ANNUAL REPORT
OF
PROGRAM ACTIVITIES
DIVISION OF RESEARCH AND TECHNOLOGY
DIVISION OF RESEARCH GRANTS
DIVISION OF RESEARCH RESOURCES
DIVISION OF RESEARCH SERVICES
Fiscal Year 1975

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service National Institutes of Health

ANNUAL REPORT

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PROGRAM ACTIVITIES

U.S. NATIONAL INSTITUTES OF HEALTH.

DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

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PUBLIC HEALTH SERVICE - NATIONAL INSTITUTES OF HEALTH

DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

Report of Program Activities

July 1, 1974 through June 30, 1975.

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ANNUAL REPORT

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DCRT Annual Report
July 1, 1974 through June 30, 1975

OFFICE OF THE DIRECTOR

This Director's Summary highlights some of the Division's FY75 activities, and provides a perspective in which to see the progress of computing at NIH, as you read the details of what the DCRT Laboratories and Branches did this year.

Ten years ago the new Division of Computer Research and Technology was organized on the NIH campus. Today computing has become an integral part of the NIH scene, and literally involves and affects work of thousands of scientists and administrators. The key to this integration is the interaction between those who provide computing capabilities and those who use these for biomedical research, health administration and program leadership at NIH.

To be useful and successful any such interaction must involve:

- a worthwhile information processing task
- a successful computer system
- a way to perform the task on the system.

Successful Computer Systems

NIH has successful computer systems, largely because NIH planned for and was willing to build its own centers of technical expertise. As a minimum, successful computer systems must be both reliable and accessible. This requires expertise in computer hardware, computer software, and electronic communications, plus an ability to combine all three appropriately for the tasks at hand.

The DCRT Computer Center Branch continues to provide NIH with responsive, reliable computer services and facilities of an unexcelled quality and diversity. To provide computing power to some 5000 users is no trivial matter. The CCB success derives largely from recognition that the key to developing a good central computing utility is high quality system software expertise, (system programmers).

The CCB report therefore emphasizes this competence and describes several improvements which balance an average of more than 10,000 computing tasks per day among several large, interlinked computer processors, while handling 80,000 on-line data sets and archiving almost 30,000 reels of computer tape. In this context, one can see the importance of the implementation of the automatic data migration facility, the automatic tape inventory and registration, the "quick" and "discount" services, and various privacy protection facilities.

These improvements carry forward the CCB philosophy of an integrated utility, based upon reliable commercially available hardware and accessible through reliable commercially available commmunications lines. Perhaps the greatest tribute to the CCB system teamwork is the recognition and emulation it receives by professionals outside the NIH, including those who provide commercial computing services.

The DCRT Computer Systems Laboratory must be viewed from another perspective since its mission and activities focus on computing tasks of a different type. It develops systems tailored to needs that cannot be met by a central computing utility. These needs fall largely in biomedical research laboratories and in clinical care areas that have requirements for real-time data collection, analysis, display or process control, as well as an interactive computing capability for research and clinical staff.

As noted in previous annual reports these tend to be longer range projects. Indeed, two of the more significant CSL projects get little discussion this year because they are not "new." One is the continuing work on systems for fundamental biochemical and biophysical investigation among the NIAMDD laboratories in Building 2. The other is the expansion and refinement of the system supporting the NHLI Intensive Care Unit.

The CSL summary notes that in addition to software competence its work involves considerable electronic engineering expertise. The intricacies of computer hardware and of directly-wired communications lines are an inescapable part of specifying or designing CSL systems. Many of these involve the acquisition, conditioning, and preprocessing of complex signals from instruments in the laboratory or at the bedside. The CSL staff too has its share of recognition and emulation by professional colleagues outside of the NIH.

Worthwhile Information Processing Tasks

There are three salient facts about the value of information processing tasks at NIH.

1. Judgements about their value rests primarily with those persons, scientific or administrative, who use the information products as part of their work, and secondarily with those who must evaluate that work.
2. The value of doing an information processing task on a computer involves a separate judgement but this also must rest with the same people who make judgements about the value of the task itself, although DCRT often provides advice.
3. Computing at NIH has flourished because there are large numbers of worthwhile information processing tasks at NIH and many of these are worth doing on a computer.

Biomedical research is, after all, a matter of acquiring and evaluating new information in the light of existing knowledge, and health science administration involves the evaluation processing of large amounts of information about research and training projects. Behind both NIH research and administration lies the considerable logistical and managerial infrastructure inherent in operating a complex organization consisting of thousands of people responsible for many hundreds of millions of dollars.

The activities of three parts of DCRT provide examples of some worthwhile information processing performed on computers.

The Physical Sciences Laboratory studies problems in physics and chemistry that relate to biological sciences. These investigations look at fundamental levels of biomedical phenomena. In general they entail theoretical studies and experimental work on interactions among molecules or the interactions of molecules or other small entities with a variety of physical force fields, e.g., centrifugal or electromagnetic.

Like much of modern physical science, the PSL work uses the precision of mathematical forms for the theoretical studies. It uses the power of computers both for numerical evaluation of mathematical statements and in experimental work as part of sophisticated instrument systems that automatically measure the changing response of the material under investigation and in many cases automatically change the force fields.

But significantly, the PSL has been rather frugal in its use of computers. In many instances it uses programmable calculators rather than full-blown computer systems because its competence in mathematics permits PSL to make appropriate simplifying substitutions in place of more complex forms. As the PSL report indicates, this mathematical talent is applied in a variety of collaborative studies with scientists outside of NIH, and the laboratory sponsors occasional meetings of experts on pertinent topics.

The Laboratory of Applied Studies operates in a similar mode with respect to problems closely related to clinical research and care. Some studies involve mathematical theory and numerical analysis, or develop statistical theory and methods for analyzing clinical data.

Others deal with complex clinical information forms such as electrocardiograms and radionuclide scintigraphs, the X-ray like images produced by the radiation emitted from minute amounts of radioactive substances administered in diagnostic tests.

Such statistical and clinical studies may involve a considerable amount of mathematical computing. They also make use of a computer's ability to organize, store, and retrieve sets of data precisely and efficiently, as well as to control the acquisition and/or conditioning of the electronic signals from which the data are derived.

Hence, it is no surprise that both LAS and PSL work with the Computer Systems Laboratory and other NIH institutes on projects which require the development of specialized computer systems and at the same time make use of the facilities of the Computer Center Branch for large scale data processing and computation.

The DCRT Office of Administrative and Management Services contains examples of the value of computing in administrative data processing. Perhaps the best example is the DCRT Project Accounting System, which handles the accounts for all DCRT services that are billable through the NIH central accounting system under the NIH Service and Supply Fund (the Revolving Fund). The system was designed by members of the Computer Center Branch and Data Management Branch. It automatically collects data on all jobs run on the CCB computer utilities and is fed supplementary information on other billable personnel, rental and service charges.

Those data are available at all times for "emergency" on-line queries. Each month's charges are billed by transfer of data on magnetic tape to the NIH Office of Financial Management. The system also makes microfiche copies of the monthly bills for ready visual reference if questions arise.

The information thus processed is absolutely essential for responsible fiscal management under the service and supply fund. Note that in this case the computer is essential for recording measurements of its own activities. It is also valuable for keeping files well organized for query and for easy transfer to other computer-based accounting systems. The microfilm records supplement and reduce the need for costly on-line inquiries.

Performing Worthwhile Tasks on Successful Systems

The mere existence of successful computer systems and worthwhile information processing tasks does not guarantee that the tasks will get done.

The DCRT tasks mentioned above benefit from close proximity within DCRT to programmers and information specialists as well as to successful computer systems.

But many computer users at NIH do not have all this talent available "down the hall." Their initial interaction with computers usually occurs first through DCRT staff and then directly through the variety of facilities which are provided and supported by the DCRT staff.

These facilities are computer programs designed to make it easier to create new programs and to use them. Indeed, this very concept of computer programs interacting with each other as well as information and people and computer hardware is absolutely essential to an understanding of modern computing.

