Plexaura homomalla "harvesting" operations; they have been dubbed "reef rape." Other powerful stimuli to this field have been provided by the discovery of halogenated antibiotics in marine organisms and by the switch of the Chemotherapy Drug Development Branch of the National Cancer Institute from its search for antitumor natural products from well-exploited land plants to the virtually untouched life in the sea.

The need was identified for more work to be done on the extremely difficult problem of studying the structure and mechanism of action of barnacle cement, and on the totally different, perhaps evolutionarily primitive, biosynthetic mechanisms that must operate in the darkness of the depths with an ever-present external high halide ion concentration.

The need was identified for faster in vivo bioassays, for the development of readily transportable in vitro bioassay kits probably based on enzymes, and for a much closer interaction between chemists, biologists and taxonomists to exploit marine biochemistry effectively. It was felt that there is little reason for the study of deep-water organisms which are relatively expensive to collect. Shallow coastal waters are rich in unstudied organisms and small boats can be used for their collection.

The Study Sections were subsequently able to formulate three guidelines for judging proposals in this area. First, the highest priority should go to those studies which are firmly based on the biological characteristics and behavior of the organisms concerned. Studies designed to elucidate the chemical basis of biological manifestations appear to offer the most promise for uncovering exciting, novel and useful chemical and pharmacological findings. Second, not having such a direct biological rationale, one should pursue those serendipitous leads already in hand which show the most promise of yielding clinically useful drugs. These leads might arise from prior random screening or from folk medicine. Finally, lacking any specific rationale, support for "look-see" studies should be provided only to the most vigorous and effective researchers based on their past track records.

A workshop on "Maturation of the Fertilizing Ability of Mammalian

Spermatozoa" in Bethesda, Maryland, January 11-12, 1973, was sponsored by the Reproductive Biology Study Section. About 160 scientists attended the sessions. Publication of an article in a journal is planned for late 1973.

Capacitation is almost certainly a normal maturing process of the sperm in several mammals. Answers to many problems will modify the certainty of the process. If it truly exists, especially in man, it might prove to be important in fertility control. Marked changes occur in the character of the plasma membrane, the nucleus, and tail fibers of human sperm, and the pattern of motility, as they pass from the head to the tail of the human epididymis. Isolated biochemical data in animals in regard to the metabolic changes in epididymal sperm are yet insufficient to provide any comprehensive understanding of this aspect. The maturation and storage of epididymal sperm appears to be androgen dependent. The ultrastructural character of the epithelial cells reflects their secretory and absorptive functions. Epididymal vasculature and blood flow is complex. Both the capacitation (maturation) and transport of spermatozoa in the female vary according to the species. The relative importance of uterus, Fallopian tube, and follicular fluids for capacitation varies considerably between species. The ability of both uterus and tubes to support capacitation is modified according to the endocrine state of the female. Capacitation itself seems to be an endogenous change in the sperm cell. The acrosome reaction is considered to be an event separate from that of capacitation.

The Nutrition Study Section and the U.S. Army Medical Research and Nutrition Laboratory sponsored a "Workshop on Digestion, Absorption, and Malabsorption" in Denver, Colorado, on January 22, 1973. About 45 participants discussed these topics: (1) new aspects of small intestinal function; (2) adaptive response of jejunal enzymes to diet with particular emphasis on carbohydrates; (3) the role of bile acid micelles in facilitating fatty acid and steroid absorption into the intestinal mucosa; (4) absorption and transport of amino acids; and (5) an approach to chronic intestinal disorders.

The fifth January conference, "Workshop on the Current Status of Hypothalamic Releasing and Inhibiting Factor", was convened in New Orleans, Louisiana, January 25, 1973, under sponsorship of the Endocrinology Study Section. About 25 participants heard presentations and discussed research in four areas: (1) recent clinical experiences with TRH and LHRH; experimental work with the release-inhibiting factor which controls secretion of MSH; evidence for so-called extrapigmentary roles for MSH, including effects on the central nervous system comparable to those reported for ACTH (i.e., extinction of conditioned avoidance behavior); (2) chemical structures of the several hypothalamic peptide molecules, now purified, identified, and synthesized; (3) studies aimed at identifying the mechanism(s) of action of releasing factors; (4) preparation of antisera against LHRH and development of a radioimmunoassay of such extreme sensitivity (0.5 picograms) that it can detect LHRH in the peripheral blood of rats.

Ten members of the Surgery A and B study sections participated in a "Trauma Workshop Conference" conducted by NIGMS in Bethesda on February 26-27, 1973. The objective of the conference was to evaluate the Institute's program on trauma research and to determine its future role in reducing the

mortality and disability of this neglected disease in modern society.

Several reports from workshops that met in earlier fiscal years were published this year. One of these reports, entitled, "High-LET Radiation in Radiotherapy," appeared in Radiology, Vol. 103, No. 1, April 1972. The journal article resulted from the January 1971, workshop of the Radiation Study Section.

The second of these reports came from the September 1971 conference of the Tropical Medicine and Parasitology Study Section. Entitled, "Disease Transmission by Arthropods," it appeared in Science, 6 June, 1972, volume 176.

A third report, "Toxicology--A Neglected Science?" published in the Journal of College Science Teaching, December 1972, presented material from the January 1972 conference of the Toxicology Study Section.

APPLICATIONS PROCESSED BY REFERRAL OFFICE, RGRB
Fiscal Year 1973: March 16, 1972 - March 15, 1973

APPENDIX

COUNCIL		NOV.72	MAR.73	JUNE 73
COMPETING				
Types 1, 2, 3	NIH -	3,538	3,689	4,045
	HSMHA -	998	955	1,152
	FDA -	29	27	33
TOTAL		4,565	4,671	5,230
Construction		126	0	2
PL 480		13	19	10
Career Development		included in NIH Count		
Subtotal		4,704	4,690	5,242
NON-COMPETING				
(All 3 PHS components)				
Type 5		3,497	2,214	2,713
Interim-Regular & Cross Fiscal		336	357	330
Subtotal		3,833	2,571	3,043
TOTALS				
(All 3 PHS components)				
Competing		4,704	4,690	5,242
Non-Competing		3,833	2,571	3,043
TOTAL		8,537	7,261	8,285

Grand Total for FY 73 (Competing and Non-Competing) 24,083

STATISTICS AND ANALYSIS BRANCH

In fiscal year 1973, the Statistics and Analysis Branch was reorganized to give greater recognition to the increasing importance of the systems, surveys, and analyses functions. A summary of this reorganization is as follows:

1. The Statistical Analysis and Surveys Section was divided into two separate sections:

   a. The Special Projects and Surveys Section
   b. The Reports and Data Evaluation Section

2. The functions of the Assistant Chief for Systems Analysis and Design, Data Processing Section, were transferred to the Office of Systems Planning within the Office of the Chief, Statistics and Analysis Branch.

With this reorganization, the Statistics and Analysis Branch has been able to be more responsive to the requirements of those using its systems and services. During the fiscal year--characterized by restrictive, budgetary, and personnel controls--the Branch, through the utilization of improved technology in systems design, hardware, and software, has been able to extend reporting services; expand the data base of its systems; and, at the same time, meet user deadlines.

The Branch continued its support of the NIH Affirmative Action Plan for Equal Employment Opportunity through an active employee training and development plan. Employees were encouraged to participate in training courses and seminars, and, as appropriate, in the Upward Mobility College Training Program. The Branch also participated in the Public Service Careers Program, hiring two employees through utilization of the Skills File, and in the Federal Junior Fellowship Program, recruiting three student trainees.

Individual training efforts, major accomplishments, and significant activities are discussed below.

1. Office of Systems Planning. The Office of Systems Planning continued its efforts to augment the base of information maintained in the IMPAC data system by expanding program coverage and adding new items of data necessary to provide a full range of management information covering the extramural activities of the NIH. Included in these new areas of coverage were the following:

Research and Project Contracts. Information on Research and Project Contracts was augmented by the inclusion of data on research involving human subjects; indirect costs; place of performance; and incrementally funded contracts. New data collection forms, including the form NIH 1759--Contract Data Code Sheet, and NIH 1688--Project Objectives and Progress Report, were designed and introduced for the purpose of collecting this new information. Additionally, on January 1, 1973, the system for numbering and identification

of NIH research and project contracts was modified to effect consistency in the systems for numbering both grants and contracts. The full conversion of the former contract numbers to the new numbering system is scheduled for completion by the end of calendar year 1973.

Interagency and Intra-agency Agreements. A new system was instituted for the collection, storage, and retrieval of information related to Inter-agency/Intra-agency Agreements between NIH and other Federal agencies. In addition to the promulgation of an NIH manual issuance defining responsibilit for reporting such agreements, special data collection forms were designed, and procedures developed for reporting this information. It is planned that all new and renewal agreements entered into by NIH components during fiscal year 1973 will be recorded in the IMPAC system by the end of the fiscal year.

Special Foreign Currency (P.L. 480) Program. Negotiations were concluded with the Fogarty International Center for reporting information relating to NIH support of biomedical research activities abroad through the use of U.S.-owned foreign currency. Collection forms were designed and directives issued to report all such projects monitored by the Fogarty International Center that were active during fiscal year 1973.

Budgeted Categories of Cost. Major systems and programming efforts have been initiated to expand the IMPAC data base to include the categories of cost budgeted by the NIH program managers for annual grant awards. This effort has required a significant reformatting of the existing computer records to accommodate some 15 budgeted categories of cost, including personnel, supplies, equipment, and travel. Introduction of the new data items into the system is expected to take place on July 1, 1973. It is expected that, with the printing of the budgeted cost on the notices of award produced by the computer, the awards will be complete at time of printing and ready for signature, thereby requiring little or no additional handling or typing by the BIDs.

Training. Personnel from the Office of Systems Planning have attended DCRT training courses, other NIH-sponsored courses, and courses outside NIH.

2. Data Processing Section. Updated methodology and newly established techniques have maximized the availability of a refined data base for customer use.

Microfilm Processing. Under the microfilm system established in the prior fiscal year, DPS furnishes to RGRB for referral purposes a completely updated microfilm file every 2 weeks. Included is information on all active research and research career awards, grants that terminated within the past year, and pending applications. During this fiscal year, all research and project contracts were added to this data base. The system permits the Project Control Unit, RGRB, to search the microfilm file upon receipt of a new or competing application and make a copy of appropriate background data. Such data can then be forwarded with the application to the Referral Officer. The provision of a computer-generated microfilm file eliminates the need for manual updating of the investigator record cards and provides a more efficient means for RGRB to continue processing applications. Additionally, the file i

utilized by both NIH grant and contract staff as a source of background information for effective program administration.

Microfiche Processing. The Programming Unit has programmed a microfiche application to replace cumbersome line item listings now in use in the Data Capture and Control Unit. Implementation of this program will occur upon receipt of microfiche readers now on order. It is expected that this microfiche technique will be fully operational in fiscal year 1974.

Training. In line with the Branch's training policy, personnel from the various units of the Data Processing Section have attended training courses both within the NIH, at the DCRT Computer Center and in other areas, and outside the NIH. In addition, personnel from the Data Capture and Control Unit are continuing their participation in the Upward Mobility College Training Program.

3. Research Documentation Section. Through the CRISP System (Computer Retrieval of Information on Scientific Projects), the Section has continued to service requests for scientific information from program administrators, scientific and information personnel in Government, as well as non-Government scientists and other individuals interested in medical research. CRISP is an independent retrieval system, on disk storage, that contains data about the scientific aspects of research grants and contract programs of the various health components of DHEW. It has the query capability of providing information ranging from a straightforward listing of grants pertaining to a single scientific subject term to a compendium of projects relating to any number of terms, using a combination of "and," "or," "not" search logic.

This year another selection option was added to the query capability to enable retrieval on primary research emphasis, as well as on program code or institution code. A variety of query output formats are available incorporating whatever fiscal, grant identification, or subject matter items the user requests. Recent improvements to the grant identification items shown on query printouts include: (1) the identification of direct or indirect costs; (2) the number of years of committed support; and (3) an average amount allocated to individual parts of multi-part projects. Refinements in indexing and vocabulary techniques were also instituted to improve the relevancy of query responses. An additional WYLBUR terminal has been added to the Section to facilitate data input into CRISP.

Research Grants Index. The scientific data used as input to the CRISP System are the indexing items that are selected to prepare the annual editions of the Research Grants Index, which is printed from a magnetic tape produced from CRISP. The twelfth edition of the Research Grants Index (NIH Publication 73-200, 2 vols.) was published in May 1973.

This year the Section has installed optical scanning typewriters for the bibliographic entries cited in Volume II, and has instituted procedures to have the entire second volume compiled by computer to replace the camera card method formerly used for printing this volume of the Index.

Medical and Health Related Sciences Thesaurus. A revised edition of the

Thesaurus was published this year and distributed on a request basis.

Other Activities. The Section compiled data on large program grants for administrative use. The compilation included: (a) a list of projects in grant-number order showing individual subproject titles, individual investigator names, addresses, bibliographies, and average subproject funds; (b) a subject-matter index to these subprojects; and (3) an alphabetical listing of investigators working on these large program grants.

Training and Presentations. During the year, nine employees of the Section participated in NIH training programs. The courses included supervisory techniques, technical writing, report writing, biochemistry, English, typing, and mailing. In addition, one employee continued to attend the Upward Mobility College.

4. Reports and Data Evaluation Section. The primary function of the Reports and Data Evaluation Section is the collection, storage, computer retrieval, presentation, and analysis of data on the extramural programs of the NIH and PHS for use in policy consideration, program planning, program analysis, and program management. In addition, the Section is responsible for the coordination of responses to inquiries about the extramural programs received from both Government and non-Government sources. The major activities and outputs of the Section during fiscal year 1973 are described below.

Publications. The following volumes of the annual multi-volume series on Public Health Service Grants and Awards were issued:

(1) PHS Grants and Awards: NIH Training, Construction, Medical Libraries, and Summary Tables, Part II, FY 1971.

(2) PHS Grants and Awards: Health Services and Mental Health Administration, Food and Drug Administration, and Environmental Health Service, Part III, FY 1971.

(3) PHS Grants and Awards: NIH Research Grants, Part I, FY 1972.

(4) PHS Grants and Awards: NIH Training, Construction, Medical Libraries, Part II, FY 1972.

(5) PHS Grants and Awards: NIH Research Contracts, Part III, FY 1972.

(6) PHS Grants and Awards: NIH Health Manpower Education, Part IV, FY 1972.

(7) PHS Grants and Awards: Food and Drug Administration, Part V, FY 1972.

Data for the pocket reference book, Basic Data Relating to the NIH--1973, were compiled in cooperation with the NIH Office of Program Planning. This publication presents information on the programs and resources of the NIH.

Reporting Activities. There are several major reporting activities, which are recurring or cyclical, and which consume a large portion of the man-hours available in this Section.

The annual survey conducted by the National Science Foundation, entitled Federal Funds for Research, Development, and Other Scientific Activities, is coordinated and prepared by this Section for the entire NIH. In general, the survey covers all the NIH intramural and extramural research activities for the past fiscal year together with estimated obligations for the next 2 future years by performer, field of science, geographic area, basic and applied research and development, and combinations of the above. A segment of the report is also devoted to Scientific and Technical Information Activities.

The CASE Report is an annual survey on support to institutions of higher education and other nonprofit organizations. The NIH response to this survey is coordinated and prepared by this Section. It requires an institution-by-institution report of all NIH extramural support, by program, for most non-profit organizations, with an individual report for each health professional school. In addition, data by field of science grouping are also requested for institutions of higher education, by program.

The HSMHA portion of this survey was also prepared by this Section for those programs regularly processed by DRG.

Obligations for Medical and Health-Related Research and Training Activities is an annual survey of all Government-sponsored medical research and training. The NIH response to this survey is also coordinated and prepared by this Section and requires data on intramural and extramural research and development by field of science, performer, programs, and State. Additional NIH data required include manpower statistics related to graduate training grants, fellowships, and research career program awards, by degree sought, institution, field of science, and institutional vs. individual support.

At the beginning of each review cycle for research and training grant applications, statistical reports are prepared, which present data on the number and dollar value of applications received for review. The presentation

is by institute, fiscal year of support, and type of application. Copies are distributed to each institute/division. In addition, statistical tables showing summaries of initial review group actions on research and training grant applications are prepared twice during each review cycle for use by the Office of Financial Management and the institutes/divisions.

Inquiries. The Section responds to hundreds of requests for information each month from Federal agencies, NIH officials, nongovernmental and other organizations. These requests are for statistical and analytical information concerning the NIH grant and award programs, and for data on the characteristics of PHS grantee institutions.

The inquiries range in complexity, as measured by man-hours, from several hundred to less than one per project. Many of these requests are satisfied by data contained in existing, but unpublished, reports, but the IMPAC system remains the primary data source and the Inquiry and Reporting System (a computer software facility) the primary method for data extraction, manipulation, and hard-copy presentation of the information requested. About 7,000 queries were processed through the Inquiry and Reporting System for this purpose during FY 1973.

Institutional Research. The Section has the responsibility for establishing and maintaining the Institution Profile File (IPF). The IPF is the central registry of names, locations, geographic and other selected data for organizations participating in the Public Health Service extramural programs. This file is the single source for organizational information established to assure uniform reporting and to eliminate the necessity for storing similar information in individual grant and award files. In FY 1973, over 1,500 new institutions were added to the IPF. The IPF now contains about 17,500 records on institutions participating in NIH programs, as well as the programs of the Food and Drug Administration and the Health Services and Mental Health Administration.

Department Coding System for Institutions of Higher Education. During fiscal year 1973, the Reports and Data Evaluation Section developed a coding scheme for departments in institutions of higher education. An individual, three-character alpha code (AAA to ZZZ) was assigned to each of the approximately 1,700 department names currently existing in our institution files. This code, coupled with the existing major component code, will facilitate retrieval of information for institutions of higher education by major component and department.

Retrieval Methodology. Three IMPAC Inquiry and Reporting System (IRS) courses were offered by the Section. Thirty-four persons attended two basic courses, and an additional eight attended a course in advanced applications. IRS is the primary instrument for extracting and reporting IMPAC data.

About ten consultations are handled each day for DRG and institute/division personnel needing assistance in debugging queries, developing more advanced queries, and applying new techniques.

Retrieval Applications and Procedures (RAP) has been developed as an informal, technical handbook to provide users with accurate information and

instructions on how to apply new or more efficient retrieval procedures, and to correct recurring IRS problems. About 50 copies are distributed, primarily in DRG.

Graphic Arts. Approximately 1,500 pieces of graphic art work were completed by the Illustrator in fiscal year 1973. This work included cover designs, charts, certificates, slides, signs, visuals, special exhibits, and illustrations for flyers and handbooks.

5. Special Projects and Surveys Section. This Section was formally established in July 1972. Its mission is to collect and analyze data on key aspects of the NIH extramural programs for purposes of program operation and management. The Section conducts surveys and special evaluation studies, prepares analytical reports, and develops statistical models and computer systems for purposes of analysis.

Manpower Analysis. The NIH Research Grant Manpower Survey of 1970, planned and conducted by the Section's staff, has provided basic data for a series of reports and special analyses. Two final reports on key aspects of the data are nearing completion. One report analyzes paid employment and earnings on research grants; the other studies the characteristics of principal and key investigators. Drafts of both reports have been circulated for review. The major findings of the manpower survey, using specially designed slides, were presented to NIH management--the Office of the Associate Director for Extramural Research and Training, OD; and the Office of the Associate Director for Program Planning and Evaluation, OD--and at a seminar sponsored by the STEP Committee.

The recent decision to eliminate the NIH training grant and fellowship programs has brought into sharp focus the need for a system that continually monitors the impact of NIH extramural programs on biomedical research manpower and research funding. To meet this need, the Section is planning mechanisms for constant surveillance of the manpower situation. These may include annual reports by recipients of research grants and contracts supplemented by sample surveys.

Preparation of the statistical data needed for the annual reports on trainees appointed under the NIH research training grants program continued. The report covering trainees appointed from FY 1965-70 funds was completed. The basic statistical data needed for the FY 1971 funded trainees have been prepared.

Evaluation Program. An evaluation project developed by the Section was approved as part of the FY 1972 NIH Health Evaluation Program. The project was designed to measure the training impact of NIH research grant programs. It utilized statistical model building techniques and was based upon selected data from the NIH Research Grant Manpower Survey. This study--carried out by a contractor in conjunction with the Section's staff--has been completed. A supplementary analysis was approved under the FY 1973 NIH Health Evaluation Program, which will develop a profile of students and postdoctorates working on NIH research grants, again using the NIH Research Grant Manpower Survey

data as a base. A contractor has been selected, bibliography developed, and work begun.

A new project approved under the FY 1973 NIH Health Evaluation Program consists of recording and analyzing the data on the Reports of Expenditures (ROE) submitted for FY 1971 research grants (the latest year for which such reports are available). Plans have been developed and a contractor selected for the data input portion of this project and for the preparation of basic reference tables. This work is now in process. Plans are proceeding for the analytical phase.

Systems and Model Development. As a means of studying the impact of program changes upon grantee institutions, the Section is designing a computer system and statistical model for estimating the amount of NIH funding that will be awarded to specific institutions during the following year. The model will allow projections based on known patterns modified by current funding levels and program decisions.

Preliminary study has been undertaken to develop data processing techniques that can be used by those with minimal computer and statistical experience. These would be used to produce data summaries, medians, standard errors of the estimate, and similar statistical measures.

Publications. A report, NIH Indirect Trainees Appointed Under Research Training Grants and General Research Support Programs, FY 1965-1970 Funds, Statistical Item No. 12.2, was issued. It is the third in a series of annual reports.

Training. During the year, 15 employees of the staff took 13 different training courses.

HOW TO USE
THESE SEPARATORS

Use one page for each separation.

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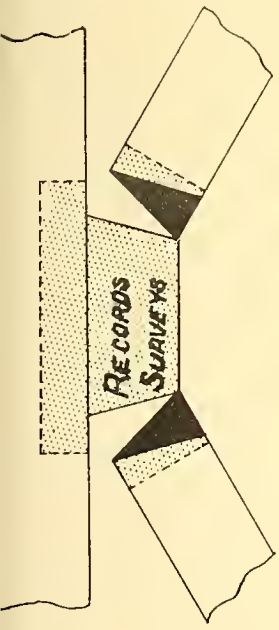
Cut off and discard all tabs except the one covered by tape.



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TABBED SEPARATOR SHEET
Form HEW-69
(3-56)

ANNUAL REPORT

FISCAL YEAR 1973
(July 1, 1972-June 30, 1973)

DIVISION OF RESEARCH RESOURCES

National Institutes of Health
Bethesda, Maryland 20014

TABLE OF CONTENTS

DRS

REPORT OF THE DIRECTOR

Dr. Thomas G. Bowery

Report of the Division Director

Fiscal year 1973 presented the Division of Research Resources with an unusual number of challenges and opportunities in administering over 224 resource type grants to support the Nation's biomedical research endeavors.

Our chief opportunity resulted from an increase of $3 million for the Minority Schools Biomedical Support Grant Program. The increase in funds allowed us to provide support for 13 additional minority institutions over the 38 which were funded in FY 1972, when the program was initiated. Further development of this program, dependent upon the additional funds requested by the President in the FY 1974 budget, will enable us to provide additional research opportunities to institutions which have not been previously recipients of NIH funds.

Challenges rather than opportunities faced the other program elements of the Division as a result of the reductions in their budgets for FY 1973. Most seriously affected were the General Research and Biomedical Sciences Support grants. With the announcement of the reduction in these programs coming late in the fiscal year, staff were unable to develop new eligibility guidelines or alert the recipient community to the impending reductions in their awards for FY 1973. The staff are currently analyzing various options for distribution of the funds for FY 1974, which are scheduled to be reduced another 50 percent.

By means of stringent budgetary negotiations we have been able to maintain approximately the same number of general clinical research centers. Additionally, we were able to initiate one discrete outpatient clinical research center. Currently, Branch staff are conducting an intensive evaluation of the clinical research centers program in an attempt to determine whether the current mode is the optimal one for carrying out clinical research throughout the Nation.

Biomedical research institutions throughout the country are seriously attempting to improve their animal research facilities in response to the Animal Welfare Act of 1970. The very limited amount of funds which we have available for assisting these institutions resulted in our making awards to only 58 percent of the applications recommended for support.

This last fall saw the dedication of the first two 1 million volt electron microscopes for biomedical research in the United States. The initiation of these programs in which the resource is utilized by scientists throughout the Nation has provided the staff with a model for sharing of resources - a concept which extends the traditional concept of institutional or regional resources. We are contemplating the resource sharing concept in terms of other programs of the Division.

The effectiveness of the National Advisory Research Resources Council has been hampered by the vacancy of three members for the past year. We sincerely hope

these vacancies, as well as the three upcoming ones, will be filled very soon, since the Council has provided us with significant guidance as we consider various alternatives and options in our program plans.

As a means of instituting more effective management techniques in the Division, my top staff and I have been working toward the institution of Organization Development-Team Building. The Division is also working toward the formalization of better management skills in all its supervisory personnel.

As we enter fiscal year 1974, the Division accepts the challenge of administering a significant portion of the NIH's extramural funds within the constraints we are facing. We will not, however, compromise the quality of our operations.

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DRS

DRR BRANCH REPORTS

Fiscal Year 1973
ANNUAL REPORT
Biotechnology Resources Branch
Division of Research Resources

INTRODUCTION

NIH-supported Biotechnology Resources continued in FY 1973 as media through which the physical sciences, mathematics, and engineering influence--and are influenced by--the domain of biomedicine. Biotechnology Resources create conditions under which the most sophisticated, health-relevant forms of digital computation, mass spectrometry, nuclear magnetic resonance spectroscopy, electron microscopy, and other technologies are spawned and evaluated in the full context of the biomedical world. These centers of technological excellence frequently offer the clientele of the NIH's categorical programs investigative opportunities otherwise unavailable to them.

The nature and scope of the various Biotechnology Resources are closely intertwined with the major technological advances and research opportunities occurring both inside and outside the biomedical research community. Beginning from almost pure service activities ten years ago, the Program has evolved to the point where, in addition to (a) furnishing research services, each resource now must (b) perform core research and development in its own area of technology, (c) enter into close collaborative activities with its user community, and (d) conduct formal and informal training to acquire new skills for its own staff and to diffuse the benefits of its technology to its user community. Incorporating all four of these activities within a resource makes the resource most responsive to the needs of its clientele. This report highlights some of the important developments in the Program during FY 1973:

STATE OF THE PROGRAM

The variety of supported Biotechnology Resources and the diversity of assistance they provide the research community are shown by the following classification of the 54 grants and three contracts active during FY 1973:

27 computer resource grants
2 resource-related projects in computer science
13 biomolecular characterization resource grants
6 biomedical image and image processing resource grants
6 biomedical engineering and other resource grants
1 electron microscopy services contract
1 high resolution mass spectrometry service contract
1 biomedical kinetics service contract

The aggregate annual expenditure level for these activities is approximately $11 million. A listing of the BRB-sponsored activities active during FY 1973 is given in Table I.

TABLE I

BRB-SPONSORED ACTIVITIES DURING FY 1973

Number	Principal Investigator	Institution	Title	FY 1973	Cumulative Awards
COMPUTER					
RR-3-12	Wilfrid J. Dixon, Ph.D.	University of California, Los Angeles, California	Health Sciences Computer Resource	$1,890,922	$16,246,247
RR-7-10	Earl H. Wood, M.D.	Mayo Foundation, Rochester, Minnesota	Computer Processing in Biomedical Systems	615,650	3,833,644
RR-11-11	David D. Mason, Ph.D.	North Carolina State University, Raleigh, North Carolina	Computer Use in the Health Sciences	17,434	1,257,829
RR-12-11	Homer R. Warner, M.D.	University of Utah, Salt Lake City, Utah	Computer Facility for Medical Community	257,105	2,109,892
RR-13-09S1	Richard H. Earle, M.D.	University of Chicago, Chicago, Illinois	Computer Facility for Medical Community	a/	2,540,071
RR-15-11	Martin Pring, Ph.D.	University of Pennsylvania, Philadelphia, Pennsylvania	Medical School Computer Facility	308,987	3,242,308
RR-16-10S1	S. James Kilpatrick, Jr., Ph.D.	Medical College of Virginia, Richmond, Virginia	Support of Scientific Computation Laboratory	33,258	671,530

RR-145-10	Josiah Macy, Jr., Ph.D.	University of Alabama Medical Center, Birmingham, Alabama	Use of Electronic Computers in Health Research	$ 122,160	$ 2,260,950
RR-241-07S1	John J. Osborn, M.D.	Institute of Medical Sciences, San Fransicso, California	Development of a Biomedical Research Data Facility	180,000	1,598,333
RR-249-08	William S. Rhode, Ph.D.	University of Wisconsin, Madison, Wisconsin	Support of Laboratory Computer Resources	229,888	1,735,156
RR-254-05	Richard T. Eastwood, Ph.D.	Texas Medical Center, Inc., Houston, Texas	Regional Computer Facility	a/	2,286,699
RR-259-07	Allan H. Levy, M.D.	Baylor College of Medicine, Houston, Texas	Computational Research Center Program	300,000	2,064,536
RR-267-08	Eugene Ackerman, Ph.D.	University of Minnesota, Minneapolis, Minnesota	Health Computer Resource	306,600	2,356,906
RR-276-08	Ivan R. Neilsen, Ph.D.	Loma Linda University, Loma Linda, California	Development of Biomedical Computation Facility	105,766	851,359
RR-291-08	Jack Leibowsky, MSEE	SUNY--Downstate Medical Center, Brooklyn, New York	Biomathematical Computer Research Center	145,354	1,346,475
RR-311-06S1	Joshua Lederberg, Ph.D.	Stanford University, Stanford, California	Advanced Computer for Medical Research (ACME)	475,158	4,135,308
RR-326-07	Cyril L. Comar, Ph.D.	Cornell University, Ithaca, New York	Computer Research Resources	60,625	522,305

RR-353-06	William J. Mueller, BSE	SUNY--Upstate Medical Center, Syracuse, New York	Research Data Processing Center	$ 92,855	$ 787,052
RR-370-04S2	Herbert M. Teager, Sc.D.	University Hospital, Boston, Massachusetts	Medical Computer Resource	94,449	541,394
RR-374-06	Theodore H. Kehl, Ph.D.	University of Washington, Seattle, Washington	Support for Physiology and Biophysics Computer	142,261	705,420
RR-396-06	Charles E. Molnar, Sc.D., E.E.	Washington University, St. Louis, Missouri	Computer Systems Laboratory	420,000	2,208,892
RR-417-03	Richard G. Cornell, M.D.	University of Michigan, Ann Arbor, Michigan	A Development Program for Biomedical Computing	a/	430,558
RR-452-02	Sidney Katz, Ph.D.	Medical University of South Carolina, Charleston, South Carolina	Research Data Processing Center	a/	163,453
RR-576-02	John Waldhausen, M.D.	The Pennsylvania State University, Hershey, Pennsylvania	Biomedical Computing Resource	123,019	284,340
RR-578-04	Robert Langridge, Ph.D.	Princeton University, Princeton, New Jersey	Special Research Resource for Biomolecular Graphics	79,200	698,622
RR-643-02	Saul Amarel, D.E.	Rutgers University, New Brunswick, New Jersey	Biotechnology Resource: Computers in Biomedicine	184,296	365,113

RR-757-01	Joseph Kraut, Ph.D.	University of California, La Jolla, California	Implementation of a Laboratory Automation System	a/	$ 192,102

RESOURCE-RELATED RESEARCH PROJECTS

RR-667-01	Harold W. Shipton, C.E.	University of Iowa, Iowa City, Iowa	A Biomedical Computer Terminal System	a/	43,310
RR-612-03	Edward A. Feigenbaum, Ph.D.	Stanford University, Stanford, California	Resource-Related Research Computers and Chemistry	$ 260,999	808,268

BIOMOLECULAR CHARACTERIZATION RESOURCES

RR-273-08	Richard Abrams, Ph.D.	University of Pittsburgh, Pittsburgh, Pennsylvania	Mass Spectrometric Facility for Biomedical Research	54,940	389,483
RR-292-08	Aksel A. Bothner-By, Ph.D.	Mellon-Pittsburgh-Carnegie Corporation, Pittsburgh, Pennsylvania	NMR Facility for Biomedical Studies	96,436	1,007,703
RR-317-06	Klaus Biemann, Ph.D.	Massachusetts Institute of Technology, Cambridge, Massachusetts	Mass Spectrometry Facility for Biomedical Research	134,122	1,261,096
RR-328-05	Jules B. LaPidus, Ph.D.	Ohio State University Research Foundation, Columbus, Ohio	An NMR Facility for Biomedical Research	a/	102,435
RR-330-06	David Rosenthal, Ph.D.	Research Triangle Institute, Research Triangle Park, North Carolina	Mass Spectrometry Center for Research Triangle Region	133,050	601,807

RR-355-07	Martin F. Semmelhack, Ph.D.	Cornell University, Ithaca, New York	High Resolution Mass Spectrometer Facility	$ 46,650	$ 477,622
RR-356-07	Seymour R. Lipsky, M.D.	Yale University, New Haven, Connecticut	Continuation of Physical Sciences Instrument Facility	206,052	1,097,223
RR-480-05	Charles C. Sweeley, Ph.D.	Michigan State University, East Lansing, Michigan	Support of Michigan State Mass Spectrometer Facility	294,274	442,266
RR-542-03	Mildred Cohn, Ph.D.	University of Pennsylvania, Philadelphia, Pennsylvania	220 MC NMR Spectrometer Facility	58,061	453,916
RR-574-02	David M. Grant, Ph.D.	University of Utah, Salt Lake City, Utah	Regional Research Facility in NMR	91,980	282,060
RR-636-01	Arthur P. Grollman, M.D.	Albert Einstein College of Medicine, Bronx, New York	Biotechnology Resource for NMR Studies of Biomolecules	a/	222,934
RR-711-01	Oleg Jardetzky, M.D.	Stanford University School of Medicine, Stanford, California	High Frequency NMR Biotechnology Resource	a/	130,989
RR-719-01	A. L. Burlingame, Ph.D.	University of California, Berkeley, California	Biomedical, Clinical Mass Spectrometry Resource	174,431	174,431

BIOMEDICAL IMAGE AND IMAGE PROCESSING RESOURCES

RR-442-04	Cyrus Levinthal, Ph.D.	Columbia University, New York, New York	Computer Resource for Image Processing and Displays	$ 329,791	$ 819,601
RR-443-05	Robert Nathan, Ph.D.	California Institute of Technology, Pasadena, California	A Computer Resource for Pictorial Data Processing	657,000	2,833,136
RR-570-03	Hans Ris, Ph.D.	University of Wisconsin, Madison, Wisconsin	Electron Microscope Facility for Biomedical Research	50,951	847,447
RR-592-03	Keith R. Porter, Ph.D.	University of Colorado, Boulder, Colorado	High Voltage Electron Microscopy of Biological Systems	287,564	920,964
RR-679-01	Clifford A. Barger, M.D.	Harvard Medical School, Boston, Massachusetts	Biotechnology Resource in Electronprobe Microanalysis	138,398	138,398
RR-715-01	Elliott N. Shaw, Ph.D.	Associated Universities, Inc., Upton, New York	Electron Microscope Facility	86,730	86,730

BIOMEDICAL ENGINEERING AND OTHER RESOURCES

RR-117-10	William A. Clark, Ph.D.	Americal Type Culture Collection, Rockville, Maryland	Preservation of the Americal Type Culture	100,000	2,116,416
RR-226-08	John C. Garver, Ph.D.	University of Wisconsin, Madison, Wisconsin	Biochemistry Pilot Plant	a/	165,965

RR-346-05	Henry G. Mautner, Ph.D.	Tufts University, Boston, Massachusetts	New England Enzyme Center	$ 36,065	$ 551,606
RR-396-06	Jerome R. Cox, Jr., Sc.D.	Washington University, St. Louis, Missouri	Biomedical Engineering Resource	805,800	4,573,955
RR-716-06	Harold W. Shipton, C.Eng.	University of Iowa, Iowa City, Iowa	A Bioengineering Resource Facility	16,220	16,220
RR-759-01	Milton Helpern, M.D.	New York University, New York, New York	The Institute of Forensic Medicine as a Research Resource	81,499	81,499
CONTRACTS					
NIH-71-444	Fred Kayne	Johnson Foundation, University of Pennsylvania, Philadelphia, Pennsylvania	Study of Fast Reaction Biomedically Relevant Chemical Systems	a/	85,000
NIH-71-2483	Rodger L. Foltz, Ph.D.	Battelle Memorial Institute, Columbus, Ohio	High Resolution Mass Spectrometry Service	a/	74,000
NIH-70-4136	Robert M. Fisher	U.S. Steel Engineers and Consultants, Inc., A Subsidiary of U.S. Steel Corporation, Pittsburgh, Pennsylvania	Access health scientists to the high voltage electron microscope located in the Edgar C. Bain Laboratory for Fundamental Research, Monroeville, Pennsylvania	40,000	175,000

a/ Active during FY 1973 but received no FY 1973 funds.

It is particularly interesting to view the BRB Program in historical perspective. In 1967, for example, the Program supported 61 resources at a cost of $12.2 million. These resources fell into the following categories:

48 computer resources
10 biochemistry instrumentation resources
3 biological materials resources

Not only the numbers but also the substantive nature of each type of resource has changed greatly during the intervening years, especially in the computer resource category. Compared to the 28 batch-processing or off-line, general-purpose computer installations in 1967, the Program will have only 1 resource of this type by 1974. Whereas in 1967 there were 15 computer resources concerned primarily with on-line, real-time interactive use, now there are 21. There seems to be little doubt that the ever more sophisticated computational needs of biomedical scientists are best met by highly specialized resources and not general-purpose ones.

Rapid and far-reaching change is not limited to the computer resource category. For example, as the requisite talent becomes available to manage mass spectrometers in a variety of biomedical settings, there is a strong trend toward the use of these instruments in clinical investigation, especially in pediatric research. It is also of interest to note that, unlike even a few years ago, all of the biochemistry instrumentation resources now contain a dedicated computer for reduction of data to a manageable form. Similarily, almost exclusively as a result of efforts by the Biotechnology Resources Program in the past several years, high voltage (i.e., one-million volt) electron microscopy services have become a reality in the United States and are now being applied for such purposes as obtaining stereo micrographs of thick-sectioned biological material and examining the surfaces and contacts of intact wet cells in a hydration chamber.

The four "new" awards made by the Biotechnology Resources Program during Fiscal Year 1973 demonstrate the continuing diversification and specialization of supported activities. These newly supported resources include a bioengineering resource, an electron microscopy resource, a resource for clinical mass spectrometry, and a resource in forensic medicine.

SELECTED PROGRAM DEVELOPMENTS

RESOURCE SHARING

The evolution of the BRB Program has produced an array of diverse Research Resources, all designed to meet one or more specific technological needs of biomedical scientists. As new advanced technological tools are shown to be both feasible and relevant to health research, the BRB increasingly experiences demands to make these tools available to the biomedical community. Because most of the new technologies are more sophisticated and costly than their predecessors, the emerging Biotechnology Resources are more complex and require a more highly specialized technical staff for their maintenance and successful operation. Moreover, because these resources are devoted more to specific research needs than to the wide range of biomedical problems served

in the traditional general-purpose Biotechnology Resources, they are usually able to make a more meaningful contribution to the activities of their clientele.

The demand for these costly specialized resources, coupled with an essentially static budget, requires the BRB to begin shifting its support from resources which exclusively serve scientists in their host institutions to national resources which serve scientists residing throughout the country. The establishment of nationally shared Biotechnology Resources is believed to be a scientifically rational and fiscally realistic way to promote the emergence and sustain the broad availability of the sophisticated research tools required by modern biomedical research.

High Voltage Electron Microscopy Resources

With the dedication of the one-million volt electron microscopes at the University of Wisconsin and the University of Colorado this fiscal year, the BRB initiated a National High Voltage Electron Microscopy (HVEM) Program. These two microscopes, as well as the microscope time supplied under a contract with the U.S. Steel Corporation on their one-million volt microscope, are now available to qualified scientists irrespective of geographical location or institutional affiliation. The establishment of the HVEM resources as national facilities is the first effort of the BRB in its Resource Sharing Program. This joint effort will give the Nation's biomedical scientists a broader range of opportunities for employing HVEM than any one resource could realistically do alone. The feasibility studies carried out under the U.S. Steel contract showed that a HVEM facility is well suited to operate as a national resource. In a course of about two years, over 26 investigators from all parts of the country used the U.S. Steel microscope very successfully. No major problems were encountered in serving these users.

A straightforward mechanism has been established to accommodate those scientists desiring to use the HVEM who are not affiliated with the host institutions of the HVEM resources. These scientists are required to submit to the BRB their proposed projects. These proposals are reviewed by an institutionally based advisory committee common to all three resources, and the successful applicants are recommended for access to that particular resource whose capabilities best match the applicant's needs.

The BRB will serve as the central point for coordinating the HVEM resources' operations. When service charges are established at the resources, the BRB will encourage uniform rates. It will also sponsor meetings for technical exchange among resource personnel and users.

Eventually the National HVEM Program will be expanded to include resources in related areas, giving an ensemble of resources specializing in the application of electron optics to biomedical problems. Examples of future resources in this group are a Crewe-type scanning transmission electron microscopy resource and an electron microprobe resource.

Biomolecular Characterization Resources

Within the Biomolecular Characterization Resources Program, increased emphasis has been placed upon resource sharing as a means of maximizing the application of sophisticated analytical techniques to facilitate biomedical research. In particular, ongoing nuclear magnetic resonance spectroscopy and mass spectrometry resources are being encouraged to expand their user communities and increase their inter-institutional commitments. New centers are programmed with greater emphasis on serving the maximum number of biomedical research scientists that can be accommodated by the capabilities presented in each grant application. Particular importance is placed upon developing strong lines of communication between resource and user community.

During Fiscal Year 1973, a study designed to examine the service component of the Mass Spectrometry Resources Program was completed. Conducted under contract with Battelle Memorial Laboratories, Columbus, Ohio, this study demonstrated that one laboratory, under proper management, could effectively meet the mass spectrometry service requirements of clinicians, pharmacologists, biochemists, and medicinal chemists located in a large geographical area.

Computers

Advances in digital telecommunications and other supportive technologies promise to make computing resources more effective in meeting health research needs by facilitating the shared use of these resources. The primary unmet needs are:

1. computing support for numerous biomedical investigators whose institutions do not host a computing resource for their problem area; and

2. specialized environments of skilled personnel, software and facilities to augment intellectual interaction among commonly interested researchers in methodologies of biomedical computing.

Refinements in inter-computer communications techniques now allow far-flung user groups to access an entire spectrum of specialized computing capabilities located at diverse geographical locations. While this technology fulfills the minimum requirements for meeting the needs outlined above, much remains to be learned about the management of technologically complex, inter-institutionally sharable resources. During Fiscal Year 1973, the BRB conducted a meeting of grantees and other biomedical computing personnel devoted to computer resource sharing. In addition, BRB staff have sought advice from numerous interested individuals and organizations on this issue. The chief conclusion drawn is that many of the technological problems of computer resource sharing have been solved or are clearly soluble, but that, in the absence of outside help, administrative barriers block all but the most energetic efforts at inter-institutional resource collaboration. Consequently, the BRB has reviewed its administrative options for grant applicants in an effort to lower barriers and target resources to meet the identified unmet needs. One change initiated by the review (and applicable

to all resources, not just in computing) is to insist that the applicant justify the full capacity of requested capabilities, and to offer a feasible plan for sharing capabilities he cannot use within his own institution. The BRB explicitly offers assistance in managing this extra capacity. A second change, likely to have high impact in computing, is to encourage applications from institutions which do not want to acquire equipment or undertake methodological research, but rather wish to gain access to existing capabilities at other institutions. Defining the role of the "facilitator" staffs which would be the interfaces between users and distant resources will be an interesting issue of scientific administration for the BRB in the next few years. It will be particularly interesting for computing, because of the wide diversity of potentially accessible resources, and hence the wide range of skills required of the "facilitators."

In the Fiscal Year 1972 Annual Report, the BRB identified a number of specialized biomedical computing areas in which sharable resources would be valuable. These were simulation techniques; file processing; numerical computation, non-numerical manipulation; remote, on-line data gathering; remote, on-line digital control of experiments; and building of special health sciences information bases. In Fiscal Year 1973, several applications for highly specialized resources of this type were received.

Unfortunately, they encountered considerable administrative and scientific problems which impair their chances for successful funding and operation. These experiences have prompted the BRB to consider alternative mechanisms, such as contracts, to support the initial operations of complex sharable computing resources. It is hoped that a way can thereby be found to answer questions of a scientific or management nature peculiar to shared resources, independent of the additional constraints imposed by inter-institutional relations. To minimize the technical support difficulties which might interfere with obtaining these answers, it seems that an area of computing with uniformly knowledgeable and experienced users should be chosen for the initial experience. For example, the "artificial intelligence" research community meets this requirements and has also shown its readiness for and interest in resource sharing.

A complete discussion of the further possibilities along this specific line is contained below in the section entitled "Automated Organization and Management of Biomedical Knowledge."

Assuming that the needs of the biomedical research community dictate and that administrative problems can be overcome, it should be possible within the next four to five years to completely reshape the nationwide ensemble of biomedical computing resources. That ensemble then would consist of specialized resources of the kinds indicated above (plus, no doubt, a few others), complemented by large, general-purpose computing facilities (probably run by contract), linked by a sophisticated data network to each other and to numerous smaller "taps" located at medical research centers throughout the Nation. All sharable and sharing resources would be staffed by "facilitators" who would be familiar with the capabilities and key personnel of all other resources. These facilitators would actively assist potential users, define their problems, locate the appropriate computing capabilities, and assist users

in utilizing them. The catalogue of capabilities and key personnel available to any resource user would be maintained and updated by a knowledgeable staff supported directly (probably by contract) by the BRB.

The existence of such an ensemble would, of course, have far-reaching effects. First, it would put the skills and products of many specialized groups literally at the fingertips of every biomedical computing user in the Nation who resided at any institution linked to the network. Second, any methodological research undertaken at any resource on the network would be supportable as resource-related research for the entire network, and in particular for that resource (or resources) specializing in that area of methodological research. Therefore, the network ensemble would directly fill the primary unmet needs of health research computing described in the beginning of this section.

CLINICAL APPLICATIONS OF BIOTECHNOLOGY

Mass Spectrometry

Over the past few years, experience gained within the Biomolecular Characterization Resources Program has demonstrated that mass spectrometry is an extremely valuable tool for analyzing substances present in biological fluids in minute amounts. During Fiscal Year 1973, increased emphasis was placed upon clinical applications of mass spectral techniques to meet the specialized needs created when dealing with medical problems. In order to take full advantage of the investment already made in basic research and accelerate the diffusion of sophisticated technology that can contribute to improved health care, clinical mass spectrometry has been designated a new initiative area in the Biomolecular Characterization Resources Program.

Developments during the last year resulted from various service and collaborative research arrangements with clinical investigators and core research activities conducted by resource staff.

At the Massachusetts Institute of Technology's Mass Spectrometry Facility for Biomedical Research, a program is being conducted for the rapid and unambiguous identification of drugs in human body fluids. Using gas chromatographic and mass spectral techniques, drugs present in the gastric contents, blood, or urine of drug overdose patients are identified and the appropriate information returned to the attending physician so that effective treatment may be initiated and proper utilization of existing facilities may be made. Of prime importance to this procedure is a digital computer. The computer accepts and processes the data from the mass spectrometer and then compares this information to a library of approximately 400 mass spectra compiled from authentic data obtained from known drugs. Thus, an automatic, rapid identification is made. The medical community has enthusiastically accepted this service and it submits only those samples that, for various reasons, have been judged to be beyond the capability of the hospital or commercial laboratories to handle appropriately. The library, compiled with the assistance of other research groups, has been distributed to other interested laboratories.

For a number of years there has been considerable interest at the Michigan State University Mass Spectrometric Facility in the structures of fatty substances that are components of normal and abnormal nervous tissue. Studies conducted at this laboratory are designed to elucidate the nature of various neurological diseases through the identification of these materials. Using mass spectral techniques on samples obtained from an 18-month-old child, the diagnosis of Sandhoff-Jatzkewitz disease, a rare variant of Tay-Sachs disease, was confirmed.

One area of clinical medicine to which mass spectrometry has proven to be of extreme value is the diagnosis of metabolic diseases. In collaboration with investigations at the Stanford Medical School, the resource-related research project, "Computer and Chemistry," being conducted at Stanford University is developing both the computer-based techniques for processing mass spectral data and the necessary laboratory procedures for handling biological specimens for analysis. As a result of the application of these techniques to urine specimens obtained from premature infants, a number of metabolic disorders have been diagnosed.

During the next year, continued emphasis will be placed upon developing clinical mass spectrometry still further. Because of the nature of a resource, the Biotechnology Resources Program provides the most effective mechanism for ensuring the success of this undertaking. Through service and collaborative research activities, adequate interaction with clinical investigators and exposure to their research problems is possible. In addition, core research carried out within a resource allows for establishment of a direct link between clinical medicine and basic research and development in the technology.

The areas of activity that will be of prime concern during Fiscal Year 1974 will involve gathering mass spectra data from normal and abnormal populations in order to characterize the biochemical profile of the normal subject and to relate abnormal profiles to specific disease states. In addition, work on developing appropriate clinical procedures and associated mass spectral techniques will be continued.

Opportunities for establishishing collaborative studies with the General Clinical Research Centers Program, DRR, will be explored. It is expected that integrated resource activities would provide the most effective means for realizing our mutual program goals.

Computer Technology

Fiscal Year 1973 also saw the continued emergence of a major new program effort involving both the BRB and the General Clinical Research Centers Branch and focusing on the potential utility of computer technology in support of human clinical investigation. Beginning in July 1971 with a DRR-organized conference attended by both computer and clinical research experts, DRR staff were able to specify a long-range series of endeavors, involving both grants and contracts, through which the role of automated information-handling in the clinical research world might be fully and accurately characterized. One of the earliest of these endeavors is a coordinated array

of four contracts designed to bring three General Clinical Research Centers and one computer technology organization together into a consortium with DRR staff and advisors for the purposes of analyzing the processes of clinical investigation and identifying their potentially viable points of intersection with computer technology.

The members of the consortium are Baylor College of Medicine, the University of Washington, the University of Oklahoma, and the Rand Corporation. These organizations were selected through a national competitive review process and began work in Fiscal Year 1973. The consortium's results are to become the primary basis upon which future implementation efforts are designed and executed.

AUTOMATED ORGANIZATION AND MANAGEMENT OF BIOMEDICAL KNOWLEDGE

"Knowledge Management" is a relatively new aspect of computer science which has radically changed the way a person can interact with a computer program. In "artificial intelligence" laboratories throughout the Nation, an individual can communicate to the computer (and it can respond) in a limited English vocabulary suited to the problem under study, rather than in a specialized computer language. Within projects where this research has been applied, the user no longer has to spell out every action the computer must perform in obtaining an answer; rather, he can pose his factual problem partly in terms of the conditions a solution must satisfy, and the computer can plan and perform much of its own search for a correct result. During that search, the computer program can ask the user for additional information to help resolve apparent conflicts in its data base or in choosing a strategy for finding a solution. The results obtained by the computer can be accompanied by a description of the problem-solving methods used and the considerations which led to the selection of those methods.

These impressive advances, it must be remembered, are the results of long-term, well-financed research (generally supported by the Department of Defense) which has occasionally explored some very long blind alleys. To date, researchers have applied the advances in but a few fields where they could represent relevant information with simplified, more manageable models. They are still far from some of their goals, such as converting a statement of a user's problem, in language appropriate to the problem area (and not the computer), into a running computer program which solves that type of problem. Currently, major knowledge management groups are actively investigating how to apply earlier advances to practical (hence, complex) problems.

The greatest assistance which knowledge management research may offer to the health fields is likely to emerge from studies of how knowledge should be organized and manipulated to facilitate the extraction of "meaningful" patterns. There is much research and speculation on a wide array of systems for helping scientific investigators construct models of their disciplines to help them quickly peruse vast and complex stores of information, to provide them with automatic references to related information, to present concise and accurate descriptive summaries of data, etc. The benefit to biomedical research will come when these systems significantly improve the

scientist's ability to form testable hypotheses from his experimental results and the collected knowledge of the co-workers in his discipline.

The propsects for significant benefit to biomedical research of advances in knowledge management are hopeful, but uncertain. Two BRB-funded activities which have tested the methodologies in the biomedical research area are described below.

Stanford University Heuristic Programming Project

This project's major activity has been the development of Heuristic DENDRAL, a program which automatically interprets mass spectra. DENDRAL reasons from data and hypotheses obtained from organic chemists, in much the same way as the chemists themselves. In fact, the major accomplishment of DENDRAL has not been to exceed the interpretive skills of mass spectroscopists, but rather to formalize their reasoning, which was formerly considered largely intuitive. A corollary effort, called Meta-DENDRAL, seeks to automate the formation of hypotheses about how organic molecules fragment inside a spectrometer. The biomedical relevance of this project is based upon the supposition that the knowledge management techniques learned here will not only improve mass spectrometry, but also will be applicable to other instrumentation or biomedical research situations.

Rutgers University Biotechnology Resource in Computers in Biomedicine

This group features broad-based core research in the methodologies of knowledge management, plus several biomedically relevant collaborative projects. Most advanced of these is the development of an interactive diagnostic/assistance computer program in glaucoma, undertaken with opthamologists at Mt. Sinai School of Medicine, New York. The program features a descriptive scheme for glaucoma in the form of a causal network of physiological/functional states of the eye. Sequential diagnostic strategies have been based upon this network of states. The group plans to develop clinical consultation and evaluation programs associated with this model. The program has already been used to study the demographic distribution of vision problems in parts of New York City. To date, the Rutgers effort is an outstanding example of successful interaction between knowledge management and biomedical research.

During FY 1973, there occurred within the NIH the first major attempt to provide support for knowledge management research efforts related to biomedicine. This was the creation of the Computer Laboratory Health Care Resource Program within the Bureau of Health Manpower Education (BHME) of the NIH. The enabling legislation (Comprehensive Health Manpower Training Act of 1971, Section 769A) mandated the support of computer laboratories to study programming languages, standards, communications, and strategies of decision making, relevant to the use of computers in health care and research. Substantial and increasing funding was projected for the first three years of the program; there were funds enough for at least a half dozen laboratories. BRB staff were active participants in the planning and establishment of this program.

Unfortunately, funding for the program was indefinitely suspended because of a BHME consolidation and reorganization, and no comparable source of stable funding for biomedically relevant knowledge management research now exists in the NIH. However, the BHME experience unequivocally demonstrates the prospects for exciting research activities in this area and has prompted BRB staff to seek ways in FY 1974 and after to facilitate the mandation of at least a few of these new interests into functioning Biotechnology Resources.

BIOMEDICAL ENGINEERING RESOURCES

Biomedical Engineering Resources are a small but significant component of the BRB Program. These resources feature the highly desirable enlistment of complex technology, equipment, and instrumentation from the engineering profession to aid medical research and medical practice. These resources operate in an environment where specialists of both sides interact in a natural, confident and mutually satisfying way. They represent a union which opens opportunities to add adaptations of revolutionary modern discoveries in the physical sciences to the progress of medical sciences and at the same time mitigates the effects of high specialization which in the past has limited interdisiciplinary collaboration.

In considering biomedical engineering resources, the following several questions can be used to form a framework for understanding the BRB's near-term and long-term objectives in this area:

1. Has biomedical engineering begun to reach a level of disciplinary competence to devote a significant portion of its activities to solving problems of other researchers as opposed to almost complete devotion to strengthening the knowledge base of biomedical engineering? i.e., are these scientists ready to become professional problem solvers?

2. What sphere or community in health research is most likely to profit from intimate interaction with biomedical engineers?

3. How does a biomedical engineering resource select problems which offer the highest payoff for health research if the resource has the following features:

    a. core research development and design activities at the highest level of its speciality;

    b. a requirement for health research collaboration to be present as represented by coauthorship of paper;

    c. less intensive activities supportive of health research akin to computer "services";

    d. continuous informal training of engineers, physicians, and support staff;

e. the diffusion of acceptable finished products (hard or soft) into health research; and

f. translation of appropriate "finished product" candidates from health research into health care from the medical center setting?

4. What are the potential benefits to the medical research community from a NIH investment into the "research overhead" of biomedical scientists?

Ameliorative Research

There is no question of appropriate roles for biomedical engineering in the ameliorative technology of medicine in compensating the incapacitating effects of certain diseases. In the biomedical engineering resource at Washington University, St. Louis, Missouri, the complete cycle of engineering action is found. The problems of radiation therapy were examined and special-purpose devices (small computers) were designed, evaluated, and carried into commercial production in the "programmed console" manufactured by Spear, Inc., and Artronix, Inc. Another example of biomedical engineering has resulted in a commercially promising device for coronary care monitoring. This product, also a small special-purpose computer for detection of irregular heartbeats, will soon be diffused into common use by Mennen-Greatbatch Electronics, Inc.

Translation of Basic Research to Medical Technology

Difficulty is found in bringing the high technology of medicine and biomedical engineering together to gain a clearer understanding of disease mechanisms. There now exists several high technologies surrounding basic research in disease. Biophysics and biochemistry go directly to understanding the disease state at the molecular level. However, there is but a small likelihood that these scientists and biomedical engineers can conceptualize, manage, or even be supportable from the NIH for the end point (verification through human experimentation) of basic research. Because the nature of the practicing engineer is to solve problems of others, the biomedical engineer's role in high technology medicine should be to continuously seek measures to reduce the research overhead of medical science and to provide new ways for the basic health researcher to interact with his engineering technologies so as to gain new information otherwise unattainable.

Notions on the Technology of Health Research

There is no doubt that this country abounds with biomedical engineering scientists performing as individual investigators forging new knowledge. It is also true that there are clusterings throughout the country of these scientists where the number exceeds the critical mass to bring about a professional problem-solving resource in the support of health research; but because of the heavy flavor of discipline-oriented investigation, little professional interaction with health scientists exists at a level that brings about a finished product. We are now observing the emergence of biomedical

engineering talent motivated toward working in the broader area of technology for health research. The BRB is exploring with engineering resources on the base provided by disciplinary activities at the institutional level.

The diffusion of technology in the service of health research is observed to be well received in the fundamental research sphere, though much remains to be capitalized there. These basic researchers all to frequently give many months or even years to their careers to add the tools of new technologies to their work. A notable lack of diffusion of technology is found in clinical investigation, for the barriers of bringing technology into the sphere of human experimentation is raised to a very high level by the concerns for the welfare of human subjects, the demanding environment of the physician, and the almost total lack of career time for these researchers to become acquainted with new or even old applicable technologies. This diffusion process must take a different and very friendly approach if its benefits are to be passed to the clinical investigator. It appears that now the NIH can further promote health research through investment in the technology of health research and that biomedical engineering resources can be a most appropriate vehicle toward that end.

AN INTERAGENCY INTERACTION

Providing the new and improved instruments and devices that are needed to support biomedical research and improve health care delivery is a problem of considerable concern that has not been satisfactorily solved. The assignment of a Department of Commerce Science and Technology Fellow to the BRB has provided an opportunity to study this problem and the role that the NIH could take in encouraging and directing the development of such instruments and devices. This study suggested that a program involving contracts with technological-oriented organizations for research, development, and prototype production, coupled with procedures that would assure frequent and open discussions between the investigators from the medical and technological communities, would be more effective than a grant-oriented program or an extensive NIH in-house effort. The study also indicates that a successful program would need to include coordinated means for matching biomedical instrumentation needs with relevant technological approaches; for ranking these needs as to medical significance and technological feasibility; for directing a research and development effort to provide the necessary knowledge base; for producing and comprehensively evaluating prototype units; for publicizing the results of the work for the benefit of the medical community as a whole; and for insuring that appropriate and adequate medical and technological inputs were made at all stages of the work.

A proposed program and NIH management scheme has been described. This program envisions participation by the NIH-related medical community in identifying and defining problems and in evaluating devices and methods developed in response to these needs. The required R and D effort and production of prototype units are expected to involve highly competent technologists from academic, industrial, and government organizations working in close conjuction with medical investigators. Frequent meetings and symposia will provide guidance, as well as the opportunity for the exchange of ideas between medical and technological investigators. Further use of the

items developed will be encouraged by descriptive publications in the open literature and by the release of plans and specifications for commercial production whenever practical.

The description of the proposed program is being reviewed at the NIH. This is not a formal BRB Program proposal, and its development has involved contacts and inputs from a number of NIH sources and outside organizations. At this time, it is not clear where the management of such a program would reside at the NIH or whether a multi-categorical coordinating system should be formed. However, the study was carried out under the auspices of the BRB, members of the staff contributed to it, and implementation of the proposal would influence the BRB Program.

PROGRAM EVALUATION AND PLANNING ACTIVITIES

Program Efforts

Two program issues received particular attention during the past year: (a) program analysis and evaluation and (b) future problems predicted to arise in resource sharing by institutions. While initial and periodic review by the Initial Review Groups and Council provide a measure of the scientific merit and effectiveness of Biotechnology Resources, program responsibilities require careful attention to the rate of diffusion of biotechnology into biomedical research; the cost effectiveness of serving that community; and the mechanism of the most effective disposition of existing, but untapped, resource capability available to and needed by the Nation's biomedical researchers. Assessment and evaluation studies of computer resources are greatly facilitated by the ease of programming to produce self-monitoring and accounting data. The annual reports provide a great amount of data acquired directly from such programs. The staff of the BRB is conducting a study using this data and other information to gain deeper insight into present and future program trends and to avoid future deficiencies by developing appropriate operational and support mechanisms.

The Rate of Diffusion of Computer Technology into the Research Community

One metric which has been developed has predictive properties regarding the development of certain resources. This measure is the ratio of productive computer hours logged by the user community of the resource to the number of full-time equivalents of programmers on the resource staff for a given year. The technical skill and interpersonal attitudes of the programmer staff seem to be important, along with the ability of the Principal Investigator to create and implement a hardware/software system matching the needs of his user community. Retrospective examination of this ratio confirms its effectiveness not only as a measure of the rate of diffusion of computer technology; but also, when combined with a cost metric (e.g., see below), it serves as a pointer to the viability of a resource relative to the review system.

Costs of Serving the Biomedical Research Community

Since it is now clear that the BRB Program can best serve the biomedical research community by encouraging the development and use of specialized resources, it is more important than ever to assess the relative costs of specialization and generality. Measures of total costs to create both generalized and specialized centers has, interestingly enough, shown little difference; and, in most cases, those computer systems especially developed for the research community are less costly than general-purpose ones, i.e., utilization by the research community is much higher when their needs are addressed directly by the staff and system of a Biotechnology Resource.

BRB interests in cost measures stem from the programmatic goal of seeing that biomedical computer technology contributes to an optimal way within the funds available. The strategy has been to create and nurture resources and then see at least their routine service components sustained without further BRB funds. Costs obviously play an important role here, for if a resource is to become self-sustaining, it must be able to compete for computing dollars within its own environment. Thus, a cost measure such as total production time in hours per year divided by the average annual BRB award dollars per year gives a measure through the BRB-support stages. Average annual amounts are used to cover rental/purchase variations introduced by alternative procurement methods selected by the grantees. Total computer production time is the total core research and user time interacting directly with the computer as is indicated in the annual resource usage summaries, i.e., total man/machine interaction time.

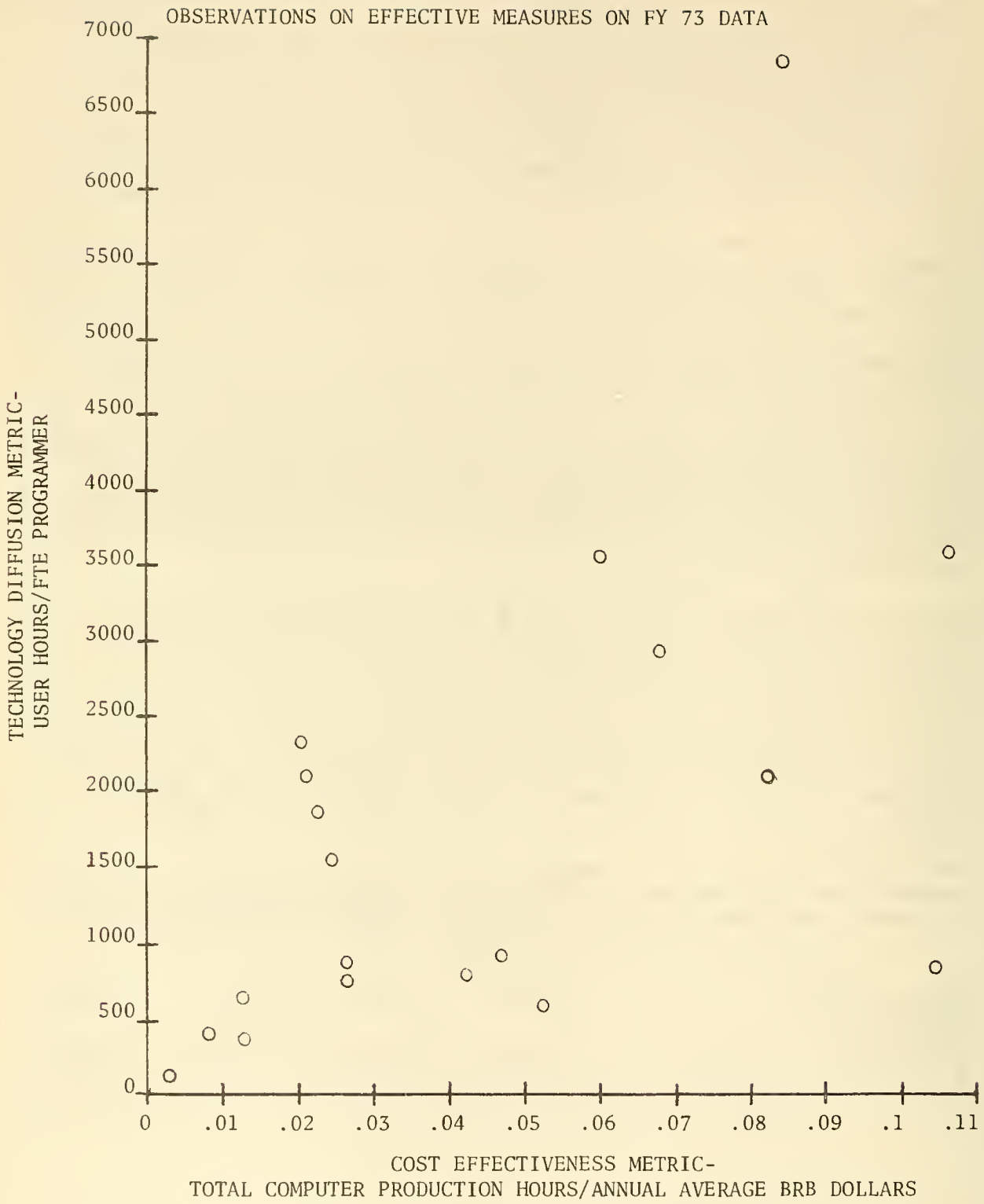
When this cost measure and the above diffusion measure are graphed and examined together for a single resource, year-by-year changes show the development of that resource in time.

When the diffusion metric and cost metric are plotted for all computer resources (Figure I), a general separation of resources into successful and unsuccessful operations is observed. Should this observation prove to be consistent in time, it can become a valuable management tool for this Program.

When taken separately over the entire computer resource program, the cost measure shows the effectiveness in moving from batch-processing systems to specialized systems developed for specific research needs, as shown in the cost/effectiveness metric during the years 1968-72.

BRB Dollars Per Computer Production Hour	1968	1969	1970	1971	1972
	$91/hr.	$70/hr.	$72/hr.	$52/hr.	$32/hr.

FIGURE I


OBSERVATIONS ON EFFECTIVE MEASURES ON FY 73 DATA
TECHNOLOGY DIFFUSION METRIC-
USER HOURS/FTE PROGRAMMER
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
0
.01
.02
.03
.04
.05
.06
.07
.08
.09
.1
.11
COST EFFECTIVENESS METRIC-
TOTAL COMPUTER PRODUCTION HOURS/ANNUAL AVERAGE BRB DOLLARS

ADMINISTRATIVE ISSUES

New Applications

Opportunities to further respond to the changing priorities through biotechnology are not limited by talent in applicant resources but by fiscal stringencies. This is apparent when only four new resources could be initiated from a population of 14 applications with outstanding priority scores (100-200). This population of unfunded applications contained 11 new applications and one supplement. Should this fiscal condition remain where priority scores in the region from 100 to 200 continue to go unfunded, this program area will be unable to attract the high-level talent wishing to contribute to biomedical research through Biotechnology Resources.

Competing Renewal Applications

Because of the length of time (upwards from three years) to bring Biotechnology Resources to optimal operations, emphasis is continuously placed in funding the first competing renewal applications. This is necessary because these resources represent a long-term development of a few comprehensive units of substantial magnitude in staff and in equipment/instrumentation, as opposed to a discipline-oriented research project.

The programmatic problem here also has its foundation in the fiscal stringencies in the grants program. These fiscal constraints permit funding of competing renewals in the upper range (100-150). Most phase-out cases occur because uncontrolled circumstances prevented the resource staff from achieving their potential contribution at the planned rate. Others are phased out because they are unable to keep pace with the technological advances, mainly because new solutions to life science research needs are constantly evolving, and it is difficult for facilities to avoid being locked up in a fixed environment. Additional program resources would permit more flexibility in recovering those resources having potential to meet the new needs of their user community.

Fiscal Year 1973
Annual Report
Chemical/Biological Information-Handling Program
Division of Research Resources

INTRODUCTION

Fiscal Year 1973 marked a major milestone in the evolution of the Chemical/Biological Information-Handling (CBIH) Program. During this year the PROPHET System--NIH's specialized computer resource for research on drugs and drug-related phenomena--emerged after over five years of intensive program-initiated design and development to become a service in support of the day-to-day information-handling requirements of more than 30 laboratory and clinical investigators at four terminal installations in three states. Moreover, as a result of a national competition conducted by the CBIH Program in FY 73 to identify additional qualified PROPHET users, another nine sites (out of 24 applying)--with, conservatively estimated, up to 70 potential additional user-scientists engaged in uniformly high quality endeavors involving chemical/biological interactions--await access to PROPHET's services as soon as contractor personnel, hardware resources, and telecommunications services can accommodate them. This is the first time that a community of geographically dispersed pharmacologists has shared a research tool of PROPHET's scope and power, and for the years immediately ahead there exists a unique opportunity to evaluate and refine PROPHET specifically--and to a considerable extent computer technology in general--in terms of its ability to catalyze the discovery, communication, and use of new pharmacological knowledge.

BACKGROUND

The CBIH Program

The CBIH Program, in keeping with the mission of the Division of Research Resources, NIH, is concerned with providing biomedical scientists with the research support capabilities they most need to pursue their investigations effectively. The focus specifically is on (a) designing and developing computer-based information-handling tools important to studies of chemical/biological interactions (a line of inquiry relevant to almost every major medical area); (b) making these tools available to the national scientific community in an easy-to-use and highly reliable form; and (c) collaborating with the users of these tools in order not only to refine and extend them but also to develop deeper insights into the investigative process itself. Particular emphasis is placed on questions of where and how computer technology and information science can catalyze the emergence of predictive capabilities regarding the interactions of chemical substances and living systems.

The PROPHET System

At the heart of the CBIH Program is the PROPHET System, a unique, large-scale computer resource designed and developed exclusively for the study of chemical/biological interrelationships. Its long-range goal is to accelerate the growth of a predictive science in this area. Its immediate objective

is to facilitate a broad spectrum of laboratory and clinical investigations concerned with how chemical substances influence--and are influenced by--life processes. PROPHET seeks to fulfill both of these purposes by making powerful computer-based information-handling methods available to individual scientists in a convenient and easy-to-use form and by encouraging computer-mediated sharing of data, programs, and the like among PROPHET users.

The PROPHET System hardware/software complex is the result of over five years of effort by contractors, advisors, and staff of the CBIH Program. The software is an extensive array of highly integrated special-purpose programs designed and developed by Bolt Beranek and Newman Inc. (BBN) of Cambridge, Massachusetts. The hardware is a large, time-shared, digital computer (a Digital Equipment Corporation PDP-10) acquired by the NIH specifically for the PROPHET project and housed and operated by First Data Corporation (FDC) of Waltham, Massachusetts. A PROPHET user accesses the System remotely via a graphic display terminal (the Computek 400) communicating over telephone lines.

The PROPHET System has five features that jointly set it apart from other research computer systems:

1. It is established as a national resource especially for the community of scientists concerned with chemical/biological interrelationships.

2. It can be mastered readily by scientists who have little or no prior computer experience.

3. It can be applied effectively to a wide range of complex information-handling tasks relevant to chemical/biological interrelationships without the user having to write <u>any</u> computer programs.

4. It can accommodate very sophisticated users/programmers, integrating user-prepared procedures automatically into the basic System.

5. Through the medium of a set of standard logical frameworks (called data types) for organizing experimental data, molecular structure descriptions, and the like, it seeks to promote the sharing of information among users.

In short, PROPHET is <u>neither</u> a general-purpose facility <u>nor</u> an information service in the traditional sense. Rather, it is a computer facility whose information-handling power is deliberately concentrated in a few specific areas and whose capabilities can grow in a highly orderly way in response to users' requirements.

In its present form, the PROPHET System is primarily a tool for the management of user-provided empirical data and molecular structure descriptions. Conversing with the computer via a high level command language (which can be mastered in a matter of hours or days), scientists can, among other things, perform the following:

(a) define--and redefine at will--the structure of tables within the computer to accommodate their personal research data and/or data which they extract from the literature;

(b) add data to these tables or alter the content of previously constructed tables;

(c) produce displays of all or any parts of these tables in either tabular or graphical form;

(d) invoke a large array of search and retrieval operations on the content of these tables;

(e) apply statistical and other mathematical procedures to the content of selected portions of these tables; and

(f) share selected tables of data and/or programs with collaborating colleagues who also use the PROPHET System but who reside at geographically distant locations.

Moreover, for the specific case of molecular structure descriptions, commands are available to receive input of two-dimensional structural diagrams drawn with a computer-controlled stylus and tablet and to produce and manipulate displays of three-dimensional molecular models. And all the operations which can be invoked through the high level command language can be embellished by a user's own procedures written in a simple programming language (PL/PROPHET).

Current plans call for future versions of the PROPHET System to offer not only extensions to and refinements of the present capabilities for handling empirical data and molecular structure descriptions, but also commands and procedures for constructing and exercising models which simulate life processes. Prototype implementation of these modelling tools already is under way, with particular attention being paid to facilitating research in pharmacodynamics. With these emerging features, as with those currently available, emphasis is on the provision of a set of basic, easy-to-use modules which users may invoke, combine, and extend as their needs dictate.

Current plans for future versions of the PROPHET System also call for expanded capabilities and procedures for user-to-user communication and intracomputer "publication" of selected data files and programs. Special emphasis is being placed upon developing an integrated body of publically available programs and data almost exclusively from the contributions of individual users. While there is no desire to abrogate each individual user's right to maintain his or her personal files in a fully private status, users are being encouraged to share the results of their work with others who also have access to PROPHET.

THE PROPHET USERS

The current array of PROPHET users presents a diversity of scientific interests and research styles. Some examples of user projects are those listed in the following outline:

A. Northeastern University (Department of Chemistry)

1. Synthesis and study of ribosylureas as potential antimetabolites.

2. Study of singlet oxygen-nucleoside reactions.

B. University of Pittsburgh (School of Medicine, Dept. of Pharmacology)

1. Metabolism of neostigmine in isolated perfused rat liver.

2. Pharmacokinetics of secobarbital.

3. Mathematical modelling of enzyme systems near equilibrium conditions.

4. Neuropharmacology of hallucinogens and narcotic analgesics in primates.

5. Studies of the mechanism and locus of phenotypic resistance of bacteria to tetracycline.

C. Boston City Hospital (General Clinical Research Unit)

1. Study of potassium metabolism in the isolated kidney.

2. Mineralocorticoids and relationship to oxygen consumption.

3. Characterization of insulin clearance in patients with renal insufficiency.

4. Hemodynamics of experimental magnesium deficiency in hamsters.

D. National Institute of Environmental Health Sciences (Intramural)

Accumulation and metabolism of selected compounds by an isolated perfused lung preparation.

As indicated in the outline, the range of projects spans a spectrum from medicinal chemistry to human clinical investigation and includes projects supported by the following components of the NIH:

National Institute of Mental Health
National Cancer Institute
National Heart and Lung Institute
National Institute of Allergy and Infectious Diseases
National Institute of Arthritis, Metabolism and Digestive Diseases
National Institute of Child Health and Human Development
National Institute of Dental Research
National Institute of General Medical Sciences
National Institute of Environmental Health Sciences
Division of Research Resources

This mix of projects not only reflects the breadth of pharmacology but also serves to exercise PROPHET's capabilities from many different points of view.

THE PROPHET SYSTEM EVALUATION/REFINEMENT

Following the successful installation of the first several PROPHET terminals in late FY 72 and early FY 73, CBIH Program staff and advisors turned their attention to the question of how best to expand the user community. An extensive national competition was mapped out and conducted over the 6-month period from October 1972 to March 1973. In brief, through advertisements in SCIENCE and the DRG Newsletter and through a series of regional briefing seminars given by CBIH Program staff, research prospectuses were solicited from scientists interested in gaining access to PROPHET. These prospectuses were evaluated by the CBIH Review Committee and detailed discussions prior to the "award" of PROPHET services are now under way between CBIH Program staff and the offerors of the several prospectuses which received the highest rankings.

Overall, the response to the solicitation was gratifying but far from ideal. On the positive side, there were well in excess of 150 separate inquiries for the detailed solicitation materials, and there were 27 prospectuses received for review. This yielded more high quality applicants than available PROPHET capacity can accommodate and gave staff and advisors a rich selection of new users to test and drive the System in various ways. On the negative side, however, many research centers and academic departments in the mainstream of pharmacologic research did not respond to the solicitation, and the majority of such research groups remain profoundly skeptical about the utility of computers in general in their discipline. Despite the success of the past several years in bringing the fruits of technological innovation into practical application in several laboratories and clinics, the burden of proof as to the efficacy of automated information-handling in the area of pharmacology still falls upon those who advocate the technology.

OPERATIONAL PROBLEMS

Large-scale, ambitious technological initiatives almost inevitably encounter frustrations--especially when their products are undergoing a "shakedown cruise"--and PROPHET is no exception. The experience of operating PROPHET as a full-scale service from April 1972 to the present has made CBIH Program staff and contractors painfully aware of areas where near-term improvements in the System are much needed. The overall success of the project and the generally high quality performance by Bolt Beranek and Newman Inc. and First Data Corporation notwithstanding, the PROPHET project faces operational difficulties which could snatch defeat from the jaws of victory if allowed to go unremedied.

Reliability of Terminals and Telecommunication Services

In sharp contrast to the central computer facility for PROPHET--where the "uptime" has consistently been in the range of 98-99% for many months--the display terminals have been chronic sources of difficulty. The terminals have almost invariably required at least two months of stringent checkout by First Data Corporation before passing acceptance tests and being judged suitable for shipment to a new PROPHET user group. Moreover, while the terminals have

generally performed well once placed in operation in the field, the few instances where there was serious malfunction after acceptance have revealed the need for improvements in field service capabilities and arrangements. The PROPHET project's corporate capability for acquiring, checking out, furnishing, and maintaining reliable display terminal equipment is currently the rate limiting step in the growth of the user community.

Telecommunications has run a close second to terminals as a source of difficulty for the PROPHET project. Even with costly dedicated, point-to-point, voice-grade lines run at 1200 bits per second (only half their maximum transmission rate), the frequency of errors such as garbled messages and extraneous lines in displays occasionally becomes annoyingly high. While careful monitoring of the line quality by First Data Corporation has rendered these problems monotonically less severe for any given installation with the passage of time, one cannot avoid labelling the current situation as suboptimal and looking for strategies that simultaneously reduce telecommunications costs and protect PROPHET users from telephone line inadequacies.

The route to solving at least part of both the terminal and the telecommunications problems seems to be selection of a second "flavor" of PROPHET terminal and development of System capability to support it. In particular, a terminal having a minicomputer built in or otherwise associated with it could be expected to do a substantial amount of error-checking on data streams and could make even noisy telephone lines routinely useful. The specifications for this new type of PROPHET terminal already are in preparation. In addition, there is also in preparation a telecommunication service plan focused on reducing operating costs and improving performance through the sharing of telephone lines among users and through the use of new digital message switching and error-correcting techniques. FY 74 should see the beginnings of implementation of these plans.

PROPHET Response Time

PROPHET's average response time--i.e., the average time interval from the issuance of a command by a user (striking the GO key) to the issuance of PROPHET's indication that it is set to receive another command (displaying the READY character)--is another source of operational woe on occasion. It is extremely difficult to promote conversational computing if the computer's average response time is anything more than a few seconds, and PROPHET--due to the size and complexity of its software--frequently exceeds this value. Slow response frustrates some users, especially those who have not worked extensively with computers before, who have only a vague understanding of what is actually entailed in PROPHET's execution of deceptively simple high-level commands (e.g., MAKE GRAPH or COMPUTE MODEL), and who--quite properly--expect machines to be responsive to their needs rather than the other way around. Improving PROPHET's average response time must be a continuing high priority item for the CBIH Program.

A major effort to improve PROPHET's responsiveness already is under way. Detailed data are being collected and analyzed on all aspects of PROPHET's performance. By relating specific events in the PROPHET software to specific events in the time-sharing monitor and the computer hardware, it should be

possible to do a substantial amount of "tuning" of the hardware/software complex to the unique requirements of PROPHET's community. This "tuning" no doubt will include changes in software and software deployment in the short run and probably will also involve hardware changes in the long run.

In addition to these technical steps to improve response time, there are administrative steps which offer some promise. As a general rule, PROPHET response time is best when the PROPHET users are not competing for hardware resources with the System developers. So long as users and developers are required to share the same computer, there will be a continuing effort to reduce the impact of these groups' conflicting demands on one another through scheduling. For the future, the feasibility of conducting PROPHET development work on a separate machine from the PROPHET service deserves serious study.

OPPORTUNITIES FOR FURTHER INITIATIVES

Looking to the future, there is much yet to be done beyond enhancing PROPHET's reliability and responsiveness and promoting vigorous proliferation of high quality users. It would be desirable, for example, if PROPHET's hardware and software capabilities for chemical information-handling were extended beyond their present state, especially in the area of constructing three-dimensional molecular models and in describing the active sites of enzymes. Similarly, development of a comprehensive set of software tools for describing and exercising models of physiological and pathological processes could add an entire new dimension to PROPHET's domain of utility. The fact that PROPHET now is functioning routinely as a shared, discipline-oriented computer resource means that the CBIH Program has an almost unique "laboratory" not only for pursuing initiatives such as the above but also for placing the resulting tools in the hands of PROPHET users literally as soon as they become available for dissemination.

The fact that there now exists a PROPHET user community of some substantial size also opens opportunities of a different sort. Most notably, it offers a ready means to explore the strengths and weaknesses of computer technology in facilitating both informal research collaboration among geographically separate scientists and formal dissemination of research results via "publication" within the computer itself. Initial efforts toward this end began in FY 73 with the first PROPHET Users' Colloquium. Efforts in FY 74 and after will center not only on the colloquium series but also on the further development and use of PROPHET features especially designed to aid user-to-user and user-to-community transfer of scientific information.

Fiscal Year 1973
Annual Report
General Clinical Research Centers Branch
Division of Research Resources

I. Introduction and Goals of the Program

The GCRC Program evolved in response to the need for specialized facilities and trained personnel to meet the complex demands required by high quality clinical research. The fundamental study of human physiology and disease with its broad implications for the maintenance and restoration of health requires the optimal environment for human study. Repeated attempts to perform high quality clinical investigation in beds scattered in the general hospital environment have proven unsatisfactory. Furthermore, a single specialized research unit effectively meets the needs of investigators studying a variety of disease problems in the most effective and economic fashion.

The objectives of the General Clinical Research Centers Program are: (1) to provide facilities and personnel sufficient to establish throughout the Nation, the optimal environment for human clinical investigation; (2) to promote the rapid application of laboratory and basic science research advances to the immediate care of the clinically diseased individual; (3) to increase the total body of knowledge of the etiology, natural history, therapy and prevention of human disease; (4) to promote the improvement of standards of medical care within grantee institutions by functioning as a model of medical excellence; (5) to train physicians, medical students, nursing personnel, dietary personnel, and paramedical personnel in the techniques and disciplines of clinical investigation; (6) to contribute to the maintenance of a national core of full-time faculty investigators and clinical educators through the support of physicians and other trained scientists; (7) to provide a resource for the hospitalization of patients being studied by investigators whose basic research is supported by peer group reviewed Federal grants; (8) to encourage and support the development and practical application of new laboratory diagnostic techniques through the sophisticated utilization of core laboratories; and (9) to promote the development of more efficient therapeutic diets and more carefully analyzed research diets through the independent research activities by program-supported personnel.

Although most of the "general" centers can accommodate both adults and children, approximately 15 percent of the supported beds and 23 percent of the supported centers focus on pediatric problems and a few have been built around premature infants, maternal-child, and acute surgical research problems. These institutional resources are available to all qualified investigators within the parent institution for use in studying patients admitted as part of approved research projects. A center consists of four to 30 beds, the average being eleven. A typical center contains bedrooms, treatment rooms, a core laboratory, diet kitchen, patients' lounge, nurses' station, and conference room.