The Data Management Branch uses many such facilities to provide practical solutions for the variety of data processing problems posed by NIH scientists and administrators. One key to the DMB success is its ability to employ, as needed, a full range of such facilities: conventional compiler-based languages, conversational programming systems and the data management program generators that DMB itself has created. During the past year DMB has improved its generators and plans to have a completely revised system available early in FY1976.

The Clinical Information Utility System segment of the DMB Clinical Center Project is an excellent example of the accomplishments which are possible through continuing interaction of knowledgeable staff in DCRT and other organizations. The CIU System addresses a long felt need for rapid, accurate and controlled retrieval of subsets from the wealth of data accumulated by the Clinical Center clinical laboratories over recent years. Development of the system involved resolution of many of the classic jurisdictional and privacy issues which appear in articles about data management in large organizations.

As in previous years, the DMB summary includes a number of projects in support of clinical research with the various NIH institutes. An excellent example is the retrospective NHLI study of pre and postoperative data on more than one thousand cases requiring surgical replacement of heart valves.

The DMB report also demonstrates a strong support for NIH laboratories and administrative areas. In the latter, a close look at the project list shows their work interacting productively with the central systems maintained and operated by the NIH Division of Research Grants and the NIH Office of Administration.

The Laboratory of Statistical and Mathematical Methodology is a counterpart to DMB. It provides practical solutions for problems involving the statistical analysis and mathematical evaluation of data. Like DMB, LSM uses a full range of facilities: compiler-based languages, interactive systems, a variety of statistical packages developed elsewhere and two facilities, MLAB and MODELAIDE, by DCRT staff members who are now part of LSM.

Here again success is a result of the interaction between the expertise of LSM and the NIH scientists and administrators who have information processing problems. The examples listed in the LSM report show that these consultative and collaborative efforts have flourished during the first year of the laboratory's activities.

The close reader of the DMB and LSM reports may note that DMB has several projects involving statistical analyses. Some of these are projects started in DMB years ago and have built up a close working staff relationship. But it is more important to realize that information processing tasks associated with sets of data do not fall into two discrete classes.

Thus, while LSM is a DCRT focus for certain statistical and mathematical disciplines, these are found elsewhere in DCRT. Similarly the research activities of LSM in size and shape and pattern recognition, computer science and various branches of mathematics have direct or related counterparts in DCRT. Without this commonality of expertise among the DCRT labs and branches much of the collaborative multidisciplinary work within DCRT would suffer.

DCRT Training Courses and Seminars are another essential element in getting the worthwhile tasks done on the successful computer systems. In many ways it is useful to view the NIH Computing System (the machines, the software, the computer science and information science expertise and the NIH staff with information processing tasks) as a learning system.

This view leads to two questions. Who needs to know what about the theory and practice of information handling and computer systems in order to achieve the best research, administration and program leadership? What kind of "educational experiences" are needed to provide that knowledge and the skills and attitudes which enable the knowledge to be used effectively? The first question tends to be answered throughout NIH by each person for his or her own perceived needs. The second is answered rather well for the specific DCRT supported programming languages and facilities by training courses given twice a year.

Future Progress of Computing at NIH

The progress of computing at NIH has followed the major outlines of the scenario envisioned in the early 1960s. Then, after a year long study (1962-63)

NIH opted for a new Division of Computer Research and Technology. This division was to be a strong central computing utility and programming resource, embellished with laboratories of excellence in computer systems engineering and mathematics. All of this came to pass.

Socalled Data Base Technology has made slower progress. There was to be a Data Systems Analysis and Design Branch in the original DCRT. The Federal enthusiasm of the late 1950s and early 1960s for central pools of systems analysts separate from computer programmers never materialized at NIH. This was due in part to the nature of NIH and in part to the state of computing at NIH and elsewhere.

There was no NIH centralization of administrative data processing systems. A group of systems analysts has functioned within the Division of Research Grants, Statistics and Analysis Branch, which operates its centralized data management systems for grants and lately for contracts. The Office (now Division) of Financial Management has in large measure obtained systems analysis, design and implementation by contract.

In spite of some promises of the late 1960s there never developed a good commercial general purpose information processing system to apply to data management. To fill the void the Data Management Branch developed a data management system for its customers in the various NIH Institutes and administrative offices.

More recently there have emerged on the market some data base management systems which begin to approach the facilities promised in the 1960s. It remains to be seen whether they will be suited to the NIH needs and whether the central NIH administrative data processing functions are suited to the concepts of integrated data base management.

Federal Automatic Data Processing regulations (ADP) still haunt computing at NIH in the form of the GSA. The general problem was discussed obliquely in last year's Director's Summary, with a historical note to show recognition in 1963 of the difference between NIH computing needs and those previously envisioned by Federal ADP philosophies. Whether or not current differences can be resolved is a matter of some concern for the future of the NIH central computer facilities.

Several trends will affect computing at NIH. One is resource constraints. The last seven years brought tighter employment ceilings to most of NIH and a call for higher productivity throughout the Federal Government. To the extent that computers can increase the "efficiency and effectiveness" of NIH and other Federal employees, we are likely to see greater use of systems like the NIH Computer Center, which are reliable, accessible and relatively inexpensive. The ultimate limit on expansion will be economic, depending on the values placed on computing compared to other activities during a period of continuing inflation.

Another trend appears in two areas which are not computers in the conventional sense. These are electric calculators and "word processing machines." The NIH property rolls currently list some 3200 "electric calculators" ranging

from $35 manual calculators to $12,000 programmable calculator systems, and the NIH rents or leases some 390 magnetic card or magnetic tape typewriters.

Programmable calculators are now available with cassette tapes and with alphabetic characters to put labels on printed results (and presumably on program statements). "Communicating" mag card and mag tape typewriters are available which send and receive messages via telephone lines, linking to the NIH central computer (or in theory to any other compatible computer in the world with telephone posts). And new product lines are announced monthly.

The significance of these trends to computing at NIH will be evolutionary rather than revolutionary. The need for a central NIH computer system will not disappear. Nor will every office and laboratory demand its own complement of number and word processing machinery and "intelligent terminals" linkable to a large computer. What will emerge is a more diverse information processing environment and a more sophisticated body of information processors (people) within NIH.

The challenge to NIH and hence to DCRT a decade ago was to make computers available and reliable. This has been met. The challenge for the decade ahead is to help computing in its increasing variety become more effective and productive as part of the "information intensive" environment of NIH. To this end one can foresee increasing, not decreasing, interaction between DCRT expertise and scientific and administrative staff as well as with policy-making groups at NIH and elsewhere.

NATIONAL INSTITUTES OF HEALTH
DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

1. DCRT

2. OFFICE OF SCIENTIFIC AND TECHNICAL COMMUNICATION

3. William C. Mohler
Director

This year DCRT established a new Office of Scientific and Technical Communications. The office formally brings together the DCRT Library and the Scientific and Technical Information Office and also is a locus of collaborative and research projects in information science and mathematics.

One domain of the office is information about information processing. Its concern is the adequacy of information reaching NIH scientific staff about computers, about their applications to scientific and administrative problems and about the DCRT activities. Another domain is application of advanced information science principles, including mathematics, to multidimensional information structures.

The office is small as well as new. Its three areas are led by Judith Prewitt, mathematician and expert on image processing, Ruth Ketler, the DCRT Scientific and Technical Information Officer, and Ellen Chu, the DCRT Librarian. Two part-time staff members and two co-workers from the Data Management Branch constitute the rest of the group. The Chief of the office is the DCRT Associate Director in a dual position.

The DCRT Library serves three functions. It is an integral working part of DCRT activities, a resource for the NIH staff, and an independent member of the network of special libraries in the Washington area. This is reflected in the 1974 circulation statistics. Some 60% of the books are borrowed by DCRT staff but over 60% of its more than 300 borrowers work outside of DCRT.

To meet these needs the library added about 230 books, 100 technical reports and theses, and 25 new periodicals this year to its collection on computer science, mathematics, engineering and related topics. It also instituted a review of holdings and subscriptions to eliminate outdated and unused materials.

As part of the library network, the DCRT library continued to include its catalog cards in the NIH Library catalog, to provide MEDLINE bibliographic services and to arrange for bibliographic searches through the NASA Scientific and Technical Information Facility and the Defense Document Center.