Over 13,000 individuals are involved with the centers. Center grants provide salary support for centers' staff numbering approximately 1,900. In addition, there are over 3,300 clinical investigators supported by other funding sources who are currently conducting medical research projects at the centers. Currently, the program, consisting of 83 centers, pays 83 percent of the extramural research patient care costs funded by the NIH. Thus, the centers are heavily interdependent with and related to the missions and programs of the categorical Institutes of the NIH. For example, during the last year investigators conducted 2,495 clinical studies in the centers. These same investigators were supported by 1,340 research project grants, fellowships, training grants, and research contracts of the NIH which totaled $94 million.

Another way of demonstrating the intimate relationship between the missions of the NIH and the research performed at the centers is to depict the broad spectrum of health problems covered. A recent classification of research activities in the centers reveals the following distribution:

Heart and Lung	33%
Arthritis and Metabolism	25
Cancer	10
Child Health	10
Allergy and Infectious Disease	5
Neurological Disease and Stroke	6
Mental Health	5
Other	10

This distribution does not represent the total distribution of NIH clinical research activities, but does show the broad utilization of the multipurpose research facilities provided by the General Clinical Research Centers. Progress and productivity in clinical research depends heavily on proper resources support including the capability to provide the specialized environment necessary for such patients. The General Clinical Research Centers provide such a national resource. Since these centers are multicategorical, research conducted therein benefits from the interaction of investigators who share experience and expertise from a variety of clinical research interests in the design, conduct, and interpretation of their investigators. Traditionally, support has been provided for a fixed number of hospital beds in a discrete area chiefly within university-affiliated hospitals staffed by specialized nursing, dietary, and laboratory personnel.

A number of mechanisms to improve the Program have been initiated or are now under active discussion. For example, rather than routinely providing a fixed number of hospital beds in a discrete geographical location staffed by specialized personnel (nursing, dietary, and laboratory), the original concept of a center as a physically discrete inpatient unit has evolved over the years in response to the changing needs of the Nation's clinical investigators. The concept has been extended beyond the research limitations of a solely inpatient unit to include facilities and personnel necessary to incorporate an outpatient or ambulatory clinical research program. During the past year, 23,000 outpatient visits were supported. The last phase of the plans for outpatient studies, that of providing geographically separate outpatient facilities is now active with one such center anticipating

5,000-10,000 outpatients visits per year. A second proposal for a geographically discrete outpatient facility is currently being activated. The additional latitude provided by this program extension represents an important complement to inpatient studies.

The GCRC Program grew at an almost constant rate between 1960 and 1967. In the past few years, rising costs and fiscal restraints have prevented expansion and have forced support for fewer centers and a decreasing number of beds. During 1973, the GCRC Program supported 83 discrete inpatient centers plus one outpatient center and one surgical scatter-bed center. Although centers currently exist in about two-thirds of the teaching medical institutions, a number of such institutions with great potential for scientific excellence do not have centers. Table I depicts this program history and indicates that since 1970 funded beds have been below the level funded in 1965. The Program has been able to operate in the face of sharp inflationary rises and modest budget increases for several reasons, such as the closing of eleven centers in 1970, the reduced number of beds supported, the savings realized through new discrete costing procedures, service patient policy, and studies being done on an outpatient basis rather than an inpatient basis. Despite budgetary constraints in recent years, the program continues to support the best available resources for clinical research. Two-thirds of all hospital beds in the Nation specialized for research on human subjects are supported by this program.

Table I. GCRC Program, FY 1960 - 1973

Fiscal Year	Institutions with GCRCs	Medical Schools with GCRCs	GCRCs Awarded	Funded Beds	Apportionment in millions of $
1965	70	58	82	891	26.9
1966	74	61	88	998	28.5
1967	75	62	91	1,056	28.5
1968	75	62	91	1,051	30.4
1969	77	64	93	1,023	35.0
1970	77	64	93 1/	940	35.0
1971	72	56	82	881	38.0
1972	74	58	84	907	42.2
1973	74	59	83	904	41.3
1974					40.6 2/

1/ In 1970, fiscal constraints necessitated a phase out budget to 11 centers and two children's centers were amalgamated with an adult center at the same institution.

2/ Estimate

The information concerning the research performed in the centers has been distributed to the medical and lay community in a variety of ways. For example, in the medical community, in fiscal year 1972 there were a total of 3,254 publications and abstracts (see Table II) which appeared in scientific books or journals. There were also 31,52 medical students, 873 interns, 1,745 residents, 1,281 fellows, 528 dietary interns, and 948 nurses who received at least part of their training through the facilities of the centers.

Table II. Center Publications

Year	No. of Publications
1967	1,477
1968	1,982
1969	2,077
1970	2,341
1971	2,242[1/]
1972	2,365[2/]

1/ Includes 246 publications involving outpatients
2/ Includes 411 publications involving outpatients

With respect to the distribution of research results to the lay community, the GCRC Branch has in recent years cooperated with Alan Landsburg Productions and the Information Office, Division of Research Resources, in the production of two hour-long television documentaries shown to a nationwide audience during prime time. This year, the GCRC Branch and the Information Office, DRR, cooperated to develop and publish a booklet titled HOW CHILDREN GROW - Clinical Research Advances in Human Growth and Development (see section VI below - Special Program Projects).

II. Training

A paramount problem today in the area of clinical research is the dwindling number of talented senior investigators with the growing demands on their research time because of increased teaching, service, and administrative responsibilities. The program serves an important function by providing institutions with an essential resource where young physicians participate in the work of experienced clinical research teams and assist busy senior investigators.

Within the centers, senior scientists, research fellows, and house staff are exposed to increasingly sophisticated methods and concepts of clinical research. Such training is essential for continued development of competent investigators and for improved medical care in the Nation. In these centers, future medical practitioners develop foundations of knowledge that facilitate critical evaluation of new medical discoveries with which they will be confronted in the course of their careers. In addition, the centers

assist in the training of large numbers of paramedical personnel. They are the primary hospital facility in which nurses, dietitians, and laboratory technicians gain practical experience in newly developed patient care techniques, generally resulting in better quality of hospital care. Table III shows the numbers of individuals receiving training in clinical centers during the past eight years.

Table III. Training in GCRCs

Fiscal Year	Medical Students	Interns	Residents	Fellows	Totals
1965	1,060	362	937	791	3150
1966	1,684	609	1,261	1,190	4744
1967	2,178	682	1,398	1,104	5362
1968	2,538	863	1,576	1,227	6204
1969	2,939	1,019	1,870	1,340	7168
1970	3,065	991	1,751	1,321	7128
1971	2,872	921	1,646	1,169	6608
1972	3,152	873	1,745	1,281	7051

III. Fiscal Summary

Figure I provides, in graphic form, program appropriations and program ceilings recommended by the National Advisory Research Resources Council since 1965. Except for 1965, appropriations have not been adequate to meet expenditures recommended by the NARRC. Figure II gives a history of expenditures since 1965. It can be seen that personnel and hospitalization costs have been the key factors in the rising costs of the Program. Because the number of active beds supported have been forced into a steady decline, personnel and hospitalization costs have stabilized since 1968.

IV. Research Highlights

Cardiovascular Diseases

Angina pectoris is caused by hardening of the arteries of the heart. Although it is common in middle-aged men, it may begin in the early twenties and can be totally disabling. At the present time, the conservative treatment of this disorder with nitroglycerin and restriction of exercise does not prevent the course of the disease. A possible major advance in the therapy of this disease has been an operation which permits a shunt of blood around the area of obstruction in the coronary arteries of these patients. Although this operation has been widely instituted, its efficacy has not as yet been fully established. Since the operation involves a significant mortality and although immediate response with decrease of pain has been achieved, complete assessment is mandatory. At Stanford University, Dr. Donald Harrison and Dr. Edward Alderman are currently undertaking a plan for a careful follow-up of 128 patients who have had bypass surgery. A

Figure 1
GENERAL CLINICAL RESEARCH CENTERS
History of Appropriations and Ceilings Recommended by the
National Advisory Research Resources Council for the
General Clinical Research Centers Program
Fiscal Years 1965 - 1973

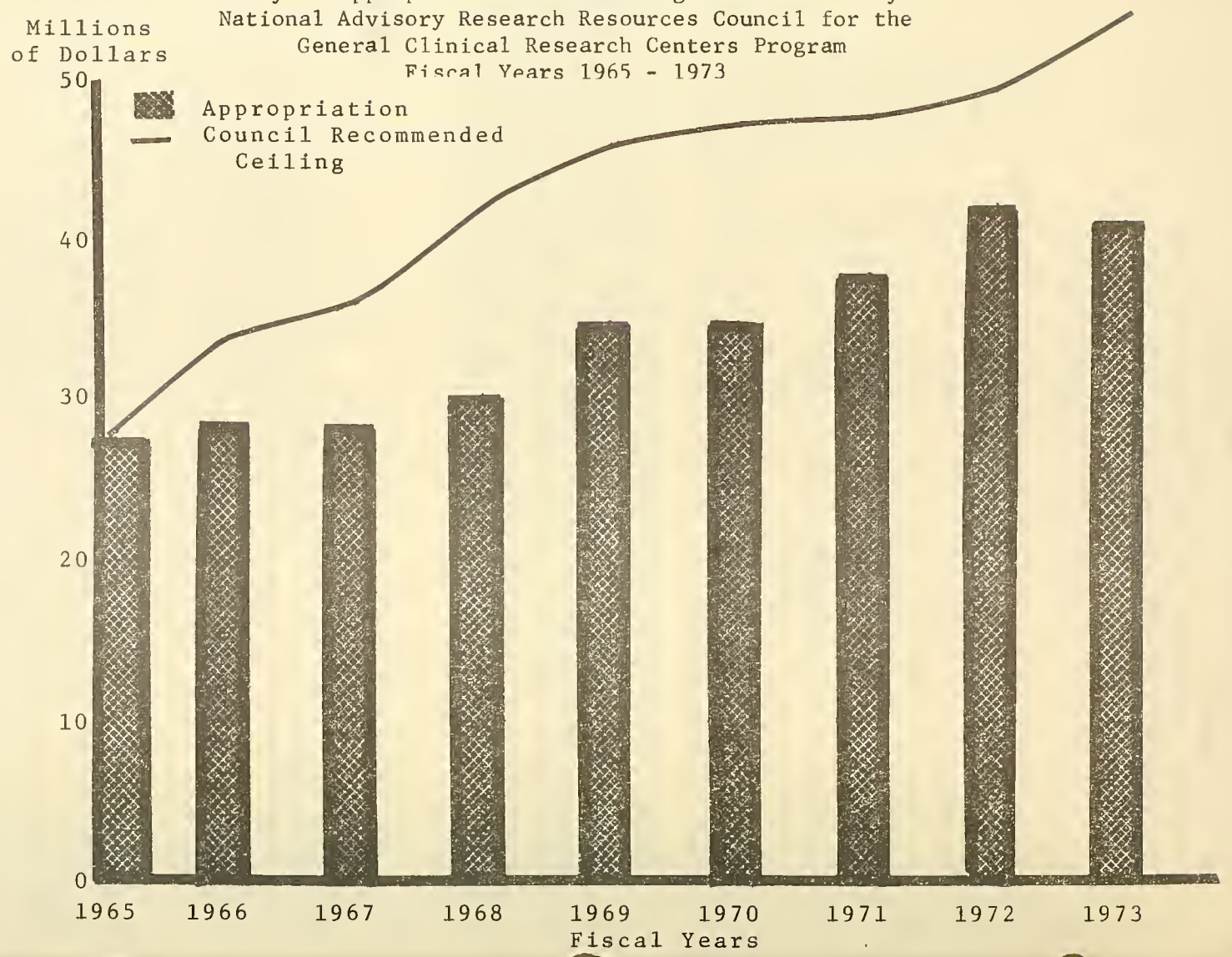
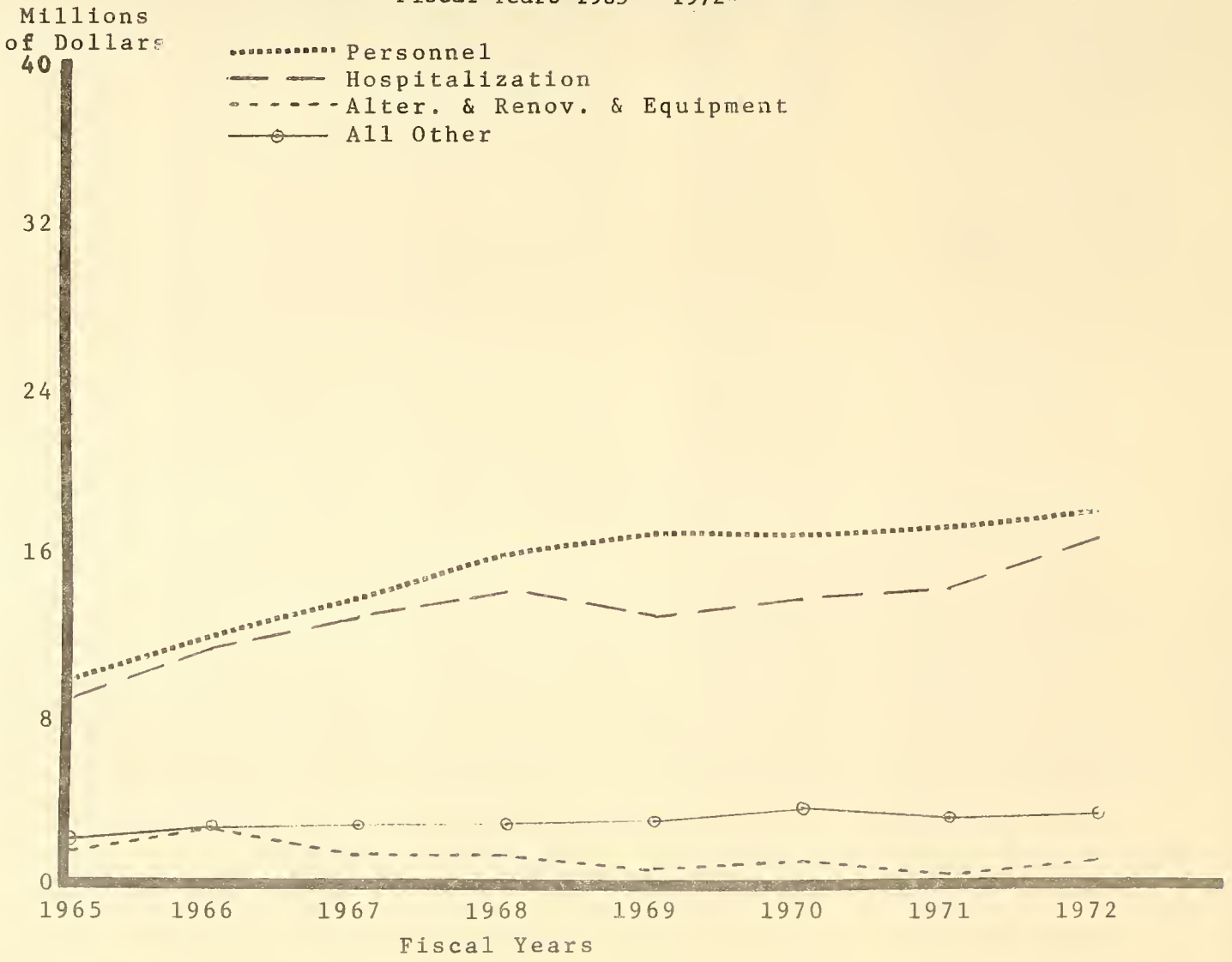


Figure 2
GENERAL CLINICAL RESEARCH CENTERS
Expenditures by Selected Budget Categories
Fiscal Years 1965 - 1972*



number of parameters are being studied and the careful documentation of the benefits and risks involved in this procedure will contribute greatly to the knowledge needed to evaluate bypass surgery.

At the Tufts New England Medical Center, investigators working on the clinical study unit have used the principle of external, counter pulsation (ECP) to increase the flow of blood to the heart and have recently shown by objective measurements of heart blood flow, as well as by striking clinical improvement, that significant changes have been made in heart function. This technique increases the pressure in the large blood vessels of the body in order to increase blood flow to the heart. In addition, the pump lowers the pressure against which the heart must work during contraction and thus decreases the work of the heart. In the patients studied with this technique, they were able to discontinue medication for pain and in several instances the patients were able to resume full employment.

Myocardial infarction, or heart attack, is a leading cause of death in this country today. At the Peter Bent Brigham Hospital, Dr. Eugene Braunwald is studying various drug and mechanical interventions in patients with acute heart attacks using various therapeutic modalities such as glucose and insulin infusions, hyaluronidase and counterpulsation in an attempt to prevent further death of heart cells. He is also using recently developed techniques involving electrocardiography and enzyme studies to define the extent of damage in these patients.

A major cause of the development of hardening of the arteries undoubtedly involves cholesterol. In order to study this relationship, Dr. Edward Ahrens and a group of investigators at Rockefeller University have developed and improved six alternate ways of measuring cholesterol absorption in man in order to determine the effects of various therapeutic agents on cholesterol absorption, cholesterol excretion, body pools of cholesterol, and rates of cholesterol synthesis in the liver and intestine. From these studies, he hopes to gain information concerning the role of cholesterol metabolism in the cause of atherosclerotic disease as well as to determine appropriate dietary and drug treatment for high cholesterol levels. Other studies in this area by Dr. William Connor at the University of Iowa are being undertaken to determine whether such dietary or drug treatment really removes stored cholesterol deposits in arteries. This information is necessary or the mere lowering of cholesterol levels in the blood would be an expensive and widespread endeavor with little recognizable gains. They have utilized radioactive cholesterol in the evaluation of patients scheduled for surgery for replacement of obstructive arteries and have found the cholesterol content of these vessels to be uniformly high. They have found through these studies that cholesterol exchange between the blood and tissue within these atherosclerotic deposits is relatively inert. For up to 14 weeks, there was low and incomplete exchange of cholesterol between the atherosclerotic lesion and the blood. Promise for rapid regression of such advanced lesions by medical means is not supported by these findings. Another important question in the studies of cholesterol and high blood fats has been the mechanism producing these high fat levels. These patients can have a defect either in the clearance of these fats or have an overproduction of them through increased

absorption, dietary intake, or synthesis in the body. Dr. Edwin Bierman at the University of Washington plans to study patients with defects in either the clearance or production of fats in order to determine the relative importance of various dietary and therapeutic agents in different groups of patients.

If, as noted above, there is not a rapid regression of cholesterol deposits, it would be important to prevent these deposits from forming as early as possible. In studies at Johns Hopkins University Clinical Research Center, investigators have participated in the initiation of one of the two initial studies demonstrating the utility of placental blood analysis of lipids for the diagnosis of certain types of high blood lipids. They are also undertaking studies to determine the natural history and appropriate therapy of certain types of disorders involving high blood fats during the first five years of life.

DRS

Hematology

Sickle cell anemia is a widespread disorder among the black population in this country. To date, therapy has been mostly symptomatic and despite early promises of other successful medications there has been no truly effective treatment which can prevent the sickling of these patients' cells. Dr. Peter Gillette and his co-workers at Rockefeller University have found that cyanide can affect the hemoglobin molecule involved in sickle cell anemia in a way that impairs sickling. He has done extensive studies of this chemical in animals to determine its efficacy and side effects, and is now undertaking clinical trials on the CRC to determine its use both orally, and taken by vein, in patients with sickle cell anemia. A major complication in sickle cell anemia is the development of infections. Dr. Howard Pearson at Yale University found that individuals with this disorder have a functional lack of a spleen and this finding may be of relevance in the propensity of these children to develop serious infections.

In another anemia, thalassemia, otherwise known as Mediterranean anemia, survival time of red cells is markedly shortened and severe chronic anemia develops. Invalidism with its profound psychological impact on both child and family is followed by death, often by the second decade of life. The only known treatment for this condition is transfusion, which increases the oxygen carrying capacities of the blood. A study under way on a Clinical Research Center, now in its sixth year, in which children are given enough blood to maintain near or normal hemoglobin levels at very frequent intervals, has found that these children maintain a relatively normal level of activity and have not thus far shown the signs of chronic iron poisoning in the degree characteristic of children treated in the conventional way. Changes in psychological state of both the child and his parents have been striking and reflect the real changes in the physical state of the patient.

In another red cell disorder, acute intermittent porphyria, Dr. Kappas at Rockefeller University has identified a deficiency of a certain enzyme activity which may be responsible for this disease. If this is indeed true, it may then be possible to provide the necessary enzyme for these patients

and provide a cure for this disease.

An attempt at therapy of individuals with deficient white cells, responsible for bodily defense against infection, is a difficult one at best. At the Children's Hospital in Boston, investigators working on the Clinical Research Center have been exploring the role of transfusion of bone marrow in the treatment of infants with severe deficiencies in immunity involving a defect in the capacity to produce lymphocytes and antibodies. While it is much too early to evaluate this form of therapy in both immune deficiencies as well as in leukemia and aplastic anemia, the studies are continuing in the hope that this approach may provide a reasonable therapy for these presently incurable illnesses. In another approach to these disorders, Dr. Martha Yow and Dr. Mary Ann South at Baylor University have raised a child with a severe deficiency in the immune system in a germ-free environment. The infant has thus far been maintained successfully and investigations are being undertaken to determine further information concerning the mechanism of this disease as well as to find a form of treatment for this particular infant.

In studies of the mechanism involved in both the production and clearing of blood clots, Dr. Victor Marder at Temple University is investigating the therapeutic effects of urokinase and other agents. Preliminary results are promising. During the course of these clinical studies, Dr. Marder and colleagues are looking into some basic and important questions related to detecting early course of clotting as well as its management. The approaches include the development of methods for detecting certain peptides in plasma which might reflect the presence of clots. Such an assay may well be valuable and, considering the magnitude of this problem, the clinical application could be enormous. In the converse of this problem, patients who cannot form clots because of the reduction in number of blood platelets, treatment has not been satisfactory. In a center study, six patients have been carefully evaluated and found to respond to Vincristine therapy with an increase in their blood platelets. Four of these patients, previously refractive to other forms of therapy, have been in complete remission for as long as five months. No serious side effects have occurred. This therapy may be a valuable asset in the treatment of patients with low platelets.

Cancer

The importance of research to determine the causes and cures for cancer is evident, considering the enormous mortality and morbidity related to this disease. Examples of research in this area at the Clinical Research Centers includes that of Dr. Olaf Pearson at the University of Cleveland, who has been investigating the area of hormonal therapy of patients with metastatic breast cancer. He has noticed that breast tumors are often sensitive to a certain naturally occurring hormone in the body, prolactin. He has undertaken tests with both stimulators and inhibitors of prolactic secretion in normal subjects and in cancer patients. He has noticed, for example, a distinctive deterrent to cancer progression in patients treated with L-dopa, a commonly used drug in Parkinson's disease, which will prevent the secretion of prolactin.

In other studies at the University of Oregon, investigators have developed a sensitive method of determining the presence of a hormone receptor which is present in the cancer cells of certain patients and not in the cancer cells of other patients. In all of the patients showing significant clinical improvement after surgery to remove the ovaries and adrenal glands, this receptor protein was present in their cancer cells. Eight patients who showed no benefit from surgery did not have this receptor present in their cells. Since only about one-third of the patients with advanced breast cancer benefit from this operation, this indicates the possibility that two-thirds of the patients who undergo this major surgery and thereafter require lifelong replacement of hormonal therapy might instead be treated more effectively in another manner.

Many drugs are being tested on Clinical Research Centers for their efficacy in the treatment of cancer. One example is being undertaken by Dr. Eugene Van Scott at the Temple University Clinical Research Center who is trying to determine the effects of external application of mechlorethamine on a cancer which begins in the skin and is known as mycosis fungoides. This treatment when begun prior to internal spread of the disease can bring about complete remission of the disease which to date has extended up to beyond two years. Thus, the cure of this cancer may now exist for the first time.

Growth and Development

Growth and development can be affected by many inherited diseases. These diseases can obviously have a number of debilitating physical effects on the involved child as well as tremendous psychological and financial impact on the entire family. Dr. Victor McKusick at Johns Hopkins University has been studying inherited diseases for a number of years on their Clinical Research Center. Indeed, two of the seven forms of a disease involving connective tissues, known as Ehlers-Danlos syndrome, have been identified through the study of patients on the center. Further studies involving replacement of deficient enzymes in certain of these inherited diseases have been undertaken by Dr. McKusick and his colleagues. It, of course, would be important to discover these metabolic disorders early in order to initiate therapy.

Dr. Henry Nadler, at Children's Memorial Hospital in Chicago, is developing protocols involving the use of amniocentesis in which amniotic fluid is taken from the expectant mother to characterize metabolic disorders that might not otherwise be detected from one to seven years. It is hoped that early detection and treatment may prevent certain of these children from a lifelong history of incapacitating illness.

Many studies involving simple but important therapy of children with growth failure are being undertaken on the Clinical Research Centers. In one study, investigators have proposed that in many instances inapparent gastrointestinal allergy to foods is closely related to the abnormal growth. They have found that a high percentage of such patients have a history of intolerance to foods, with a definite history of allergic disease, and it has been possible to increase remarkably the linear growth rate in some of the children by diets which exclude these foods. In other studies, it has been found that

infants with chronic diarrhea and failure to thrive can be successfully managed by oral feedings in nearly all cases studied. Future studies on this center call for the examination of the basic mechanisms of the abnormalities in these children, their absorption defects and the reasons for the eventual growth and development of the infant.

In the maternal deprivation syndrome, Dr. Charles Whitten at the Wayne State CRC has recently challenged certain notions, in particular one widely held that in this syndrome there is large food intake to no avail. Dr. Whitten has documented that these subjects eat poorly and can grow significantly better on small improved food intake.

Corneal Transplant - Ophthalmology

Corneal transplantation has been a remarkable advance to provide vision to patients whose corneas had opacified to the extent that they could no longer see. However, there have been many problems involved in this procedure, among them rejection of the transplanted cornea. In a study at Boston University, it has been found that a postoperative course of Imuran and steroids provided greatly increased success rates for this operation. A randomized study of these drugs is now planned to accurately determine their place in corneal transplantation. In addition, Dr. Herbert Kaufman at the University of Florida has been investigating the factors which he hopes will be predictive of success or failure in corneal transplants. In addition, Dr. Kaufman has been attempting to determine the mechanisms by which clearing of the cornea occurs in corneal transplantation.

Neurology

Many studies are under way concerning the evaluation of L-dopa in Parkinson's disease. Although this drug has been responsible for considerable improvements in patients with this disease, there have been a number of problems involving appropriate administration and side effects secondary to the L-dopa treatment. Dr. Fletcher McDowell at Cornell University has been among the investigators studying this drug on the Clinical Research Centers. Among his important findings has been that of the intermittency of response to L-dopa, which demonstrated that a much lower dose of the drug can be instituted after a temporary withdrawal of the medication. He has also made significant contributions on the effects of other drugs such as alpha methyldopa on the success of L-dopa therapy in Parkinson's disease.

Gastrointestinal

A major cause of morbidity in this area is secondary to the development of cholesterol gallstones. The first real possibility of medical therapy for gallstones has come from the Mayo Clinic Clinical Research Center where Dr. Hoffman has already found significant successful resolution of cholesterol gallstones by the administration of bile acids. Further studies on the benefits and side effects of this therapy are currently in progress. In addition, Dr. William Admirand at the University of California has described encouraging results of preliminary studies directed at dissolving retained postoperative gallstones by washing the bile duct with certain solutions

containing a chemical, sodium cholate. With a more acceptable method and greater experience, this practice may become applicable outside of the research setting.

A common medical problem, particularly in large cities, is the treatment of alcoholic cirrhosis of the liver. The patterns of blood flow to the liver are of extreme importance in the understanding and management of patients with this disease who frequently bleed to death because of a blockage of blood flow through the liver. Studies concerning these patterns of blood flow are currently being undertaken by Dr. Frederick Reichle at Temple University who has already gathered much potentially important data for the management of the patient with cirrhosis and portal hypertension. Through the understanding of these patterns, successful treatment might be possible, such as the operation developed by Dr. Dean Warren using the CRC at Emory University in which he uses a new operation to direct blood flow away from the liver, known as a splenorenal shunt. This technique may bring new hope to patients with this disorder who otherwise have a grim prognosis.

A disease of the body's connective tissue which has significance for the gastrointestinal system is scleroderma. Dr. Gerald Rodnan at the University of Pittsburgh has studied an extensive group of these patients on the CRC who have been referred from all over the country. Dr. Rodnan has shown that many patients with active scleroderma have increased daily excretion of certain chemicals known as hydroxyproline peptides. Dr. Rodnan hopes to further study these peptides to determine their origin and role in the production of this disease. In many disorders like scleroderma, therapy is not available and means must be developed to care for the symptoms of these diseases. One mechanism to prevent the large amount of time spent in hospitals by certain patients with malabsorption diseases has been the development of an artificial gut by Dr. Belding Scribner at the University of Washington. This involves a home program of self infusion of daily nutritional requirements by patients who can no longer ingest or absorb food normally.

Renal Disease

To better understand the pathogenesis of kidney diseases, Dr. Norman Hollenberg at the Peter Bent Brigham Hospital has explored the distribution of kidney blood flow using radioisotope techniques. He has already determined alterations in kidney blood flow in various types of renal failure and he now hopes to provide treatment for these disorders by correcting these abnormalities in blood flow.

The area of renal transplantation has brought new hope to patients with previously incurable kidney diseases. Dr. John Najarian at the University of Minnesota Clinical Research Center is presently working in this area to understand, and to treat or prevent, naturally occurring immunologic renal diseases in man. He also hopes to provide a means of predicting which classes of renal diseases might benefit from renal transplantation. In the course of their studies, they have gathered the world's largest collection of

renal transplants in diabetics.

In another major means of palliating kidney disease, investigators at the University of Utah have developed a new technique in maintenance hemodialysis which obviates one of the most bothersome problems in this therapy--namely, the placement of a second needle for the dialysis. In other studies there, a new artificial kidney has been developed which utilizes a disposable insert. This is important since these new machines cost about one-third the price of the units currently in use.

Mineral Metabolism

Two major causes of disease leading to frequent hospitalization are the formation of calcium stones and osteoporosis. At the University of Florida, Dr. William Thomas has been performing research concerned with the characterization of inhibitors of the formation of calcium stones, present in the urine of normal individuals but not in formers of certain types of kidney stones. Studies are now under way to further identify this substance with the possible aim of its use for therapy in the treatment of kidney stones. Dr. Thomas has also been actively involved in the use of orthophosphates in the treatment of this disorder. The treatment of osteoporosis with calcitonin is being investigated in a number of Clinical Research Centers. It has been estimated that four million Americans have the disease, experiencing back pain or fractures in the areas of the hip and wrist. From the financial point of view, the cost to the taxpayer has been estimated to be $3 billion. The use of calcitonin has had preliminary indications of success in this disorder. Also, at the Mayo Clinic Clinical Research Center a treatment consisting of a combination of sodium fluoride, calcium, and vitamin D has been undertaken. The evidence thus far indicates that this combined form of treatment produced an increase in bone mass, and it is estimated that in five years the patient studied will have reached the state where the bone mass has increased to a point where further fractures will not occur and further pain and disability should cease.

Body Fuel Utilization

Two important areas concerning aberrations of body fuel utilization are diabetes mellitus and obesity. Diabetes mellitus is one of the most common diseases in the country today and, indeed, in populations over 60 years of age the prevalence may be as high as 10 percent. The regulation of glucose, a body fuel, and insulin, one of the body hormones which control glucose levels, has been a subject of major study on the Clinical Research Centers. Dr. Stephen Fajans at the University of Michigan is performing studies involving the regulation of insulin release by different amino acids. His studies indicate that the responses to these amino acids are secondary to two separate sources or pools of insulin: an initial or labile pool and a secondary or synthetic source. Dr. David Kipnis at Washington University in St. Louis is studying the effects of various carbohydrate and caloric intakes on insulin release mechanisms. He is studying subjects after six weeks of prolonged fasting in order to determine body responses and their development. They have the potential for synthesizing certain radioisotopic hormones

which should increase the probability of providing new information on insulin release.

The major approach to the treatment of diabetes and the relationship to its complications will probably depend on whether there is a relationship between diabetic control of blood sugar levels and these complications. At the Peter Bent Brigham Hospital CRC, Dr. Stuart Soeldner has been working on the development of a glucose sensor which can be incorporated into a system by which insulin could be infused in response to high blood sugar. The ability to control blood sugar within the physiological range for the first time provides an opportunity to adequately examine the question of whether diabetic complications are related to the degree of control of blood sugar. In other studies at this hospital, Dr. George Cahill has made fundamental contributions to the interrelationship of hormones and fuels during various nutritional conditions. He plans to continue his studies on the influence of insulin-altered body states, and hormonal manipulations in order to further understand the mechanisms of body fuel utilization.

Obesity represents a major health problem in the United States. At Harbor General Hospital, they have embarked on a multidisciplinary project to evaluate the effects of radical treatment for the massively obese individual. Using the technique of bypassing part of the intestine, they indicate that patients have been losing weight at the rate of 10 to 15 pounds per month during the first months after the operation with very few complications. Attention should also be placed on the prevention of obesity, and at Rockefeller University Dr. Jules Hirsch, who has made contributions on the relation of the size of cells to obesity, is now concentrating his efforts on behavioral studies concerning the psychological factors of obesity and weight loss. He hopes to determine those factors most important in both the development of obesity as well as its treatment. In order to further understand the problem of obesity, Dr. Philip Felig at Yale University is undertaking studies concerning the relationship of various hormones and fuels in diabetes, obesity, and obese diabetics. He is also studying food and hormonal relationships in pregnancy in order to determine appropriate diets and diet therapy for pregnant women.

Thyroid Disease

The area of thyroid disease is currently undertaking dramatic developments secondary to the development of new assays for hormones involved in thyroid function and its abnormalities. Dr. Charles Hollander at New York University is currently working on studies using thyroid releasing hormone in order to determine, for use in major clinical testing, the exact location of the abnormality when increased thyroid hormone is present in the blood. At the University of Pittsburgh, Dr. P. Reed Larsen has developed a good assay for triiodothyronine, which is secreted by the thyroid gland, and he now plans to apply this assay method to the physiologic and pathologic secretion of this hormone in man. Since T3 seems to be physiologically more important than thyroxine, a thyroid hormone which has received the most attention to date, this investigative program is of major medical interest.

A new method for the treatment of hyperthyroidism has been developed at the University of Southern California by Dr. John Nicoloff and involves the use of I^{125} for treatment of patients with overactive thyroid glands. Since 1941, over 200,000 patients had received treatment with another radioactive compound, I^{131} for this disorder. It is estimated that 70 percent of all patients with hyperthyroidism receive I^{131} as a definitive mode of treatment for this disease. It has been recently recognized that many of the patients treated in this center eventually develop underactive thyroid function. I^{125}, unlike I^{131}, can selectively damage the hormonal producing portions of the cell while sparing those portions which contain the genetic information required to maintain and reproduce thyroid cells. Initial results of their clinical trials indicate that I^{125} can be successfully employed to manage hyperthyroidism and will result in a substantially lower instance of hypothyroidism from this treatment.

Growth Hormone

The use of growth hormone to correct growth abnormalities in individuals deficient in this hormone has been a recent medical advance. The recent development by Dr. Robert Blizzard at Johns Hopkins University, of an instrument which withdraws a small amount of blood at a constant rate, has allowed them to study the role of growth hormone in the adolescent growth spurt. Using this device, they have concluded that, contrary to previous published articles, growth hormone does not increase because of testosterone, a "male" hormone, at puberty.

Information on hormonal levels during normal adolescence will allow them to investigate more completely the boys who have abnormality of growth at puberty. A constant problem in the treatment of patients deficient in growth hormone has been the availability of enough growth hormone to meet this demand. In order to meet this demand, Drs. Wilhelmi, Kostyo and Rudman at Emory University are searching to find a smaller portion of the growth hormone molecule that is active and either abundant in some accessible animals or easily synthesized. The early studies in animals are promising and the studies of these fractions of the hormone in human subjects appears likely to yield information which may soon allow them to achieve their aims and provide a means of treatment of certain children with growth failure.

Hypertension

High blood pressure, or hypertension, affects millions of individuals in the United States and leads to the early onset of coronary, artery, and cerebral vascular disease. The relationships of certain hormones, among them renin, aldosterone, and angiotensin are extremely important in the development of this disorder. Dr. Gordon Walker at Johns Hopkins University has headed a group working on the CRC concerned with the evaluation of this system in patients with hypertension, have developed a new assay for plasma angiotensin II, and now plan to screen for the association between this hormone and several types of hypertension. One of the curable forms of hypertension involves the overproduction of one of these hormones, aldosterone. It can be caused by a number of mechanisms that are important to define as the

treatment for these mechanisms is radically different. At the University of California, Dr. Edward Biglieri has developed a combination of tests which he feels can separate all but a few difficult cases. This is important since no single criterion has proved to be consistently useful in the differential diagnosis. At the University of Southern California, Dr. Richard Horton has developed a rapid and accurate method for the measurement of aldosterone which allows a precise diagnosis of increased aldosterone to be made in patients suspected of this disease. In addition, measurement of levels of aldosterone in the blood flow from the adrenal gland can localize the site of a tumor responsible for the increased aldosterone and hypertension. Predetermination of where the tumor resides thus allows the surgeon to do a much safer and simpler operative procedure for removal of the tumor.

Immunology

At the University of Minnesota Clinical Research Center, Drs. Robert Good and Soo Duk Lim successfully treated leprosy by immunotherapeutic methods. Dramatic clinical improvement was shown in a dozen leprosy cases by creating an immunologic attack against a drug-resistant disease. Similar studies on the center at the University of Rochester now give hope to approximately 15 to 50 million lepers in the world who are resistant to drug treatment. This new treatment also opens new research parameters in the use of thymus-type white cells against disease.

Drug Abuse

The problem of narcotic addiction has a tremendous impact upon both the system of medical care delivery and the entire economic sphere. Much of the work concerning the clinical development of the methadone program was undertaken by Dr. Vincent Dole on the CRC at Rockefeller University. Many other units have also undertaken studies concerning this problem. Among the examples of such studies are those at the University of California in San Francisco where a unique computer-driver mass spectrometer has been developed which allows detection of drugs and their metabolites in urine and breath. Chronic narcotic addiction is recognized by production of certain end products of morphine found in the urine of heroin addicts. Methadone and its metabolites can also be detected. Specific new research programs will involve the use of propranolol, a drug now used to treat certain patients with heart disease, in order to prevent the euphoric actions of heroin addicts, and also to control alcohol withdrawal syndromes. With the widespread use of marijuana, it has become essential to determine any side effects or possibility of addiction to this chemical. Researchers at the University of Chicago CRC have developed both the instrumentation and techniques for standardizing the administration of marijuana to human subjects and for quantitating with reasonable reliability the amount of the active compound absorbed through the lung of these subjects. Although drug tolerance has been described in animals, no such phenomenon was evident in these studies in humans. These subjects showed heart rate elevation characteristic of marijuana effect. Several subjects lost their capacity to detect time, and there was some evidence of mental aberrations at higher doses. This is just the beginning of a scientific investigation of

marijuana influence, which should ultimately provide society with a firmer base for making appropriate judgments concerning marijuana usage.

Opportunities

There are, in addition to the studies mentioned, abundant future opportunities for research progress on GCRCs. For example, in the area of cardiac disease studies involving the pathogenesis of atherosclerosis, the effectiveness and new techniques for specific risk factor reduction in this disease, the mechanism of biochemical and genetic control of blood lipids, behavioral intervention methods, and hypolipidemia regimens are all in progress in centers. Centers are also intimately involved in determining simple, safe, rapid, noninvasive methods for the detection and quantification of coronary atherosclerosis, myocardial ischemia, and methods of therapy for these disorders. In the area of hypertension, most of the current knowledge developed in the important area of the renin-angiotensin-aldosterone hormonal axis has been distilled from studies involving the controlled environment of the GCRC necessary to adequately define hormonal interrelationships. These studies are continuing on the centers and the current wealth of data available promises that the future may soon hold new and exciting developments for understanding this disease, as well as therapeutic implications.

In the area of endocrinology, particular attention is being devoted in GCRCs to the study of diabetes mellitus, thyroid disorders, obesity, adrenal hormones, and hormones concerned with growth and development. At the present time, the development of assays for specific hormones, as well as their synthesis, promises exciting new areas in the development of diagnostic and therapeutic regimens for endocrinological diseases.

V. Future Objectives and Trends

A. Resource-related project grants

Authority was received in the fall of 1972 to award resource-related research project grants. These grants would be funded either as supplemental grants to centers or as project grants to individual center personnel who seek support for a specific activity designed to serve as a prototype model for conducting high quality clinical research. The program will serve as an administrative locus for projects which aim to upgrade clinical research capabilities through development or adaptation of technical or conceptual tools for use in GCRCs. The Branch has not implemented this project because of fiscal constraints in the entire Program.

B. Clinical Research Center Associates Program

The implementation of clinical research demands assistance for the clinical investigators. This assistance takes a variety of forms, many of which are currently part of a research resource on the clinical research center. Until recently, professional assistance in the implementation of clinical research has been provided by young physicians whose support came from other sources. In the absence of the latter, it will become increas-

ingly difficult to carry out the objectives of the Clinical Research Centers Program. To ensure that the greatest potential for clinical investigation can be appropriately achieved, it is necessary to supply additional professional (MD) research assistants. Authority to implement a program to support clinical associates on a competitive basis is being sought.

C. Outpatient Activities

Starting in 1970, the General Clinical Research Centers Program allowed grantee institutions to complement their inpatient research programs by incorporating outpatient admissions into their research efforts. In 1971, twenty-nine centers were responsible for 13,100 outpatient days. In 1972, approved outpatient protocols showed that the number of grantees using outpatients for clinical research increased from 29 to 44, accounting for 25,000 outpatient visits. For 1973, the Branch estimates that 47 to 50 of the total of 83 grantees will be doing outpatient work with approximately 30,000-35,000 outpatient visits. The Branch estimates that the level of outpatient activity in 1974 will remain essentially at the 1973 level until additional discrete outpatient centers are operational.

DRS

VI. Special Program Projects

A. Public Information

A public service activity which the Branch has undertaken has been the preparation of a second booklet* entitled "How Children Grow - Clinical Research Advances in Human Growth and Development." This booklet, designed for the layman, but of sufficient sophistication to be useful to medical students and to the nonspecialist physician,undertakes to review new clinical research findings which have been derived from research in child growth and development within the past several years. The majority of the work detailed within the booklet has resulted from efforts on General Clinical Research Centers; however, clinical research results from efforts other than on these centers have been included and given prominence consistent with their importance. The booklet, published in late summer of 1972, serves to underline the importance of clinical research in one circumscribed area and to demonstrate the degree to which work supported by the GCRC program is involved in that effort. The booklet recently was acclaimed by Parade Magazine, a Sunday supplement in many newspapers in the United States, as ..."one of the most outstanding publications made available by the government." To date, about 50,000 individual requests for copies have been received.