During her first year as librarian, Mrs. Chu has made several changes to improve effective service and operating efficiency, based on her questionnaire survey of library users and on the advice of her ten member DCRT Library Committee. For the coming year she ambitiously proposes: 1) a complete inventory of the collection, 2) an update of the catalog, shelf list and journal holdings list, 3) modifications to the automated circulation list, 4) improvements in

the work area and library layout, 5) investigation of microform reading equipment, and 6) revision of the reference collection. She also plans further cooperative efforts with other local libraries.

The Scientific and Technical Information Office began to enlarge its scope this year. It initiated new steps to analyze the needs of the NIH staff for information about computers, about their applications and about DCRT activities. A questionnaire survey of some 500 NIH laboratory, branch and department chiefs and administrative officers disclosed a broad expression of interest in, or need for those three kinds of information. This response is indicative of the extent to which computing has generated application and interest in all parts of NIH.

The new STI Officer, Mrs. Ketler, arrived in the midst of the DCRT preparations for the Alumni Reunion, the Public Open House and the Bicentennial Exhibit. In conjunction with the Computer Systems Laboratory and other members of DCRT, she helped to implement an exhibit about computing at NIH incorporating a slide show with sound track and a supplementary brochure. In addition to the exhibit DCRT presented five examples of computing via remote terminals to demonstrate the broad capability of human interactions with computers, by such means as graphic displays and audible responses including computer-generated speech.

During the fall, the STIO assisted the Computer Systems Laboratory in preparation for a conference on Computers in Cardiology which was sponsored by DCRT in conjunction with NHLI, The European Congress of Cardiology and the American IEEE.

As in previous years, the Scientific and Technical Information Office answered many queries from both inside and outside the NIH. The majority of these requests were for technical reports, for specific software programs and for information about computer applications. The office continued to handle a number of information reporting functions required by Federal regulations.

In the coming year, the office plans both to better define the interests and needs expressed in this year's questionnaire survey and to develop a set of presentations to meet them.

The work on multidimensional information structures has several dimensions. Mrs. Prewitt has been a leader as well as a collaborator in programs of three divisions of the National Cancer Institute. These include development of new techniques for diagnostic radiology, advances in automated clinical cytology, and analytic studies of subcellular cell and tissue characteristics of several types of neoplasms. On the NIH campus she has begun several collaborative projects in data analysis with scientists in the National Heart and Lung Institute.

Her active participation in these programs entailed many site visits and conferences. She was also an invited speaker or participant at some two dozen conferences, seminars, and workshops in the United States, Europe and Japan. These all related to her interests in development of rational bases for utility and effectiveness of both diagnostic and therapeutic procedures.

Summary of the Assistant Director

July 1, 1974 through June 30, 1975

The Office of the Assistant Director, DCRT, provides three basic capabilities:

1. The Office serves NIH as the focus for coordination of ADP policy matters and thus also as a central point of NIH contact with PHS, the Office of the Secretary, other DHEW agencies, GSA and OMB for NIH ADP policy questions and relative to NIH participation in the development thereof.

2. The Office supports the Director of DCRT by providing a point of reference and coordination to insure that DCRT's own ADP activities are consistent with NIH, PHS, O/S, GSA and OMB policy directions, and

3. The Office supports the Directors of DCRT and NIH by providing advice on ADP resource acquisition and allocation necessary for DCRT and NIH mission performance.

During the year the role of the Office of the Assistant Director, DCRT, as the NIH-wide coordinator of ADP policy needs and its role as the central point of contact on ADP policy questions with PHS, OS, OMB, GSA and other Federal Agencies was given added status by its formal recognition as the Office of ADP Policy Coordination. This change solidifies the role of the Director, DCRT, as the principal advisor to the Director of NIH on all ADP matters. This is also a first step in the implementation of the organizational alignments recommended by the AMETA Study of 1973.

A major continuing undertaking started during FY72 and continuing thereafter is the technical and management leadership in development of NIH's annual ADP Plan. This plan attempts to lay out a two year projection for ADP equipment, manpower and ADP support contracts for all components of NIH. This planning process creates an orderly opportunity for ADP users to take stock of their goals and accomplishments. The most recent annual plan covered NIH ADP efforts exceeding $34 million for FY75, $34 million for FY76 and $38 million for FY77. Through extensive coordination with PHS and the Office of the Secretary, the office was able to integrate several GSA and OMB reporting requirements into the NIH ADP planning process, thereby reducing the administrative burden which would otherwise be entailed in the current trend toward "overmanagement" of ADP.

In serving as a central point of contact for NIH on ADP related matters with PHS, DHEW, GSA, OMB, etc., a large number of NIH research and research support staff members are spared the agony of becoming expert in the many nuances of ADP related regulations. Since these regulations are generally written from a second generation business data processing point of view, a thorough understanding of their purpose and operation often allows beneficial interpretations of their application to the NIH research environment.

During FY75 the ever-increasing "overmanagement" of ADP by OMB and in particularly GSA, has resulted in the need for the Office of the Assistant Director, DCRT, to spend an ever-increasing percentage of available man-hours on the paper work associated with ADP procurements. Notwithstanding the increased burden of paper work, the office has been able to make technical contributions which have assisted the National Library of Medicine in making an orderly upgrade of the MEDLINE capabilities and assisted the Clinical Center in the installation of a new clinical chemistry system and in the selection of a total Hospital Information System. In addition, numerous small laboratory computer systems have either been installed or placed on order. In each case the office provided both advice and assistance with regard to procurement and policy considerations as well as technical advice.

The NIH policy coordination role is exercised in part by review of all NIH proposals for contracts or procurement actions involving ADP equipment, services or programming which must all be cleared through this office prior to being executed. This provides a continuous opportunity to alert program or contract officials to opportunities to avoid duplications, reduce costs or, importantly, to avoid difficulties with higher echelons.

With regard to the role of assisting the Director, DCRT, with technical coordination of internal DCRT operations, the office provided technical leadership with regard to two major physical plantundertakings initiated during FY75. The office coordinated an architectural and engineering study which will eventually result in the conversion of the second floor of Building 12 into space usable for computing equipment. This innovated approach to overcoming the natural limitations of the size of a building will, when brought to fruition, result in the novel but functionally effective concept of a two-floor computer room. Secondly, during the year the office coordinated for Engineering Design Branch the ADP technical aspects of an entirely new building, 12B, which will allow for expansion of the computational functions of the Division.

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Automated Processing of Medical Language

Previous Serial Number: 4.9

Principal Investigators: A.W. Pratt, M.G. Pacak

Other Investigators: P. Graepel, G. Dunham, S. Harper, M. De Meyts-Graitson

Man Years:

Total:	2.5
Professional:	2.5
Other:	

Project Description:

Background:

For the past several years, an effort has been underway to develop a linguistically-oriented system for automated processing of medical language, and the program for information storage and retrieval of pathology data. The system includes the acquisition of textual information, the interrogation of a medical dictionary (SNOP), a set of transformational morphosyntactic and morphosemantic rules which are required for the identification of the information content of the input messages. The system for automated indexing of pathology data became operational in 1971 and is going to be extended to other subfields of medicine.

FY 74-75 Activities:

Development of a procedure for automated morphosyntactic analysis of medical language. The program was written in RMAG and PL-1 and is fully operational.

The model for the construction of a computer-oriented medical micro-glossary for cancers and the design of a semantic model for the interpretation of medical records are being tested.

A program for automated encoding of French pathology data was developed and successfully tested. This program is compatible with the program

which was developed for the encoding of English pathology data which became operational in 1971.

Preliminary design of lexical processor and manipulator for study, comparison and maintenance of medical lexical material. Feasibility trials for the implementation of the lexical processor indicate that NIH 370 system would serve as a base.

A program was developed for the identification and transformation of terminal morphemes in medical French (M. Graitson) which became a part of the French medical encoder (see appendix).

Analysis of a set of German language autopsy reports in preparation of an automated preprocessing method for medical German. Special attention was given to the problem of segmentation of compound words in German (Dr. Graepel). The preliminary results of the segmentation algorithm were used for the development of a statistical model for word segmentation by Dr. Mosimann and C. Clark.