B. Clinical Information (CLINFO) Contracts

In a cooperative effort with the Division's Biotechnology Research Branch, the GCRC Branch has been participating in the initiation of project CLINFO,

*The first booklet was entitled "Research Advances in Human Transplantation"

a scientific inquiry aimed at identifying and characterizing the intellectual tasks and information flows in clinical investigation. Project CLINFO is also designed to develop methods for facilitating these tasks and flows, possibly with the aid of computers.

As CLINFO studies have progressed, a large proportion of clinical investigators interviewed indicated that they spend roughly half their time in manual information processing. Furthermore, their research suffers often because investigators do not have time, background, facilities, staff, and interest for appropriate information processing. This is borne out by many cases in which complete data are not collected or are not recorded in an accessible form, in which recorded data are not accurate or are otherwise not suitable for analysis, in which data are not available for timely decision-making, in which analyses are confined by an investigator's personal statistical background, and in what can be done with limited computational facilities, and in which results are not presented in a form that can be interpreted by the investigator and his colleagues.

To develop a detailed knowledge base, the CLINFO investigators have observed a number of clinical research applications of automatic data processing and have discussed a number of computer resources available to clinical investigators. Almost universally, these computer resources are considered "unfriendly," posing overhead barriers and are extremely difficult for investigators to interact with. Clearly, these computer systems were not originally intended for clinical research. The goal of the CLINFO project, on the other hand, is to develop a friendly automatic information processing system especially designed to facilitate many of the fundamental aspects of clinical research. Such a system will help the investigator handle the complexity and magnitude of his information processing tasks. Its capabilities will most likely include recording and validating data, transcribing data from one place to another, transforming information from one form to another, searching for previously recorded information, organizing and reassembling existing information, and analyzing information. Such a system will also help investigators increase their own productivity. This increased productivity is particularly important when analyzed from the point of view of limited availability of funds, subjects, beds, laboratory equipment, etc., that constrain additional investigation time and talent. As a number of investigators have indicated, a friendly information processing system will encourage investigators to shift their time from routine processing tasks to the more intellectual activities of clinical investigation. In sum, nearly all investigators interviewed have expressed their concern about their data handling methods. Many investigators use completely manual methods that are inadequate for the large complex collections of data generated in clinical investigation. Such information processing is central to clinical investigation. The CLINFO contractors believe that a substantial portion of clinical research information processing operations can be acceptably automated. Current plans call for a review of specific subsystem proposals.

C. GCRC Program Evaluation

GCRC grants were awarded first in FY 1960. Activities of the centers have been monitored by staff. Center programs have been reviewed periodically by consultants (principally through the GCRC Advisory Committee and the NARRC), and staff has conducted studies of (1) specific operational components, such as core laboratories, dietary activities, bed support systems, and space usage charges, and (2) certain scientific areas of investigation such as human transplantation and inherited metabolic diseases. GCRCs have not been evaluated systematically in a manner that measures (1) the degree to which GCRC program objectives are being met, (2) the quantity and quality of research output of the centers, and (3) the impact of the program on the biomedical research community, medical education and training, and health care. The accrued experience among the centers warrants an evaluation, in terms of these factors, and to determine whether new objectives should be sought through program modification.

The GCRC Branch has developed an over-all scheme to conduct such an in depth evaluation. The scheme has the following three phases and related input:

Phase 1. Review and clarification of program objectives and execution of appropriate study techniques to determine whether or not these objectives are being met. These studies will also provide important data for assessment of program impact.

Phase 2. Evaluation of specific components of the resource, i.e., core laboratory, diet kitchen, outpatient program, etc.

Phase 3. Review of data obtained in Phase 1 and Phase 2 to determine: (1) the need for changing the objectives, (2) mechanisms for program modification, and (3) the need and recommendations for continuing evaluation.

A subcommittee of the GCRC Advisory Committee has been participating in both the development and the execution of the evaluation plan. Qualified ad hoc consultants have agreed to prepare contribution papers which will be designed to document the contributions that the GCRCs have made to the advancement of research knowledge in specific human disease areas. Contribution papers have been received in the area of growth and development and are almost completed in diabetes and serum lipid disorders. In addition, research profiles of the aggregate GCRCs have been developed. In 1971, information on every project conducted on GCRCs for the grant period October 1, 1969, through September 30, 1970, and October 1, 1970 through September 30, 1971, was obtained. This information includes the project title, an anatomic-pathological code assigned by the investigator, the name of the investigator(s) conducting the project, the number of discharged patients and discharged patient days. The data also include NIH, other Federal and nonfederal grant support. All NIH grants were verified against Division of Research Grants records. The data captured will

enable staff to determine the spectrum of research conducted in GCRC resources. In addition, information concerning the number of projects conducted in various research fields has been compiled. The cost per patient day in each center is also being included in the data so that corresponding dollar figures will be available for protocols in specific areas.

Some of the methodology for Phase 2 is being prepared in conjunction with the CLINFO project being undertaken by the GCRC and BRB. A major task of CLINFO initially will be the description of how the clinical investigator relates to the structure and function of the GCRC and how this affects the investigative process.

Fiscal Year 1973
Annual Report
Animal Resources Branch
Division of Research Resources

INTRODUCTION

The overall objective of the Animal Resources Branch is to support resource projects that provide, or enable biomedical scientists to effectively use animals in human health related research. Special attention is given to those animal resource activities that are broadly supportive of the missions of the various NIH components. The Branch objectives are accomplished through a Primate Research Centers Program, a Laboratory Animal Science Program, and Research Contracts.

PRIMATE RESEARCH CENTERS PROGRAM

The Primate Research Centers, established and operated by Federal grant funds, provide a unique research environment where biomedical research in a number of important areas is being conducted. These Centers continue to provide leadership in the rapidly expanding field of medical primatology, and during this year numerous contributions were made in the areas of reproductive biology and population control, cardiovascular diseases, infectious diseases, and neural and behavioral disorders.

The core support provided by this program permitted the 114 core staff scientists to conduct research on a total of 113 grants and contracts totaling $4.4 million. As a result, a total of 608 scientific publications were published during this year. Some 399 collaborative scientists from a number of universities utilized these facilities to conduct their research; and in addition, 372 scientists were provided with biological specimens. The Centers were active in both technical and research training, and a total of 136 graduate students participated in the research activities as part of their theses requirements. The program provided salary support for 135 doctoral level staff members and 656 technical and administrative personnel.

The research missions previously identified for each Center have been implemented during the year. These missions map on national health needs permitting the Centers to engage in research activities which will assist in solving some of the major health problems.

The Centers realize that primates are becoming increasingly more difficult to obtain from their native habitats and are rapidly developing primate breeding programs. During the year, more than 1,000 primates were born in the Centers. In addition, primate population surveys are being conducted, and steps are being taken to establish a primate breeding station in the Canal Zone.

The missions and research activities of the Centers are as follows:

Oregon Primate Research Center

The missions of this Center are reproductive biology, cardiovascular and metabolic diseases and immune diseases. The following are examples of their research accomplishments:

1. Mechanisms of Sexual Maturation

Intrauterine contraceptive devices (IUDs) were implanted into several female Japanese macaque monkeys to test the hypothesis that endocrine events related to pregnancy interact with other conditions to end the mating season. The six-month mating season was extended by one month, and the females with IUDs were courted with greater fervor than females which had become pregnant. To prove a direct measure of female macaque sexual motivation, several macaques were trained to release vasectomized males from an apparatus that enabled the animals to see and hear each other but to come into social or sexual contact only when the female pressed a switch to release the male. It is now evident that females have partner preferences and that regardless of the stage of their menstrual cycle they release favorite males.

2. Effects of Vasectomy on the Reproductive System

The effects of vasectomy on the reproductive tract system are being investigated in the rhesus monkey. In intact animals, spermatozoa leave the testes and travel through the epididymis to the vas deferens. After vasectomy, the ejaculate consists of the fluids secreted by the accessory glands, and the spermatozoa are trapped in the epididymis. The body must provide a mechanism for their disposal, and to define this mechanism is the purpose of this research. Biopsy specimens from the epididymis of rhesus monkeys vasectomized for 1 to 7 years show many morphological and functional changes. After vasectomy, in both men and rhesus monkeys, there is an increasing level of antibodies, which probably aid the phagocytic cells to recognize spermatozoa as foreign. These morphological and physiological changes after vasectomy indicate that long-term vasectomy results in an autoimmune response to spermatozoa that may aid in disposal of many spermatozoa still being produced by the testes.

Washington Primate Research Center

This Center continues to pursue its original mission, namely, neurophysiology relating to cardiovascular function and the development of an extensive collaborative program in many areas of biomedical research. The following are examples of work being conducted at this Center:

1. Sickle Cell Anemia

A research program which will result in information that is directly applicable to human illness is the study of cyanate to combat sickle cell anemia. Cyanate binding to hemoglobin prevents sickling of the

red blood cells but has no toxic effects. Monkeys have been used to determine the effects of exposing blood to cyanate solution and then returning the washed red cells to the animal. Oxygen affinity for hemoglobin is altered, and cyanate, which is not bound to hemoglobin, has the capacity to bind to other body proteins. No evident toxic effects have been found, and on the basis of these results, clinical studies in man have begun.

2. Methyl Mercury Poisoning

A project which is of great importance in the field of environmental safety is methyl mercury teratogenesis. Man may directly consume methyl mercury as an occupational hazard or may indirectly acquire chronic intoxication as the final consumer in the biological food chain. This material is widely distributed in the body tissues and can freely pass through the placental barrier in pregnant women. In some cases, brain injury to the fetus is extensive. Defective formation of the brain and other organs occur, and genetic damage is also produced. Scientists at this Center are investigating the effects of methyl mercury as a teratogen using the monkey as a model for the human situation. Adult monkeys and developing fetuses are exposed to methyl mercury, and damage to control of movement, to vision, to learning ability, and to other neural functions are evaluated.

California Primate Research Center

The missions of this Center are respiratory diseases and environmental toxicology.

1. Simian Lymphosarcoma

This Center has experienced a spontaneous outbreak of cancer in monkeys, and during the past four years, 38 monkeys have died from cancer of the lymphatic tissues. This cancer outbreak is of international importance because the only other known outbreaks of cancer in monkeys are occurring in the Soviet Union and Thailand, where they are associated with the introduction of human materials, possibly cancer viruses. The possibility that human cancer viruses are causing cancers in monkeys is under active investigation. Thus far, evidence has been obtained for the presence of 12 as yet unidentified viruses in tumors from nine monkeys. The investigators have been successful in transmitting cancer to newborn monkeys thus providing a model for the study of early cancer detection and treatment.

2. Pulmonary Biochemistry

Scientists at this Center have demonstrated that significant abnormalities occur in the lungs of rats exposed to as low as 0.2 ppm ozone for seven days. There is an increase in amount of glutathione peroxidase in these lungs. This has two major implications--first, that glutathione peroxidase levels are an extremely sensitive indicator of pulmonary oxidant damage; second, that the glutathione peroxidase pathway represents a newly discovered system for protection against oxidant damage. These findings

are of potentially great importance relative to human exposure to oxidants, since this work was conducted at ambient concentrations. The results obtained with rats are now being tested in nonhuman primates in order to see whether extrapolations can be made with reasonable confidence to man.

Delta Primate Research Center

The primary mission of this Center is infectious diseases, and an example of this research is as follows:

1. Immunity to Enteric Diseases

This project involves the study of circulating and local antibody formation, with special regards to immunologically competent cells and their formation in cholera, bacillary dysentary, and enteropathogenic E.coli infections. The immunologic responses in monkeys have been studied. Three classes of antibody were found, and the role they play in immunity to these diseases was established. This research was aimed at understanding the disease processes and to use this information for appropriate prevention and control of these diseases.

Wisconsin Primate Research Center

The areas of neural and behavioral sciences and reproductive biology are being continued as the missions of this Center. An example of this research is as follows:

1. Thyroid Deficiency and Retardation

Learning handicaps caused by thyroid deficiency known as cretinism can be partially offset by the provision of a stimulating environment. Center investigators selected retarded animals, provided them with abundant sensory and social stimulation and then placed them in a variety of learning situations. The retarded monkeys performed tasks which normally they would be expected to fail, thus demonstrating the importance of an enriched environment. Based on these studies, it is believed that thyroid deficiency need not lead to totally irreversible retardation, a finding that hopefully can be applied to people with the same condition.

Yerkes Primate Research Center

The research missions of this Center are neurophysiology and neuroanatomy and the study of neoplastic and degenerative diseases. This Center also maintains the largest colony of great apes available anywhere in the world for biomedical research.

1. Histocompatibility Typing in Chimpanzee Families

Histocompatibility typing on six chimpanzee families shows that the genetics of the factors involved confirms that the chimpanzee

has a major histocompatibility locus that is similar to the HL-A locus in man. The investigators have adapted mixed lymphocyte reactivity to the chimpanzee population and have demonstrated a correlation between the degree of lymphocyte stimulation and the genetic distance of chimpanzee families. The Yerkes Center, because of its several generations of related chimpanzees and because the identity of both mother and father of infants is known, is the only place in the world where this work could have been done. The significance of this research is to establish the chimpanzee as an ideal animal for transplantation and tumor research. The establishment of the sharing of antigens of the major histocompatibility loci is important and allows one to apply interpretations to the human with a great deal more confidence.

2. Development of a Computer-Controlled Language for Great Apes

A computer-controlled environment within which the language-relevant behavior of young apes is studied has been developed. The system allows for objective inquiry into ape language skills and for the systematic inquiry into the conditions that differentially foster the development and expression of such skills. A special language has been devised for this project. Words are color-coded geometric symbols which are on the keys of the console on which the animal works. The system allows for conversation between the ape subjects and the human experimenters. A young chimpanzee has already reached significant levels of achievement in the mastering of this language.

New England Primate Research Center

This Center supports an extensive collaborative research program; and in addition, programs in infectious diseases and pathology are conducted by the core scientists.

1. Isolation of a New Virus Causing Malignant Lymphomas in Primates

A new virus, Herpesvirus ateles, from a spider monkey (Ateles geoffroyi) has been shown to induce malignant lymphoma and leukemia in marmosets. The disease is similar to H. saimiri lymphoma which was also isolated at this Center. This finding further stresses the importance of members of the herpesvirus group as oncogenic viruses and the importance of nonhuman primates as potential health hazards as little is known of their normal viral flora.

LABORATORY ANIMAL SCIENCES PROGRAM

The overall objective of the Laboratory Animal Sciences Program, Animal Resources Branch, is to support activities that provide or enable biomedical scientists to effectively use animals to develop knowledge for the prevention and treatment of diseases in man. This objective is accomplished through grants supporting animal colonies of unusual and special value for research; studies directed at finding animal models which are needed for research on human diseases, projects to assist institutions to comply with the legal and policy requirements for care of laboratory animals and which also improve the quality and economy of research with animals; laboratories for the diagnosis and control of disease of laboratory animals; research related to improving health care and determining environmental requirements of animals used in research; and training of specialists in the field of laboratory animal medicine. The program received appropriations of $6.007 million in fiscal year 1973, which supported 78 discrete animal research and resource projects, 9 training programs, and 3 fellowship awards.

Research and Resource Projects

The Laboratory Animal Sciences Program (LASP) has provided support to a relatively small number of discrete research projects over the past several years. This may be summarized as follows:

Research Related to Animal Resources

	FY 70	FY 71	FY 72	FY 73
Number of Projects	5	4	6	8
Awarded (in thousands)	345	403	449	593
Percentage of Total $	8%	9%	7%	10%

Projects falling into this category generally have one of the following objectives: (1) to investigate the etiology, pathogenesis, and control of laboratory animal disease problems, (2) to determine various environmental requirements of laboratory animals. As an example, a grant was recently awarded to Kansas State University to continue studies concerning heat, moisture, and ammonia production from various species of animals. Considerable definitive data has been accumulated already which bears on ventilation requirements for animal facilities. Future work will focus on the effects of ventilation system and cage design on air distribution.

New information and technology have also been major goals of diagnostic laboratories supported by LASP. For example, one laboratory reported the first occurrence of measles as a disease problem in squirrel and cebus monkeys. The safety and efficacy of measles vaccination for squirrel monkeys are now being evaluated. Another laboratory developed an indirect fluorescent antibody test to detect circulating antibody to Nosema. This test should be a valuable addition to efforts to detect and

eliminate this organism from rabbit and rodent colonies used for research. Indepth studies of laboratory animal disease problems resulted in over 70 publications and presentations during the past year. An important facet of the diagnostic program has been the elucidation of new laboratory animal models of human disease. One laboratory reported the occurrence of a nephrotic syndrome in laboratory born and reared squirrel monkeys. Preliminary investigation of this animal health problem indicates that it has potential as an animal model of the human disease. Several of the laboratory programs provide diagnostic support for zoos. This association has provided much valuable material from unusual species which have been maintained for long periods in urban settings. One laboratory became extensively involved in a study of aquatic birds exposed to an oil spill. Much information relating to the epidemiology, microbiology, and pathology of this incident of environmental pollution was accumulated and prepared for publication. The laboratories have also played a major role in training in laboratory animal medicine and comparative pathology. Laboratories are currently located in all institutions where Animal Resources Branch training programs are active. In the future, the support of research associates, etc., by diagnostic laboratories appears to be an attractive way to continue to bring new people into the field and provide training "on the job."

There are 16 diagnostic laboratory programs which are currently active. By undergirding an institution's animal health program, these laboratories have made a direct contribution to approximately 1,400 NIH-supported research projects, with total funding of nearly $70 million. A shortage of appropriately trained specialists (veterinary pathologists, microbiologists) has been a limiting factor precluding any rapid establishment of new laboratories. No new projects were funded during the current year although it is anticipated several new groups with excellent potential will submit applications in the near future.

Institutional Animal Resource Improvements

Development and basic improvements of institutional animal resource programs have continued to comprise an extremely active program area during the current fiscal year. Institutional needs normally include larger and more comfortable animal cages, cagewashers and other types of general sanitation equipment, renovations of animal housing facilities, and addition of better trained professional/technical personnel. This program has received special emphasis since FY 1972 when Congress appropriated $1.5 million for assistance to research institutions in upgrading their animal resource programs to achieve compliance with the Animal Welfare Act of 1970 (P.L. 91-579). The NIH policy on "Care and Treatment of Laboratory Animals" (issued on June 14, 1971) has further contributed to the high amount of institutional interest and overall response to this program area.

As a measure of progression, 14 active improvement grants in FY 1971 accounted for 11 percent of the total LASP budget; 24 active projects in FY 1972 represented 35 percent of the total budget; and 28 of these projects in FY 1973 currently account for 41 percent of the total LASP budget. Although funds available for this particular program unit were actually reduced to $1.1 million in FY 1973, critical needs for such assistance have necessitated

withdrawal of some funds for its support from other areas of the LASP budget. During the current fiscal year (FY 1973), 86 basic improvement applications were received and reviewed. Of this total, 61 applications received scientific approval. Fifteen new awards were made during FY 1973, with new awards totaling $1,727,040. Forty-four (44) approved applications (total value of approximately $5 million) are currently on hand and will be carried over to compete for funds in fiscal year 1974. Institutional needs for assistance in this area are expected to continue at a rather high level for the foreseeable future.

Animal Models and Special Colonies

The objectives of this program are (1) to characterize and determine the usefulness of particular animals which display potential for broad biomedical research utility, (2) to establish, improve, or expand special animal colonies that are valuable for specialized research, but which are not generally available, and (3) to preserve valuable animal stocks which might otherwise be lost (e.g., because of the temporary lack of project support).

Support for characterization and development of animal models and for establishment of special colonies of valuable research animals has remained at a rather constant level during recent years (20 projects in FY 1973 @ $1.141 million) as compared to 21 projects in FY 1972 ($1.250 million) and 21 projects in FY 1971 ($1.342 million).

Most of the currently active projects in the animal models and special colonies area are related to vertebrate species. However, staff analysis and plans have been further developed during the past year to stimulate the future inclusion of appropriate invertebrate animals for model definition and development. A project on characterization and development of Xyleborus (wood-boring beetle), which appears to have potential for diverse biomedical research uses, is currently being initiated at the University of Wisconsin. Another project, also initiated during FY 1973, concerns the maintenance of a number of rare species of Drosophila as a biomedical resource at the University of Texas, Austin. A panel of marine invertebrate specialists was convened in February 1973, to discuss resource-related problems, model definition, and development of appropriate marine invertebrate organisms (e.g., mollusks, arthropods, echinoderms, annelids) for biomedical research utility. Many of these organisms offer unique advantages (e.g., simple anatomic and physiological systems) for investigations. A modest beginning for support in this area is planned during FY 1974.

Animal model development (characterization and definition) projects are limited to those species which have been shown to demonstrate good potential for broad biomedical research utilization (i.e., potential use for two or more categorical areas of research). Particular attention has been given to the qualifications of investigators who are responsible for conducting this developmental work, since a multidisciplinary approach is usually required to achieve maximum information on such animal models. Such projects normally require a rather extensive period of support to fully define and exploit their potential as new and useful models.

Examples of projects on animal models which are currently under development by this program include (1) miniature swine (University of Missouri) as models for studies on chronic alcoholism and associated liver pathology and withdrawal symptoms; (2) hereditarily obese ("fatty") rats (Red Acre Farm, Inc., Stow, Massachusetts) for metabolic and hormonal studies on growth and obesity; (3) a colony of mink (Washington State University, Pullman) with inherited myopathy for studies on muscular dystrophy; (4) several colonies of lemming species (University of Alaska, Fairbanks) for studies on body composition, chronic interstitial nephritis, atherosclerosis, mammary gland tumors and diabetes; and (5) a colony of Siamese cats (University of Alabama, Birmingham) with inherited GM_1 gangliosidosis for studies on human ganglioside storage disease (Tay-Sachs disease).

Examples of active projects which provide support for maintenance of special animal colonies with unique characteristics and which serve as both local and national resources include (1) inbred and mutant mouse stocks (University of Kansas, Lawrence) for studies on host-parasite interactions and ecology, mammalian genetics, energy metabolism of nervous tissue, and genetic influence on ovulation; (2) inbred and mutant strains of rabbits (Jackson Laboratory, Bar Harbor, Maine) which are useful for studying processes related to constitutional diseases, growth, and reproductive disorders in man; (3) beagle dogs (Oklahoma State University, Stillwater) with deficiencies of Factors VII, VIII, and IX for studies on hemophilia; (4) amphibians (University of Michigan, Ann Arbor) which are well defined and useful for many types of biomedical research; and (5) well-defined miniature swine (University of Missouri, Columbia) for various types of biomedical investigations including atherosclerosis and whole/partial body irradiation. During FY 1973, twelve special colonies with core support from the Laboratory Animal Science Program undergirded approximately 52 NIH-funded research projects with total funded value of $4,013,000 and 50 biomedical research projects funded by other sources (total funded value of $749,000).

DRS

Institutional Primate Resources

Five institutional resource projects have received core support for maintenance and care of special colonies of nonhuman primates during the current fiscal year. Total funding in this area currently constitutes approximately 6 percent (@ $342,000) of the total LASP budget. This is in contrast to 14 percent (7 projects @ $879,000) in FY 1972 and 20 percent (9 projects @ $805,000) in FY 1971. This steady decline reflects the continuing implementation of program policy relating to phase-out of DRR support for such resources after their firm establishment.

During FY 1973, these primate resources have undergirded 99 NIH-funded research projects (accumulated funding value of $5,858,000) and 75 biomedical research projects supported by other sources (accumulated funding value of $1,998,000). Research utilization has included investigations in the areas of atherosclerosis, reproductive physiology and fetal development, chronic alcoholism, infectious hepatitis, organ transplantation and experimental epilepsy. Support for initial establishment of primate resources for multidisciplinary biomedical research utilization within institutions is expected to continue as a rather small but viable portion of the overall program.

Reference Centers and Information Projects

The program has continued to support several reference center and information projects. Examples of these are:

1. A simian virus reference laboratory at the Southwest Foundation for Research and Education at San Antonio, Texas. It now has a working repository of over 60 virus reference reagents and reference antiserums. Ongoing activities of the project are designed to give information regarding the immune status of subhuman primates and the possible cause of outbreaks of overt diseases. Institutions throughout the country have taken advantage of this program. For example, during the past year, nine laboratories submitted a total of 1,435 sera from various nonhuman primates for B virus antibody testing.

2. The Registry of Comparative Pathology, located at the Armed Forces Institute of Pathology. The Registry has continued to augment its collection of specimens from primates and other laboratory animals, domestic and wild animals, fish and birds. Material has been made available to others and utilized for the preparation of exhibits, lantern and microscopic slide sets, and as the basis for a number of publications. In addition to publication of a quarterly "Comparative Pathology Bulletin," the Registry sponsors publication of an animal model in each issue of the American Journal of Pathology. A handbook entitled "Animal Models of Human Disease" was prepared for sale during the past year. This initial fascicle contains descriptions of 16 models, and future additions are planned. During the past year, a "Symposium on Fish Pathology" was jointly sponsored with the University of Wisconsin Sea Grant Program. The 150 participants included fish biologists, zoologists, and medical and veterinary pathologists. The potential of fish as animal models for a number of human diseases was pointed out by the various speakers.

3. The Laboratory Primate Newsletter which now has a mailing list of nearly 2,000 individuals. The Newsletter provides information on maintenance, breeding, and procurement of nonhuman primates for laboratory studies. It also serves as a general source of information through announcement of meetings, nomenclature changes, etc., and aids investigators by publishing requests for materials.

Training Grants

The Animal Resources Branch has supported training programs in laboratory animal medicine since 1967. At that time, six programs were transferred from the National Institutes of General Medical Sciences, which initially supported training in this area. Three new programs were subsequently funded and several additional programs were approved, but remained unfunded. The programs are all located in medical research environments. Diagnostic laboratories are also supported in each of these locations, and the laboratory resources have provided major input to the training experience.

Training in laboratory animal medicine is intended to prepare individuals to provide professional care of the many species of laboratory animals, to manage central animal resources, and to give special assistance to investigators through superior knowledge of laboratory animal biology and understanding of research methods. In addition, the trainees are prepared to participate in the teaching of graduate students and young investigators and to pursue their own research interests either as independent investigators or as a member of a research team.

Currently available figures indicate that 70 trainees have completed training since the inception of training grants in laboratory animal medicine. Thirty-one of these are employed by medical schools and 28 by other academic, research, or governmental organizations. The majority (42) are functioning as directors or staff members of a vivarium, 24 are engaged in research or are obtaining additional training, and 4 are engaged in public health and other activities. Retention in the field of laboratory animal medicine has been excellent, and the graduates have filled vitally needed leadership roles.

A decision to phase out research training programs supported by the National Institutes of Health is reflected in the 1973 budget. Under the phase out of all ongoing programs, trainees with commitments made prior to January 29, 1973, will be supported until the end of their normal training period. There are 25 trainees currently enrolled in the 9 active training programs. The usual training period is 2 to 3 years. It is expected that 19 trainees will be supported beginning July 1, 1973. Four of the programs should complete training activities during fiscal year 1974, and all trainees should complete their programs by February 1976.

Fellowship Awards

The laboratory animal science fellowship program was supported by an appropriation of $32,000 for fiscal year 1973. Three fellows are being funded during fiscal year 1973. This fellowship program includes both postdoctoral and special fellowships available to qualified individuals who hold the DVM, MD, PhD, or similar degrees. Candidates can engage in indepth studies in a discipline or specialty such as surgery, anesthesiology, pathology, virology, nutrition, or immunology through which they can contribute to research animal resources. This program was designed to produce the highly specialized person who can make significant contributions to knowledge regarding laboratory animals.

RESEARCH CONTRACTS

The Animal Resources Branch has used the research contract mechanism as an adjunct to its resource grant programs to support specific, essential services or to initiate activity in vital resource areas that have not responded or are not eligible to respond to the grant mechanism. Although research contract funds for ARB were $1,039,000 for FY 1973, $800,000 of this was specifically designated to maintain operation of two large primate resource colonies.

The remaining, limited funds were used to continue four contracts that contribute significantly to the advancement of laboratory animal science. In addition, two projects funded in FY 1972 were completed in FY 1973.

Partial Support for the Institute of Laboratory Animal Resources

The Institute of Laboratory Animal Resources (ILAR) is a subsidiary of the National Academy of Sciences, established as a coordinating agency to disseminate information, survey existing and required animal resources, establish standards and promote education in the field of laboratory animal science. Since July 1953, ILAR has received financial support from NIH. These activities are a valuable adjunct to the Animal Resources Branch program. The ILAR meets ARB needs for writing standards and guidelines for animal facilities and care, furnishing information on sources and users of laboratory animals, and providing survey information on the status of animal resources. Special activities include an information service on the sources and availability of over 450 animal models and genetic stocks and a field survey on the abundance and distribution of primates of biomedical interest in selected areas in South America.

Development of a Training Program for Entry Level Animal Care Technicians

This program, developed at the University of California, San Francisco, is specifically designated to instruct entry level animal technicians who are recruited from the socio-economically disadvantaged. Traditional programs have failed to identify minimal skills required for acceptable performance, to properly motivate, and to train this group. Programmed learning techniques are being developed; guidance for instructors and supervisors and identification of the level of skill and knowledge required for acceptable performance as a journeyman animal technician have also been developed. Progress has been excellent, and the program should be ready for distribution in the late fall of 1973.

Domestic, Commerical Primate Production

ARB has renewed for a second year a contract with Charles River Breeding Laboratories to provide partial support in determining the feasibility of domestic production of free ranging rhesus monkeys on an island in the Florida Keys. Although the need for this type of program has long been accepted, the low cost of imported wild-trapped monkeys, and long-term investment in a breeding program has discouraged commercial firms from developing this concept. NIH support has stimulated interest in this

area and has helped assure a quality program. If this program is successful and significant numbers of primates are produced in this country, it will eliminate the many disadvantages in the use of wild caught primates. These include hazards to human health, variability and political uncertainty of supply, and depletion of wild species. The project is progressing well. Three hundred specially trapped primates are in quarantine. The first 100 will go on the island in May 1973.

American Association for Accreditation of Laboratory Animal Care

The Animal Resources Branch is providing through a small contract partial support for site visits at a number of institutions that were accredited by AAALAC 3 to 5 years ago. This effort is important to maintain quality in the accreditation program. NIH officially recognizes AAALAC accreditation as meeting the requirements of its policy on the care and treatment of laboratory animals.

DRS

Holloman Primate Facility

This contract is to provide basic support for a large chimpanzee colony and other primates formerly supported by the Air Force at Holloman Air Force Base, New Mexico. These primate colonies have been used as a resource for biomedical research activities oriented towards environmental health and toxicology. This contract has provided required interim support of the chimpanzee facility, and it is expected that users of the resource will provide its full support in FY 1974.

Caribbean Primate Center

This primate resource is being supported by funds transferred from the National Institute of Neurologic Diseases and Stroke which formerly supported the Center. The Center includes several semi-free ranging primate colonies on islands off the coast of Puerto Rico. The Center is a valuable resource for research on social behavior and neurologic-behavioral relationship and has the potential to be an important breeding center.

Environmental Requirements for Laboratory Animals

The general aim of this project at Kansas State University is to determine ventilation and air conditioning requirements necessary to maintain optimal conditions for laboratory animals with respect to temperature, humidity, odor, gases, particulate matter, and microbial content of the air. Definition of these requirements for laboratory animals may provide considerable savings in construction and operating costs in the programs supported by NIH. Prior to the initiation of the project, there was almost no scientific data on these requirements in laboratory animals. Findings to date indicate that heat produced by most laboratory animals is two to three times as great as their standard metabolic rate. The DRR-directed contract will be completed in FY 1973.

Public Service Announcement

The Animal Resources Branch and the American Association for Laboratory Animal Science have shared in the development of a 60 second public service announcement designed for TV. The theme of the message is that biomedical research institutions are concerned about animal care and devote significant effort to this area. A secondary theme is that animals are important to the research effort to solve human health problems. The spot is narrated by Danny Thomas. It will be ready for distribution in the summer of 1973.

Table 1 - Primate Research Centers Program Applications, FY 1973

Type	Number Received	Amount Requested	Number Approved	Amount Approved	Number Funded	Amount Funded
New	-	--------	-	--------	-	---------
Renewal	2	4,330,380	2	4,208,810	2	3,848,973
Supplemental	7	734,164	6	466,534	-	---------
Continuation	5	8,447,948	5	6,771,280	5	6,998,027
Totals	14	13,512,492*	13	11,446,624*	7	10,847,000**

*Direct Costs Only
**Includes Indirect Costs

Table 2 - Laboratory Animal Sciences Program, FY 1973

Type	Number Received	Amount Requested	Number Approved	Amount Approved	Number Funded	Amount Funded
New	109	11,603,467	71	6,114,840	21	2,002,812
Renewal	11	734,675	6	297,143	4	245,067
Supplemental	4	180,956	4	180,956	4	227,342
Continuation	55	4,385,383	55	3,119,921	53	3,224,779
Totals	179	16,904,481*	136	9,712,860*	82	5,700,000**

*Direct Costs Only
**Includes Indirect Costs

Table 3 - Training Grant Applications in Laboratory Animal Medicine, FY 1973

Type	Number Received	Amount Requested	Number Approved	Amount Approved	Number Funded	Amount Funded
New	-	-------	-	-------	-	------
Renewal	3	228,137	3	150,935	2	68,247
Supplemental	2	23,673	2	23,673	2	15,265
Continuation	5	337,077	5	329,447	5	191,488
Totals	10	588,887*	10	504,055*	9	275,000**

*Direct Costs Only
**Includes Indirect Costs

Table 4 - Fellowship Applications in Laboratory Animal Science, FY 1973

Type	Number Received	Number Approved	Number Funded	Amount Funded
New	7	6	2	22,639
Renewal	1	1	1	5,262
Supplemental	-	-	-	-----
Continuation	-	-	-	4,099*
Totals	8	7	3	32,000

*Supply grants and tuition costs for ongoing fellowships

Table 5 - Laboratory Animal Sciences Program Resource and Research Grants, Project Distribution, FY 1972 and FY 1973

Project Type	1972 Number of Projects	1972 Amount in $1,000's	Number of Projects	Amount in $1,000's
Basic Improvement (Animal Welfare)	24	2,211	28	2,313
Special Colonies and Models	21	1,250	20	1,141
Primate Resources	7	879	5	342
Resource Research	6	449	8	593
Diagnostic Laboratories	16	1,162	16	1,026
Reference and Information Centers	5	279	4	285
Totals	79	6,230	81	5,700

Table 6 - Laboratory Animal Sciences Program, Research Utilization of Selected Animal Resource Colonies - FY 1973

Number of Colonies	Number NIH Grants	Dollar Value NIH Projects in $1,000's	Number Other Projects	Dollar Value Other Projects in $1,000's
Primate Resources - 7	99	5,858	75	1,998
Other Special - 12	52	4,013	50	749
Total - 19	151	9,871	125	2,747

Total Research Colonies - 19
Total Research Projects - 276
Total Funding of Research Projects Using Resource Colonies - $12,618,000

ADMINISTRATION

Major administration activities of the Animal Resources Branch in fiscal year 1973 consisted of follow-through on previous initiatives.

Program plans formulated late in 1971 have been implemented. The Primate Centers Program is making good progress in building programs of scientific excellence for each Center around one or two major themes in important biomedical research areas. The administrative policy statement for the Centers program is being revised. A decision was made to allow additional institutions to compete for primate centers.

Program plans in the Laboratory Animal Sciences area to emphasize those projects that advance animal resources through production of new knowledge or through development of new technology have been implemented. Through selective programing and award of grants, our dollar investment in resource-related research and diagnostic laboratories has increased by 15% over the past 2 years. Conversely, our investment in special colonies and institutional primate resources has decreased by 30% over the past 2 years.

Throughout fiscal year 1972, we became increasingly aware that animal resources in many institutions were in financial difficulty. As a result, we have underway a joint effort with the Business Officers Group of the Association of American Medical Colleges to develop a manual on cost analysis and rate setting for animal resource facilities. The draft manual is complete and it will be use tested in 6 to 8 animal facilities in the summer of 1973. The manual will facilitate cost analysis in animal resource facilities; and this will lead to better cost control, management, and establishment of rates that will provide sufficient income for animal resource facilities. It is our intention that the manual be the basis for informing and educating investigators and sponsors of research that full animal care costs should be supported by funding agencies through fees charged to users.

Fiscal Year 1973
Annual Report
General Research Support Branch
Division of Research Resources

The General Research Support Branch in FY 1973 administered the General Research Support Grant, the Biomedical Sciences Support Grant, the Health Sciences Advancement Award, and the Minority Schools Biomedical Support programs.

GENERAL RESEARCH SUPPORT GRANT AND BIOMEDICAL SCIENCES SUPPORT GRANT PROGRAMS

The General Research Support Grant (GRSG) program was initiated in 1962 after the passage of Public Law 86-798. GRSG funds are awarded for the general support of health-related research activities to medical and other health professional schools, hospitals, and other non-academic research institutions. In 1966, the companion Biomedical Sciences Support Grant (BSSG) program was initiated. This program is conceptually identical to the GRSG program, but provides funds to academic institutions other than health professional schools.

The GRSG/BSSG programs advance and strengthen the medical and health-related research and training programs of academic and scientific institutions by complementing the research project system by providing continuing funds to be used flexibly by the institution. More specifically, the objectives are (1) to cultivate scientific excellence through building institutional strengths, (2) to contribute to the stable support and development of institutional programs, (3) to enable an institution to balance its programs, (4) to enhance the institution's role and initiative in determining the direction of its programs, (5) to meet emerging opportunities in research via support and pursuit of unorthodox ideas, (6) to enable earlier recognition and support of scientific talent, and (7) to add to rather than supplant other support.

The most significant thrust of the GRSG/BSSG programs is that it permits the grantee institution to make its own judgments and decisions at the local level over the emphasis, direction, content, and quality of its biomedical research efforts, so that their self-conceived goals and aspirations can best be achieved.

The availability of GRSG/BSSG funds to use flexibly, as different situations arise, has been of extreme importance to an institution. For example, an institution could immediately initiate support of a pilot project for an exciting new idea for the possible cure or treatment of a disease. This inherent flexibility provides an institution with an instrument to support young investigators with seed funds while they develop more detailed and extensive research ideas. Also, because of the flexibility, an institution can use GRSG funds for the stabilization of research faculty support. For example, a faculty member may, temporarily, not receive outside support because of a shift in priorities, i.e., the termination of a research training grant which supported

the faculty member. The GRSG could support such a person until such time as other support is obtained and thus help stabilize the research base of the institution.

GRSG/BSSG funds are used to support a variety of biomedical research activities, such as: pilot projects, exploration of novel ideas by young investigators, unanticipated expenses in established research projects and programs, central research resources, and for short-term biomedical research training experiences.

Fiscal year 1971 funds have been used in the following manner:

	Number	Dollars (millions)	% of Total Dollars
Pilot Research Projects	3,411	$ 9.079	18.1
Regular Research Projects	5,436	20.307	40.4
Central Research Resources	--	11.438	22.8
Research Training	--	3.648	7.3
Other	--	5.728	11.4
Total		$50.200	100.0

In addition, some 2,334 trainees participated. A 10 percent sample of GRSG/BSSG programs indicates about 1,400 principal investigators on NIH research grants received research project support through GRSG/BSSG funds.

Fiscal and Administrative Considerations

Due to the fiscal situation it was necessary for NIH to change program priorities. It was decided to re-allocate funds from the GRSG/BSSG programs to specific research project grant activity of the NIH. The FY 1973 level of support available for the GRSG/BSSG programs was about 60 percent less than for FY 1972. The GRSG awards were $17,234,000 compared to $44,298,000 in FY 1972, and the BSSG awards for FY 1973 were $2,690,000 compared to $6,914,000 in FY 1972. Tables I and II show for the GRSG and BSSG programs respectively, (1) the trend in allowable research grants awarded by NIH and NIMH to eligible GRSG or BSSG institutions (entitlement) since the initiation of the programs, (2) the trend in award funds, and (3) the relation between entitlement and awards.

TABLE I

GENERAL RESEARCH SUPPORT GRANT PROGRAM
Trends in NIH/NIMH Research Grant Awards
(Entitlements) 1/ and in General Research Support Grant Funds, FY 1962-1973

Fiscal Year	NIH/NIMH Awards (Entitlement)	GRSG Funds Awarded	Ratio (%) GRSG/Entitlement
1962	$108,234,000	$20,000,000	18.48%
1963	192,408,000	30,000,000	15.59
1964	241,426,000	35,000,000	14.50
1965	286,832,935	43,985,365	15.33
1966	320,415,167	39,200,000	12.23
1967	354,893,188	41,700,000	11.75
1968	393,366,592	48,174,445	12.25
1969	441,064,040	48,200,000	10.93
1970	448,080,707	45,802,000	10.22
1971	430,721,426	43,423,000	10.08
1972	495,806,184	44,298,000	8.93
1973	577,966,843	17,234,000	2.98

1/ Previous Fiscal Year Awards Received From the NIH Institutes and NIMH by GRSG Awardees

TABLE II

BIOMEDICAL SCIENCES SUPPORT GRANT PROGRAM

Trends in NIH/NIMH Research Grant Awards
(Entitlements) and in BSSG Funds, FY 1966-1973 1/

Fiscal Year	NIH/NIMH Awards (Entitlement)	BSSG Funds Awarded	Ratio (%) BSSG/Entitlement
1966	$ 80,233,656	$ 5,000,000	6.23%
1967	87,564,767	6,000,000	6.85
1968	108,925,527	7,500,000	6.89
1969	119,007,903	7,500,000	6.30
1970	123,150,660	7,125,000	5.79
1971	122,385,049	6,777,000	5.54
1972	138,129,124	6,914,000	5.01
1973	160,949,957	2,690,000	1.67

1/ Previous Fiscal Year Awards Received From the NIH Institutes and NIMH by BSSG Awardees

Because the revised FY 1973 budget for the GRSG/BSSG was not received until January 1972, a decision was made not to change the eligibility requirements or formula for the FY 1973 awards. Approximately the same number of institutions received GRSG/BSSG awards as in FY 1972, but at a greatly reduced funding level, as shown in Tables III, IV, and V below.

TABLE III

GENERAL RESEARCH SUPPORT GRANT PROGRAM

Number of Grantees by Type and Funds Available for the General Research Support Grant Program FY 1966 - 1973

Type of Grantee Inst.	FY 1966	FY 1967	FY 1968	FY 1969	FY 1970	FY 1971	FY 1972	FY 1973
Medicine	89	90	95	99	100	100	101	104
Dentistry	49	49	49	49	49	33	34	34
Osteopathy	5	5	5	5	5	0	0	0
Pub. Health	12	12	12	12	12	12	12	12
Pharmacy	5	9	10	12	15	15	16	14
Vet. Med.	9	13	15	17	17	17	16	15
Nursing	0	0	0	0	0	2	4	3
Allied Health	0	0	0	0	0	0	0	1
Hospitals	51	64	71	75	79	76	79	71
Health Dept.	3	3	3	3	3	2	2	2
Res. Inst.	41	49	51	58	64	69	75	71
TOTAL	264	294	311	330	344	326	339	327

Total General Research Support Grant Funds Awarded (In Millions)

	FY 1966	FY 1967	FY 1968	FY 1969	FY 1970	FY 1971	FY 1972	FY 1973
Total Funds Awarded	$39.2	$41.7	$48.2	$48.2	$45.8	$43.4	$44.3	$17.2

TABLE IV

GENERAL RESEARCH SUPPORT GRANT PROGRAM
Distribution of General Research Support Grants by Size of the Awards

Size of Grant (in thousands)	Number of Institutions FY 1966	FY 1967	FY 1968	FY 1969	FY 1970	FY 1971	FY 1972	FY 1973
Under - $ 30.0	14	22	27	30	49	34	46	135
$ 30 - 49.9	49	58	54	46	47	51	54	54
50 - 99.9	59	60	74	80	85	77	78	92
100 - 149.9	29	36	41	49	41	50	36	46
150 - 199.9	35	40	40	36	34	36	45	---
200 - 249.9	29	26	21	21	26	25	26	---
250 - 299.9	13	17	19	29	31	25	21	---
300 - 349.9	17	14	13	12	8	8	10	---
350 - 399.9	11	9	13	9	23	20	23	---
400 - 449.9	3	12	9	18	--	--	--	---
450 - 499.9	5	--	--	--	--	--	--	---
500 - 599.9	--	--	--	--	--	--	--	---
TOTAL	264	294	311	330	344	326	339	327

Grant Range (All Inst.)	Amounts (In Thousands) FY 1966	FY 1967	FY 1968	FY 1969	FY 1970	FY 1971	FY 1972	FY 1973
Low	$ 14	$ 14	$ 13	$ 12	$ 5	$ 11	$ 12*	$ 8
High	459	441	424	429	396	383	367	134
Average	149	142	155	146	133	133	130	53
Number of Inst. Receiving Maximum Grant	5	6	7	7	10	17	21	23

*Represents award to an institution phasing out of the GRSG program. Lowest award for a fully funded grant was $20,725 in 1972.

TABLE V

BIOMEDICAL SCIENCES SUPPORT GRANT PROGRAM

Number of Biomedical Sciences Support Grants Awarded From 1966 Through 1973 by Size of Award

Size of Grants (In thousands)	Number of Institutions							
	FY 1966	FY 1967	FY 1968	FY 1969	FY 1970	FY 1971	FY 1972	FY 1973
Under - $ 30.0	4	-	-	1	8	8	14	89
$ 30 - 49.9	36	32	27	36	35	36	36	20
50 - 99.9	47	54	60	59	59	57	59	4
100 - 149.9	3	6	11	11	9	9	5	-
150 - 199.9	1	1	3	2	2	1	2	-
200 - 249.9	-	-	1	1	-	1	1	-
Total No. of Grants	91	93	102	110	113	112	117	113
Total Amount Awarded (in millions)	$ 5.0	$ 6.0	$ 7.5	$ 7.5	$7.1	$ 6.7	$ 6.9	$ 2.7

Grant Range (All Inst.)	Amounts (in thousands)							
	FY 1966	FY 1967	FY 1968	FY 1969	FY 1970	FY 1971	FY 1972	FY 1973
Low	$ 29	$ 33	$ 36	$ 29	$ 15	$ 12	$ 15*	$ 10
High	160	179	219	220	199	210	212	83
Average	55	65	74	68	63	61	59	24

* Represents an award to an institution phasing out of the BSSG program. Lowest award for a fully funded institution was $28,598 in 1972.

Numerous Congressional and grantee institution letters were received concerning the funding level budgeted for FY 1973 and FY 1974. The concern was not only because of the greatly reduced funding level, but the timing: The grantees had no advance indication as to the severity of cut. Institutions were of the opinion that they were receiving in FY 1973 approximately the same level of funding as in FY 1972 and had planned accordingly. There was also great concern as to which institutions would receive awards in FY 1974 with only $9,500,000 in the President's budget.

It was the opinion of staff, because of the FY 1974 funding level, that it will not be possible to provide support to all the institutions which are currently eligible under the programs' existing guidelines. Of primary concern is the need to maintain the strength, viability, and the flexibility of those institutions which are of critical importance to the conduct of the NIH mission. It is hoped that GRSG support in the future will allow the recipient institutions the ability to support those areas which are of the highest priority to them in maintaining a strong biomedical research environment, pilot research, stabilization of faculty support, and funding the young investigators.

The General Research Support Program Advisory Committee formed a subcommittee to study the problem and to make recommendations concerning the restructuring of the GRSG/BSSG programs. At a special meeting of the General Research Support Program Advisory Committee, it was recommended, based upon FY 1974 funding level, (1) that the GRSG/BSSG should be combined into one program; (2) that the minimum amount of entitlement (base used to calculate awards) should be $800,000, rather than the $100,000 and $200,000 currently used for the GRSG and BSSG respectively; (3) that no entitlement over $6,000,000 should be allowed; and (4) that $20,000 be the minimum amount of award. The recommendations of the General Research Support Program Advisory Committee are being considered along with other staff studies. Final staff recommendations will be made early in FY 1974.

Another subcommittee of the General Research Support Program Advisory Committee made a study on Small Grants. The General Research Support Program Advisory Committee recommended that NIH initiate an Institutional Small Grant Program. One of the purposes for which the General Research Support (GRS) program was initiated was to take the place of small grants awarded by NIH categorical institutes other than NIMH. In FY 1972, over 3,400 small research projects were supported by GRS funds.

The need for an Institutional Small Grant Program has developed in part because the expected level of GRS funds in FY 1974 will reduce awards to about 100 institutions compared to 440 awards in FY 1973. Most GRS grantee institutions have reported that small grants have been one of the most important uses to which GRS funds have been put.

New and young investigators have fared well in competing for NIH grants in the past, but with a shrinking proportion of grant funds available for competing grants, it will become increasingly difficult for new grant applications to compete successfully, and this is the category of applications that come from new and young investigators. It is likely that some of the success that new

and young investigators have had in competing for NIH grant support is attributable to small grants and pilot projects conducted with GRS support. Therefore, an Institutional Small Grants Program becomes increasingly important for this purpose as major curtailments in GRS awards occur at the same time that funds available to support competing regular research grants are diminishing.

HEALTH SCIENCES ADVANCEMENT AWARD PROGRAM

The moratorium on new applications for Health Sciences Advancement Awards will result in complete phase out of the program by the end of 1974. In FY 1973 only two non-competing continuation awards were made to the following:

University of Kansas
Duke University

Kansas and Duke will receive their final award in FY 1974, thereby fulfilling pre-existing commitments.

During FY 1973 it had been planned to make site visits and to initiate an in-depth evaluation of the institutions that have completed the HSAA program. Because of the limited number of staff, who were primarily involved with the Minority Schools Biomedical Support program and GRSG/BSSG budgetary problems, the study was not initiated.

MINORITY SCHOOLS BIOMEDICAL SUPPORT PROGRAM

The Minority Schools Biomedical Support (MSBS) program, initiated in fiscal year 1972, is designed to strengthen the capabilities for biomedical research in institutions of higher learning with predominantly ethnic minority student bodies (i.e., black, Chicano, American Indian, or Oriental). It constitutes part of the concentrated effort by the National Institutes of Health to involve minority school scientists in biomedical research and to bring to minority students the challenges and opportunities in biomedicine.

Although the objectives of the MSBS program cover a rather wide scope of activities, they include substantial opportunities for research progress. Among these are:

- Salary support for time or effort, as a substitute for a portion of teaching responsibilities.

- Provisions for supporting student research efforts which primarily involve undergraduates, but may include both pre- and postdoctorals.

- Opportunities for both investigator and student to participate in biomedical research during the summer as well as throughout the academic year. Summer research participation which is of paramount importance for establishing a continuation of activities throughout the year has been traditionally absent in this group of institutions.

- Chances for investigators at minority institutions to obtain seed funds for promising biomedical research ideas or initiation of full-scale research projects.

- Opportunities for minority institutions to secure additional research resources, such as specialized items of equipment, animal facilities, etc., which will provide for the kind of research and teaching environment necessary to attract quality faculty and students.

Fiscal and Administrative Considerations

Table VI below shows the number of MSBS applications received and awarded for FY 1972 and 1973. In FY 1973, a total of 51 awards were made involving 57 institutions. There were 14 new, 1 renewal and 36 non-competing continuation awards. The 14 new and 1 renewal award were made for seven months for the first budget period. This allowed several additional institutions to get started in FY 1973.

TABLE VI

MSBS APPLICATIONS

FY 1972

Type	Number Received	Amount Requested	Number Approved	Amount Approved	Number Funded	Amount Funded
New	75	$11,689,831[1]	42	$3,815,408[1]	38	$2,000,000[2]

FY 1973

Type	Number Received	Amount Requested	Number Approved	Amount Approved	Number Funded	Amount Funded
New	43[3]	$ 6,390,717[1]	33	$3,315,755[1]	14	$ 968,551[2]
Renewal	2	234,511	2	155,596[1]	1	54,947[2]
Supplemental	10	838,828	2	40,428[1]	--	---
Continuation	36	6,198,327	36	3,527,722	36	3,976,502[4]
	91	$13,662,383	73	$7,039,501	51	$5,000,000

1/ First Year
2/ Seven-Month Budget Period
3/ Includes 6 deferrals from prior year
4/ Increase due to adjustments caused by seven-month funding for 01 budget period

Awards have been made to 20 states, District of Columbia, and Puerto Rico.

The MSBS program major objective is to involve faculty and students in biomedical research. Table VII shows the involvement to date.

TABLE VII

Faculty and Students Being Supported by the MSBS Program

358 Faculty Receiving Released-Time Salary Support
643 Undergraduate Research Participants
95 Graduate Research Assistants

Minority Group	Undergraduates	Graduates	Institutions
Blacks	494	83	45.5
Mexican-American	102	9	7.5
Puerto Rican	24	3	2.0
American Indian	17	0	1.0
Hawaiian and Other Polynesian	6	0	1.0
	643	95	57.0

The GRSPAC recommended modification of the MSBS program to provide opportunities for a greater number of Chicano, American Indian, and Puerto Rican students than there have been under the present program. This is a recognition that there are no institutions established for Chicanos, American Indians or Puerto Ricans on the mainland generally comparable to the traditional black schools.

There are large numbers of Chicano, American Indian, Puerto Rican and black students enrolled in institutions that are not now eligible for the present MSBS program. In order to provide opportunities for these minority students in biomedical research, expansion of the MSBS program to these other institutions, with less than 50 percent minority enrollment, is planned for 1974 on a limited basis.

Another recommendation was to broaden the MSBS program to provide research participation and opportunities for ethnic minority persons to work as research assistants and research associates under well-qualified senior biomedical research scientists. This type of support will complement the present MSBS program by providing research opportunities to minority persons who are beyond the level served by the MSBS program, but not yet independent investigators who are fully competitive in the field.

Staff is preparing a final position paper on the above recommendations which will be forwarded early in FY 1974.

During the past year, new application forms and instructions for the MSBS program were put into effect. The application forms and instructions are unique for NIH in that they can be used for either a new, supplemental, renewal, or continuation application.

PROGRAM ANALYSIS BRANCH

The Program Analysis Branch collects and maintains on a regular basis a large volume of data relating to the four programs of the Division. The source documents for these data are grant applications, award statements, expenditures reports and annual reports submitted by grantees. From this data bank, PAB produces annual and periodic publications such as:

(1) The "Research Resource Grants" booklet which contains highlights, graphs, highlight tables, summary tables and listings that pertain to the DRR grants and that reflect the magnitude, scientific and technical diversity, geographical coverage, and general vitality of these programs of support for resources;

(2) A publication for the National Advisory Research Resources Council, "Division of Research Resources Handbook," which is a compendium of current and historical data on the appropriations and awards of the Division and its four programs, and which presents a brief description of the goals, objectives and general activities of the Division's programs. This booklet was redesigned this year to include new arrangements of data and a great deal of pictoral illustrations.

(3) The General Research Support Program Awards History Booklet which lists the name, location, type of institution, grant number and amount of award for each recipient of general research support since the inception of the program in 1962, and includes summary tables by type of institution within fiscal year and by geographic division within fiscal year:

(4) A Biomedical Sciences Support Program Awards History Booklet which contains the same type of information for this program as described under (3) for the GRS program;

(5) The General Research Support Expenditures Booklet which shows the data over a six-year span as tabulated from the Annual Report of Expenditures filed by all recipients of General Research Support; the booklet includes summary tables for all types of institutions according to the type;

(6) A Biomedical Sciences Support Program Expenditures Booklet similarly constructed as that described in (5) above.

PAB is still developing a "Division of Research Resources Basic Data Book" which will be a collection of highlighted DRR data

and related facts in a pocket-size booklet. Considerable historical tabular data has been compacted into various creative displays to experiment with and select those which will be most communicative.

The data system established by PAB for the Division contains approximately 309 data items which are defined and described in the PAB Handbook of Definitions and Specifications for the three distinct master files maintained, as well as in the documentation for the Publication Retrieval System master files. A completely computerized system has been established and, depending on the nature of the task, access to the data is accomplished through the 360/20 remote or the IBM 2741 Communication Terminal. Various methods are used such as computer programs, the Inquiry and Reporting System (IRS), and the Publications Retrieval System (PRS) which is similar to the Administrative Inquiry Reporting System (AIRS) introduced by the Division of Computer Research and Technology.

During the past year PAB restructured its data capture and retrieval procedures to accommodate the revised forms for the Annual Report of the General Clinical Research Centers and the Report of Expenditures and Annual Report of the General Research Support grantees. PAB has now completed a major part of the project to review, edit and collect research project data from pages 2 through 5 of the GRS Annual Report on the IBM 2741 Communications Terminal in PAB. The research project data now in the system includes the project title, name of investigator(s), amount of support and type of project. Guidelines for editing the reports and procedures for capturing the data have been written by the PAB staff. This system employs the Publication Retrieval System in a similar manner, as established for the GCRC Annual Report research projects, by using the WYLBUR text editing and remote job entry facility supported by the Division of Computer Research and Technology for keying in and editing of the data. PAB will coordinate the input activities, transfer the data to tape, maintain the tape files and be responsible for all facets of the project. With the system PAB can identify the scientific content of the GCRC research studies at various depths, including specific diseases, disciplines and techniques. The same is possible for the GRS projects. Some of the coding has been accomplished for the BSS program as well.

The PAB continues to assist the General Clinical Research Centers Branch in establishing criteria and processing appropriate data to be used in evaluating characteristics of the center's program.

PAB has written and now maintains and executes a series of computer programs and subroutines which calculate the GRS and

BSS awards, punch the cards which are used to prepare the award statements by computer, and produce listings and tables which when xeroxed and reduced in size are bound and distributed as the Final GRS Awards Booklet. This publication shows for each institution form of control, entitlement and a comparison of the newly calculated award with the amount awarded the previous year. The awards are presented by eligibility within type of institution and within each category arranged by size of entitlement, amount of difference between the new award and the previous year's award, percent of difference, amount of new award, and grant number. When the need arises, PAB adapts these programs and subroutines to produce experimental manipulation of the GRS and BSS data in order to analyze the effect of various alterations of the formula and the resulting impact on the BSS and GRS programs. PAB developed a taxonomy of a number of possible alternatives for merging the GRS and BSS programs. In the past year, the Branch calculated a vast array of experimental awards to assist the GRS staff in redesigning the GRS awards program in this regard.

The above exemplify some of the Program Analysis Branch efforts to meet the Division's requirements for data reporting and program evaluation as they fit into the decision making process. During the coming year PAB will continue to study the Branches' data needs in order to expand its data base for analysis. In 1973, PAB organized and held a number of cross orientation meetings with DRR Branches. As a result PAB is now initiating

1 - a new data collection system for BRB to be compatible with their PROPHET system; and to provide BRB expanded graphic analysis services

2 - an analysis of GCRC protocols by disease category

3 - an historical data analysis study of the primate centers program

4 - system for and collection of data on MSBS program

5 - automatic editing of GRS expenditures report data

"Ladies, if you're pregnant or plan on having a child, send for a 56-page booklet, "How Children Grow. . ."

Those were the words of Parade Magazine's "Special Intelligence Report" which on April 29 informed its 18 million readers of the excellence of the Division of Research Resources publication--one that is becoming one of NIH's "best sellers." Parade went on to tell its readers that the "booklet, informative and authoritative," was "one of the most outstanding publications made available by the government."

This particular promotional project, plus 12 other varied activities during the year, offer prime examples of how the Information Office works to inform various publics about the programs of the Division.

The American people responded in large numbers to the Parade article. More than 45,000 requests were received by DRR within the first several weeks. The enthusiastic cards and letters, many of which contained multiple requests, caused the "NIH Weekly Activities Report" to headline HIGH DEMAND FOR DRR PUBLICATION. This headline followed by several weeks the "Activities Report" featuring the placement of the item in the high circulation Sunday magazine.

The Parade special report culminated months of Information Office activity involving the booklet, which began last October with its first full-scale release.

As a result of the Information Office's activities:

United Press International in syndicated material to hundreds of newspapers called the publication "up-to-date information on children's growth". . . containing "useful background on fetal growth, low birth weight babies, childhood growth (including sections on hormones, nutrition, illness, and emotion)."

Enterprise Science News distributed an 800-word Information Office generated bylined feature signed by the Division Director which was sent to 140 top newspapers with an accompanying picture. It had a direct tie-in to the booklet. The article said: "Perhaps the most crucial period in any person's life from conception to maturity is before birth when they spend 7 to 10 months inside their mother's womb. The following is based on a comprehensive new National Institutes of Health report about advances in clinical research, 'How Children Grow.'"

The Human Growth Foundation urgently requested 2,000 copies to distribute to its members throughout the country after its medical advisor, Dr. Robert M. Blizzard, called the booklet an "excellent manuscript" that could be used advantageously by the chapters.

In the spring, the American Pharmaceutical Association distributed over 8,000 copies of the booklet through its Health Information Centers in 350 pharmacies throughout the United States.

The American Academy of Pediatrics put "How Children Grow" on its "suggested reading" list and said: "The National Institutes of Health has prepared a booklet. . . which tells the remarkable story of how a human being evolves from two germ cells into an adult made up of 100,000 billion cells."

The 8th Edition of "1001 Valuable Things Free," published by Bantam Books, said: "If science is your bag, send away for this special. . . It's theme is based on the fact that the mature human body is the end result of a growth process that requires almost two decades for completion."

The International Medical News Service and the Physicians International Press highlighted the booklet to their physician readers, many of whom wrote for single copies.

Children Today, Medical Lab, Health Services Reports, Pediatric World, the Journal of the American Dietetic Association, World Medical Reports, the Newsletter of the American Orthopsychiatric Association, Scholastic Teacher, and the Counselors Information Service, to mention only a few professional publications, all featured the booklet for their readers.

The M.D. editor of the Nebraska Medical Journal, in reviewing the booklet for his readers, said: "I have seen not as good books sell for ten times this one's price. It is called 'Clinical Research Advances in Human Growth and Development,' and if that is what you want, fine."

Earlier in the year, a television documentary which was an office project had a repeat showing over hundreds of TV stations of the ABC network. On December 29, "Life, Health, and the American Woman," initially titled "Life, Death, and the American Woman," produced dozens of news clips which were directly connected with the Information Office's activities. About the repeat showing, the St. Petersburg, Fla., Times reviewer said: "Rich, poor, old, young, black or white, all those with the common bond of being women should be seeing a doctor regularly, eating wisely, exercising, and taking better care of themselves.

"That, in a line, was the message of 'Life, Health, and the American Woman,' an absorbing informative special on women's medical problems and what can be done about them."

As part of the show, arrangements were made for NIH's clinical research centers to receive billing next to the main title of the special. As participants, each of the Division's grantee program director experts and his institution received additional billing. At the end of the special, the Division received full credits.

In the news material which appeared in hundreds of papers prior to the repeat, "National Institutes of Health physicians and their patients at NIH research centers throughout the country" were widely featured. The "active participation of the National Institutes of Health" was also heavily acknowledged.

An outstanding cover story on the Division's General Clinical Research Centers appeared in the July 1972 issue of Laboratory Management. The piece featured

a picture of the Chief of the General Clinical Research Centers Branch, the Assistant Chief, and the Director of the Division on the cover of the journal. Later, reprints were ordered for distribution as a GCRC handout.

The Information Office exhibited at the Fourth International Congress of Primatology, Portland, Oregon, last summer. "NIH Primate Research Centers: A Major Scientific Resource," the new DRR primate booklet, upon which the exhibits were based, was received with enthusiasm by many of the primatologists at the Congress. A Voice of America announcer interviewed Dr. William Goodwin, Chief of the Primate Centers Section, DRR, Dr. William Montagna, Director of the Oregon Center, and several key scientists, and news material was also provided to United Press International and to other outlets.

In addition, the new NIH primate centers booklet was distributed widely throughout the professional community and received active promotion last summer. The 74-page booklet, produced by the Information Office, describes the centers in detail and includes 78 photos of animals, facilities, and researchers in action.

As the year drew to a close, the primate booklet won a 1973 publications award for its total communications effect from the Federal Editors Association which was presented to the DRR Information Officer.

In an effort to tell various publics about the use of advanced technological tools in biomedical research, the Information Office assisted in the dedication of the DRR-supported million volt microscopes at the University of Wisconsin, Madison, and the University of Colorado, Boulder. The Office helped the University of Wisconsin plan the special event. In addition to developing a press kit, the Office placed articles and photos on the dedication of the Nation's first such microscopes for biomedical research with numerous publications ranging from Drug Research Reports, the Milwaukee Journal, the Denver Post, Chemical and Engineering News, Industrial Research News, Medical Tribune, Biomedical News, Archives of Internal Medicine, and the Journal of the American Medical Association, to the NIH Record and the HEW Newsletter. Covering on television were CBS, NBC, and ABC affiliates.

Giving further visibility to the activities of the Biotechnology Resources Branch, a feature article was placed in Laboratory Management by the Information Office. The article covered the history, function and thrust of BRB in detail and has been reprinted for general distribution.

A filmstrip on the Division and its programs was completed by the Information Office. Using a unique documentary style, it was shot and taped on location at four Division-supported resources and at the locale for two General Research Support Grants. Viewers were able to see the actual day-to-day work of the resources through the eyes of the center director and individual scientists. Dr. Thomas G. Bowery, Division Director, was host/narrator for the 28-minute show which was premiered before the March National Advisory Research Resources Council meeting and the May Animal Resources Advisory Committee, with favorable comment. At the NARRC meeting, the Information Office worked closely with the Animal Resources Branch to present an exhibit and publication display for the Council.

The fourth revised edition of the "Guide for the Care and Use of Laboratory Animals," formerly the "Guide for Laboratory Animal Facilities and Care," was edited and produced by the Information Office. Revised by a study committee of the Institute of Laboratory Animal Resources of the National Research Council, under contract to the Animal Resources Branch, DRR, the Guide provides standards for professionally appropriate care for laboratory animals. In addition to editing and producing the booklet, the Information Office promoted the new revision in the trade press.

The Information Office originated and placed articles and pictures on "Developing the Frog as a Biomedical Model," "Yerkes Primate Research Center," "Albino Bullfrogs," "NIH Lends a Hand in Animal Welfare Act Compliance," "Upgrading Entry Level Animal Technicians," "Alaska Wild Rodent Possible Research Model," "The Deer in Sickle Cell," and "Miniature Swine as Animal Models" in Lab Animal, U.S. Medicine, and ILAR News during the year. The articles and photos gave wide coverage and high visibility to the Animal Resources Branch.

A one-minute television spot on the professional care given to research animals was filmed at the New England Regional Primate Research Center, Southborough, Massachusetts, during the year. The idea was an unsolicited proposal from the American Association for Laboratory Animal Sciences. In addition, AALAS agreed to reproduce and mail the spot upon completion, and to assume all management costs associated with distributing the message to 750 television stations. The Information Office and the Animal Resources Branch worked closely on the project from its inception, talking to the producer, revising the script, and making arrangements for filming, editing, etc.. Danny Thomas did the narration for the spot which will be ready for release sometime this fall, after it has been pretested on television stations in several university communities. As the fiscal year drew to a close, the Information Office was preparing a leaflet which would explain the Animal Resources Branch philosophy on good care for laboratory animals. This leaflet would be distributed by AALAS to television viewers who write in after viewing the spot.

Working in close cooperation with the News and Feature Service of NIH, the Information Office helped produce an exciting Minority Schools Biomedical Support Portfolio. Showing MSBS researchers in action at various funded schools, the Portfolio was widely distributed to daily newspapers, professional journals, black, spanish-speaking and Indian newspapers, as well as broadly at NIH and within the grantee community. Next, operating in close cooperation with Xavier University of New Orleans, a reprint was produced on the First Annual Xavier-Minority Schools Biomedical Support Program Biomedical Symposium. This reprint, which originally appeared in The Louisiana Weekly in late April, showed representative pictures taken at the Symposium of students and scientists, representing 42 colleges and universities from 18 states, who attended and participated. The Information Officer and Assistant Information Officer attended the meeting and coordinated closely with the Xavier Department of University Relations to provide broad coverage. The reprint from The Louisiana Weekly article was distributed widely at NIH, to MSBS program directors, and by Xavier to presidents, development directors, and public relations directors of 75 predominantly black colleges and

universities, officials of the Southern Association of Colleges and Schools, all board members of the United Negro College Fund, etc.. Featured prominently were the Chief, Assistant Chief, and Program Director, General Research Support Branch, in addition to major mentions for the Division of Research Resources and the National Institutes of Health.

As the year ended, the Information Office was developing a heavily illustrated booklet on the UCLA Health Sciences Computing Facility for the Biotechnology Resources Branch. Working closely with the staff at UCLA, the Information Office covered the activities of the center, wrote the narrative for the booklet, developed a layout and dummy, and checked these with the scientists and administrators who were involved. A beautiful publication on this strongly-supported BRB resource should result in the months to come.

These 13 activities were selected to show the span of the Office's work during the year. This report does not address itself to the many individual placements or projects, too numerous to mention, which the Office was involved in during the year.

DRS

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Use one page for each separation.

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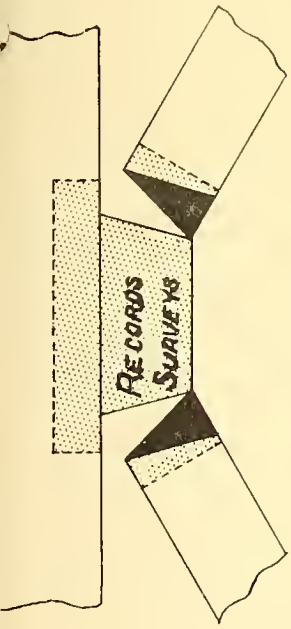

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DIVISION OF RESEARCH SERVICES

Report of Program Activities
July 1, 1972, through June 30, 1973

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NATIONAL INSTITUTES OF HEALTH

DIVISION OF RESEARCH SERVICES -- DR. JOE R. HELD, DIRECTOR

Report of Program Activities
July 1, 1972, through June 30, 1973

A. Objectives

The Division of Research Services supports other NIH components by providing centralized scientific, technical, and engineering services essential to biomedical research. Division programs function through a staff of professional and technical personnel organized into five Branches: Biomedical Engineering and Instrumentation, Environmental Services, Library, Medical Arts and Photography, and Veterinary Resources.

B. Current Programs

A broad range of central research support services and products are provided by the Division of Research Services. These currently include the following:

1. The application of engineering principles and techniques to the solution of biomedical problems.
2. The design, fabrication, and maintenance of special research instruments.
3. Environmental surveillance to detect and eliminate conditions adverse to conducting high quality research or hazardous to patients, employees, or the community.
4. Library and bibliographic services.
5. Foreign language translation.
6. Still photography and motion picture production.
7. Graphics arts services and exhibits design.
8. Medical illustration and model making.
9. Animal production, procurement, conditioning and holding.
10. Animal health services.
11. Experimental surgery and related activities.
12. The production of tissue cultures, microbiologic medias and animal biologics.
13. Central processing and sterile preparation of laboratory glassware.

C. Program Progress and Accomplishments

1. Biomedical Engineering and Instrumentation

Personnel ceiling restrictions forced curtailment of scientific equipment preventive maintenance services and constrained the number of innovative ventures. There were fewer requests for the fabrication of new apparatus, but increased demands for maintenance and repair services. This shift is presumably the result of budgetary restrictions within the Institutes. Substantial effort was devoted to improving the effectiveness of current programs. The development and application of pharmacokinetic models was

continued and significant extensions were made in the areas of toxicity, tumor behavior, dialysis therapy, and techniques for inhibiting growth of certain cancerous cell types.

Investigation of polymer kinetics and fabrication techniques enhanced the application of implant materials. Preliminary studies indicated that atherosclerotic plaque formation and distribution is dependent, in part, on blood flow dynamics. New transducers, improved video signal processing, and noninvasive ultrasonic scanning systems provided more versatile tools for the study of cardiovascular and neurologic conditions. An automated testing apparatus increased the reliability and economy of procedures for safety checking hospital electrical equipment. Significant refinements in Nuclear Magnetic Resonance, mass spectrometry, fluorometry, and thermometry were achieved. Automation and mechanization of routine laboratory procedures were advanced through innovations in electromechanical and fluidic techniques. Concomitants of head injury and concussion were substantially clarified by theoretical analysis and new experimental devices.

2. Environmental Services

Major efforts were devoted to biological control and pollution abatement during the year. This emphasis resulted from internal NIH program needs and external requirements related to the Occupational Safety and Health Act and the National Environmental Policy Act. These two Acts required surveys of laboratories and employee work places, preparation of environmental impact statements, specific actions relating to collection and disposal of solid waste, and assistance to NIH management on the environmental impacts of contract and grant programs.

Biohazard control activities were enhanced by the appointment of an NIH Biohazard Committee. A specification for laminar flow biological safety cabinets was developed which should result in greater competitive bidding for purchasing quality safety cabinets. The testing and maintenance of biological safety cabinets, high efficiency filters, and other bio-control systems demonstrated the need for quality control testing of equipment using HEPA filters. Three epidemiologic investigations of human illness associated with handling non-human primates were carried out.

Noise pollution problems continued to increase. Identification and evaluations were carried out at the power plant, the printing plant and other mechanical rooms with work interference situations. Air pollution was primarily monitored by a Maryland State Air Pollution Monitor located on the NIH grounds. State officials routinely make the data collected available to NIH. Water pollution problems at the NIH Animal Center were controlled and water pollution at the NIH Campus was reduced. Solid waste management and disposal studies were a major staff effort and special environmental impact studies were carried out in relation to the Tri-Service Incinerator.

Under a new plan, a hospital environmentalist provided surveillance of Clinical Center and associated laboratories coordinating the efforts of other ESB personnel required to maintain the desired environment. A plan was developed for restructuring the Clinical Center water supply system to

protect it from internal contamination and assistance was given in preliminary planning for eight major Clinical Center construction and renovation projects.

Detailed environmental evaulations of animal room facilities were conducted for various I/D's. Substantial upgrading of NIH food service establishments began and assistance was given to a number of I/D's in solving a variety of environmental problems.

3. Library Services

A number of measures were taken to generally improve library services with special efforts taken to improve photocopying and stacks maintenance of the collection. Automatic data processing system applications were also improved and expanded for better control and cataloging of acquisitions and holdings. Wider use was made of MEDLINE Services and a pilot study was carried out in the preparation of recurrent bibliographics related to subjects of multi-institute interest. A new policy relative to written translations became effective wherein more translations are handled by contract and the cost charged to the requesting B/I/D.

4. Medical Arts and Photography Services

With a sharp increase in demand for services coupled with loss of personnel in FY 1973, medical arts and photography services kept well abreast of its program commitments by use of new and improved technology, operational improvements, training and a 100 percent increase in outside contract services. With advanced technology the micrography skills and service output increased.

5. Veterinary Resources

The production and services related to animals, tissue culture, media and glassware continued to rise to meet increasing demands of expanding intramural B/I/D programs. Increased services with decreased personnel were accomplished by the extensive use of overtime, improved animal production methods, automated processing, limited use of temporary positions, and contracting.

Rodent, rabbit, and cat production dropped from last year, while laboratory reared dogs, timed-pregnant non-human primates, and ungulate production increased. Contracting supplemented canine, primate and ungulate production. Procurement of non-human primates continued at a level similar to recent years. With the renovation of Building 14D, protected facilities will be available for holding over 650 non-human primates. Random source dog procurement continued to increase.

Tissue culture and media production increased 25 percent, while glassware issues decreased 11 percent reflecting personnel reductions and increased use of disposable supplies.

Over 110 investigators world-wide were supplied with nucleus inbred breeders from VRB rodent genetic reposistory pedigreed colonies. The Frederick Cancer Research Center was provided with inbred strains to assure the reliability of nucleus stock.

Surgical activities and support continued to increase and surgical facilities were used at near maximum capacity.

Calls for the Animal Disease Investigation Service increased and included several special, in-depth surveys of Institute animal care programs.

D. Division Management

1. Appointment of a New Director

Dr. Joe R. Held, former Chief of the Veterinary Resources Branch, was appointed Director of DRS effective July 10, 1972. Dr. Held replaced Dr. Roger Estep who resigned to return to Howard University.

2. Additional Appointments

Mrs. Ruth Smith, former Director of the Scientific Documentation Division in the Naval Ship Systems Command, U. S. Navy, joined DRS in April 1973 as Chief of the Library Branch. Mrs. Smith replaced Mr. Seymour Taine who accepted a position with the National Library of Medicine.

Dr. Robert Whitney, Jr., accepted the position of Chief, Veterinary Resources Branch in November 1972, replacing Dr. Joe R. Held. Dr. Whitney transferred to DRS from the Division of Research Resources where he was Assistant to the Chief of the Animal Resources Branch.

Mr. James Byrne, formerly with HSMHA, joined DRS in October 1972 as the Division Training Officer. Mr. Byrne replaced Mr. Fred Fagan who left to accept another position at NIH.

3. Equal Employment Opportunity Program

Mr. Lawrence Cundiff, formerly with the National Bureau of Standards, joined DRS as Equal Employment Opportunity Specialist on April 16, 1973. Mr. Cundiff will serve as the DRS focal point for all EEO matters. The Division's Human Relations Committee channelled significant employee problems to Branch management and the OD, DRS. The Director and Executive Officer worked closely with this committee to implement recommendations for improvement of working conditions and morale of employees.

As part of its Affirmative Action Plan, the Division instituted a mid-year performance evaluation system. Many employees had expressed concern when discovering their performance was not considered to be average in various job aspects. To provide opportunity for every employee to improve before the formal rating in June, all supervisors discussed performance on an individual informal basis, emphasizing areas where improvement is essential.

Mrs. Smith, new Library Branch Chief, became the first minority group member and the first woman to occupy one of the top five program positions in DRS.

At the suggestion of the Division's Human Relations Committee, the outstanding work performance of the employees in the Media and Glassware Section, VRB, was reviewed and a group performance award was approved.

To increase understanding of the purpose of the Official Personnel File and in response to implementation plans of the Affirmative Action Plan, the Division instituted a procedure to provide opportunity for every employee to review the contents of his OPF on an annual basis. DRS Personnel Office staff is also available at that time to answer inquiries and clear up misunderstandings.

4. Employee Development

The Division continues its long history of being a leader in the field of training and career development at the NIH campus. The training function during FY 1973 exceeded the FY 1972 figures for (1) number of DRS employees included, (2) man-hours expended and (3) dollars spent.

The Division intensified its efforts to develop upward mobility training opportunities for its lower graded employees. This training was aimed at first providing a good basic understanding of specific branch occupations and secondly developing employees with ability toward greater career opportunity.

The Veterinary Resources Branch and Environmental Services Branch conducted training in laboratory animal sciences for 28 B/I/D employees. Forty-eight hours of intensive training was provided in such topics as physiology, genetics, nutrition, vermin control, disease, medical terminology, techniques of surgery and many others. Twenty-three completed the course with three becoming certified by the American Association of Laboratory Animal Science (AALAS) as Assistant Laboratory Animal Technicians and one as Laboratory Animal Technician.

The Office of Personnel completed an individual training agreement with the Civil Service Commission to begin developing a senior personnel assistant in the personnel management field. Through a diverse program of on-the-job and formal training the incumbent will be working at the full operating level of a personnel management specialist at NIH (GS-201-09) after one year.

The Biomedical Engineering and Instrumentation Branch has established two new career training positions in which trainees enter as Glassblower and Machinist (trainees). Through a well-structured career program of on-the-job training and formal classroom instruction at local universities each apprentice progresses to the journeyman level in these highly specialized fields. Efforts are now being initiated to secure two additional positions for traineeships in Medical Equipment Repair and Glassblowing.

The Library Branch established the position of Library Technician (trainee). Selection was made of a Library employee for a comprehensive training program that combined rotational assignments within several sections of the Library Branch, on-the-job training and specialized training courses given by the USDA Graduate School and U. S. Civil Service Commission. The effort has been successful by every measure and permanent placement was made of the trainee recently. A Branch employee was selected for long-term training and is currently attending the Massachusetts Institute of Technology.

The Medical Arts and Photography Branch initiated a series of technical seminars for all employees. Outside experts were invited to visit MAPB, make a presentation, and assist in specialized problems in their area of expertise.

The Veterinary Resources Branch used the newly approved NIH Omnibus Training Agreement to establish the position of Administrative Technician (trainee) in the Office of the Chief. Content area modules have been arranged by the

immediate supervisor in such areas as Budget, Personnel, Space-Management, and Procurement. Formal classroom training will compliment the administrative training as the Technician progresses. The length of the training will be one year with several periods of career counseling and evaluation scheduled intermittently. Promotion is assured with the successful completion of the training period.

Again, as in the past, DRS continued to give full support to the Adult Education Program at NIH. Progress is now being made by several DRS employees toward their GED certificate. Also, 15 DRS employees are making continued advancement toward their B.A. in the Upward Mobility College at NIH.

Every effort has been made to assure that all these positions fulfill the letter and the spirit of the Upward Mobility Programs at NIH.

5. Management Analysis Projects

The Division's general management information system, the Data Reporting System (D*R*S), continued to be improved and expanded. A new report generator now enables the system to selectively display up to five years of annual totals for data distributed either on a customer basis or on a total item basis. The D*R*S, now in its third year of operation, collects distributed data on approximately 1,200 different line items and generates an average of 500 Trend reports per month.

Working with the Administrative Office and the Personnel Office, the Management Analysis Office has developed and installed a computerized subsystem of the central NIH personnel ARMS. This subsystem monitors the accuracy of ARMS and, on a timely basis, provides average grade and budgetary information distributed according to each funding mechanism. Special inquiries concerning various employment profiles of DRS personnel are now available as needed.

The Management Analysis Office continued to provide technical assistance and problem-solving services to the Branches throughout the year. Major effort was devoted to the BEIB interface requirements of a job-costing and inventory control system that is being developed centrally by NIH. A computerized system was developed and installed to help the Systems Maintenance Section of BEIB keep track of maintenance jobs undertaken by them or through contract. This system is being expanded to collect workload data and to link with the central D*R*S. A training course was held to teach Branch secretarial personnel how to make use of the text-editing facilities of the Wylbur system. A special computer program was developed for the Personnel Office which automatically addresses and prints standard personnel letters on NIH stationary with visual quality sufficient for distribution.

Howard B. Kelly, the Management Analysis Officer, left DRS in November to accept another position. Michael J. Kremer was named Acting Management Analysis Officer. The staff's capabilities were augmented by the selection of a full-time computer programmer December 26, 1972.

6. Personnel Management

During the past year, two of the three personnel generalists transferred to other B/I/D's. Replacing them, Mr. Joseph Whitaker joined the staff as a Personnel Management Specialist, and Miss B. Louise Monroe was promoted from a clerical position to a professional job as a Personnel Management Specialist.

Since July 1972 the Personnel Office staff has interviewed all DRS employees in Grade 7 and below for inclusion in the Opportunity Skills File. Inclusion in the file should assist people in these grade levels in locating positions with enhanced upward mobility.

A formal job restructuring program was initiated in September 1972, and since that time 15 persons in the Division have been placed in restructured positions which will either immediately or ultimately improve their career potential.

In October 1972, a blanket training agreement for non-professional NIH employees was approved by the Civil Service Commission. Two DRS positions have been filled using the training agreement and its use will be expanded in the future.

E. Visual Communications Projects

Visual communications projects continued to expand within the Division and, more broadly, across the B/I/D's of NIH.

The Visual Communications Project Officer provided consultation and advice on audio-visual problems and specific projects throughout NIH, particularly OD-NIH, NCI, DCRT, NEI, NLM. He gave illustrated lectures to a variety of NIH and NIH-research related audiences on effective uses of visual aids in communicating scientific material. Advice on audio-visual training materials was also provided.

To date, about 500 copies of the kit, "Preparation and Presentation of Effective Slides and Visual Aids" have been distributed to provide desk-top assistance to investigators and technicians in preparing illustrated lectures, papers, and presentations.

Liaison and coordination were provided for NIH with the Office of the Assistant Secretary for Health, OS, DHEW for an HEW exhibit on technology which included NIH; the Federal Design Council; the Endowment for the Arts in connection with the First Federal Design Assembly; and, for DRS, with the NIH Office of Information.

Work continued on building a centralized file of original slides. It primarily depicts work of the Division, but also includes subjects of broad current and historical interest to NIH. This resource was of significant value in preparing visual presentations, particularly on short notice, for the NIH Office of Information, DRR and DRS. Duplicates of slides of pertinent interest were made and distributed to Branches of DRS for staff use.

Slide presentations and accompanying manuscripts on programs were developed for OD-DRS and DRS Branches. One overall presentation was seen by all DRS employees at a series of orientation seminars.

A group of historic NIH slides was gathered, background information and identification were developed, and they were transmitted for preservation to the historic collection of the National Library of Medicine.

The Visual Communications Project Officer participated on ad hoc committees for NCI and DRS in screening contract bids where visual presentation and graphic production were involved. He assisted in developing improved audio-visual capabilities in several NIH conference areas.

The slide/tape presentation, "MEDLARS, What It Is, What It Does," prepared for the National Library of Medicine, won an award for writing/editing from the Federal Editors Association.

A training slide/tape presentation, modeled after the above NLM product, on "Effective Use of the Laminar Flow Biological Safety Cabinet" was completed for the Office of Biohazards and Environmental Control, NCI. Consultation continues on additional training vehicles stemming from the initial presentation.

DIVISION OF RESEARCH SERVICES

Summary of Branch Activities July 1, 1972, through June 30, 1973

BIOMEDICAL ENGINEERING AND INSTRUMENTATION BRANCH Dr. Lester Goodman, Chief

I. SUMMARY

Activity during FY 1973 was devoted primarily to further development and refinement of programs initiated in previous years. Reduced personnel and fiscal uncertainties for BEIB and the entire NIH intramural operation constrained the number of innovative ventures. Substantial improvement and expansion have been achieved, however, in major projects begun earlier.