Future Efforts:

Improvements of English and French encoders on the syntactic and semantic levels (development of paraphrasing rules, classification of semantic operators, etc.).

Construction of computer-oriented microglossaries for tumors and cardiology.

Application of statistical linguistics to medical data processing, and the construction of medical dictionaries.

Publications:

1. Pratt, A.W.: Medicine and Linguistics, MEDINFO 74, North Holland Company (1974).

2. Pratt, A.W.: Representation of Medical Language Data Utilizing The Systematized Nomenclature of Pathology, Proceedings of Symposium "Computers in Laboratory Medicine, Univ. of California, San Francisco, February 1975.

3. Pratt, A.W.: Organizing the Medical Data for Pattern Generation, Proceedings of IRIA Medical Data Processing Symposium, Toulouse, France, March 3-5, 1975.

4. Pratt, A.W.: Computer-Based Information System for the Research Environment, Proceedings of IRIA Medical Data Processing Symposium, Toulouse, France, March 3-5, 1975.

5. Pacak, M.G.: Computational Linguistics and Information Handling, Management of Information Handling System, ed. P.W. Howerton, Hayden Book Co., New Rochelle Park, N.Y., 1974; pp. 19-47.

PUBLIC HEALTH SERVICE-NATIONAL INSTITUTES OF HEALTH
DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

1. DCRT-2
Serial Number

2. COMPUTER CENTER BRANCH

3. J. D. Naughton
Branch Chief

MISSION

The Computer Center Branch designs, implements and operates a large general-purpose computer utility to meet most effectively the dynamic and diverse requirements of both N.I.H. research investigators and managers in the support of modern medicine. This charge includes the original development of new system facilities to meet the unique requirements of the NIH mission in order to bring the full power of the computer to bear on problems at every level of biomedical research in many remote locations. The core of this computer utility is a network of computers and remotely located terminals, which, by means of a modern communications network, extends the power of the computer directly into research laboratories and administrative offices throughout N.I.H. This provides immediate access to the computer thus minimizing delays in the research program and making more efficent use of critical manpower than more traditional methods. An inherent responsibility of the Computer Center is the continued research and development of new methods to extend the network even further into the research environment while continually adapting to the constant impact of new knowledge and program direction.

A full spectrum of computational services is provided to all Institutes and Divisions of the NIH on a fee-for-service (cost recovery) basis. These facilities include conversational programming, graphics, microfilm output, text editing, remote job entry, time sharing, data base management and batch processing. Large systems as well as mini-computers and terminals are tied together providing a "distributed capacity" available at many levels. Research into the computer and information sciences coupled with close cooperation between the N.I.H. medical investigators and the computer scientist have introduced computers directly into the research environment where they can perform most effectively in attacking the complex problems of medical research.

The medical research programs of N.I.H. require the most powerful and flexible of computer services and tools available today. The computer network provided must have a distributive power that is easily accessible when needed to scientists in the laboratory itself. The goal is to mold, polish and, in general, enhance the computer into a complete tool for medical research and its administrative support. New areas of computer applications are sought out continuously in conjunction with a comprehensive training program to inform research investigators of the latest methods in the use of computers to most effectively meet the unique requirements of their individual laboratories.

1974 ACTIVITIES

In spite of a general upwards spiraling of costs throughout the country, the NIH Computer Center began the year with the announcement of the most significant rate reduction ever offered NIH computer users. Rates were reduced 22.8% for all work processed on both the IBM System 370 and the DECsystem-10. In addition, the Night Service discount rate was increased to 25% for all work processed between the hours of 6 p.m. and 8 a.m. Increased workload, larger computer systems and internal modifications to the operating system resulting in improved system performance, combined to maintain the lower rates throughout the year in spite of continually increasing operating costs.

As the effects of the manpower shortage continued to become even more acute throughout NIH, many areas turned to "automation" as a means of compensating for decreased manpower without curtailing programs. Existing computer programs were modified or extended to accommodate new applications and entirely new programs were designed and implemented specifically to automate procedures that had previously been done by hand. As a result, the demand for computer services from the Center continued to increase dramatically throughout the year. Total workload increased 25% to 205,000 jobs/sessions processed per month. Interactive terminal systems provided service to 3000 sessions daily and the number of on-line disk datasets increased to 80,000 while the printers produced over 150 million lines of printed output per month. NIH is undoubtedly the most "automated" Agency of the Federal Government.

Two new processing services, "discount" and "quick" were introduced this year. These services were designed to encourage the shifting of workload from the peak load period during the daylight hours to overnight service. Users electing to use the discount service have their jobs automatically held until after

6 p.m. when the job is run at a 25% rate reduction. This has a double effect in that it also improves turnaround time for all daylight work and reduces the user's cost for computing services. Quick service, on the other hand, provides a facility to insure fast turnaround for users who choose to work at night. Through the quick service, jobs submitted during evening hours are run ahead of the large overnight production runs, thereby eliminating the long waits and making the user's time much more productive. Quick service also receives the night-time discount.

Because of the increasing national concern for personal privacy and the security of information stored and used in computers, the Computer Center designed and implemented a number of security improvements for the NIH Computer Utility. Most significant of these was the development of an automatic data encoding (scrambling) facility which is usable in all languages and from all systems supported by the Center. This facility permits a user to easily encode sensitive data in such a way that even the Computer Center could not decipher it. In addition, "keyword" protection became mandatory for both batch processing work and interactive terminal sessions while access to registered initials and account numbers was restricted. Additional facilities to further insure the confidentiality of sensitive data and the physical security of the Computer Center itself were designed and implementation was begun.

Many new or improved software services were introduced this year. The Integrated Plotting Package provides the user with a mechanism to generate intermediate text which will be processed, possibly after storage on an external file, by a variety of different plotting devices.

The Extended Printing Facility which provides a convenient means of printing mathematical expressions containing superscripts and subscripts as well as greek letters was improved to provide additional function and convenience for the user.

This year saw many improvements for TSO users, especially in the area of performance. After a slow start, internal systems software and hardware modifications brought TSO response up to an acceptable level. A new function gave users the ability to monitor CPU time used during a TSO session. With this facility users had more control over their terminal environment and "runaway" TSO programs became a thing of the past.

Many additional internal system changes were made that were transparent to the user, except that the changes increased the efficiency and reliability of the system and therefore either improved turnaround time or kept it from increasing as the

workload grew. The disk accounting system was modified to improve internal performance and provide more effective dataset recovery facilities. As the size of the tape library increased to over 27,000 reels, an automatic tape inventory and registration was implemented. In addition to insuring more accurate handling of tapes and reducing the manual burden for machine operators, this facility consolidated the "Tape Listing" and "Dataset Listing" into one convenient report for users.

The usefulness and popularity of many of the software systems and improvements designed by the NIH Computer Center was illustrated by numerous requests for copies received from other facilities throughout the world. Over 150 copies of software packages such as SHARED SPOOL, WYLBUR, DATASET MIGRATION, SPOUT, HASP, OCR, COM etc. have been distributed to federal and state governments, academic institutions and commercial organizations. The superiority of the Shared Spool package over other ways of controlling multiple CPUs was illustrated when IBM announced Multiple Access Spool, which is their version of the NIH Shared Spool System.

The DECsystem-10 was expanded to meet the demands of the workload which increased throughout the year. April 1, 1974 saw the addition of a second KI-10 CPU as a slave processor. The dual master-slave KI processors have provided the increased capacity needed to maintain excellent time-sharing services as well as CPU redundancy assuring continued service in case of failure of one processor.

The rapidly accelerating use of this system for time-sharing, laboratory-oriented programs, graphics problems required a continuous enhancement of both the software and hardware of the DECsystem-10. Plans were developed to provide additional on-line disk storage capacity and improved magnetic tape drives for this system next year.

Selection of the NIH Computer Center as one of two test sites for advanced monitor software paid dividends in terms of increased system reliability and early availability of new features, e.g., virtual memory.

The telephone line capacity of the DECsystem-10 was increased to 41 lines thus reducing the frequency of busy signals experienced by users. In addition, this year saw the introduction of support for 2741 terminal users by single-digit dialing on the NIH dataswitch.