The validity of pharmacokinetic models was increased and significant extensions were made in the areas of toxicity, tumor behavior, dialysis therapy, and techniques for inhibiting growth of certain cancerous cell types. Fundamental investigation of polymer kinetics and novel fabrication techniques enhanced the application of implant materials. The dependence of atherosclerotic plaque formation on blood flow dynamics was clarified. New transducers, improved video signal processing, and noninvasive ultrasonic scanning systems provided cardiovascular and neurological researchers with tools of unprecedented versatility. An automated testing apparatus markedly increased the reliability and economy of procedures for safety checking hospital electrical equipment. Significant refinements in Nuclear Magnetic Resonance, mass spectrometry, fluorometry, and thermometry were achieved. Automation and mechanization of routine laboratory procedures advanced with innovations in electromechanical and fluidic techniques. Concomitants of head injury and concussion were elucidated via theoretical analysis and new experimental devices.

Substantial professional consultation was provided to the intramural, collaborative, and extramural programs of all categorical institutes and divisions.

Emphasis on cost reduction throughout the NIH decreased the number of requests for fabrication of new apparatus and, simultaneously, increased demands for maintenance and repair services. Reduced personnel ceilings forced curtailment of preventive maintenance routines and restricted operations of the scientific equipment rental program. Improved management practices and training were important in economically maintaining high levels of service and support.

II. BRANCH PROGRAMS

A. Objectives

To provide direct and consultative engineering support to clinical and biomedical research projects, including advice on systems analysis, experimental design, and synthesis of technical expedients.

To design, develop, fabricate, and evaluate special-purpose devices and systems not commercially available.

To maintain and repair scientific laboratory and clinical equipment.

To obtain and disseminate information on developments and improved production methods in the biomedical engineering and instrumentation fields.

B. Current Programs

The primary purpose of the Branch is to provide service and support to the intramural program of the NIH. Its activities, therefore, are identified with many individual programs of the intramural research effort. The overall program is best described as the coordinated effort of operating units.

1. Instrument Fabrication

Production, modification, and minor design of medical equipment and instrumentation systems requiring special tools and skills in the electronic, electrical, glass, mechanical, optical, rubber, plastics, welding, and sheet metal categories.

2. Systems Maintenance

Maintenance and repair of biomedical equipment and instrumentation systems and instruction of technicians and scientists in the proper use and operation of especially complex instruments and devices.

3. Supply

Acquisition and disposition of materials, parts, and equipment required for branch operations and maintenance of controlled inventory stocks and records.

4. Engineering and Applied Science -
Chemical, Electrical and Electronic, and Mechanical:

   a. Direct and consultative professional services for fundamental and applied projects relevant to biomedical research and health care at NIH.
   b. Research, design, development, and evaluation related to new instrumentation and equipment.
   c. Communication between NIH and the scientific community on engineering support to biomedical research and clinical practice.

5. Satellites

These technical support units, composed of selected engineers and technicians with appropriate shop facilities, are located in certain areas where it is beneficial to make typical BEIB support and service immediately available via a controlled degree of decentralization. They are responsive to demands of local programs and operate as integral parts of the resident team but are administratively responsible to the central Branch. Each satellite is especially tailored to meet specific needs of the host institute or division,

supplying it with advantages of a proprietary technical group while maintaining the chief benefits of centralized resources.

C. Program Progress and Accomplishments

1. Technical Services

a. Instrument Fabrication Section

Workload during FY 1973 remained relatively stable through the first and second quarters; an upsurge was experienced in the third quarter, with a return to normal for the fourth quarter. Despite reductions in staff, the section was able to meet promptly most demands by increased productivity from its available personnel. The section completed approximately 4,600 projects valued at $936,000 compared with 4,800 projects valued at $907,000 in FY 1972.

b. Systems Maintenance

Service was restricted almost completely to meeting immediate demands as staff reductions forced curtailment of preventive maintenance routines. Training and improved management helped to reduce the average time per job by 10 percent from the previous year. SMS performed approximately 9,600 assignments at a cost of $910,000 compared with 11,600 and $960,000 in FY 1972.

Space previously made available for the Scientific Equipment Rental Program has become inadequate. The number of instruments in the equipment pool is approaching 350; approximately 160 items were rented to intramural investigators during FY 1973. Five thousand dollars' worth of new apparatus was added to inventories from net operating proceeds.

c. Supply Unit

Benefits of attention to improvement of operational and administrative procedures, in previous years, were clearly evident as the unit processed approximately 22,000 transactions compared with 15,000 in FY 1972; dollar value of material handled increased to $425,000 from $400,000 in FY 1972.

2. Engineering and Applied Sciences

a. Chemical Engineering

Considerable progress was made in applying principles of chemical reaction engineering to problems of drug, metabolite and trace contaminant distribution in the body. Pharmacokinetic modeling has permitted the elucidation of species differences in both metabolized and non-metabolized substances. It also permitted operational assessment of the quantitative importance of physiologic processes and biochemical interactions which determine uptake, distribution and elimination. Of primary concern was the assessment of toxic risk to man of drugs and environmental contaminants on the basis of experiments conducted in animals or from simplified *in vitro* screens. Similar concepts have been applied to the quantification of dialysis therapy.

Better understanding of pharmacokinetic principles together with the invention of a device for slow controlled release of an anticancer drug provided greater comprehension of the biological response of tumor and sensitive normal tissue and suggested methods for improved therapy.

Substantial effort was devoted to synthesis and characterization of metal complexes with biological activity. Two palladium compounds were prepared which inhibit the growth of L-1210 leukemia in culture. Platinum complexes were successfully assayed in body fluids of monkeys. Improved analytical methodology should lead to better understanding of mechanisms of action and suggest more effective chemical structures.

Biomaterials research progressed along several lines. Analytical methodology was established for measurement of plasticizer migration from medical grade vinyl. This was accompanied by thermodynamic and kinetic studies of the system. Segmented polyurethane was demonstrated stable for periods of more than three years when implanted in animals. Tissue pathology revealed a low order of reactivity. New fabrication techniques were developed for a variety of special purpose devices and sterilization procedures examined.

An electrochemical technique was employed to measure shear stress distribution at the wall of a model of the canine aorta. Preliminary findings indicate high shear stresses near bifurcations. These are also regions of atherosclerotic plaque formation in experimental animals. The effect of pulsatile flow and distensible walls was investigated. The role of lipoprotein diffusion is being studied both experimentally and theoretically.

Extensive consultation was provided to a variety of intramural, collaborative, and extramural programs.

b. Electrical and Electronic Engineering

As implied elsewhere in the report, BEIB completed a substantial number of new designs for electrical and electronic apparatus for the NIH research program.

Major new developments in the general area of video signal processing include a new technique for directly determining net forward ejection fraction with an order of magnitude reduction in the amount of radio-opaque dye required, and a system for quantifying metabolic activity in the brain by measuring fluorescence of the exposed cortex with an image intensifier-camera tube combination, followed by specially tailored signal processing. The use of ultrasound for routine noninvasive diagnosis was advanced by innovations in the acquisition, recording, presentation, and interpretation of scan data.

Primary emphasis in the area of patient electrical safety was placed on the development of automatic test apparatus needed for a comprehensive scheduled inspection system in the Clinical Center which is expected to substantially improve the NIH position regarding electrical safety.

In the area of laboratory instrumentation, considerable effort was continued on the superconducting Fourier transform NMR system in collaboration with NIAMDD. Significant new projects were carried out in connection with mass

spectrometry, rapid precision temperature measurement, absorption and fluorescence measurements in T-jump and stop flow systems, and laboratory automation systems.

Extensive consultation was provided to a number of intramural collaborative and extramural programs.

c. Mechanical Engineering

Continued close collaboration with research and service staff throughout the NIH resulted in several substantial developments. Mechanization and automation of routine procedures received emphasis. Efficiency and effectiveness of biological sample analyses were enhanced via several new automatic manipulator devices for aliquots and reagents. Distinct improvements were achieved in methods for large-scale processing of laboratory glassware and media. These systems continue to reduce the cost and time of routine manual tasks and enable reallocation of manpower to more productive and challenging duties.

Considerable attention was devoted to fundamental and applied research on the mechanisms of head injury. New testing apparatus was designed to provide heretofore unobtainable information for improved analyses of relevant phenomena leading, eventually, to the design of improved protective devices. The state of the art in recording electrical signals from the brain, in vivo, was advanced with the innovation of devices for precise atraumatic insertion of electrodes into cortical regions.

A new dimension in cardiac diagnosis was provided with a chest mounted servo-controlled ultrasonic scanning device that can be used with upright exercising subjects.

Extensive consultation was provided to intramural, collaborative, and extramural programs.

3. Technical Advances

BEIB delivered a considerable number of special purpose devices and systems in support of research programs. Significant items of interest follow:

A LOW LIGHT LEVEL IMAGE INTENSIFIER CAMERA, together with UV illumination and video densitometry, provides a new fluorescence method for sensing NADH changes on exposed cat cortex in response to cortical stimulation.

A SEMIAUTOMATED SPECTROFLUOROMETER advances research on tissue metabolism by accurately measuring small changes in sample fluorescence resulting from enzymatic reaction.

A NOVEL ALL-GLASS FUSED MULTIPLE CHAMBER cell significantly expedites gel slab electrophoresis processes.

AN AUTOMATED MICRO-VIDEO SYSTEM calculates cell cross-sectional areas under microscopy and enables human intervention to isolate particular cells with minimum overlap.

A DATA PROCESSING SYSTEM for use with a commercial instrument which uses scattered light to sense cells in capillaries. The system performs pulse height analysis and refined analog information processing.

A DATA PROCESSING SYSTEM FOR ULTRASONIC ECHOCARDIOGRAPHY simultaneously displays signal time, distance, and intensity, together with four channels of pressure and ECG data.

AN IMPROVED RATIO SPECTROPHOTOMETER measures absorption and dichroic ratio of specimens containing chlorophyll with automatic control of wavelength and data readout.

HIGH DENSITY MAMMALIAN TISSUE GROWTHS, in vitro, are achieved with a revolutionary device based on a mixed bundle of semipermeable polymeric capillaries.

AN INTERFACE AND CONTROL SYSTEM synchronizes repetitive sweeping of a mass spectrometer and data acquisition by a minicomputer.

A SPECIAL PURPOSE LABORATORY FACILITY TO STUDY HEAD AND NECK INJURY will be used to investigate human cadaver response to predetermined translational and rotational loads. A NOVEL ACCELEROMETER, of density equal to brain tissue and displacing only 450 µl, is expected to enable improved prediction of head injury effects.

CONTROLLED DELIVERY OF ANTINEOPLASTIC DRUGS FROM IMPLANTS achieves prolonged drug administration in vivo.

A HETERONUCLEAR SPIN DECOUPLER used with a superconducting pulsed NMR system includes a digital pseudorandom noise generator, phase modulator, 220 mhz power amplifier, and related components.

A NEW ISOMETRIC MUSCLE FIBER FORCE TRANSDUCER features displacement detection to within 1 micron, sensitivity of 4 volts/gram, noise level equivalent to 2 milligrams, and 90 percent response time of $2\frac{1}{2}$ milliseconds.

AN ULTRASONIC SCANNING SYSTEM displays density as a function of position in two dimensions on hard copy for expediting dynamic noninvasive cardiovascular studies.

A HIGH PERFORMANCE THERMAL FEEDBACK CONTROL SYSTEM enables freezing of white cells from bone marrow with minimum cell damage.

NEW VIDEO-FLUOROSCOPY APPARATUS determines the net forward left ventricular ejection fraction on patients undergoing LV angiography.

AN AUTOMATED EQUIPMENT TEST SET provides new dimensions of speed and economy of monitoring for hazards in clinical and surgical apparatus.

4. Training

An effective professional and technical training program was essential in maintaining high quality support and service to the NIH program. Fifty-eight employees participated in 70 academic, administrative and technical courses. Seventeen (187 man-days) undertook formal education and training courses. Seven (30 man-days) received specialized training on scientific equipment at manufacturers' facilities and at the NIH. Two members attended Basic Schools programs at the sub-high school level and five were enrolled in the Upward Mobility College.

The Machinist and Glassblower Trainees, hired under the Affirmative Action Program, were promoted to the Intermediate level, after demonstrating proficiency at the higher grade. These two WG-8 employees continue to receive academic instruction at Washington Technical Institute and Frederick Community College, respectively, as well as intensive on-the-job training.

Under terms of Contract #NIH-73-P-(A)-106CC, BEIB/SMS and Beckman Instrument Company jointly conducted two courses. The first was on the elutriator rotor and covered basic operational techniques and the separation of cells and large particles in an isotomic medium. Thirty-three scientists and technicians from NIH and other agencies attended.

The second, under the same contract, was offered in liquid scintillation. This covered basic theory and practical operations related to isotopes, nuclear disintegration, detection processes, theory of liquid scintillation counting and basic operational procedures. Forty-seven scientists and technicians from NIH and other agencies attended.

D. Program Plans

BEIB will continue to respond to intramural requests for service and support. Since these consume nearly all available time and resources, few changes in current patterns of operation can be contemplated. Several relatively minor innovative activities, already begun, should receive added emphasis during FY 1974. For the areas of long-term commitment cited below, it is felt that meaningful work can be done without sizable increases in staff. Given more resources, much more could be accomplished.

1. Extension of the comprehensive biomaterials research, development, and evaluation program.

2. Enhancement of university-BEIB cooperation in biomedical engineering via arrangements with Howard University and other institutions.

3. Improvement and expansion of the Scientific Equipment Rental Program which is now well received and used by a rapidly growing number of intramural investigators.

4. Extension of the patient safety program now conducted primarily by BEIB electrical and electronic engineers, assisted by Systems Maintenance technicians with the cooperation of Clinical Center staff. Substantial progress has already been made; much more remains to be done.

5. Increased attention to collaborative intradivision research and development activities to improve the manner in which DRS, as a whole, serves and supports NIH. Closer interaction and collaboration among the branches should be highly advantageous to all of NIH; particular projects should be defined and pursued.

6. Continuation and expansion of the technician training program under the auspices of the Affirmative Action Plan.

E. Publications and Patents

1. Publications

Boretos, J. W.: Communication to the editor--Tissue pathology and physical stability of a polyether elastomer on three-year implantation. Journal of Biomedical Materials Research, 6: 473-476, 1972.

_____: Concise Guide to Biomedical Polymers--Their Design, Fabrication and Molding. Springfield, Ill., Charles C Thomas, 1973, 179 pp.

_____, Detmer, D. E., and Braunwald, N. S.: Factors influencing longevity of low-profile prosthetic heart valves. Journal of Biomedical Materials Research, 6: 185-192, 1972.

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Dedrick, R. L.: Animal scale-up. In Pharmacology and Pharmacokinetics: Problems and Perspectives. (In press)

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_____ and Forrester, D. D.: Blood flow limitations in interpreting in vivo Michaelis constants for ethanol oxidation. Biochemical Pharmacology. (In press)

_____, _____, Cannon, J. N., ElDareer, S. M., and Mellitt, L. B.: Pharmacokinetics of Ara-C-deamination in several species. Biochemical Pharmacology. (In press)

_____, Zaharko, D. S., and Lutz, R. J.: Transport and binding of methotrexate in vivo. Journal of Pharmaceutical Sciences. (In press)

Dehn, W. R.: An all-glass device for fabricating gel electrophoresis slabs. In Proceedings of 18th Symposium of the American Scientific Glassblowing Society. (In press)

Dvorak, J. A., Clem, T. R., and Stotler, W. F.: The design and construction of a computer-compatible system to measure and record optical retardation with a polarizing or interference microscope. Journal of Microscopy, 96: 109-114, 1972.

Friauf, W. S.: An aversive stimulator for autistic children. Journal of Medical and Biological Engineering. (In press)

Gaasterland, D., Kupfer, C., Ross, K., and Gabelnick, H. L.: Studies of aqueous humor dynamics in Man III. Measurements in young normal subjects using norepinephrine and isoproterenal. Investigative Ophthalmology. (In press)

Gabelnick, H. L.: Biorheology. In Lapedes, D. N. (Editor in Chief): McGraw Hill Yearbook of Science and Technology. New York, McGraw Hill, 1973, pp. 66-74.

_____ and Litt, M.: Preface. In Gabelnick, H. L. and Litt, M. (Eds.) Rheology of Biological Systems. Springfield, Ill., Charles C Thomas, 1973, p. ix.

_____ and _____ (Eds.): Rheology of Biological Systems. Springfield, Ill., Charles C Thomas, 1973, 319 pp.

Gennarelli, T. A., Thibault, L. E., and Ommaya, A. K.: Pathophysiologic responses to rotational and translational accelerations of the head. In Proceedings of Sixteenth Stapp Car Crash Conference, Nov. 8-10, 1972, Detroit, Michigan. New York, Society of Automotive Engineers, Inc., Lawrence M. Patrick, Chairman, pp. 296-308.

Goldstein, S. R.: Atraumatic recording from exposed pulsating human cortex--a new mechanism. In Proceedings of the 25th Annual Conference on Engineering in Medicine and Biology 1972, Bal Harbour, Florida, vol. 14. Arlington, Va., The Alliance for Engineering in Medicine and Biology, Samuel P. Asper, M.D., Chairman, p. 190.

_____ and Salcman, M.: Mechanical factors in the design of chronic recording intracortical microelectrodes. IEEE Transactions on Biomedical Engineering. (In press)

Goodman, L.: Book review: Concise Guide to Biomedical Polymers, Their Design, Fabrication and Molding. Journal of the Association for the Advancement of Medical Instrumentation. (In press)

_____: Instrumentation for health care. IEEE Transactions on Biomedical Engineering, BME-20: 185-189, 1973.

_____: Quality in preventive maintenance and equipment control. AAMI Tutorial Proceedings, The Clinical Engineer in Today's Hospital. (In press)

_____: The engineer and advanced medical systems. In Proceedings of the Annual Scientific Meeting of the Society for Advanced Medical Systems. (In press)

Kazama, S., Chotiner, B., Metz, H. D., Lerner, E. H., Waldhausen, J. A., and Pierce, W. S.: Left ventricular bypass in the dog. Arch. Surg., 105: 607-610, 1972.

Knazek, R. A., Gullino, P. M., Kohler, P. O., and Dedrick, R. L.: Cell culture on artificial capillaries: An approach to tissue growth in vitro. Science, 178: 65-67, 1972.

Larson, S., Bailey, J., Griffith, J., Schall, G., and Johnston, G.: Radioisotope technique for measuring regional organ blood flow. Int. Journal of Applied Radiation and Isotopes, 23: 388-390, 1972.

Leighton, S. B. and Kent, K. M.: A precision gas mixing technique for medical applications. Journal of Applied Physiology. (In press)

Lutz, R. J., Litt, M., and Chakrin, L. W.: Physical-chemical factors in mucus rheology. In Gabelnick, H. L. and Litt, M. (Eds.): Rheology of Biological Systems. Springfield, Ill., Charles C Thomas, 1973, pp. 119-157.

Ommaya, A. K., Gennarelli, T. A., and Thibault, L. E.: Traumatic unconsciousness: Mechanics of injury to the brain in violent shaking of the head. In Proceedings of the American Association of Neurological Surgeons, 1973. (In press)

Riggle, G. C., Bennett, S. H., and Hoye, R. C.: Regional anticoagulation for intraoperative reinfusion of autologous blood. In Proceedings of the 25th Annual Conference on Engineering in Medicine and Biology 1972, Bal Harbour, Florida, vol. 14. Arlington, Va., The Alliance for Engineering in Medicine and Biology, Samuel P. Asper, M.D., Chairman, p. 196.

Schuette, W. H. and Whitehouse, W. C.: Television video measurement techniques for medical research. In Proceedings of the 25th Annual Conference on Engineering in Medicine and Biology 1972, Bal Harbour, Florida, vol. 14. Arlington, Va., The Alliance for Engineering in Medicine and Biology, Samuel P. Asper, M.D., Chairman, p. 318.

Vurek, G. G., Kolobow, T., Pegram, S. E., and Friauf, W. S.: High precision oxygen saturation monitor for extracorporeal circulation applications. Journal of Association for Advancement of Medical Instrumentation. (In press)

Zaharko, D. S. and Dedrick, R. L.: Applications of pharmacokinetics to cancer chemotherapy. In Proceedings of the 5th International Congress on Pharmacology. (In press)

_____ and _____: Pharmacokinetic models: Antineoplastic agents. In Handbook of Experimental Pharmacology. (In press)

_____, _____, and Oliverio, V. T.: Prediction of the distribution of methotrexate in the sting rays dasyatidae sabina and sayi by use of a model developed in mice. Comparative Biochemistry and Physiology, 42A: 183-194, 1972.

2. Patent

G. L. Norris: Laboratory Homogenizer. U. S. Patent No. 3,666,187, May 1972.

III. INDIVIDUAL PROJECT REPORTS

Serial No. DRS-BEIB-1
1. Biomedical Engineering and Instrumentation Branch
2. Chemical Engineering Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1972, through June 30, 1973

Project Title: Pharmacokinetics

Previous Serial Number: Same.

Principal Investigators: Robert L. Dedrick, Daniel S. Zaharko

Other Investigators: Vincent T. Oliverio, Henry L. Gabelnick, Anthony M. Guarino, Donald D. Forrester, Robert J. Lutz, Kenneth B. Bischoff, Joseph N. Cannon

Cooperating Units: LCHPH-NCI, LT-NCI (Project No. NCI-3502), OD-NIEHS, Howard University

Man Years:

Total:	3.0
Professional:	2.0
Other:	1.0

Project Description:

Objectives: To improve and extend mathematical models for the distribution and disposition of drugs and environmental contaminants in animal and man to:

(1) Account for species differences in drug distribution.

(2) Provide rational bases for extrapolation of toxicity from animals to man.

(3) In conjunction with cytokinetics, provide a basis for optimization of cancer chemotherapeutic regimens.

(4) Enable rational transfer of *in vitro* metabolic data to *in vivo* cases.

Methods Employed: Mathematical models are developed using physicochemical, physiological and anatomical information and the principles of chemical reaction engineering. Resulting differential equations sets are solved analytically or numerically and compared with experimental data. Uncertainties are clarified by additional experiments and model modification.

Major Findings:

(1) A mathematical model was developed that permits enzyme kinetics determined in vitro for Ara-C to be used in predicting plasma and tissue drug concentrations in several mammalian species.

(2) A device was invented to permit controlled slow administration of MTX to mice.

(3) The role of hepatic blood flow in influencing ethanol metabolism in vivo was clarified.

(4) The relationship between pharmacokinetics and drug effect of MTX has been partly clarified.

Significance: Drugs and other chemicals are tested for toxicity in animals; the extrapolation of the results to predict risk in man is a subject of serious concern. At issue are both the risk associated with environmental contaminants and the optimal use of drugs in therapy.

Proposed Course: Continued emphasis on pharmacokinetic modeling with particular attention to incorporation of metabolic processes. Increased emphasis on biologic effects through both experimentation and use of cytokinetics in conjunction with pharmacokinetics.

Honors and Awards: None.

Publications:

Bischoff, K. B., Himmelstein, K. J., Dedrick, R. L., and Zaharko, D. S.: Pharmacokinetics and cell population growth models in cancer chemotherapy. Advances in Chemistry Series. (In press)

Dedrick, R. L.: Animal scale-up. In Pharmacology and Pharmacokinetics: Problems and Perspectives. (In press)

_____: Physiological pharmacokinetics. Proceedings of the IFAC Symposium, 1973. (In press)

_____ and Forrester, D. D.: Blood flow limitations in interpreting in vivo Michaelis constants for ethanol oxidation. Biochemical Pharmacology. (In press)

_____, _____, Cannon, J. N., ElDareer, S. M., and Mellitt, L. B.: Pharmacokinetics of Ara-C deamination in several species. Biochemical Pharmacology. (In press)

_____, Zaharko, D. S., and Lutz, R. J.: Transport and binding of methotrexate in vivo. Journal of Pharmaceutical Sciences. (In press)

Zaharko, D. S. and Dedrick, R. L.: Applications of pharmacokinetics to cancer chemotherapy. In Proceedings of the 5th International Congress on Pharmacology. (In press)

_____, Dedrick, R. L., and Oliverio, V. T.: Prediction of the distribution of methotrexate in the sting rays dasyatidae sabina and sayi by use of a model developed in mice. Comparative Biochemistry and Physiology, 42A: 183-194, 1972.

Serial No. DRS-BEIB-2
1. Biomedical Engineering and Instrumentation Branch
2. Chemical Engineering Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1972, through June 30, 1973

Project Title: Development of Metal Complex Compounds for Control of Tumors

Previous Serial Number: Same.

Principal Investigators: André F. LeRoy, Anthony M. Guarino, Richard H. Adamson

Other Investigator: Rebecca E. Munroe

Cooperating Unit: LCHPH-NCI, LT-NCI

Man Years:

Total:	1.2
Professional:	0.8
Other:	0.4

Project Description:

Objectives: Development and characterization of metal complex molecules with organic and inorganic ligands that exhibit significant biological effects. Chemical synthesis, purification and analysis of platinum metal complexes whose anti-tumor activity merits careful study.

Methods Employed: Established chemical synthesis techniques are used when possible with novel procedures devised when necessary, for preparation of new compounds. Available methods permit characterization with gravimetric and volumetric chemical analysis. Atomic absorption spectrophotometry is used to assay metal content of body fluids. Cell culture techniques and *in vivo* testing with mice and other animals are employed.

Major Findings: Cis-diamminedichloropalladate, prepared with an improved technique, and ammonium tetrachloropalladate inhibit growth of L-1210 cells in culture. Platinum complex species can be assayed at the parts-per-million level of concentration in urine from test monkeys. Platinum complexes in urine can be fractionated by electrophoresis into positively and negatively charged species eluted and assayed for metal content.

Significance: Identification of metal complexes that inhibit tumor growth is an important contribution to cancer therapy. Characterization of such compounds and assay for the metals in body organs and fluids can help identify modes of action and suggest other potentially useful compounds.

Proposed Course: Broaden ability to synthesize, analyze, and characterize complexes. Improve sensitivity of analytical methods for measurement, identification and distribution of metal complex species in organs and body fluids of test animals.

Honors and Awards: None.

Publications: None.

Serial No. DRS-BEIB-3
1. Biomedical Engineering and Instrumentation Branch
2. Chemical Engineering Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1972, through June 30, 1973

Project Title: The Role of Fluid Dynamics and Mass Transfer in Development of Atherosclerosis

Previous Serial Number: None.

Principal Investigators: Robert J. Lutz, Joseph N. Cannon

Other Investigators: Robert K. Stiles, Kenneth B. Bischoff, Robert L. Dedrick, Donald L. Fry

Cooperating Units: OD-IR-NHLI, Howard University

Man Years:

Total:	1.5
Professional:	1.5
Other:	.0

Project Description:

Objectives: To measure shear stress on the inner wall of simulated arteries and correlate data with localization of atherosclerosis as found in experimental animals.

Methods Employed:

(1) An electrochemical technique, based on an oxidation-reduction reaction at electrodes implanted at a fluid-solid interface, is used. Mass transfer rates of redox ions are determined. Velocity gradients at the wall (shear rate) can be calculated from mass transfer rates by use of suitable boundary layer equations.

(2) In vitro experiments involve the measurement of diffusion rates of radio tagged lipoproteins and albumin into excised sections of canine thoracic aorta. A special constant temperature-humidity chamber has been designed to conduct these transport studies.

Major Findings: Preliminary findings from shear stress experiments in rigid casts of the canine arterial tree indicate peaks in shear stress near bifurcation points and branches, which are also regions of high plaque involvement in experimental animals. Results of the diffusion experiments indicate increased flux of lipid and protein into the arterial wall of excised sections

of canine aorta after exposure of the tissue to shear stresses which can damage the endothelial surface.

Significance: Elucidation of the role of hemodynamics and mass transfer in the development and progression of atherosclerotic plaques is fundamental in the study of vascular disease.

Proposed Course: Extend experimental studies in rigid casts of arteries with steady flow to pulsatile flow in distensible arterial models and further animal experimentation.

Honors and Awards: None.

Publications: None.

Serial No. DRS-BEIB-4
1. Biomedical Engineering and Instrumentation Branch
2. Chemical Engineering Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1972, through June 30, 1973

Project Title: Tumor Growth on Semipermeable Membranes

Previous Serial Number: Same.

Principal Investigators: Richard A. Knazek, Pietro M. Gullino, Robert L. Dedrick

Other Investigator: William R. Kidwell

Cooperating Unit: LB-NCI (Project No. 5219)

Man Years:

Total:	1.4
Professional:	1.3
Other:	0.1

Project Description:

Objectives:

(1) Develop effective devices and techniques for culture of solid tumors *in vitro* to study physiology, biochemistry and drug effects.

(2) Elucidation of transport mechanisms between tumors and implanted membrane cells in the study of metabolism and drug concentration *in vivo*.

Methods Employed: Tumor cells have been grown on the outside of capillary membranes perfused with oxygenated nutrient solution within a new device composed of capillary membranes which are permeable to nutrients, metabolites, oxygen and carbon dioxide.

Major Findings: L-cells formed nodules 1-2mm in diameter suggesting a release from contact inhibition. Human choriocardinoma also grew to multilayer depths. Commercial interest in the technique is intense.

Significance: It may be possible to grow cells *in vitro* to densities that approach those of solid organs or tumors. Resulting structures are expected to possess properties that differ from those of cells grown in monolayer culture. They may approach behavioral potential of the *in vivo* state and permit study of metabolism and drug sensitivity. High cell densities could also be useful in production of large quantities of cellular products.

Proposed Course: Further investigation of transport characteristics and development of improved devices. Application of existing system to new cell lines.

Honors and Awards: None.

Publication:

Knazek, R. A., Gullino, P. M., Kohler, P. O., and Dedrick, R. L.: Cell culture on artificial capillaries: An approach to tissue growth in vitro. Science, 178: 65-67, 1972.

Serial No. DRS-BEIB-5
1. Biomedical Engineering and Instrumentation Branch
2. Chemical Engineering Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1972, through June 30, 1973

Project Title: Multicomponent Plastics in Biomedical Use

Previous Serial Number: None.

Principal Investigator: Henry L. Gabelnick

Other Investigators: Rebecca E. Munroe, John W. Boretos, John I. Peterson

Cooperating Units: None.

Man Years:

Total:	1.0
Professional:	0.6
Other:	0.4

Project Description:

Objectives: To define the interaction of plastic systems with the biological environment with emphasis on the kinetics of additives elution from polymers and absorption of body constituents.

Methods Employed: Determination of concentration vs. time profiles of migrating species by means of quantitative analytical techniques. Parameters under investigation include fluid composition and flow conditions.

Major Findings: Analytical techniques have been established for the di-2-ethylhexylphthalate-polyvinyl chloride system exposed to a "pseudo-serum" consisting of a soybean oil emulsion. Equilibrium uptake by the "pseudo-serum" has been determined.

Significance: Physiologically compatible, stable materials with desirable physical properties are needed for many biomedical research and clinical applications. Characterization of desorption rates for additives from polymer systems and absorption of bodily constituents are important aspects in determining the utility of biomaterials.

Proposed Course:

(1) Kinetic studies of elution in a flow system which will simulate typical conditions in a heart-lung bypass procedure.

(2) Equilibrium and kinetic studies of phthalate elution into serum.

(3) Absorption studies including effects on physical properties.

Honors and Awards: None.

Publications:

Boretos, J. W. and Gabelnick, H. L.: Letter to the Editor--Characterization of biomedical polymers. Journal of Biomedical Materials Research. (In press).

Gabelnick, H. L.: Biorheology. In Lapedes, D. N. (Editor in chief): McGraw Hill Yearbook of Science and Technology. New York, McGraw Hill, 1973, pp. 66-74.

_____ and Litt, M. (Eds.): Rheology of Biological Systems. Springfield, Ill., Charles C Thomas, 1973, 319 pp.

Serial No. DRS-BEIB-6
1. Biomedical Engineering and Instrumentation Branch
2. Electrical and Electronic Engineering Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1972, through June 30, 1973

Project Title: Nuclear Magnetic Resonance Techniques for Biochemical Analysis

Previous Serial Number: Same.

Principal Investigators: Thomas R. Clem, Walter S. Friauf, Edwin D. Becker

Other Investigator: James A. Ferretti

Cooperating Units: LCP-NIAMDD, PSL-DCRT (Project No. DCRT 5.11)

Man Years:

Total:	4.0
Professional:	3.0
Other:	1.0

Project Description:

Objectives: Innovate and implement improved methods for structural elucidation of organic molecules by means of nuclear magnetic resonance with emphasis on ^{13}C.

Methods Employed: Develop and evaluate novel technique for improving sensitivity and versatility, including use of a superconducting magnet, pulse train excitation with digital programming of the sequences, heteronuclear decoupling, real time computerized data acquisition, digital averaging, phase correction, matched filtering, Fourier transformation, and printout of spectra.

Major Findings: A custom probe has been built to optimize conflicting electrical, magnetic, thermal and mechanical requirements. Completion of the heteronuclear decoupling and resolution of system integration problems have permitted quantitative sensitivity evaluation. Sensitivity achieved is close to the calculated theoretical limit.

Significance: The system provides a powerful new tool for elucidating the structure of organic molecules. It provides information on the location of carbon atoms that is used with information on hydrogen atoms obtained by proton NMR. The high sensitivity allows study of specimens with natural abundance of ^{13}C, and relaxes stability requirements by shortening the time needed to attain an adequate signal-to-noise ratio.

Proposed Course: Refine sensitivity and ease of use and develop more effective and convenient operating features.

Honors and Awards: None.

Publications: None.

Serial No. DRS-BEIB-7
1. Biomedical Engineering and Instrumentation Branch
2. Electrical and Electronic Engineering Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1972, through June 30, 1973

Project Title: Television Image Processing Techniques for Use in Research and Medicine

Previous Serial Number: None.

Principal Investigator: William H. Schuette

Other Investigators: James A. Dvorak, Leonard E. Grauer, Darrell V. Lewis, David R. Redwood, John M. Van Buren, Richard L. Webber, Willard C. Whitehouse

Cooperating Units: LPD-NIAID, CB-IR-NHLI, EEG-NINDS, SN-NINDS, OMS-NIDR, ADM-CC

Man Years:

Total:	3.0
Professional:	2.0
Other:	1.0

Project Description:

Objectives: Develop and apply new techniques for analyzing television signals available in medical research. Increase the use of television based systems for the collection of medical research data.

Methods Employed: The following systems have been developed as part of this program:

(1) A semiautomatic method for calculating left ventricular volumes directly from televised fluoroscopy. Traced ventricular silhouettes are electronically analyzed and volumes calculated automatically, utilizing realistic geometrical assumptions.

(2) A logarithmic television densitometer for obtaining the net forward ejection fraction of the left ventricle. The exponential decay of the washout curve obtained as a result of an LV X-ray dye injection is utilized to determine the ejection fraction.

(3) A television based system for analyzing changes in fluorescence that occur in exposed cortex during neurosurgery. The changes in fluorescence, which are related to metabolism, may be studied over large areas and the activity from several areas can be compared simultaneously.

(4) A quantum limited dental X-ray system, under development, with the first successful test of a prototype completed.

(5) A television based system for measuring cell areas and volumes, employing two TV cameras. The cell areas and volumes are automatically calculated from tracings and readout on a digital display.

(6) A system for inserting analog data into the television format so that auxiliary data may be correlated with video signals.

Major Findings: Image amplifiers have extended the use of television into low light level applications previously reserved for photomultiplier tubes. Video signals obtained for other purposes often can be processed to obtain valuable new quantitative data. Semiautomatic processing with analog circuitry and human involvement, at the proper level, is usually more cost effective than fully automated computer processing.

Significance: These developments extend noninvasive testing and provide increased quantitative data for research and treatment. Cell sizing by televised microscopy makes certain important measurements feasible which would otherwise be impractical. The televised fluorometer has launched a new area of investigation, the metabolism of exposed human cortex.

Proposed Course: Work will continue in order to improve available systems. New technologies will be incorporated and new applications explored.

Honors and Awards: None.

Publication:

Marcus, M. L., Schuette, W. H., Whitehouse, W. D., Bailey, J. J., and Glancy, D. L.: An automated method for the measurement of ventricular volume. Circulation, XLV: 65-76, 1972.

Serial No. DRS-BEIB-8
1. Biomedical Engineering and Instrumentation Branch
2. Electrical and Electronic Engineering Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1972, through June 30, 1973

Project Title: Diagnostic Ultrasound

Previous Serial Number: None.

Principal Investigator: James M. Griffith

Other Investigators: Walter L. Henry, Chester E. Clark, P. David Meyerowitz

Cooperating Units: CB-IR-NHLI, SU-IR-NHLI

Man Years:

Total:	5.0
Professional:	3.0
Other:	2.0

Project Description:

Objectives: To noninvasively obtain dynamic measurements of cardiac geometry, using ultrasound, to clarify the relationships of wall thickness, transverse ventricular dimensions, and valve motions to assess health state and diagnose disease.

Methods Employed: A unique interface between the ultrasonic scanner and a high speed fiber optic recorder was developed to expand the dynamic range of recorded information. A semiautomatic data reduction system including human interaction and video scanning is used to extract parameters of primary interest.

Where a two-dimensional display is required, an angular scan at 20 hz is utilized to best use of the small observation window available in the human chest. A synchronized scope display is monitored with CCTV to facilitate recording and analysis.

Major Findings: These systems enhance the amount of quantitative data obtainable from ultrasonic scanning to the point where it is useful as a routine diagnostic tool. The two-dimensional presentation makes it possible to observe the aortic and mitral valves simultaneously, which is of great value in analyzing certain cardiac problems.

Significance: A safe noninvasive method for making quantitative measurements of cardiac dynamics region has substantial value for diagnostic and research purposes.

Proposed Course: Refine present systems and extend techniques to animal studies to assess potential use in humans for flow measurement, study of drug effects, etc.

Honors and Awards: None.

Publications: None.

Serial No. DRS-BEIB-9
1. Biomedical Engineering and Instrumentation Branch
2. Electrical and Electronic Engineering Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1972, through June 30, 1973

Project Title: Instrumentation for Measurement of Low Level, Rapid Chemical Reaction Rates by Temperature Jump and Stopped Flow Meter Techniques

Previous Serial Number: None.

Principal Investigators: Michael Greifner, P. Boon Chock

Other Investigators: None.

Cooperating Units: LB-IR-NHLI

Man Years:

Total:	1.0
Professional:	0.75
Other:	0.25

Project Description:

Objectives: Measure incremental parameter changes corresponding to important biochemical reactions over a wide dynamic range. System response shall be capable of detecting and displaying chemical reaction rise times of less than 100 nanoseconds.

Methods Employed: Absorption and fluorescence are monitored with photomultipliers. Dynode switching provides wide dynamic range without impairment of frequency response, linearity or accuracy. Cooling the photomultipliers and using a magnetic lens assembly further increase instrument dynamic range.

Major Findings: Increased stopped flow meter sensitivity yielded an order of magnitude improvement in absorption level detections over those commercially available. Higher sensitivity is important, since enzyme reactions are generally low level in nature.

Significance: Improved system sensitivity and frequency response opens exploratory investigations into the complex mechanisms of various enzyme functions. State of the art instrumentation for temperature jump apparatus and stopped flow meters can provide information on the incremental, fast interactions between antibiotics and enzymes or proteins.

Proposed Course: Complete evaluation of stopped flow meter reaction times. Check out and evaluate temperature jump apparatus.

Honors and Awards: None.

Publications: None.

Serial No. DRS-BEIB-10
1. Biomedical Engineering and Instrumentation Branch
2. Electrical and Electronic Engineering Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1972, through June 30, 1973

Project Title: Automatic Test Set for Evaluating Electrical Safety of Clinical Equipment

Previous Serial Number: None.

Principal Investigators: Walter S. Friauf, Horace E. Cascio

Other Investigator: Anthony J. Vita

Cooperating Unit: ESC-CC

Man Years:

Total:	1.5
Professional:	0.5
Other:	1.0

Project Description:

Objectives: To improve performance and economy of routine electrical safety testing required for hospital equipment and enhance accuracy, reliability, and safety.

Methods Employed: Design, construction, test, and evaluation of an automated test system that satisfies published criteria on electrical safety standards.

Major Findings: The instrument performs the five most needed tests fully automatically and meets all specified technical requirements. The high accuracy and digital readout promise to provide trend information which can greatly increase the value of scheduled inspections.

Significance: Hospital electrical safety depends on a great number of routine tests at relatively short intervals. This can be done satisfactorily only with the aid of automatic test equipment of the type described. This is especially important in a clinical research environment, where more equipment (and greater variety) than usual is encountered.

Proposed Course:

(1) Complete evaluation and check out of the test system.

(2) Use test set to accumulate data for design of comprehensive test program.

(3) Design a test program for high priority areas in Clinical Center to include establishment of test limits and inspection interval for each piece of equipment, trend review procedures, files, etc.

(4) Design and build a second generation test set.

Honors and Awards: None.

Publications: None.

Serial No. DRS-BEIB-11
1. Biomedical Engineering and Instrumentation Branch
2. Mechanical Engineering Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1972, through June 30, 1973

Project Title: Biomechanical Concomitants of Head Injury/Head Injury Model Program

Previous Serial Number: Same.

Principal Investigators: Ayub K. Ommaya, Lawrence E. Thibault, Thomas A. Gennarelli

Other Investigators: None.

Cooperating Unit: SN-NINDS

Man Years:

Total:	2.5
Professional:	1.2
Other:	1.3

Project Description:

Objectives: Define head injury mechanisms for a variety of mechanical loading configurations; develop reproducible models for cerebral concussion, cortical contusion and cavitation injury in order to perform intensive pathologic, neurochemical and electrophysiological investigations.

Methods Employed: Mathematical analysis of mechanical phenomena; experimental stress analysis (i.e., photoelastic and Moiré); animal experimentation and appropriate physiologic transduction.

Major Findings: Somatosensory evoked responses (employing median nerve stimulation in the experimental animal) are a quantifiable index of level of consciousness and cerebral concussion.

Significance: Somatosensory evoked responses may prove to be a valuable tool in head trauma research and clinical diagnosis of closed head injuries.

Proposed Course: Now that a reproducible model for cerebral concussion has been developed, the resultant physiology will be studied in detail with the intention of deriving a data base with clinical significance; extend the investigation to models for cortical contusion and cavitation injury.

Honors and Awards: None.