A very stable version of the SAIL programming language was introduced and generated very few problems. A new Fortran compiler with excellent optimization was added to decrease

running time for compute-bound programs. The double-precision hardware features of the KI-10 processor further helped decrease execution times.

Dataset controls were added to improve the computer's handling of dial-in telephone lines. With the dataset controls, the computer detects when a telephone connection has been broken and suspends or detaches the session. The line is then re-initialized and freed for the next caller.

Omnigraph, the graphics system on the DECsystem-10, has been extended and improved both to achieve more efficient utilization of the entire computer system and to provide more flexible facilities. The Omnigraph system was modified to allow the executable code of large Omnigraph programs such as MLAB to be shared among many users. This has resulted in a saving of as much as 150K core at a time. In addition, new routines were added to facilitate the use of vertical text and raster mode on the DEC340 display. Support for the new DEC Fortran, Fortran-10, was also implemented.

TXTCOM, an additional microfiche package, was made available to DECsystem-10 users. This package provides ASCII characters not normally available, giant lettering of file titles and index lettering across the top of the fiche. The transfer of data files between the DECsystem-10 and the IBM370 System was made even easier by the development of several 370 catalogued procedures, which are used with corresponding DECsystem-10 command files and the EBCDIC program. In addition, a new operational procedure was implemented to aid in the physical transportation of tapes between the DECsystem-10 and the System 370.

Changes in both the System 370 and the DECsystem-10 required significant revisions to Computer Center technical documentation to update and describe new standards and facilities. The Computer Center Users Guide was updated while new editions were issued for the NIH TSO Command Reference Manual and the WYLBUR Reference Manual. Documentation revised during the year included: the CPS Basic Primer, RHB Routines, the DECsystem-10 Timesharing Guide and DECsystem-10 Display Systems Manual. In addition, the MLAB Manual was revised, and three new RMAG manuals were published.

The Technical Information Office was kept busy distributing these new manuals as well as those provided by vendors. Altogether, 35,646 pieces of documentation were distributed to users of the NIH Computer Center during the year. Most distributions were done through the Automatic Documentation Service which served the needs of 2,606 customers whose

Individual documentation profiles are kept on-line by the office.

The PAL unit, the interface between our users and the Computer Center, continued to provide aid and assistance to the 4500 registered users of the Center. Individual assistance to users, on specific problems, was given over the counter, by telephone (in numbers too numerous to count) and by written responses to 2000 Program Trouble Reports (PTRs). A new PTR facility was developed called the "Remote PTR". This facility allows a user to submit a Programmer Trouble Report by using the TSO interactive terminal system. This aid was developed to help in problem determination for remotely located users who need help but do not have convenient access to the PAL Unit facilities, and whose problem cannot be solved through telephone conversation. Between calls the PAL Unit wrote over 100 pages of technical information to users thru the "Diagnostics, Bugs, & Hints" section of INTERFACE, developed a new version of PALTAPE, contributed to numerous system reconfigurations and applied over 458 major fixes to the vendor supplied software to improve the reliability and efficiency of the Computer Utility. These changes were made with minimal effect on the user community.

The training activities of the Computer Center were in great demand in 1974. Forty-three different courses and seminars were given covering general purpose programming languages, operating systems, terminal systems, and special facilities and programming aids, etc. Over 2000 requests to train people to use both the System 370 and the DECsystem-10 were received this year. Although 82% of all requests for training were accommodated, it was, unfortunately, necessary to reject 364 applicants due to lack of staff.

The requests for the elementary training courses were particularly strong as more and more NIH researchers, administrators and clerical employees discovered the usefulness of the computer in their daily work. It was necessary to teach eight complete sessions of the two week "Introduction to WYLBUR for Administrative and Secretarial Personnel" course this spring and summer in order to satisfy the requests made during the spring of 1974. Even so, the number of requests received for this course is still far greater than we can satisfy.

INTERFACE, the Computer Center's vehicle of communication with the users, was published 8 times during the year, an increase of one from the previous year. 307 pages of documentation on all phases of computing were distributed in these issues.

To give complete coverage to all facets of computing a Diagnostics, Bugs, & Hints section for the DECsystem-10 was

added to INTERFACE this year. This, along with the regular Diagnostics, Bugs, & Hints section, provides the users with the detailed technical information necessary to process work using both systems. The Compleat Computor and the Programming Methods sections appeared regularly covering timely topics. The third Annual Index through 1974 was the last issue of INTERFACE to be published in calendar year 1974.

Since over 95% of all work processed by the NIH Computer Center is received via the teleprocessing network, the communication facilities of the system were improved considerably. Conversion from Model 2703 teleprocessing units to the newer more powerful Model 3705 teleprocessing unit was completed. These new units permitted the addition of more lines but more importantly led to the announcement of new teleprocessing services not possible with the displaced units. Autospeed came first, allowing 2741's and teletype terminals to use the same communication port at varying speeds up to 300 baud. The data switch was expanded to provide additional lines for WYLBUR and TSO users and also to provide 1200 baud service. Over 850 terminals are available for use with the NIH Computer Utility and the number of lines accessible to the system was increased to over 300 to handle the work load. The expansion of lines was timely since the number of daily interactive sessions passed 3000. New highs for the number of simultaneous users were established when WYLBUR reached 239 simultaneous sessions and TSO hit 38.

The major hardware change of the year was the replacement of a 370/165 and a 360/65 by a 370/168-MP. This increase in computer power was installed behind schedule, but its impact was soon felt as turnaround time returned to the limits normally expected by the Center and its users. The continual increase in workload necessitated not only an increase in computational power but also an increase in peripherals as twenty-two new tape drives and three 1500 lines per minute printers were added to the system. The need for additional on-line disk storage space was met by converting the Model 2314 disk units to Model 3330 units. The 3330 units have from two to four times the capacity of the older 2314 units and transfer data two and one-half times faster. The 3330 conversion started in July and was completed in early 1975. The transfer of over sixty thousand on-line datasets was accomplished with no interruption in service. With the completion of the disk conversion, the shortage of on-line space should be over. Data migration of inactive data sets continues to insure that disk space is always available for current active projects.

Directly addressable memory on the 370/145 was doubled to two million bytes. The additional memory will enable more thorough testing of the large software systems to be done independently of the main CPU's in the system.

As the use of microfiche as a computer output medium increased to over 5.7 million images per month, a second COM unit was added to the system. The ease of use of the system, the reduction of bulk and an interest in saving paper all contribute to the constantly growing popularity of microfiche.

Year end saw the last major hardware announcement, the availability and support of high speed CRT display terminals for users of the NIH Computer Utility. Operating at 120 characters a second, the CRT's will provide users with transmission speeds four times faster than previously available. In addition to new functional capability, the new CRT's offer shorter sessions (more efficient use of lines), and better data entry and editing capabilities. Using an attached hardcopy printer remote users will be able to receive more printed output at their location. The CRT is usable with all systems supported by the Center on both the System 370 and the DECsystem-10. Users will have little difficulty using the CRT with existing programs or designing new programs specifically oriented to the CRT as an input/output device.

As the year came to a close, a Request for Proposals (RFP) for a major equipment upgrade to the NIH Computer Utility to provide additional capacity to meet the projected workload over the next three years was written and forwarded to GSA for appropriate action.

1976 Plans

In order to provide effective computational support to meet the constantly changing and diverse requirements of the NIH biomedical research activities, the Computer Center maintains a continual program of expansion and development. In addition to a significant increase in computational capacity to support existing programs, the Computer Center plans to implement a number of new computational facilities and services in support of new research and administrative programs during the coming year.

To accommodate the increasing demand for service in a responsive manner, the processing power of both the IBM system 370 and the DECsystem-10 will be increased significantly.

Procurement actions, begun last year, should result in the exchange of a presently installed IBM 370/165 with an IBM 370/168-MP central processing unit. This will represent an increase of approximately 28% in raw processing power as well as provide the capability for operation under the newer Virtual Operating System. This change will also include a corresponding increase in peripheral devices. Additional disk drives will

provide more on-line storage capacity for data and programs; new communication facilities will allow interactive access to the system using high speed (120 characters per second) CRT terminals; additional fixed-head-storage devices will be installed to improve system performance and efficiency; and high speed tape drives will allow faster tape processing.

During the same period, the DECsystem-10 will experience an even more significant increase in computational capacity. Both of the present processors in this system will be replaced by faster and more sophisticated KL-10 units providing a 200% increase in processor power as well as the ability for directly coupled multiprocessor operations; a direct communications link (PDP-11) will provide for automatic on-line data transfer to and from the System 370; new disk drives will provide double the present on-line data storage capacity; new 1200 baud dial-up communication facilities will provide more effective access for remote timesharing users; and replacement of the existing tape drives will improve reliability significantly and will provide a dependable facility for transfering large volumes of data to the System 370.

The present graphics display equipment (AGT 30 & DEC 340) will be replaced by a more modern surface display unit(s) to facilitate molecular structure research and biomedical image processing.

A standard interface will be designed and built to permit the interconnection of laboratory computers to the central DECsystem-10 without requiring "special" software to accommodate the differences between various manufacturers' equipment.

A new higher resolution incremental digital plotter will be installed this year to replace the present obsolete plotter. In addition to providing finer plotting increments the new unit is twice as fast as present equipment and considerably more reliable. This should result in reduced turnaround time for plotter users as well as improved accuracy and increased productivity of the operator. Procurement actions to provide new higher speed interactive hardcopy terminals, portable interactive terminals, terminal plotter, communication line scramblers, and batch RJE terminals for computer users will be issued this year.

To accommodate the planned hardware conversion, major modifications to the physical plant will be initiated but will not be completed for several years. Although a long range architectural plan has been completed for a total renovation of the second floor of building 12 to provide sufficient environmental support facilities (power, air conditioning,

water) to house both major computer systems, only phase 1 will be completed during this year. This phase will provide only temporary facilities to house a small number of disk drives. A roof-top "penthouse" will be partially completed to provide additional chilled water and electrical generators required for the immediate hardware expansion planned for this year. The administrative processes necessary for scheduling and implementation of the overall renovation plan will be initiated this year.

New software facilities and services planned for this year will have an even greater impact on the effective use of the computer in support of the NIH mission.

A completely new version of WYLBUR, which has been under development for the past two years, will become operational this year. The new WYLBUR will provide a multitude of new functions designed specifically to meet the unique requirements of the NIH research and administrative programs. Its new macro processing facility will allow applications not previously possible and the document preparation features will permit more effective preparation of research manuscripts as well as administrative documents and reports. Multiple active files, an expression evaluator, more flexible file searching features, and many other new facilities will make NEW WYLBUR one of the most usable computational services available anywhere.

A newly designed MILTEN, a communication line handler, will provide software support for high speed interactive CRT terminal access to the system for the first time. In addition to providing forms entry, block text editing, multiple type fonts, and character sets, and communications across virtual address spaces NEW MILTEN can accommodate thousands of simultaneous terminal users and at the same time simplify operator interaction.

The most complex software conversion effort ever undertaken by the Computer Center, conversion from OS/MVT, Release 21.6 HASP 3.1 to OS/VS2, Release 3, JES2, will be started during this year and is scheduled to be completed 18 to 24 months later. This new "Virtual" operating system will permit larger programs to be developed/processed without the delay and overhead introduced by segmenting or overlaying programs. Improved system integrity and reliability will facilitate a more dependable service with fewer interruptions due to software failure. Dynamic address translation will permit more efficient use of critical system resources as well as more effective manipulation of user data on the basis of application requirements.

It is anticipated that the Computer Center will offer the service of a data base management system, IMS (Information

Management System) for the first time this year. This new capability will provide NIH with the ability to develop multiple transaction-oriented applications using large centralized, but independent, data files. Conversational applications may be developed and maintained independent of terminal/communication technicalities, input/output traffic, and terminal and program message switching. IMS also provides automatic journaling and checkpoint/restart facilities to provide maximum data base integrity and minimum "out-of-service" time. Extremely elaborate control mechanisms provide the maximum possible protection against unauthorized access to the system or modification of the data base. This system will be available only on a restricted basis during fiscal year 1976.

During the coming year a new version of the timesharing monitor will be installed on the DECsystem-10 to provide new function for users as well as improved internal system performance and reliability. This new software operating environment will provide a facility for interprocess communications which will result in more effective scheduling and control of the entire system. A more flexible software interrupt facility will permit dynamic switching among tasks and expanded virtual memory support will permit both the servicing of a larger number of simultaneous users and the development of larger applications programs.

Because of the plans for major changes in both hardware and software for both the System 370 and the DECsystem-10, it will be necessary to completely rewrite almost all technical documentation published by the Computer Center. Five major new documents are planned for NEW WYLBUR/MILTEN and an extensive users' manual describing the use of the NIH5200 CRT terminal will be published this year. A completely new comprehensive Time Sharing Guide for the DECsystem-10 has been outlined and will be completed and available to users this year. In addition, the DECsystem-10 Display Systems manual will be updated to reflect the incorporation of new displays into the OMNIGRAPH system. Technical documentation for TSO, SPOUT, CICS, COM, OCR, CPS, HASP (SHARED SPOOL), etc., as well as Job Control Language will be extensively re-written to reflect the new virtual operating environment, and an IMS Users Guide will be finalized.

All on-going activities including support activities, problem consulting, documentation distribution, and training will continue at an increased pace. The task of fine tuning the NIH Computer Utility to keep it responsive to the changing needs of the NIH, and the investigation of new computational techniques must continue so that the Utility can best support the NIH mission.

July 1, 1974 thru June 30, 1975

PUBLIC HEALTH SERVICE - NATIONAL INSTITUTES OF HEALTH

DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

Summary of Branch Activities

1. DCRT

2. COMPUTER SYSTEMS LABORATORY

3. Alan M. Demmerle
Chief

INTRODUCTION

The primary mission of the Computer Systems Laboratory (CSL) is to identify problem areas in biomedical research and clinical care in which the computer offers a potential for improved research productivity or improved health care. The concentration of work is on applications where real-time data collection, analysis, display, and experiment control are required, where economic considerations favor a small computer or where equipment proximity is important.

The staff of CSL has, in addition to expertise in both the engineering and programming aspects of laboratory computing and automation, extensive experience in working on problems in the biomedical area. Many of the laboratory's projects require a coordinated effort between engineers and computer scientists from CSL and researchers from other Divisions and Institutes.

I. COMPUTER SUPPORT FOR AUTOMATION OF LABORATORY EXPERIMENTATION

CSL is engaged in a number of projects supporting research in the physical sciences. The primary goal of this support is automation of the collection, processing and display of laboratory data. Achievement of this goal has, generally, involved the design, and implementation of a number of computer systems of varying sizes. The larger systems, usually, serve a number of users simultaneously and require several years of effort to attain full operational status. An example of such a system is the NIAMDD System which serves several NIAMDD Laboratories, permitting a number of experiments to be processed simultaneously. Smaller laboratory systems are usually dedicated to a single user at a time, and can usually be implemented in less time. The NMR System in NIAMDD, which is used for Fourier Transform Spectroscopy calculation, is typical of this class of system, as is the NIAID System which is used with experimentation concerning the structure of immunologically important proteins.

During the past year, the CSL engineering staff has been involved in various phases of the implementation of 10 systems aimed at automating laboratory experiments. The capabilities of the NIAMDD System, mentioned above, have been expanded to include processing of data from an EPR Spectrometer and McPherson Spectrophotometer. A system for the Laboratory of Vision Research (NEI) which was started the previous year has been made operational during this past year. Analog voltage data relating to the photo transduction process in the retina are collected and processed and analyzed data are displayed. Further work has proceeded on automation of a Flourescence

Activated Cell Separator for NCI. This system was also started in the preceding fiscal year. A computer for this system has now been procured and the utility programs written to allow it to use the DCRT PDP-10 interactively for data storage and complex mathematical analysis. Interfacing to the cell sorting instrument has begun. A second system for NEI was started. This system is to be used for two different studies. The first is a study aimed at understanding the normal and pathophysiological mechanism for the control and production of eye movements. Normal volunteers as well as patients with all forms of disturbance of eye movement will be studied with mechanized visual stimulation equipment. Eye movements over a range of 0-45 degrees will be analyzed in detail. The second use involves analysis of data concerning pupil movement.