Publications:

Gennarelli, T. A., Thibault, L. E., and Ommaya, A. K.: Pathophysiologic responses to rotational and translational accelerations of the head. In Proceedings of Sixteenth Stapp Car Crash Conference, Nov. 8-10, 1972, Detroit, Michigan. New York, Society of Automotive Engineers, Inc., Lawrence M. Patrick, Chairman, pp. 296-308

Ommaya, A. K., Gennarelli, T. A., and Thibault, L. E.: Traumatic unconsciousness: Mechanics of injury to the brain in violent shaking of the head. In Proceedings of the American Association of Neurological Surgeons, 1973. (In press)

Serial No. DRS-BEIB-12
1. Biomedical Engineering and Instrumentation Branch
2. Mechanical Engineering Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1972, through June 30, 1973

Project Title: Atraumatic Electrical Sensing in Brain Cortex

Previous Serial Number: DRS-BEIB-10

Principal Investigator: Seth R. Goldstein

Other Investigator: Edward M. Schmidt

Cooperating Unit: LNLC-NINDS NDS-(I)-69LNLC/OC-1687

Man Years:

Total:	1.5
Professional:	1.5
Other:	.0

Project Description:

Objectives: Achieve stable electrode location next to neuron for reliable acute recording of brain cell activity within the pulsating cortex at prescribed depths up to 0.5 cm with minimum tissue damage.

Methods Employed: A conducting wire electrode is advanced by a fine lead screw within a frictionless pneumatically balanced piston-cylinder retainer that "floats" on the cortical surface and automatically compensates for axial pulsations of the cortex.

Major Findings: Instrument has been successfully bench tested and is ready to be tested on animals.

Significance: Electrical recording from cerebral cortex in humans has been limited because of difficulty in achieving atraumatic intervention. This new method, if successful, is expected to enable a considerable increase in acquisition of information necessary to enhance understanding of brain function.

Proposed Course: Testing and evaluation with animals and humans, refinement of techniques and apparatus, if necessary; clinical applications; enlargement of device family for related types of measurement requirements.

Honors and Awards: None.

Publications:

Goldstein, S. R.: Atraumatic recording from exposed pulsating human cortex--a new mechanism. In Proceedings of the 25th Annual Conference on Engineering in Medicine and Biology 1972, Bal Harbour, Florida, vol. 14. Arlington, Va., The Alliance for Engineering in Medicine and Biology, Samuel P. Asper, M.D., Chairman, p. 190.

_____ and Salcman, M.: Mechanical factors in the design of chronic recording intracortical microelectrodes. IEEE Transactions on Biomedical Engineering. (In press)

Serial No. DRS-BEIB-13
1. Biomedical Engineering and Instrumentation Branch
2. Mechanical Engineering Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1972, through June 30, 1973

Project Title: An Electrohydraulic System for Ultrasonic Echocardiography on Exercising Patients

Previous Serial Number: None.

Principal Investigator: Seth R. Goldstein

Other Investigator: David R. Redwood

Cooperating Unit: CB-IR-NHLI

Man Years:

Total:	1.0
Professional:	1.0
Other:	.0

Project Description:

Objectives: To achieve scanning and stable orientation of ultrasonic transducers mounted on chest of exercising patient for echocardiography studies of heart left ventricular wall motion and thickness.

Methods Employed: An ultrasonic transducer contained in a hemispherical bearing is oriented by two perpendicular servo actuators mounted on a small platform strapped to the chest and connected by an "umbilical" cord to a hydraulic power supply and feedback control electronics.

Major Findings: The overall system allows echocardiography studies to be performed on upright and exercising patients.

Significance: Echocardiographic studies have previously been confined to patients at rest in the supine position. Studies can now be extended to conditions of varying load on the heart. Phasic left ventricular transverse dimension and, in some instances, wall thickness can be observed.

Proposed Course: Clinical use of the device; testing and further development for possible indication of cardiac output measurement.

Honors and Awards: None.

Publications: None.

Serial No. DRS-BEIB-14
1. Biomedical Engineering and Instrumentation Branch
2. Mechanical Engineering Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1972, through June 30, 1973

Project Title: Mechanically Induced Somatosensory Evoked Responses/A Technique for Studying Closed Head Injury in the Clinic

Previous Serial Number: None.

Principal Investigators: Ayub K. Ommaya, Thomas A. Gennarelli, Lawrence E. Thibault

Other Investigators: None.

Cooperating Units: SN-NINDS

Man Years:

Total:	1.0
Professional:	0.5
Others:	0.5

Project Description:

Objectives: To study the somatosensory evoked response on patients with closed head injuries and utilize data obtained to improve clinical diagnosis.

Methods Employed: A stimulator was developed to evoke a cortical response by mechanical manipulation of the wrist; the response is recorded on tape and analyzed with a PDP-12 computer. This system is portable for use in the clinic.

Major Findings: The technique has been validated and is ready for evaluation in the clinical environment; a data base for human normals is currently being developed.

Significance: More complete understanding of the physical and physiological concomitants of head injury is required for diagnosis, assessment, and therapy.

Proposed Course: Refine and extend experimental and theoretical methods; correlate the findings from the animal experiments in head injury to clinical data for a variety of pathologic states.

Honors and Awards: None.

Publications: None.

Summary of Branch Activities July 1, 1972, through June 30, 1973

ENVIRONMENTAL SERVICES BRANCH Vinson R. Oviatt, Chief

I. SUMMARY

The Environmental Services Branch devoted its major program effort to biological control and pollution abatement during the year. This emphasis resulted from internal NIH program needs and external requirements related to the Occupational Safety and Health Act and the National Environmental Policy Act. These two acts required surveys of laboratories and employee work places, preparation of environmental impact statements, specific actions relating to collection and disposal of solid waste, and assistance to NIH management on the environmental impacts of contract and grant programs. The Laboratory Section was eliminated, and the manpower resources gained were diverted to these two major efforts.

The Biological Control Program was enhanced by appointment of the NIH Biohazard Committee. The Chief, ESB, was appointed Secretary, and two other Branch members serve on Sub-committees. A specification for laminar flow biological safety cabinets was developed in collaboration with Materiel Management, National Cancer Institute, and representatives of the affected industries. Materiel Management will develop a qualified products list using the specifications. This should result in greater competitive bidding in the purchase of quality safety cabinets for NIH and for other Government and private laboratories.

The Branch collaborated with the Engineering Design Branch, OES, in development of biohazard procedural manuals for entrance requirements for contractors working in Building 41 and the 5-C Corridor of Building 36. The testing and maintenance program of biological safety cabinets, high efficiency filters, and other bio-control systems revealed that 61% of associated HEPA filters failed the initial "leak" test. This demonstrates the need for testing HEPA filters prior to certification that equipment is safe. A new activity of this program is the coordination of epidemiological investigations with the Employee Health Service. Three investigations were carried out; all involved handling non-human primates. The Veterinary Resources Branch participated in these investigations.

The 15th Biological Safety Conference, cosponsored by NCI, was held at the NIH for the first time. Eighty participants represented both Government and private biomedical research laboratories. Staff visited several university environmental health and safety programs to assist in establishing biological control programs. Visitors from domestic and foreign laboratories involved in biological safety programs were received and briefed.

Noise pollution problems continue to increase. Identification and evaluations of work interference situations were carried out at the Power Plant, the printing plant, and other mechanical rooms. The Branch supported the NIMH in setting up the special hearing test environment in Building 10.

Air pollution monitoring by ESB staff was drastically curtailed during the year. This was possible due to the location of the Maryland State Air Pollution Monitor on the NIH grounds. State officials routinely furnish ESB with magnetic tapes of collected data for NIH use.

Water pollution problems at the NIHAC are under control with the new Water Pollution Control Plant in complete operation. The plant has met design requirements. Discharge effluent now produces only a minimal effect on Broad Run. Automated water quality monitors have been installed upstream and downstream of the plant providing around-the-clock water quality data. Progress was made in reducing water pollution at the NIH Campus. Two major sources of pollution of the NIH storm drain were eliminated by construction of an interceptor for diversion of trash and ash washings to the sanitary sewers and a vehicle wash facility for trucks, dumpsters and related equipment. The amount of waste elemental mercury and mercury compounds was further reduced through orientation of investigators in the use of mercury and provision of facilities to concentrate compounds containing this pollutant.

Solid waste management and disposal studies were a major staff effort. Assistance was provided the Federal Engineering and Construction Agency in the form of technical development of the environmental impact statement for the Tri-Service Incinerator. Preliminary investigations were made for contract proposal which will result in a comprehensive study of solid waste handling and disposal procedures at the NIH main Campus. The program to eliminate the use of metal G.I. cans for solid waste collection began with the installation of a paper bag disposal system in the laboratories of NIAID.

The ESB completed the first year of total Building 10 environmental control under a revised plan worked out jointly with the Clinical Center. Under the plan the Hospital Environmentalist provides surveillance of Clinical Center and associated laboratories. He coordinated the efforts of other ESB personnel required to maintain the desired environment. Both ESB and the Clinical Center are satisfied that this approach provides essential services when needed, adequate surveillance, and the best use of limited manpower. Substantial staff effort was devoted to problem diagnosis and solution. A plan for restructuring the building water supply system was worked out with the Engineering Design Branch, OES, to protect it from internal contamination. Assistance was given in preliminary planning for eight major Clinical Center construction and renovation projects.

Detailed environmental evaluations were conducted in the NCI, Clinical Center, and NICHD animal room facilities in cooperation with the Veterinary Resources Branch. The creation of individual institute animal care committees has greatly aided the effectiveness of this program. Substantial upgrading of NIH food service establishments began as a result of ESB surveys coupled with management cooperation in provision of major items of equipment. Industrial hygiene activities were limited as a result of staff assistance in the NIH

Occupational Safety and Health survey required by DHEW. Problems for which significant solutions were provided included asbestos contamination in the BEIB Glassblowing Shop, design of a special hood for control of chemical carcinogens in a feed mixing operation, and noise problems in the Power Plant and other areas.

Environmental studies completed during the year included an experimental high purity water distribution system via the use of polytetrafluoroethylene tubing, a disposable filter assembly for removal of virus in fluids; evaluation of the Sorvall cell washing centrifuge, a new high purity water processing system; and modification of two laminar flow biological safety cabinets; one to provide a heating system and controls, and one for containment of a centrifuge. The latter two projects were in collaboration with BEIB.

ESB extended its efforts via the use of contracts. Two contracts were continued; one for testing and maintenance of biological safety cabinets, and one to identify research needs for high purity water. A contract was initiated for the development of an NIH biohazard safety guide. Contract efforts planned for the coming year include chemical fume hood monitoring; animal room surveillance; a comprehensive study of NIH waste production, management and disposal; and management of the ESB training effort for biological control, use of pesticides and hazardous environmental chemicals, and animal caretaker training.

ESB continued its effort in improvement of human relations. The implementation of the Branch Human Relations Committee proved most successful to employees and management.

II. BRANCH PROGRAMS

A. Objective

The Environmental Services Branch objectives at NIH, Bethesda, Maryland, and field station facilities are:

1. To locate and solve environmental problems.

2. To assure a safe, compatible environment for patients, staff, and the surrounding community.

3. To promote an environment conducive to a quality research program.

B. Current Programs

The Branch objectives were attained through the following closely coordinated program areas:

1. Biohazards and Contamination Control

The biohazards and contamination control program is designed to promote a safe environment for personnel and to protect research work at all NIH facilities in Bethesda and in the field. There is regular surveillance of potentially hazardous laboratory and animal room areas, control equipment, and facilities. Consultation is provided on a case-by-case basis for laboratory arrangements needed to protect the investigator and the public.

2. Industrial Hygiene

The industrial hygiene program recognizes, evaluates, and controls environmental factors and stresses which may cause illness or significant discomfort among workers or citizens of the community. Gaseous and particulate air contamination (including air pollution) potentially or actually generated at NIH are major surveillance activities. Problems connected with noise, temperature extremes, and non-ionizing radiation are also dealt with by this program.

3. Hospital Environmental Control

The hospital environmental control program in the Clinical Center is designed to protect patients, employees, and visitors from environmental influences which may be unsafe, unhealthful, or uncomfortable. This program includes regular surveillance of patient care areas and support departments. It also provides consultative services to programs in these areas.

4. General Sanitation and Sanitary Engineering

The general sanitation and sanitary engineering program is concerned with basic environmental factors affecting the health of NIH employees, visitors and the quality of the research environment. These factors include food

sanitation, water supply, solid and liquid waste disposal, housekeeping practices, pesticides, and water pollution control.

5. Environmental Studies for Support of Research and Patient Care

Continuing environmental studies are conducted as a necessary adjunct to surveillance and consultation activities. Studies are oriented to environmental systems and problems; evaluation of new equipment and methods; quality glassware, animals, and water; environmental stresses related to light, heat, noise, food, water, and waste; and the identification of environmental contaminants.

6. Training

Training to promote job effectiveness is provided for ESB personnel and staff members at NIH. This training is particularly related to environmental control devices and practices in the general research environment which require special training for proper operation and handling.

C. Program Progress and Accomplishments

1. Biological Control

A standing NIH Biohazard Committee was established by the Deputy Director for Science. The Chief, ESB, was appointed Secretary, and two other Branch members served on the training and risk assessment sub-committees. ESB continued to provide basic services in biohazards control to the B/I/D. Initial action was taken in the surveillance of laboratories handling class 3 and 4 pathogens. A new questionnaire for the registry of micrcbial agents, tissue cultures and animals was developed on a "check off" basis to ease and speed investigator responses.

The ESB supervised contract NIH 72-C-7-CC for testing and maintaining biological safety cabinets, high efficiency filters, and certain other bio-control systems. Of the various problems uncovered during the contract period, the most noteworthy deficiency was failure of HEPA filters. Sixty-one percent, or 141 of 230 hood filters, failed the initial filter leak test. These results demonstrate the need for testing to certify that the equipment is safe. Equipment requiring upgrading not covered by the contract was handled in-house by work request. This testing program has been well received by the I/D. The contract was negotiated for another year.

A technical evaluation committee reviewed nine proposals resulting from RFP, NIH-DRS 73-1, for development of a biohazard safety guide. Three offers were acceptable, and a contract was negotiated.

A comprehensive NIH specification for a laminar flow biological safety cabinet was completed. This specification was developed in collaboration with Materiel Management and National Cancer Institute. A one-day meeting was held at NIH with 47 laminar flow equipment manufacturers represented to explain the specification and administration of the Qualified Products Listing (QPL) and to receive industry comments. This specification should

provide for greater competitive bidding and a better quality safety cabinet for NIH. Other Government and private agencies should benefit from the QPL development.

A decontamination chamber is currently under design to be located on the Third Floor of Building 13. The facility will be used to decontaminate equipment to be repaired or surplused.

Major program emphasis continued in the area of consultation with NIH research personnel in assessing potential biological hazard problems, equipment use, and procurement. ESB served as technical advisor to Materiel Management in review of procurement documents with respect to biological safety; collaborated with Engineering Design Branch, OES, in the development of biohazard procedural manuals on entrance requirements during construction contracts in Buildings 41 and 36 (5-C Corridor).

Several plan layouts were reviewed for the proposed renovation of Building 376 at Fort Detrick. The building will house the NINDS research program presently located at the Patuxent Wildlife Refuge. The objective has been to establish levels of biohazard existence in areas of office, laboratory, and animal holding and to control access to these areas by means of shower-locker complexes, double-lock doors, and unidirectional traffic flow. The integrity of all architectural barriers was examined and an effective barrier system established. Also, autoclaves have been positioned to best ensure against contamination spread between different levels of containment. Biohazard barrier systems at the Middle America Research Unit in Panama were tested and maintenance provided to correct deficiencies. This included decontamination of exhaust plenums and installing new HEPA filters. Safety cabinets and other equipment were checked to certify that they were safe to use.

A new activity for the biological control program is coordination of epidemiological investigations with the Employee Health Service. Three investigations were carried out as a result of: (1) two cases of hepatitis "A" among animal caretakers, NINDS; (2) three tuberculin skin test conversions in animal caretakers, two in NEI and one in DRS; and (3) three cases of shigellosis among animal caretakers, DRS. Handling of non-human primates was involved in all cases. The Veterinary Resources Branch participated in these investigations. In addition to alerting all principals about the infections, substantial recommendations were made. Better management practices to protect personnel who work with non-human primates are needed. In two of the three situations investigated, the primate facilities were sub-standard.

The ESB staff provided extensive professional and technical advice to other governmental organizations and private institutions. In addition to numerous telephone conferences, these consultative services are frequently comprehensive reviews of records and/or literature with written response to the requestor; review and critiquing of environmental control standards, such as those promulgated by the Joint Commission on the Accreditation of Hospitals and the National Sanitation Foundation; protracted consultations with domestic and foreign visitors at the NIH Reservation; and travel from the assignment station for such purposes. The Fifteenth Biological Safety Conference was held at NIH for the first time, cosponsored by the NCI and DRS. Over 80

attended.

Regular sampling surveillance was continued through the year providing microbiological analyses of NIH potable water, NIHAC waste effluent, distilled water, milk and food samples, animal feed and bedding, sterility and other tests.

Arrangements have been made with the NCI to evaluate prototype laminar flow biological safety cabinet designs for acceptance on the Qualified Products List. This verification of containment performance is a requirement of a new specification to upgrade quality of equipment and to enhance industry competition.

Poor construction practices in laboratories were reviewed, and detailed methods for sealing various types of wall, ceiling and floor penetrations to meet up-to-date construction practices were developed.

2. Industrial Hygiene

Industrial hygiene activities ranged from careful plan reviews of new or remodeled facilities to specific occupational health problems such as: (1) A study of asbestos contamination of the air in the BEIB Glassblowing Shop following discovery of a serious employee health problem. While after-the-fact evaluations did not reveal excessive air concentrations, procedural changes and ventilation controls were recommended, and will be implemented by BEIB. (2) Design of a special hood for control of chemical carcinogens in a feed mixing operation. (3) Identification and evaluation of noise problems which continue in areas of the NIH Power Plant, and in various printing operations and building mechanical rooms. Nuisance and work interfering noise complaints were at a high level this year. Significant program support was given NIMH in setting up a sound controlled out-patient test environment in Building 10.

A team survey for compliance with the Occupational Safety and Health Act was conducted with representatives from ESB, Radiological Health and Safety, and Plant Safety jointly surveying the facilities. Surveillance of chemical fume hood performance was continued during the year. About one-third of the 800 hoods at NIH were monitored.

The Maryland State Air Pollution Monitor located at NIH was operational throughout the year. ESB has been working with state officials and regularly receives magnetic tape copies of the data. A computer program to read the tape and print a report of selected parameters has been prepared. Air quality was generally quite good in this location except for relatively brief episodes occurring when the wind direction is from the Power Plant and incinerator.

3. Hospital Environmental Control

For the first time, ESB provided total surveillance of the Clinical Center environment and provided environmental control services to the Clinical Center staff. This resulted from the ESB Building 10 environmental control program plan, approved by DRS and CC administration. The principal innovation is that

the ESB hospital environmentalist coordinates all Building 10 environmental control problems related to patient health. The CC administration expressed satisfaction with this approach.

Substantial staff effort was devoted to problem diagnosis and solution typified by the following: formulation of guidelines for cleaning and disinfecting fiberoptic endoscopes; definition of a method for effective, non-damaging sterilization of methacrylic prosthetic implants; prescribing a method for generating high quality steam for autoclaves in such sensitive areas as surgical suites and the pharmacy; development of a cleaning method for removal of deposits from heart-lung machine oxygenation discs; high frequency bacteriological testing of patient dairy product supplies due to sub-standard flavor and microbial quality, culminating in a different source of supply; and ongoing testing of sterile supplies of varying age to provide a data base for realistic shelf-life policies.

Many months of effort by ESB and the Engineering Design Branch, OES, resulted in formulation of an engineering policy for protecting the Building 10 water supply system(s) from possible internal contamination. Due to the magnitude of the task, it will be executed in stages beginning in FY'74.

Significant staff time was devoted to review of environmental aspects of documents and plans for NIH construction projects. Prominent among eight Clinical Center projects were the preliminary Program of Requirements for the Ambulatory Care Research Facility (Building 10-B) and the industrial and environmental engineering study of the laundry.

4. General Sanitation and Sanitary Engineering

The NIHAC water pollution control plant completed its first year of operation. ESB provided technical assistance, consultation, and training for its operators. ESB provides monthly surveillance of the potable water and wastewater. It also conducts special chemical and biological studies of the receiving stream (Broad Run) to ensure compliance with water quality standards. The plant met design requirements, and discharge of the effluent produced a minimal effect on the stream. Automated water quality monitors have been installed upstream and downstream from the effluent discharge point on Broad Run. Around-the-clock water quality data will soon be available.

Some progress was made in reducing water pollution by NIH. Control measures were effected for two major sources of pollution of NIH storm drains and thus Rock Creek. An interceptor ditch was constructed for diversion of trash and ash washings to the sanitary sewer behind Building 11; and a vehicle wash facility for trucks, dumpsters, and equipment was built near the Building 12 Fire Department Station. The program continued to reduce the amount of waste elemental mercury and mercury compounds released into the sanitary sewer by orienting investigators and providing facilities to concentrate compounds containing mercury.

ESB continued to monitor building and individual high purity water supplies during FY'73. Distilled water was regularly monitored for conductivity, and quarterly for copper content. Consultations on problems with existing

systems and recommendations for special new high purity water systems were provided.

An experimental polytetrafluoroethylene tubing high purity water distribution system was installed in the ESB laboratories and at several other NIH locations. Studies were made indicating that this tubing has excellent qualities and does not contribute measurable contaminants to water.

Problems associated with the disposal of solid waste were at a peak. ESB contributed critical review and revisions for the environmental impact statement for the Tri-Service Incinerator; baseline noise surveys at the Walter Reed Annex where the incinerator is to be located for future assessment; initiation of a contract for an independent, comprehensive assessment of all waste handling and disposal systems at NIH; and planning and effecting improvement in waste handling procedures through new equipment and limited conversion to a paper bag waste container system. A special metal funnel was engineered for use of the bag system in animal rooms.

Detailed sanitation evaluations were conducted in the NCI, CC, and NICHD animal room facilities in cooperation with the VRB to evaluate animal room facilities for conformance with existing standards and ability to meet program needs.

A general program for upgrading NIH public food service establishments was conducted. ESB pressured managers and encouraged cooperation of NIH funding groups. Special problems and complaints were handled immediately.

5. Environmental Studies

ESB collaborated with BEIB in modifying a laminar flow biological safety cabinet for the NHLI to provide a heating system and controls; and for the NIAID, a centrifuge containment system.

The Branch evaluated contamination problems and attendant occupational risks in operating Sorvall cell washing centrifuges in the CC Blood Bank, including experimental assessment of potential aerosol discharge. Biological tracers disclosed two significant avenues of aerosol discharge from the operating system. Comprehensive recommendations were submitted concerning hygienic use of the device, effective washing and disinfection, and proposed modifications of the system to control aerosols.

A disposable filter assembly, which is pretested to remove all particles 0.25 micrometers (mm) or larger in size and 98% of all particles 0.12 mm in size or larger, was evaluated to determine filtration efficiency against viruses. The filter effectively removed virus particles in aerosols but permitted passage of viruses in fluids. The filter, combined with a flask, provided a trap to prevent contamination of vacuum lines. The system was described in Environmental Control Note, No. 3, entitled, "A Secondary Reservoir and Filtration Apparatus for Vacuum Systems."

A contract was negotiated with the University of Minnesota to study research water quality requirements. ESB is providing its existing data base and

supporting the part of the study being conducted at NIH. The report will be completed in FY'74.

6. Training

The ESB training program offered to NIH employees was below last year's greatly reduced level. ESB cooperated with the Veterinary Resources Branch, DRS, in one animal caretaker training course.

ESB personnel received 526 hours of training at designated short courses or in classroom experience at local community colleges and universities. ESB seminars were continued to provide "state-of-the-art" information to staff and other interested personnel.

Two PHS Co-step trainees contributed to the Branch mission in sanitation and biological control.

D. Problems

Some rather serious deficiencies exist in a number of NIH facilities which periodically forces reaction on an emergency basis to health or pollution related problems. Some situations are slowly in the process of correction; for example, Building 37 air intake contamination by trucks at the loading dock, mentioned in last year's report.

Air handling systems, construction and architectural details of some of the older NIH laboratory buildings make the space unsuitable for hazardous biological work and vulnerable to contamination of research work. Most notable are Buildings 7 and 9. Neither building is safe for work with potentially infectious agents, nor for safe housing and experimentation with non-human primates. Availability of space at the Frederick Cancer Research Center should be explored for NIAID hazard work. Primates should not be housed in Building 9. Space should be made available for this purpose that will meet the criteria established in DHEW-NIH guide #73-23.

Manpower shortages caused a virtual discontinuance of ESB sponsored training in most program areas.

E. Program Plans

A greater use will be made of the contracting mechanism to accomplish Branch objectives in FY'74. The present high purity water study contract and the bio-control cabinet surveillance and servicing contract will be continued. Contracts for chemical fume hood monitoring a total waste survey of NIH, an annual animal room surveillance program, and an animal caretaker training program by a contractor are also under consideration.

Specific ESB personnel will be assigned the B/I/D interface responsibility in an attempt to provide better communication and to permit ESB to better carry out its environmental control programs. This concept has already been adopted with Building 41, NCI staff, Building 10 in general, and with the Engineering Design Branch, OES, with good results.

On occasion, problems have occurred where PEB personnel have attempted to perform work in biohazard restricted areas without prior safety clearance. Discussions have been held with PEB toward development of a procedure for ESB to review work requests involving biohazard restricted areas.

A modest effort was begun toward surveillance of those laboratories working with potentially hazardous class 3 and 4 agents. Although this effort falls far short of what was projected in last year's program plan, it will be a high priority activity in FY'74.

Different approaches have been discussed with EDB and a system formulated for streamlining the plan review process. It is expected this system will maximize efficiency and allow ESB an opportunity to have input on the environmental aspects at an early stage of the project.

F. Publications

Oviatt, V.R.: Environmental Health Concerns. Journal of the American Hospital Association. 47:83-85, 1973.

Wilkinson, T.K., Morrison, R.P., and Oviatt, V.R.: Control of Physical and Chemical Agents. Journal of the American Hospital Association. 46:9-102, 1972.

Karamian, N.A.: Ventilation of Electron Capture Detectors. Health Physics. 23:257, 1972.

Falcao, D.P., Mendonca, C.P., Scrassolo, A., De Almeida, B., Hart, L., Farmer, L.H., Farmer, J.J.III: Nursery Outbreaks of Severe Diarrhoea Due to Multiple Strains of Pseudomonas Aeruginosa. The Lancet. 2:38-40, 1972.

U.S. Patent 3,713,778 issued January 30, 1973, on "Karamian Separatory Funnel" innovation.

DIVISION OF RESEARCH SERVICES

Summary of Branch Activities July 1, 1972, through June 30, 1973

LIBRARY BRANCH Ruth C. Smith, Chief

I. SUMMARY

The position of Branch Chief became vacant in August 1972, and the Director, DRS, served as Acting Chief until the present Librarian entered on duty on April 30, 1973.

The suit of Williams and Wilkins Company against the Government for alleged infringement relating to the photocopy service of the NIH Library and NLM and the copyright law has been presented to the full Court of Claims by the Department of Justice and is still pending.

New photocopy equipment has improved this important service to the NIH investigators and supporting staff.

A new policy relative to written translations became effective January 1. Written translations, with the exception of letters and similar items, are handled almost exclusively by contract with the cost of the translation charged to the B/I/D concerned.

A limited informal survey of users' attitudes toward the Library as it currently functions and a review of suggestions for improving services to fit their research needs was conducted. The returns will be analyzed.

The semiannual review of employee performance by supervisors instituted by DRS this year was completed in January. An informal unstructured approach provided a relaxed atmosphere for employee-supervisor discussions.

The Branch Human Relations Committee conducted a general meeting of nonsupervisory employees and held several meetings with the Acting Branch Chief to discuss employee criticism and suggestions. Representatives on the Committee were chosen by each Section and the Office of the Chief.

The FY 1973 Branch Training Program met individual and organizational needs on a group basis continuing the policy of the last few years.

Exhibits displayed by the Library featured services of the NIH Library, Dr. Christian B. Anfinsen, one of the 1972 Nobel Prize Winners in Chemistry, and a history of the Public Health Service.

II. BRANCH PROGRAMS

A. Objectives

The primary mission of the Library Branch is to operate an efficient, comprehensive library in support of NIH scientific, medical, and administrative programs. Activities of the Library include selection, acquisition, organization, maintenance, and circulation of literature pertinent to the programs; operation of a photocopy service; provision of interlibrary loan service; provision of informational, reference, and bibliographical services; provision of Library services advisory assistance; and provision of a translating service for foreign scientific and medical literature. To fulfill its mission, the Library is responsive to changing literature needs of the NIH investigators, is knowledgeable of current developments in manual and machine methods of communication and information retrieval, and is alert to adjustment of procedures for improved Library services.

B. Current Programs

Readers Services

The Circulation staff provides a charging system, making available books and journals. The staff issues Library Identification Cards; operates the Library's security system; provides an overdue recall system; issues Pagemasters; and makes assignments to locked study carrels.

The Interlibrary Loan staff obtains from other libraries literature required by NIH investigators which is not included in the collection.

The Stacks and Copy Service staff maintains the stacks, carrels, reference and Reading Room areas and reshelves books and journals to facilitate access by the Library clientele. A copy service is provided which allows greater use of the Library's journal collection.

Translating Service

The Translation Unit provides oral, recorded, and written translations as requested. Oral translations are emphasized in-house, and a written translation service is provided through contractual firms.

Reference and Bibliographic Services

The Library Services Adviser Program provides an integrated response to the information needs of the NIH scientific community. This may consist of utilization of external resources in addition to the resources and services available in the NIH Library, such as specialized information centers, computerized information retrieval systems, and clearinghouses. The Reference staff supplies ready response to questions, verifies citations, and compiles short reference lists upon request at the Reference Desk in the Upper Level Reading Room or by telephone. Reference Librarians answer difficult reference questions and compile literature searches as requested. They serve as selectors for Library acquisitions by continually searching for literature

pertinent to the scope of the Library. They also maintain the collection of basic Reference Books. The Section staff provides bibliographic assistance with experienced searchers to conduct requested MEDLINE computer searches from the National Library of Medicine.

Technical Services

The Acquisitions staff provides for the acquisition of books, journals, technical reports, and microfilm materials by purchase, gift, and exchange which have been selected as pertinent to the scope of the Library. The staff is responsible for the maintenance of accession records through input to automated systems used by the Library and for the preparation of completed journals for commercial binding. Computer printout includes daily and monthly cumulated listings of current journals and their holdings and weekly listing of books on order or in preparation.

The Cataloging staff organizes the acquired book literature through classification, cataloging and subject heading, and processes it for inclusion in the collection. The staff is responsible for the maintenance of the Library's catalog and the maintenance of catalog records for journals through input to the automated systems.

C. Program Progress and Accomplishments

Two Library Consultants were appointed to advise the Branch Chief. Dr. Estelle Brodman, Librarian at Washington University School of Medicine Library, served as consultant on overall library matters and Mr. Glyn Evans, Coordinator of Library Systems, Five Associated University Libraries, Syracuse, New York, as library automation consultant.

Demands, later withdrawn, by Williams and Wilkins for increased subscription rates to include "license fees" resulted in some delay by NIH Procurement in processing subscription renewals of their journals. NLM and the NIH Library would have been required to accept the principle of licensing for making single photocopies of articles for researchers and of paying page charges for copying for Interlibrary Loan. The DHEW Office of General Counsel and the Department of Justice helped negotiate the change in position and to establish and maintain the Government's position. The suit filed in 1968 by Williams and Wilkins against NLM and the NIH Library for alleged copyright infringement is still pending before the U. S. Court of Claims.

The annual registration of Library Identification Cards has been postponed until September 1973.

Library employees in GS 1-5 grades were interviewed for the NIH skills file prepared for job availability purposes.

A Library User Study is underway involving in the first phase an in-depth analysis of reader use of monographs, journals, and other materials held by the NIH Library using a variety of input sources and techniques. The study includes analysis of all materials borrowed for NIH research staff to meet their needs.

The FY 1973 Branch Training Program was designed to meet the needs of all Library employees by group category and developed this year to bridge the groups. Emphasis for Group I, Professional group, was given to the promotion of professional development through in-Library lectures, attendance at NIH lectures and individual enrollment in academic courses. Group II, GS 5-7, was included in the in-Library lecture program arranged for the Professional group. Group II employees were given a short course designed to enable them to distinguish foreign languages and another in simplified medical etymology both of practical use to Library Technicians. Group III, GS 1-4, was included in the two short courses prepared for Group II. Group III was also provided a rotational program to learn more about other Library functions. Groups II and III continued to have the opportunity for enrollment in Library science courses for nonprofessionals, Basic Adult Education, the Upward Mobility Program, and courses to further individual job skills.

Translation

Effective January 1, written translations with the exception of letters and similar items, are handled almost exclusively by contract and the costs of translations are charged to the B/I/D concerned. Oral and recorded translations continue to be emphasized in-house.

Technical Services

Data input for current journals to the PHILSOM computer journal control system designed by Washington University School of Medicine Library has been completed. A cumulated monthly list of current journals including holdings is received from this system. Decision was made to input journal receipt information to DCRT's computer in order to have available a daily cumulated listing of journals received as well as an alphabetic listing of current and noncurrent journals in the NIH Library's collection. Full data for noncurrent journals including holdings is being coded for incorporation into the PHILSOM journal control system. In addition to the above lists, computer output, such as the PHILSOM binding control slips, journal receipt cards, claim, renewal, and current titles by source lists are markedly increasing the efficiency of various journal operations.

The FY 1973 contract for journal subscription was awarded to the F. W. Faxon Company. The Library had the opportunity to review and rate the bids in relation to the resources, subject specialization, follow-up system, and computer expertise of the bidding firms.

Subscription renewals for 30 Williams and Wilkins journals for 1973 were held up for some weeks by NIH Procurement until the publisher withdrew demands for increased subscription rates to include "license fees."

Readers Services

All procedures of the Stacks and Copy Service were examined and analyzed to discover and eliminate problems experienced by the Library users relative to photocopy service and the condition of the volumes on the stack shelves.

Installation of new photocopy equipment eliminated complaints from NIH clientele about poor quality of photocopy, frequency of fires, equipment breakdown, and long-time lag for mailed copies. Two pieces of equipment were installed for a 90-day trial period for long, continuous operation evaluation.

Reference and Bibliographic Services

Computer bibliographic searching is now conducted by remote terminal through National Library of Medicine's on-line MEDLINE computer system. The MEDLARS system in use for many years was gradually reduced by NLM, terminating in December. Recurring demand searches are also processed through NLM's SDILINE system via the remote terminal. NIH Library's senior professional staff in this Section has received training in MEDLINE searching at NLM.

A redistribution of activities in the Section was made following the loss of three senior professional staff in order to maintain regular services and absorb the increasing demand for MEDLINE searches.

A series of Library orientation sessions for NIH clerical, secretarial and laboratory assistant employees was initiated this year. The course conducted by senior professional staff gave practical "how to" instruction on use of the Library and on the forms of citation for books and journals.

Teaching tapes on the use of Index Medicus and Science Citation Index have been obtained for the use of the NIH clientele. If this type of instruction proves beneficial for user needs, other similar teaching tapes may be developed.

Members of the Reference and Bibliographic Services Section staff contributed to the evaluation project of Library services in Region IV (Washington, D.C., Maryland, Virginia, West Virginia and North Carolina) of the Regional Medical Library Program. Two questionnaires developed by the NIH Library group will be submitted by the Task Force of the Region IV Program to hospital librarians and physicians in the Region.

The Chief of the Section presented the first lecture of the DRS Program Seminar on March 28 in the Library. He spoke on Computerized Bibliographic Search Services.

D. Problems

The services provided by stacks maintenance, acquisitions and other services to NIH users are affected by present limitations.

E. Program Plans

Upon review of the Library's organization, operations, staffing and the services, the new Branch Chief will develop a priority of plans and program emphasis.

DIVISION OF RESEARCH SERVICES

Summary of Branch Activities July 1, 1972 through June 30, 1973

MEDICAL ARTS & PHOTOGRAPHY BRANCH Mr. Arthur F. Moore, Chief

I. SUMMARY

With a sharp increase in demand for services coupled with loss of personnel in FY 1973, the Medical Arts & Photography Branch kept well abreast of its program commitments by the use of new and improved technology, operational improvements, training and a 100 percent increase in outside contract services. With advanced technology the micrography skills and service output increased. These factors, pride, and healthy morale added quality, quantity and speed of production from the Branch.

II. BRANCH PROGRAMS

A. Objectives

The objectives of the Branch are to provide consultation and production services to the NIH; to visually communicate program effort and research results; to provide knowledge, skills and techniques in visual design, medical art, applied arts, still photography and cinematography for solving problems of recording, communicating and presenting research activity; and to investigate, develop and apply new visual techniques.

It is also the objective of the Branch in meeting NIH research program demands to provide services on a professional basis, competitive with commercially obtainable services at the lowest possible cost, and to develop specialized capabilities, particularly in graphic presentation, still photography, cinematography, and medical arts, tailored to NIH needs.

The Branch monitors procurement of art and photography services by outside contract, serving as technical adviser in obtaining needed additional services at the lowest cost consistent with high quality.

B. Current Programs

Programs of the Branch are still and motion picture photography, including photomacrography, photomicrography, high-speed cinematography, general photography, and related laboratory services; visual arts production including publications design and general graphics; visual aids including slides, vu-graphs, and other projectables; animation art work; technical, general and medical illustration; exhibit design; statistical drafting display charts; medical models; and computer-generated graphics.

C. Program Progress and Accomplishments

1. Accomplishments

Six 30" X 40" easel art silk-screened illustrations depicting the six classical surgical procedures for removal of breast cancer were prepared for the NCI and presented to the President's Council on Cancer at the White House. Forty publications of the same material were also prepared for those in attendence.

A long term project for NEI was completed with a three-dimensional reconstruction of the Canal of Schlemm. Three models were constructed in serial section using both fetal material, 3-month term and postpartum material through adulthood. Special attention was paid to the development of Schlemm's Canal and the differentiation of septa. The appearance and disappearance of septa with age may have a bearing on the etiology of glaucoma.

The Laboratory of Perinatal Physiology, National Institute of Neurological Diseases and Stroke, received a total of seven drawings made of various facets of the dual circulation of the rhesus monkey placenta which clarify the rather complex and intimate relations between the fetal and the maternal circulation. The work entailed drawings as well as representations of its microstructure and its intricate configuration. Overlays were also created to express some of the physiological relationships and alterations that occur in relation to the flow of maternal blood through the placental cotyledons. Color was used in these illustrations to meet the requirement for slide projection and black and white ink drawings were used for journal illustration of the nature of the primate placenta. Some aspects of this work were completely original and represented, in themselves, concrete contributions to our knowledge of placental morphology and function.

2. Operational Improvements

Photographic end product prices were revised to reflect a more accurate balance of profit and loss margins. With less than one year experience on the revolving fund, the Branch was able to project its operation costs within 3% of its break-even point. Total revenues were in excess of $400,000.00.

Within close proximity of the scientific camera unit, an additional darkroom was constructed and custom equipped for the printing and finishing of technical photography. This has increased production and quality printing of photomicrographs and photomacrographs. Advanced equipment was identified, purchased and installed in the technical areas as well as the laboratory areas. This equipment and technology have provided photomicrography that previously was not possible at the NIH.

The entire Photo lab was completely renovated on the B1 level of the Branch and new equipment was installed.

3. Service Contracts

With another sharp rise in demand for services and reduction in productivity from some loss of personnel, the Branch used more outside contract services. An increase of over 100% in the use of such services over FY '72 clearly indicates a trend in NIH service needs.

Projections indicate substantial increases in contracting will be necessary as requests increase and the personnel ceilings fall.

With training and experience, MAPB, during FY '73, developed an effective technique for the extended use of contract services--a technique that will easily expand as conditions dictate. Additional training in this area is planned for FY '74.

4. Training

As the MAPB professional staff continues to gain national and international recognition for excellence in their fields, formal training for these professionals as such has become non-existent. As a result MAPB has and will continue to identify and select professional meetings and/or seminar-workshops for attendance by those employees of advanced skills.

Sixteen Branch employees received formal training in management, administration and technical categories.

5. EEO Developments

Equal employment opportunity goals continued to be pursued vigorously. Emphasis was placed on identifying minority members who were contributing significantly to the overall effectiveness of the Branch. Although promotion actions were limited, the Branch was successful in promoting four minority members for their outstanding abilities and initiative in accepting higher level responsibilities.

MAPB was able to fill two full-time vacancies and occupy several stay-in-school positions with highly qualified minority members.

6. Labor Relations

In May, the Branch completed the second year of a two-year negotiated agreement with Local 2419 of the American Federation of Government Employees. This agreement was automatically renewed for two more years. Relations between management and Local 2419 were without incident.

D. Problems

There is a critical need for members of the NIH community using MAPB services to allow more lead time for planning and execution of their audio-visual material. The Branch has extensive expertise in the planning and conversion of raw data into effective multi-media presentations. Planning counsel is readily available in all areas of MAPB.

E. Program Plans

MAPB will continue to improve, enlarge, and extend its services. It will seek new ways to acquaint the NIH community with its skills and in this effort the Branch will heavily emphasize the real necessity of counsel and planning for optimum results.

DIVISION OF RESEARCH SERVICES

Summary of Branch Activities July 1, 1972, through June 30, 1973

Veterinary Resources Branch Dr. Robert A. Whitney, Jr., Chief

1. SUMMARY

The Veterinary Resources Branch provides NIH investigators with living models and life support systems for biomedical research. The branch also provides facilities and services related to the use of these models and systems.

The production and services of VRB continued to rise to meet increasing demands of expanding intramural BID programs, although branch personnel ceilings have been reduced 17 percent over the last 5 years.

The increased services with decreased personnel were accomplished by the extensive use of overtime, improved animal production methods, automated processing of glassware and production of media, limited use of temporary positions and, of most significance, contracting.

Contracting for 126,000 noninbred rodents reduced in-house production from the previous year and allowed for increased VRB production of inbred strains used at NIH, but not commercially available.

Contracting continues to expand, with anticipated procurement of most species commonly available commercially. The expansion of contract supply will, hopefully, free personnel necessary to initiate high priority experimental animal holding programs for primates and research rodents.

While rodent, rabbit, and cat production dropped from last year, laboratory reared dogs, timed-pregnant nonhuman primates, and ungulate production increased. Contracting was used to supplement canine, primate, and ungulate production.

The procurement of nonhuman primates continued at a level similar to recent years. Random source dog procurement continues to increase every year.

Tissue culture and media production increased 25 percent over last year. Glassware issues decreased 11 percent over last year, reflecting personnel reductions and increased use of disposable supplies.

Animal biologics production remained relatively constant.

Over 110 investigators world-wide were supplied with nucleus inbred breeders from VRB rodent genetic repository pedigreed colonies. The Frederick Cancer Research Center was also provided with inbred strains to assure the reliability of nucleus stock for their large program.

Surgical activities and support continued to increase from 700 procedures last year to over 900 this year. Surgical facilities are now used at near maximum capacity.

Experimental animal holding increased for dogs and ungulates. With the renovation of Building 14D, protected facilities will be available for holding over 650 nonhuman primates.