The Hybrid Computer, purchased about 10 years ago as a general utility for the NIH research community, is now being used primarily on NHLI research projects. This system and its supporting staff occupy 5 modules of Building 10. The demand for this space has become so acute that the system will be replaced with newer and more compact equipment, thereby making available 3 of the 5 modules for other purposes. Elements of the new system have been ordered and will be made operational before the old system is dismantled and removed during the coming fiscal year. The new system is to provide a comparable facility for general purpose data acquisition, A/D conversion, plotting and display.

II. CLINICAL CARE & RESEARCH

CSL has, for the last several years, become increasingly involved in the support of several clinical care and research functions at the NIH. This has occurred because of an increased understanding and awareness by clinicians of the potential of computers and automation, and also because of advances in medical instrumentation and techniques which have led to the generation of voluminous amounts of data that must be analyzed and examined prior to use in patient diagnosis and treatment.

The role of the computer in the clinical environment is still evolving. Currently, it performs functions that cannot be accomplished by manual means, provides the physician with a valuable tool in decision making and promotes direct patient care activities by relieving highly trained medical personnel of routine clerical functions. The technical requirements in this environment include the acquisition, storage, analysis and display of clinical data. For the most part, these functions are performed on-line and in real-time. All require extensive cooperation among engineers, computer scientists, programmers and medical personnel.

THE NHLI INTENSIVE CARE UNIT

This project provides for the continuous monitoring of patients in the heart surgery recovery area in order to provide the earliest possible detection of abnormal or dangerous conditions. For the past two years, the ICU System has collected and analyzed ECG, temperature, fluid loss, arterial pressure and venous pressure data from a single patient. During the past year this capability has been extended so that these same functions can be provided

simultaneously for four patients. This extension has required the optimization of the processing of the ECG and pressure wave forms. Much of the analysis of these signals is now done external to the computer using special purpose hardware developed here over the past several years. Further development of these techniques using the new microprocessor technology is now underway. These preprocessors will be used on a number of projects. An ECG preprocessor implemented with a microcomputer, for instance, will be used in the ICU System and also in conjunction with an NHLI project that requires the analysis of PVC's obtained from ambulatory patient electrocardiograms.

NUCLEAR MEDICINE DEPARTMENT

CSL has continued to contribute engineering expertise to a joint project with LAS, DCRT and the Clinical Center's Nuclear Medicine Department. We have worked toward more fully developing the potential of a computer system which has been operational for several years and an additional system which was acquired this year. The accomplishments of this project are described in the LAS report.

PHONOCARDIOGRAM RESEARCH

For the past three years, CSL has collaborated with the Surgical Branch of NHLI in the development of methods by which characteristics of the phonocardiogram can be used as diagnostic indices of prosthetic heart valve performance. We are searching for a reliable, easy to apply, non-invasive indicator. For more than one year now, phonocardiograms have been routinely taken on about six patients per week and analyzed on the hybrid computer. The analysis involves beat-to-beat correlation of heart sounds, a determination of the ratio of the amplitude of the opening sound to that of the closing sound and sound spectrographic analysis. Current indications are that the correlation technique offers no significant improvement, as a diagnostic indicator, over the opening to closing sound ratios, particularly for the SE1000 series values. Attention is now being directed to the 1200 series values, for which much less data is currently available. Partly as a result of this project, it became clear that a computerized retrieval system for the patient data collected in the Surgery Branch of NHLI was needed. The data base includes demographic data, laboratory tests, surgical notes, autopsy report data, catheterization data and phonocardiogram data on all patients. The development of this information retrieval system began this fiscal year.

CATHETERIZATION LABORATORY SYSTEM

An extensive dual goal project was started this year with the Catheterization Laboratory of NHLI. The first goal envisions on-line computer support in the acquisition and processing of data acquired during catheterization procedures. Electrocardiogram data, several blood pressures, dye concentration measurements, thermal dilution cardiac output signals, phonocardiograms, HIS bundle electrograms, and possibly other physiologic parameters are to be processed. CSL, after exploring several alternative methods of implementation recommended that an existing commercial system be procured and modified to meet specific NHLI requirements. That purchase, however, was not made this year.

The second goal of this project is to organize the medical data associated with the NIH patients who have been catheterized, into a computer-based data

management system that can readily provide answers to complex research oriented queries. Very considerable emphasis is attached to the problem of developing techniques that will promote simple flexible data retrieval capable of being initiated and operated by the scientific user. As such techniques are perfected, it is planned to integrate them into other projects using similar data bases. An example of this projected transfer is provided by an on-going project with the Microbiology Service of the Clinical Center's Clinical Pathology Department. That Service is, among other things, (1) actively studying methods of organism identification, (2) developing resistance patterns of organisms to antibiotics, and (3) attempting to trace the existence and source of hospital infections. This effort has been greatly facilitated by a retrieval system, utilizing GNR data and antibiotic sensitivity data, that has been implemented by CSL during the past year. Although operational, however, the complexity of system use is such that CSL rather than the Microbiology Service remains responsible for operation.

III. OTHER COMPUTER SUPPORT PROJECTS

Two projects were started this year which are neither exclusively for laboratory nor clinical support. The NIEHS in the Research Triangle, North Carolina has, during the past few years, developed an increased need for computer support beyond that available to them from a keyboard terminal connected to a computer utility. Their four basic requirements are: 1) a high speed data entry facility to a remote computer utility, 2) a high speed printing and graphic output facility from a remote computer utility, 3) a capability for elementary processing of data produced by laboratory instruments such as spectrometers which produce data in a form and on a medium suitable for computer processing, and, 4) the collection, processing and retrieval of data relating to their animal colony. Analysis of these requirements led to the purchase, this year, of computer equipment capable of satisfying their first three requirements. Work has not begun on the fourth requirement. Also started this year is a computer system for the NIH Library that is designed to automate the collection and maintenance of daily transaction information (charging, discharging, reserving and reviewing library materials). The system is based on a computer to be located in the library along with optical scanning devices, a CRT terminal and other specialized input devices. Every day or so, the data collected on the library computer will be transferred to the DCRT central facility where master files will be maintained. This system is to start out as a near duplicate of one developed at the University of South Carolina and is to be further developed here in accord with NIH specific requirements.

IV. GENERAL RESEARCH

While the bulk of the work in CSL is connected with laboratory automation and clinical care, there is considerable effort devoted to other areas of computer research related to biomedical applications. Currently, there are two major areas of general research, the use of computer pattern recognition methods in biomedical problems, and the development of a medical telecommunications system.

PATTERN RECOGNITION STUDIES

Work in applying pattern recognition techniques to predict structure-activity

relationships was continued. An on-line system which attempts to predict the pharmacological activity of drugs was developed. This system, using pattern recognition and substructural analysis methodology assigns pharmacological activity in two ways. First, the methodology attempts to find overall similarity in molecules by determining how "similar" a compound is to known drugs by using the Euclidean distance criteria. Then the compound is assigned the activity of the "most similar" compound. The second procedure predetermines those substructural units that are most indicative of a pharmacological class using the learning machine. Then if a compound possesses these common substructural units, it is predicted to possess this activity. In addition, the structures of the known drugs used in assigning the activity can be displayed to check the pharmacological assignment. Thus, this empirical approach allows past biological data to guide current testing.

MEDICAL TELECOMMUNICATIONS SYSTEMS

For several years, CSL has been engaged in the development of a technology by which computer services can be made available to the medical community using only a conventional touch tone telephone as a computer terminal. The plan has been to make such services readily available so that the power of the computer can be applied in assisting physicians in such areas as diagnosis, treatment and therapy planning. A prototype system was completed more than one year ago which permits use of the push buttons on the telephone as a means of providing input to the computer, while the computer responds in voice over the telephone. Six medical application programs have been developed which are indicative of the types of applications which might be used. The medical school of the University of Wisconsin has been demonstrating this system in their hospital. Improvements to the system during the past year have been directed toward making the speech generation more economical. It is expected that a voice generator, tied to a microcomputer, will permit the use of this technology with only a modest hardware addition to any commercial time-share facility. Thus, the current need for an entire dedicated computer (SEL-810B) will be eliminated.