The number of calls for the Animal Disease Investigation Service increased 17 percent over last year, from 128 to 150 calls, including several special, in-depth surveys of animal care programs requested by NIH Institutes.

Several key personnel changes occurred in this fiscal year. In November, Dr. Robert A. Whitney, Jr. was selected as branch chief, VRB. Dr. Steven Potkay was appointed chief of the Animal Center Section in May 1973, replacing Dr. Amos Palmer who transferred to NINDS.

II. BRANCH PROGRAMS

A. Objectives

The primary objectives of the Veterinary Resources Branch are:

1. Issuance of research animals, animal biologics, tissue cultures, tissue culture media, bacteriologic media, and laboratory glassware.

2. Maintenance of a centralized genetic repository of valued animal strains for the international scientific community.

3. Provision of facilities and professional staff for experimental surgery to include postoperative care and roentgenography and other special procedures.

4. Maintenance of animals during experimentation.

5. Acquisition of information, through research, on animal health, care, and husbandry.

6. Provision of consultative services on animal health and husbandry, use of experimental animals, tissue cultures, and bacteriologic media.

B. Current Programs

1. Research Animal Production

Rodents, rabbits, dogs, cats, and primates are bred and reared in the Branch's colonies. Some are characterized genetically and some are microbiologically defined. Care is taken to maintain the genetic integrity of inbred strains and minimize inbreeding of random bred stocks. Germ-free and specific pathogen-free (SPF) rodents are produced for intramural research programs requiring them and for replacement breeders to enhance the health status of production and genetic colonies.

2. Research Animal Procurement and Conditioning

Primates, dogs, cats, and feral animals are procured and conditioned. Generally, these animals can neither be characterized genetically nor well-defined microbiologically and are of lower quality than NIH-bred animals; but their cost is less and they are adequate for many studies. These species are held for a period of several weeks before they are issued, during which time they are clinically examined and tested for a variety of infectious agents. Treatments and immunizations are administered when indicated during the conditioning period.

Noninbred rodents are procured through contracts to supplement in-house production. They are delivered directly to NIH investigators. Quality control of these species is maintained through monitoring of the various producers' facilities and operations by Branch staff members.

3. Tissue Culture and Media Production

Several continuous cell line tissue cultures are maintained, propagated, and produced in large volumes to supplement I/D requirements not met by commercial sources or individual laboratory preparation. Media for the culture of bacteria, fungi, and tissue cells are produced to meet the needs of NIH investigators. A stringent quality control program insures that only high quality products, free of contamination and true to formulation, are issued. As a service to investigators, valuable cell lines are frozen and stored for long-term preservation.

4. Processing Laboratory Glassware, Animal Cages, and Miscellaneous Items

Laboratory glassware is decontaminated, sorted, cleaned, inspected, plugged, wrapped, sterilized, and issued to NIH investigators. The overall operation includes processing of used glassware received from investigators and the introduction of new glassware from replacement stock. In addition to cleaning animal caging for its own programs, the Branch furnishes cagewashing services to investigators in the Clinical Center and the Buildings 14-28 complex. Clinical Center rubber-backed carpets are also washed. A service is provided for ethylene oxide sterilization of heat labile patient and laboratory equipment from the Clinical Center and other I/D's.

5. Animal Biologics Production

A dog blood donor colony is maintained for the production of Canine Erythrocyte Antigen (CEA) 1, 2, & 3, formerly A-negative, blood for research use. Ungulates are maintained to produce a variety of antisera, blood, and tissue specimens for investigators. RIF-free and Marek's disease-free eggs used in NIH research are produced from flocks of chickens free of these agents maintained in isolators.

6. Genetic Repository and New Animal Models Program

Genetically defined rodents that are valuable models in biomedical research are derived and maintained to support I/D requirements and serve as a genetic repository for the international scientific community.

7. Experimental Surgery, X-ray and Related Activities

Facilities are provided for investigators to perform experimental surgery on any size domestic animal. These facilities include modern equipment for the proper anesthesia, handling, and physiological monitoring of experimental subjects under aseptic conditions. Upon request, staff veterinarians will perform special surgical procedures for investigators needing surgically prepared animals for their studies. Radiographic facilities and services are also made available for use on animals of any size.

8. Experimental Animal Holding

Dogs, primates, ungulates, and germfree rodents are held for varying periods of observation while under test by NIH investigators. Provision is made for physiological sampling and collection of specimens.

9. Disease Investigation, Research, and Quality Control within VRB

The professional staff consists of persons trained in general clinical veterinary medicine and specialists in laboratory animal medicine, pathology, microbiology, epidemiology, nutrition, and animal husbandry. All efforts are oriented toward improving the Branch's programs by gaining new knowledge through research and monitoring the quality of procured and produced animals.

10. Consultative Services

Information and assistance are available to NIH investigators for solving problems relating to animal experimentation, health, care, and husbandry. Through the Animal Disease Investigation Service (ADIS) "house calls" are made to the I/D's to provide investigators with clinical veterinary services for their research animals. There is also a program to furnish each I/D a comprehensive review of its animal care programs with evaluations and recommendations for improvement. Consultative services are available regarding the use of tissue cultures and microbiologic media. A training program is offered to I/D animal technicians and related personnel.

11. General Support and Management

These basic programs listed above are also supported by Branch-wide administrative and management staff and transportation/delivery service.

C. Program Progress and Accomplishments

Approximately 502,000 VRB-produced rodents and rabbits were issued to investigators, a reduction from 532,000 issued the previous year.

Progress was made in establishing hysterectomy-derived, barrier-maintained, foundation colonies and clean conventional expansion and production colonies for all strains and stocks of mice. Nucleus colonies of the General Purpose and NIH mice have been established in the barrier. Over 200 successful hysterectomies were required to maintain the genetic diversity of these noninbred stocks. The new pathogen-free production colony of General Purpose mice was established. Clean conventional inbred expansion colonies of the major strains were established from the barrier-maintained, foundation colonies. Two new production colonies are being established from these colonies which will support a total estimated production of 750,000 mice per year. The production at the Frederick Cancer Research Center (FCRC) is supported by these colonies as well as VRB's. Those few mouse strains that have not adapted to the barrier and the mutant stocks are being hysterectomy derived directly into the clean conventional facility.

General Purpose mouse production was decreased from three breeding rooms to one as a result of contracting for noninbred mice. An improved harem mating system was devised for this stock using larger cages, which improves production, efficiency, and husbandry conditions.

The pathogen-free rat colonies in the barrier and clean conventional environments continue to demonstrate excellent health and reproductive performance. A major effort was made to sort out the genotypes of 14 mutant stocks that are maintained in the barrier. A trial automatic watering system for clean conventional rats was evaluated and found promising.

Inbred guinea pig production was converted to a permanent harem system rather than the old system of isolating pregnants. All guinea pig production is now on this system which provides more efficient production.

Two pathogen-free colonies of Hartley guinea pigs were established. They are fed an autoclavable diet and vitamin C is added to the drinking water. One was received from Edgewood Arsenal and the other was hysterectomy derived from the salmonella-infected NIH colony. Two colonies are being perpetuated because they have immunogenetic differences.

Studies are being conducted on diets and methods to hysterectomy derive inbred guinea pigs so the foundation colonies of the Strain 2 and 13's can be maintained within the barrier.

A disposable cardboard dropping pan that would reduce cagewashing is being evaluated for guinea pigs. Large plastic cages for breeding guinea pigs are being evaluated.

A nucleus of hysterectomy-derived rabbits was obtained and is being isolated from the conventional colony. These rabbits are used as foster mothers for developing pathogen-free colonies of rabbits with defined allotypes and complement 6 deficient rabbits. Six closed lines of rabbits were established, each homozygous for a particular allotype specificity. The levels of inbreeding progressed to an equivalent of six generations of brother-sister mating in one line and the remainder between three and five generations.

Methods and diets for hysterectomy-derived rabbits continue to be studied. Progress was made in developing successful methods of hand nursing.

b. Large Animal Production

The canine breeding colony currently consists of 119 foxhound bitches and seven dogs. Culling during FY 1972 eliminated poor producers and animals with hip dysplasia. Production was increased from 1,019 pups in FY 1972 to approximately 1,100 colony reared dogs issued in FY 1973. Three of four proposed inbred lines of American foxhounds were established during FY 1973. Development of these lines will be directed principally towards providing a genetically uniform research dog for NIH investigators by crossbreeding the lines.

The cat breeding colony was reduced from 37 to 25 queens and from eight to five toms. Approximately 250 colony reared cats were issued.

The goat breeding herd was expanded to include 10 does and one buck. Twenty-four kids were born during the fiscal year. Goats produced from the breeding herd will be held until approximately 1 year of age before issue.

c. Nonhuman Primates

The rhesus monkey timed-pregnant breeding colony was enlarged from a total of 64 animals to 140 females and 25 males. In addition, a colony of 40 breeding female rhesus monkeys was managed for NINDS. A minimum demand of 200 pregnant females is expected in FY 1974. To supplement this activity, two short-term contracts were awarded to provide 35 to 45 timed-pregnant rhesus monkeys over the last 3 months of FY 1973, and the first 3 months of FY 1974. In FY 1974, new contracts for timed-pregnant rhesus monkeys are planned to further meet the acute demands of B/I/D investigators.

2. Research Animal Procurement and Conditioning

a. Rodents

Approximately 126,000 noninbred rodents were purchased from contractors compared to 75,000 in FY 1972. The increase resulted primarily from the use of contract Swiss mice. Arrangements were initiated to award a new contract for Hartley guinea pigs which are presently bought through blanket purchase order or acquired by transfer from the Frederick Cancer Research Center. Sprague Dawley rats and Golden Syrian hamsters were supplied predominately by contractors.

b. Large Animals

Random source mongrel dogs and random source foxhounds were purchased after 30 days of preconditioning by the vendor. Illness among animals was minimal and losses have been virtually eliminated. The trend in issues of random source dogs of both types continued to increase. Estimates indicate that approximately 1,250 to 1,350 random source dogs (mongrel and foxhound) were issued. Foxhound-type dogs rather than mongrels were supplied whenever possible.

Random source cat programs declined markedly since mid-FY 1972. Issues for this fiscal year were about 500 cats.

Approximately 450 ungulate animals were purchased, quarantined, conditioned, and issued. In addition, some 50 domestic fowl, including ducks, chickens, and turkeys were utilized.

The primate quarantine facility completed its first year of operation. Most deficiencies in the building and equipment have been identified, and corrective measures were implemented.

Because of contractual problems, rhesus (Macaca mulatta) monkey issues were about 2,000, short of the 2,300 required. Other species of monkeys and apes (M. fascicularis, M. radiata, M. arctoides, Saimiri sciureus, Cercopithecus aethiops, Papio spp., Aotus trivirgatus, Saguinus oedipus and Pan sp.) contributed about 9 percent to the overall quarantine and conditioning program.

3. Tissue Culture and Media Production

The estimated number of requisitions processed for tissue culture and media totaled 13,900; a slight increase over last year. The volume of media produced was 53,000 liters of bacteriologic media and 90,000 liters of tissue culture media for a total of 143,000 liters. This total represents a 25 percent increase over last fiscal year, primarily in tissue culture media. The trend noted last year of larger volumes per request continued.

Issues of tissue culture cells as cell suspensions continued to increase with a projected total of 183 liters of suspension, sufficient in quantity for 183,000 tubes, an 8 percent increase over FY 1972. The continued increase in requests for cell suspension reflects the trend noted over the last 2 years to use cells in suspension rather than tubes or bottles as in the past.

Tissue culture cell freezing and storage services continued to be popular. A projected total of over 1,700 ampoules of cells were frozen and over 2,100 ampoules of cells were maintained in the frozen cell bank to support research programs.

The quality control program was expanded to include osmolarity testing of each lot of tissue culture media and many lots of bacteriologic media, where appropriate. Testing was accomplished with an automatic osmometer utilizing the freezing-point depression method to provide an additional safeguard for media users.

Several steps were taken to improve working conditions. Among these were provision of safety shoes, reduction in the noise level of automatic bottling equipment by installation of a plastic coated cap delivery system, and general painting of areas with minor renovations to provide more pleasant surroundings.

4. Processing Glassware, Animal Cages and Miscellaneous Items

Glassware issues totaled about 9,460,000 pieces; a 10.8 percent decrease over FY 1972. A total of 235,000 cages, racks, and associated pieces of equipment were processed for B/I/D's, not including rubber carpets washed for the Clinical Center. Cage wash support for VRB production and holding programs is not included in the above totals.

Introduction of a new disposable container for pipettes has proven to be a successful means of eliminating periodic backlogs. Costly purchase of stainless steel pipette cans on a monthly basis was eliminated.

5. Animal Biologics Production

Domestic turkeys and ducks were utilized in small numbers to produce normal blood and antisera for specific research projects.

The canine blood donor colony, consisting of 247 dogs, produced an estimated 3,264 units (1 unit = 500 ml) of blood. This quantity represents a savings of 1,600 dogs that would otherwise have been exsanguinated.

Biologics production from ungulate animals decreased somewhat to about 1,500 liters. The size of the ungulate herd maintained for all purposes increased from 450 to 515.

Inbred Line 6 chickens produced 560 dozen eggs. The chickens were maintained in isolators and are RIF-free and susceptible to all Rous Sarcoma (RS) viruses (C/O).

6. Genetic Repository and New Animal Models Program

The genetic repository received increased emphasis. Rodent and rabbit colonies represent the most diversified multispecies rodent collection maintained at any centralized facility. In addition to supplying animals for intramural investigators, these colonies serve as a resource for the international scientific community. Many of the stocks, strains, and substrains are not available elsewhere, and investigators throughout the world are supplied breeding nuclei. This year, approximately 110 investigators were provided with litters of inbred animals to start colonies and several hundred noninbred animals were provided as breeders. For the first time, breeding nuclei were made available to commercial breeders as well as nonprofit organizations. The strains in greatest demand were the hypertensive rat and the normotensive control, the rat with diabetes insipidus, and the C4 deficient guinea pig.

Arrangements were made to support inbred animal production at the Federal Cancer Research Center by providing pedigreed animals from the repository as breeders for their expansion and production colonies. Therefore, production at that facility and NIH both stem from the NIH foundation colonies, assuring comparable research animals from either place.

A program to assist investigators in obtaining new animal models to meet previously unfilled research needs continued. In some instances, new strains of existing laboratory animals exhibiting unique physiological or anatomic characteristics were used. In others, animals having characteristics required in a particular research problem were adapted from nature. New models are hysterectomy derived and foster nursed or hand nursed prior to introduction into the NIH colonies. Fifteen new strains or stocks were added to the repository at the request of NIH investigators. They are listed below:

Inbred mice: CBA/CaHN, CBA/CaHN-T6, STAR/N, B10.D2/oSnN, B10.D2/nSnN

Mutant mice: Nude, Brindled, Dappled, Blotchy, Tortoise, Sex-Linked anemia

Inbred rats: LEW/SsN, BN/SsN

Mutant rabbits: Complement 6 Deficient

Other stock: Cotton Rat (Sigmodon hispidus)

Of greatest interest was the introduction of the Nude (athymic) mouse. It is immunologically incompetent and accepts transplants or tumors from virtually any host. Also, the introduction of the mammary tumor virus (MTV) into the pathogen free C3H/HeN mouse makes available the same C3H strain for the first time with or without MTV.

7. Experimental Surgery, X-ray, and Related Activities

a. Building 28 Facilities

The surgical facilities are primarily available to B/I/D investigators; however, surgery was frequently performed by veterinarians assigned to the section at the specific request of investigators. Assistance to investigators was provided in anesthesiology, surgical support, diagnostic radiology, and postoperative care of animals.

Surgical procedures increased from 700 last year to over 900 this year. Surgical facilities were used at near maximum capacity. A projected increase of only 5 percent is anticipated next year, due to limitations of building size and room arrangement. There was also a marked increase in the amount of time devoted by Experimental Surgery Unit personnel in providing better technical and professional assistance to investigators conducting research in this surgical facility.

b. Animal Center Ungulate Surgery

Activities in ungulate surgery declined. Projects utilizing sheep for intrauterine fetal surgery generated approximately 60 surgical procedures. Swine breeding was undertaken to develop four inbred lines of immunologically distinct animals. Four pairs of swine produced 22 progeny. Approximately eight skin transplant procedures were performed in connection with this project.

Radiographic procedures remained constant with 250 exposures projected for the year.

8. Experimental Animal Holding

a. Primates

Renovations were completed for Phase I of Building 14D, a nonhuman primate facility. This centralized holding activity is a new service available to the B/I/D's providing professional service, technical management, and

care for approximately 650 nonhuman primates on scientific studies. Renovations for Phase II of Building 14D are expected to be initiated and completed in FY 1974. This will expand holding capacity for 250 additional nonhuman primates.

b. Canine

The population of long-term dog holding increased from a mean population of 310 dogs per month to 429 dogs per month. Holding space for dogs on scientific studies was at maximum capacity. To meet continuing demands of B/I/D investigators, a joint DRS-NHLI contract was awarded to hold dogs essential to research projects but not requiring frequent handling by investigators. This allows a greater proportion of space for dogs which must be available for frequent observation or handling by investigators, as dictated by specific research protocol.

The south wing of Building 14E was equipped to hold 40 dogs for an atherosclerotic study for the NHLI. Additional space in this wing was allocated for postoperative care of pregnant sheep which have undergone intrauterine-fetal surgery.

c. Ungulates

Several species of ungulates are held under observation for NIH investigators during investigative studies. Physiological sampling and specimen collections are provided in association with these studies.

9. Animal Nutrition

The open formula rat and mouse ration has been used throughout NIH for approximately 1 year. The only reported problem associated with this product was corrected by altering the materials used in packaging. Use of this ration will result in an estimated annual savings to NIH of $30,000. Savings are possible because the standardized diet can be advertised and awarded on a low bid basis rather than awarded to a sole source. An open formula laboratory rabbit ration was developed and tested. Advertised contract arrangements were made to purchase this ration for use throughout NIH.

Contract arrangements were completed for an independent laboratory to conduct estrogen assays and a limited number of nutrient analyses on samples collected from all animal feeds manufactured under NIH contracts. This is in contrast to the requirement that each feed contractor provide results of an estrogen assay for feeds delivered to NIH. More reliable and uniform assay results should be obtained from the independent laboratory.

The use of succulent feedstuffs as a supplement to rodent rations is gradually being eliminated. The bread, milk, and kale supplement for inbred mice was eliminated as was feeding kale to guinea pigs in most production colonies.

Various nutritional studies with rats and mice are being conducted in cooperation with other VRB investigators and investigators from other Institutes.

10. Animal Health

a. VRB Animal Health Problems

Salmonellosis occurred in the VRB guinea pig colony for the third time in the 15-year history of the colony. The outbreak was a major one affecting three rooms. The causative agent was identified as S. typhymurium var. copenhagen. An epidemiologic study conducted by the staff of the Center for Disease Control failed to prove the source of the infection. Fresh kale fed as supplement to the commercial pelleted ration was a suspected source because, as in the two previous outbreaks, guinea pigs were the only animals receiving kale and the only ones to develop the disease. The guinea pigs in two of the rooms were being fed one brand of commercial pelleted ration, those in the third room a different brand. Subclinical infections in two animal caretakers during the outbreak were thought to be acquired from the guinea pigs. The disease was eliminated in 4 months by testing all animals caged with diseased animals.

Subclinical nephrocalcinosis was found in a large number of guinea pigs examined during the salmonellosis outbreak. Previous data indicate that magnesium deficiency may be the cause. Studies are planned to determine levels of magnesium in the diet relative to other minerals.

Hemothorax continues to occur at a low incidence in the barrier-maintained mouse colonies. As previously described, the disease appears to be a noninfectious condition of male mice characterized by myocarditis and prolonged prothrombin time. In contrast to the first outbreak which involved 10 to 12 week old G.P. mice, the disease is now recognized in all strains at 4 to 6 months of age. Efforts to reproduce the disease experimentally by feeding vitamin K deficient diets have been unsuccessful.

The B10.D_2/nSnN strain of mice has been found to produce a high percentage of hydrocephalic offspring. An attempt is being made to breed the condition out of the primary colony and retain the gene in a second colony for further study.

Nephrosis has been found to interfere with studies of aging in rats in certain NIH laboratories. Experiments are underway to determine whether the level of protein in rat diets influences the onset of this condition.

During studies of chronic respiratory disease in rats a significant discovery was made concerning the mechanism of spread of Mycoplasma pulmonis. The agent was found to be either noncontagious or to spread extremely slowly among animals in close contact in the absence of bacteria. The findings suggested that mycoplasma adhered to the surface of bacteria may be transported from animal to animal.

The fecal cultures for Mycobacterium paratuberculosis from the goat herd were continued. No new cases were identified. Culturing will continue for at least another year.

Brucellosis was diagnosed in the swine herd during the first quarter of the fiscal year. Reactors were killed and the remainder of the herd was placed on antibiotic therapy for 3 months. Monthly serologic tests have inconsistently revealed suspicious results, but no reactors have been detected for 6 months. Testing will continue on a bimonthly basis well into the next fiscal year. More stringent quarantine measures will be employed to preclude reintroduction of the disease.

The canine breeding colony was surveyed radiologically for hip dysplasia. American foxhounds are relatively free of the disease while 90 percent of the English hounds are affected. Distribution of dysplasia in the crossbred stock was largely a function of their English ancestry. Dysplastic stud dogs were immediately retired from service, and affected bitches are being removed from production as suitable replacements become available.

b. BID Animal Health Problems

Tuberculosis was diagnosed in a rhesus monkey which had been maintained nearly a year on prophylactic isoniazid in an NIH laboratory. The animal was sacrificed when its tuberculin test became positive. A small primary lung lesion and a caseous peritracheal lymph node were found at autopsy. Numerous acid-fast bacilli were demonstrated in the lesions which have been cultured for the purpose of identifying the bacillus. The animal caretakers in contact with these animals are being monitored by the Employee Health Service.

Simian hemorrhagic fever was diagnosed in an NIH laboratory colony of 212 rhesus monkeys. There were 119 deaths from the disease and euthanasia was performed on the remaining animals when they developed signs of the disease. Previous studies showed that the disease is of viral origin and is characterized by fever of sudden onset, severe proteinuria, consumptive coagulopathy and a tendency to hemorrhage at sites of mild trauma, terminal shock, and nearly 100 percent mortality in clinically evident cases. Although the disease is remarkably similar to certain of the Asian hemorrhagic fevers of man, to date it has been found only in Macacca spp monkeys. The current outbreak was the third one of major proportion known to occur in the United States since 1964 when the disease was first recognized in the NIH primate quarantine colony and the primate colony at the Sukumi Institute of Experimental Pathology and Therapy in the U.S.S.R.

Following the outbreaks of cervical lymphadenitis of guinea pigs in four NIH laboratories last year, extensive follow-up studies have shown that survey of animal colonies for Streptococcus zooepidemicus by throat or nasal culture methods is not practical.

11. Animal Disease Investigation Service

The number of calls by animal disease investigators has increased by 17 percent, from 128-150 calls. These involved consultative, diagnostic, and therapeutic activities. Animal species encountered were quite varied including rodents, rabbits, primates, carnivores, and marsupials. The complexity of these calls also varied and involved most institutes. This service, well received by the B/I/D investigators, has gradually increased in scope. It has been mutually beneficial to investigators and to the VRB professional staff in providing an overview of laboratory animal facilities and practices at NIH. Two special ADI services were accomplished this past year; comprehensive reviews were made of the NICHD Gerontology Research Unit, Baltimore, Maryland, and of the laboratory animal programs of the intramural NCI program. Significant disease problems investigated by the ADI are described in the section on Animal Health.

D. Problems

Problems of Animal Disease are referred to in Part II, C 10.

There is a serious understaffing problem in each of the sections in spite of existing contracts to reduce levels of in-house production. The problem is further aggravated by many employees attending authorized classes during working hours. To compensate for this shortage, many employees were required to work an unreasonable number of overtime hours and several necessary activities, such as the increased production Strain 2 guinea pigs, were postponed.

There was a large revolving fund deficit for rodent and rabbit production. This indicates the need for financing research and development, strain development, and genetic repository activities from sources other than animal issues.

The diagnostic service for the rodent colonies declined this year with the loss of an experienced laboratory animal clinician resulting in the loss of necropsy service for all sick and dead rodents in the colonies. As a result, an accurate, timely profile of the health status of the colonies is not maintained.

Personnel losses in the Media and Glassware Section affected the ability to continue responsibility for regeneration of three large mixed-bed deionizers. Regeneration of these units requires an average of 3-4 hours per day for one person in order to maintain an adequate supply of deionized water to not only meet the glassware operation needs, but also those of the Media Unit and Clinical Center Pharmacy.

Transportation of media and glassware to outlying buildings and return of dirty glassware for processing continued to be a problem. Irregular pickup of dirty glassware caused needless variations in workload. Some days almost no glassware was returned and other days there was too much to be processed efficiently. On slow days new glassware was placed

into circulation in order to meet demands. A more regular rate of return might conceivably lessen the need for endless supplies of new glassware.

Several problems with suppliers of screw-cap tubes occurred. Tubes were received that did not meet the rigid specifications required for use of the tube in automatic tubing equipment. Variations in tubes received caused many breakdowns in operation, with loss of time and media.

Cramped quarters for both personnel and efficient utilization of equipment continued to be a serious problem in the Media Unit. Despite several attempts to renovate existing areas, overcrowding prevented necessary expansion in such areas as media storage at cold room temperatures and further automation of tubing and bottling operations. Increased individual requests for media make additional space mandatory if demands are to be met without greatly increased backlogs in production.

The supply of rhesus monkeys was terminated for 12 weeks during the third and fourth quarters of the fiscal year because of procurement oversights and contract default by the supplier. Consequently, issues of monkeys to the B/I/D's were completely halted for several weeks.

Plastic water manifolds on 252 new primate cages required replacement because of deterioration produced by cage washing procedures.

Provision of contractor-supplied, timed-pregnant ewes was erratic during FY 1973, and pregnancy diagnoses were frequently incorrect. It is expected that the situation will be rectified by changing the source of supply.

Availability of quality, blood group CEA 1, 2 & 3 negative, microfilaria negative, dysplasia-free dogs as additions to the breeding colony was extremely limited. The rigid selection requirements will continue to retard the full development of the breeding colony.

Attempts continue to improve physical working conditions in Building T-8. Lighting improvements and interior painting of the building remain outstanding up to 18 months after initiation of requests.

E. Program Plans

The search for a suitable disposable container for return of dirty glassware continued. Samples of various types of containers which will withstand autoclave sterilization were tried with limited success. The most promising is a plastic small animal cage of the same approximate dimensions as the present stainless steel discard container. Use of this container for disposal of all nonreturnable items of glassware would eliminate time-consuming sorting of disposable items from reusable glassware.

Studies are in progress to obtain basic data for developing open formula, autoclavable rations for rats, mice, and guinea pigs. The use of stabilized vitamin preparations for these rations will be explored.

A Rodent Research Facility is planned to provide centralized professional care for animals under investigation and technical assistance to investigators. This could alleviate severe overcrowded conditions in NIH animal research laboratories and best utilize space available in VRB. One building in the 14 complex could be devoted to this activity. It has been proposed to establish a rabbit contract and divert the savings in manpower to the Rodent Research Facility.

The program to free all rodent strains and stocks of disease through hysterectomy derivation will continue. Techniques will be developed for applying this practice to guinea pigs and rabbits. This requires a cooperative effort in areas of nutrition, microbiology, and genetics and the development of methods for hand and foster nursing these species. In addition, the feasibility of converting additional buildings into barrier facilities to better protect the health status of SPF animals will be explored. New strains of animals in danger of extinction that have significant potential for research will be added to the colonies. An attempt will be made to support these activities from the Management Fund rather than the Revolving Fund. This is necessary because the decreased in-house production activity can no longer support research, development, reference stock, and genetic repository activities and still maintain reasonable prices for animals produced.

It is anticipated that the feed assay program by an independent laboratory will be expanded to include assays for pesticide residues, heavy metals, and possible bacterial contamination.

Present data indicate that there are considerable differences in nutritional requirements among various strains of inbred rodents. Studies will be initiated to define these differences.

Continued efforts will be made to develop open formula rations that can be purchased through advertised contracts to replace closed formula rations purchased through negotiated contracts on a sole source basis.

In order to meet increasing demands of the research community in the face of manpower reductions, continued efforts will be made to expand or improve automation needed for media production. Automatic labeling equipment to make labels as well as apply them will be added to the filling conveyor system to eliminate time-consuming manual application. Necessary modifications to increase tolerances will be made to eliminate variations in tubes received from the suppliers. A method of handling the larger ball mill grinding jars necessary to keep pace with the large volume orders of media is being designed by BEIB. The large jars now needed are too heavy to lift manually and require some mechanical method for lifting and handling to remove the ground powdered media.

Renovations to rooms housing tubing and bottling equipment are planned to provide a filtered air system to allow aseptic automatic filling of containers which now must be filled manually. This capability will require further changes in production techniques to provide for large volume lots of standardized media prepared as stock from which requests can be filled as needed.

To solve delivery problems of finished media, the possibility of contracting for direct delivery to the users' laboratory is being explored. A service contract, with the contractor responsible to the Media Unit, should provide vastly improved control over deliveries as well as eliminate costly remakes of expensive media lost through mishandling.

Extensive renovations in the glassware sorting area are needed to provide automation and safer methods of handling dirty glassware. Three separate proposals have been received. Negotiations are underway with SMB to determine the best method of obtaining the necessary renovations as soon as possible.

A concerted effort will be made to encourage investigators to expand their use of culture tubes directly from the factory package without further processing. Money savings to the I/D's as well as manpower savings to the Glassware Unit could result if this practice were used on a regular basis. In an effort to obtain more dust-free packaging that would encourage this type of usage, contacts with suppliers of these tubes will be continued.

The feasibility of a contractor to pick up and deliver glassware to the investigator's laboratory will be investigated. Regular deliveries under control of Glassware Unit personnel would substantially decrease breakage of glassware and assure regular return of dirty glassware for processing. The possibility of contracting for supply of deionized water will also be investigated.

Plans are underway to design and implement a new form for glassware issue. This will eliminate unnecessary paper work by providing a VRB record of quantities and types of glassware issued and a record of glassware ordered for the requestor. Present methods do not provide a permanent record of orders received.

Continued expansion of the canine breeding colony by purchase of quality dogs from outside sources will be pursued. Special attention will be directed towards obtaining a nucleus of stock for a fourth inbred line, preferably English foxhound. Contract production of purebred foxhound puppies (200-600/yr) will also be undertaken during the last quarter of this fiscal year.

The dairy goat and burro breeding herds will be expanded, pending installation of appropriate fencing around existing pasture land and erection of shelter.

Plans for outdoor, nonhuman primate breeding facilities will be finalized and pursued as a high priority item.

Further definition of the blood groups of dogs in the canine donor and breeding colonies will be undertaken. Typing antisera for groups CEA 4 (formerly B), CEA 5 (formerly C), Cea 6 (formerly D) and groups He and Tr should become available during FY 1974 from outside sources.

Final reduction of the feline breeding colony to 20 individuals will be accomplished. The colony will fill requests for timed-pregnancies and neonates.

It is anticipated that RIF-free avian activity will be terminated early in the next fiscal year.

F. Publications

Amsbaugh, D.F., Hansen, C.T., Prescott, B., Stashak, P.W., Barthold, D.R., and Baker, R.J.: Genetic control of the antibody response to type III pneumococcal polysaccharide in mice. I. Evidence that an x-linked gene plays a decisive role in determining responsiveness. J. Exp. Med. 136: 931-949, 1972.

Ganaway, J.R., Allen, A.M., Moore, T.D., and Bohner, H.J.: Natural infection of germfree rats with Mycoplasma pulmonis. J. Infect. Dis.

Goldman, P.M. and Moore, T.D.: Spontaneous Lancefield group G streptococcal infection in a random source cat colony. Lab. Anim. Sci.

Hansen, C.T.: A genetic analysis of hypertension in the rat. In Kozo Okamoto (ed.): Spontaneous Hypertension - its Pathogenesis and Complications. Tokyo, Igaku Shoin, Ltd., 1972, pp. 15-28.

Pucak, G. and Johnson, D.K.: Sarcocystis in a patas monkey (Erythrocebus patas). Lab. Anim. Digest 8: 36-39, 1972.

Serial No. DRS-VRB-1
1. Veterinary Resources Branch
2. Animal Center Section
3. Poolesville

PHS-NIH
Individual Project Report
July 1, 1972 through June 30, 1973

Project Title: ERYTHROCEBUS PATAS MONKEY AS AN ANIMAL MODEL FOR CARDIOVASCULAR RESEARCH

Previous Serial Number: None

Principal Investigator: George Pucak

Other Investigators: Donald Fry, NHLI

Cooperating Units: Section on Experimental Atherosclerosis, ODIR, NHLI

Man Years:

Total:	0.3
Professional:	0.2
Other:	0.1

Project Description:

Objectives: 1) To determine the suitability of the patas monkey for atherosclerotic studies as they relate to humans. Positive findings would provide an additional animal model and the first primate atherosclerosis model from an African source. 2) To determine whether the patas monkey would be a better model for cardiovascular studies than those species presently available.

Methods Employed: Fifty patas monkeys (Erythrocebus patas) were purchased and maintained on monkey chow for 4 months while base line data was obtained. They were then randomly divided into one group of 10 animals and two groups of 20 and are currently being fed atherogenic diets. Blood samples are being drawn monthly and a variety of hematologic, serum chemical, and serum lipid data are being obtained.

Major Findings: None

Significance: If a model for atherosclerosis can be provided from an African nonhuman primate it will enlarge the sources of models for this important research.

Proposed Course: Completion in October 1973.

Honors and Awards: None

Publications: None

Serial No. DRS-VRB-2
1. Veterinary Resources Branch
2. Animal Center Section
3. Poolesville

PHS-NIH
Individual Project Report
July 1, 1972 through June 30, 1973

Project Title: IDENTIFICATION OF NATURALLY OCCURRING HYPERLIPIDEMIC RHESUS MONKEYS (MACACA MULATTA)

Previous Serial Number: None

Principal Investigator: George J. Pucak

Other Investigators: None

Cooperating Units: Comparative Pathology Section, VRB, DRS

Man Years:

Total:	0.2
Professional:	0.1
Other:	0.1

Objectives: To identify rhesus monkeys that have a natural hyperlipoproteinemia, especially the Type II. These have been reported and indications are that they occur in approximately 1 percent of the rhesus population.

Methods Employed: A single channel autoanalyzer will be used to determine the total serum cholesterol of each animal after it has been in quarantine for at least 4 weeks. If an animal is hypercholesterolemic, further tests such as lipoprotein electrophoresis will be done to evaluate whether the hypercholesterolemia is primary or secondary.

Major Findings: Data are insufficient to evaluate at this time.

Significance: A method of identifying this disease will provide the NIH investigators with animals that have naturally occurring hyperlipidemias rather than having to rely on the experimental production of hypercholesterolemia.

Proposed Course: Continuation

Honors and Awards: None

Publications: None

Serial No. DRS-VRB-3
1. Veterinary Resources Branch
2. Comparative Pathology Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1972 through June 30, 1973

Project Title: PATHOLOGY OF ADJUNCTIVE EFFECT OF IMMUNOSUPPRESSION AND THYMECTOMY ON CANINE PULMONARY ALLOGRAFTS

Previous Serial Number: None

Principal Investigator: Dawn G. Goodman

Other Investigators: Richard Scott, NHLI
Tom Bowles, NCI
Glenn Gaelhold, NCI
Paul Chretien, NCI
Thomas Moore

Cooperating Units: Comparative Pathology Section, VRB, DRS
National Cancer Institute
National Heart and Lung Institute

Man Years:

Total:	1.0
Professional:	.5
Other:	.5

Project Description:

Objective: To evaluate the role of thymectomy on decreasing the immune response using the K-9 lung allograft as a model.

Methods Employed: Dogs which are 4 years or older and weighing 15 kg or more are used. Fifteen dogs have been thymectomized as puppies. Four groups of dogs are used:

1. Controls--no immunosuppression or thymectomy
2. Standard immunosuppression (prednisone and azothioprine)
3. Standard immunosuppression plus thymectomy (performed at age 4-6 months).
4. Thymectomy without immunosuppression

Major Findings: Not available at this time.

Significance: The effect of early thymectomy, with and without immunosuppressive therapy, on pulmonary allograft rejection has never been studied.

Proposed Course: Continuation

Honors and Awards: None

Publications: None

Serial No. DRS-VRB-4
1. Veterinary Resources Branch
2. Comparative Pathology Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1972 through June 30, 1973

Project Title: DIFFERENT LEVELS OF DIETARY PROTEIN FOR LABORATORY RATS

Previous Serial Number: None

Principal Investigators: Anton M. Allen
Joseph J. Knapka

Other Investigators: K.P. Smith

Cooperating Units: Comparative Pathology Section, VRB, DRS
Rodent and Rabbit Production Section, VRB, DRS

Man Years:

Total:	1.0
Professional:	0.25
Other:	0.75

Project Description:

Objectives: To evaluate the effect of various levels of dietary crude protein on the reproductive performance, various physiological systems, pathology and longevity of noninbred stocks of rats.

Methods Employed: A series of factorial designed long-term feeding trials are conducted involving rations containing various concentrations of crude protein. Throughout the study various reproductive trials and physiological determinations are recorded. At predetermined intervals, rats from each treatment group are sacrificed for pathological evaluation.

Major Findings: Analyses of data have not been completed.

Significance: It is extremely important to determine and feed optimal levels of nutrients to laboratory animals. Reproductive performance, longevity, disease processes, and costs of operation all may be related to proper diet.

Proposed Course: Continuation

Honors and Awards: None

Publications: None

Serial No. DRS-VRB-5
1. Veterinary Resources Branch
2. Rodent and Rabbit Production Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1972 through June 30, 1973

Project Title: GENETIC ANALYSIS AND ANIMAL MODEL DEVELOPMENT

Previous Serial Number: DRS-LAB-5

Principal Investigator: C.T. Hansen

Other Investigators: K.P. Smith
W.J. Hinkle
W.J. McEleney

Cooperating Units: Laboratory of Bacterial Products, DBS
Laboratory of Immunology, NIAID
Laboratory of Pathology, GLC, NCI
Laboratory of Biology, GLC, NCI
Laboratory of Microbial Immunity, NIAID

Man Years:

Total:	1.0
Professional:	.5
Others:	.5

Project Description:

Objectives: 1) To study the role of genetic and environmental components involved in the dynamics of reproductive performance of inbred strains of animals, 2) to conduct genetic monitoring of inbred strains, and 3) to develop new animal models utilizing the existing gene pool and new and exotic species.

Methods Employed and Major Findings: Analysis of long-term reproductive records of inbred strains has shown that the most important component of reproductive yield is the frequency of litters weaned rather than the more traditional average litter size at weaning. The frequency of litters weaned is determined by both genetic and environmental factors.

Studies are underway to establish characteristic strain frequencies of various tumors and age of onset of leukemias in both SPF and conventional environments.

Blood pressure levels of inbred rat strains are being monitored. The range in systolic blood pressures of 17 inbred strains is from 116 mm. Hg. to 182 mm. Hg. in males at 10 weeks of age. F_1 hybrids of these strains demonstrate that blood pressure is inherited in a complex manner.

Selective breeding for the sensitivity and resistance to effect of histamine after treatment with B. pertussis has reached the 13th generation. Sensitivity has been increased to about 75 percent in the sensitive strain and decreased to about 3 percent in the resistant strain from an average sensitivity of 30 percent in the unselected base population.

A number of oriental mouse species have been introduced into the colonies for the purpose of studying additional genotypes involved in the immunoresponse mechanism.

The development of closed lines of rabbits continues. Four lines have been established homozygous for a pair of genes which control the gamma globulin allotypes. Work has been undertaken to study the inheritance of tissue antigens in these species. Also, preliminary analysis of long-term reproductive records has also been undertaken in the rabbits.

Significance: The significance of these projects is to develop, by the use of genetic procedures, new animal models which have an application to biomedical research.

Proposed Course: Continuation.

Honors and Awards: Dr. Hansen was invited to present a paper entitled "A Genetic Analysis of Hypertension in the Rat" at the U.S. Japan Symposium on the Spontaneously Hypertensive Rat in Kyoto, Japan, October, 15-22, 1971.

Publications: Hansen, C.T. and McEleney, W.J.: Strain and season differences in the reproductive performance of inbred strains of mice, rats, and guinea pigs. Proceedings of the IV ICLA Symposium, NAS, 179-202, 1971.

Amsbaugh, D.F., Hansen, C.T., Prescott, B., Stashak, P.W., Barthold, D.R., and Baker, R.J.: Genetic control of the antibody response to type III pneumococcal polysaccharide in mice. I. Evidence that an x-linked gene plays a decisive role in determining responsiveness. Journal of Experimental Medicine. 136: 931-949, 1972.

Serial No. DRS-VRB-6
1. Veterinary Resources Branch
2. Rodent and Rabbit Production Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1972 through June 30, 1973

Project Title: DEVELOPMENT OF DIETS FOR LABORATORY ANIMALS

Previous Serial Number: DRS-VRB-6

Principal Investigator: J.J. Knapka

Other Investigator: F.J. Judge

Cooperating Units: None

Man Years:

Total:	2.0
Professional:	0.5
Others:	1.5

Project Description: Objectives: 1) To formulate and evaluate open formula rations designed to improve the nutritional status of laboratory animal colonies, 2) to accumulate data regarding the specific nutrient requirements of various strains of inbred laboratory rodents.

Methods Employed: A series of factorial designed feeding trials are conducted to determine the effect of various diets differing in nutrient concentrations and physical form on the growth and reproductive performance of the species involved. Criterion of evaluation includes number of pregnancies, number of litters born, number of litters weaned, number of offspring weaned, weight of offspring weaned, and the post-weaning, growth rate of offspring. These data are coded for computer analysis by the appropriate statistical methods.

Major Findings: An open formula ration for laboratory rabbits and conventionally reared mice and rats has been evaluated. The performance of animals fed these new rations was equal to those fed commercial rations. Open formula rations for barrier reared mice, rats, and guinea pigs are being evaluated. A limited amount of data has been accumulated that indicate there are considerable differences in the major nutrient requirements of various strains of inbred mice. These data also indicate the reproductive performance of many inbred strains of mice can be improved by feeding rations lower in crude protein than is contained in conventional commercial rations.

Significance: The development of open formula rations for NIH production and research animal colonies is advantageous because, 1) production of rations is not restricted to a single mill in the event of a fire or bacterial contamination, 2) investigators have the opportunity to know the complete nutritional status of animal colonies, 3) a basis is provided for the improvement of rations for particular stocks or strains of animals, and 4) competitive procurement of essentially the same product can be accomplished over many years.

The efficiency of maintaining production and research colonies of laboratory animals can be markedly improved if rations can be developed that supply nutrients in concentrations nearly equal to the requirements of the strain of animal involved.

Proposed Course: Continuation

Honors and Awards: None

Publications: None