V. CONSULTATION

In addition to the work described above, CSL consults with researchers in need of computer expertise. This consultation can be simply providing advice on a specific problem or can result in the design of special purpose hardware or in the writing of special software. A typical example of this type of supportive work occurred with a data collection problem in NCI. Help was sought in determining the optimum method of replacing an old unreliable noisy punch paper tape system. CSL examined alternatives, specified a programmable calculator with cassette tape for the collection of long runs (24 hours) of diet intake of animal colonies, and will soon interface the new system to the instrumentation involved. Five other projects of comparable size were undertaken this year, each one consuming 3-6 man-months of effort.

CSL Summary of

LEVEL OF EFFORT AND EXPENDITURE

BY PROJECT

Project Name	Project Leader	DCRT Man-Power (M-Y/Year)		DCRT Capital Invested ($ X K) Including Maintenance		Central Facility Charges ($ X K)
		FY-74	FY-75	FY-74	FY-75	FY-75
Bldg. 2 516	Schultz	2.0	1.5	2.0	8.0	2.0
NMR	Schultz	2.0	1.5	24.8	12.0	
NIAID	Plexico	3.0	1.5	9.0	5.0	
NEI	Schultz	1.5	1.5	1.0	3.0	
NEI	Plexico		0.5			
NCI	Schultz	1.0	1.5		2.0	
ICU	Syed	7.0	5.0	80.6	90.0	11.0
Nuclear Med.	Schultz	0.5	0.5	40.0	3.0	1.0
Phonocardio-gram	Schultz	0.5	1.0	0.5		20.0
Medical Tele-communications	Plexico	1.0	1.5	14.5	17.0	
Pattern Recognition	Chu	3.0	1.0			50.0
NIEHS	Plexico		0.5			
NIH Library	Plexico		0.5		1.0	
Hybrid Replacement	Plexico		2.0		10.0	1.1
Cath Lab.	Syed		2.0			5.0
Special Consultation			3.0			
Support			3.0			
Microbiology			1.0			5.5

July 1, 1974 through June 30, 1975

PUBLIC HEALTH SERVICE - NATIONAL INSTITUTES OF HEALTH

DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

Summary of Branch Activities

1. DCRT

2. PHYSICAL SCIENCES LABORATORY

3. Dr. G. H. Weiss

I. OBJECTIVES

The Physical Sciences Laboratory is devoted to the study of problems in physics and chemistry that relate to the biological sciences. Several disciplines are represented in the membership of the laboratory. These include applied mathematics, theoretical chemistry, and theoretical physics. Whenever possible the theoretical studies are performed in conjunction with experimental work, either in collaboration with workers in outside units, or by members of the Physical Sciences Laboratory working in other laboratories at NIH. In addition to performing research of its own choosing, members of the Physical Sciences Laboratory provide consultation to other researchers at NIH on different topics in the disciplines represented in the Laboratory. These services are enumerated in the project reports.

II. SUMMARY OF LABORATORY PROGRAMS

1. The Physical Sciences Laboratory together with the Fogarty Center held a symposium celebrating the fiftieth anniversary of the ultracentrifuge. Speakers from all over the world participated and proceedings of the meeting will appear, hopefully within a year. We have continued our own research on numerical solutions of the Lamm equation. These solutions have enabled us to obtain new insight into the Johnston-Ogston effect in interacting species. We have also begun a study of the wall effect in cell separation by the ultracentrifuge.

2. Our studies in the forces important in biological phenomena have continued, and in collaboration with Professor R. P. Rand of Brock University we have succeeded in measuring the repulsive forces between membranes of the phospholipid lecithin. This experimental arrangement allows us to further study the effects of sugars on the model membrane. A theory for the anomalous swelling pressure of the cornea has been derived. This new theory is in agreement with experimental results which show that the pressure can decrease with increasing temperature. All previous theories came to the contrary conclusion. The suggested theory can be further tested experimentally. Further work on the van der Waals forces has included the development of methods for converting absorption spectra into intermolecular forces.

3. Considerable effort has been devoted to a project on laser light scattering in biological systems. We are currently constructing an inelastic light scattering spectrometer for use at NIH to be located in Building 4. Most of the work on this apparatus has been concluded and we hope to begin actual experiments shortly. We have continued work on cellular motility and chemotaxis. In particular, we are engaging in joint experimental and theoretical studies of the cellular mechanisms of the MIF assay and in particular the use of fluctuation spectroscopy to determine mobility parameters.

4. Our work on nuclear magnetic resonance spectroscopy has focused mainly on the rapid scan technique. This allows a considerable improvement in signal to noise ratio. We have continued our studies of helix-coil transformation of polypeptides in solution, concentrating on the effects of finite chain lengths. The usual theories of this phenomenon are based on the approximation of infinite chain length. We have shown that the effects of finite chain length are important for peptide numbers up to 1,000.

5. A collaborative study with Dr. William Caveness on the long range effects of head injuries is presently being concluded. Our studies of the mortality rate and other details of death on German veterans injured in World War I has shown that severe head injuries lead to increased mortality in later life and increased deaths due to cerebrovascular causes over a control population. We have also collaborated with Dr. Eugene Fischmann of Freedmen's Hospital on the possible improvement of electrocardiographic techniques through the use of increased numbers of leads. We have so far identified the most appropriate sets of leads for new techniques of data processing of this information.

6. Our work on the use of adaptive sampling in clinical trials has consisted in the application of the likelihood methodology for treatment-control comparisons. We have shown that the likelihood selection and likelihood stopping techniques offer a considerable improvement over sequential procedures already in the literature. Another study concluded is the effects of covariant information on the performance of different adaptive sampling rules. The inclusion of covariant information is found to be mandatory for adaptive sampling.

Project No. Z01 CT 00014-08 PSL
1. Physical Sciences Laboratory
2. Not Applicable
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1974 through June 30,1975

Project Title: Theory of Biochemical Separation Technique

Previous Serial Number: 5.1

Principal Investigator: George H. Weiss, Ph.D.

Other Investigators: None

Cooperating Units: David Yphantis, Ph.D., University of Connecticut, David Rodbard, M.D., Reproductive Research Branch, NICHD, Thomas Pretlow, M.D., University of Alabama Medical School, Marc Lewis, Ph.D., Laboratory for Vision Research, NEI.

Man Years:

Total:	0.2
Professional:	0.2
Others:	0.0

Project Description:

Objectives:

To determine the physico-chemical effects influencing different biochemical separation systems such as ultracentrifugation, chromatography, and electrophoresis. To determine the quantitative significance of these effects. To devise numerical techniques for processing data from chemical separation procedures to determine properties such as molecular weight and diffusion coefficients.

Progress in FY 1975: A symposium celebrating the fiftieth anniversary of the ultracentrifuge was held jointly with the Fogarty Center. Proceedings of the meeting jointly edited by G. Weiss and Marc Lewis are to be published as a special issue of Biophysical Chemistry within a year. We have continued our study of the resolving power of one and two dimensional separation systems, finding that almost any criterion gives the same result for optimizing parameters provided that it takes into account the phenomenon of over-resolution. Results of the investigation are applied to determining optimal gel parameters in pore gradient electrophoresis. We have completed a numerical and analytical study of the Johnston-Ogston effect in ultracentrifugation, finding that results previously obtained for special systems have

much wider application. We have begun a study of the wall effects in the density gradient centrifugation of cells, in collaboration with Dr. Thomas Pretlow of the University of Alabama, with the object of relating the cell loss to the initial configuration and other parameters of the experiment. We have developed a technique for extrapolating the concentration profiles in equilibrium centrifugation experiments to infinite time using an Aitken transformation. The procedure requires relatively noise-free data but has the potential of reducing experimental times by factors of at least two under almost all experimental conditions.

Keyword Descriptors: Ultracentrifuge, electrophoresis, resolution in chromotography, wall effect.

Honors and Awards: none

Publications:

Weiss, G. H., Rodbard, D.: Resolution of species showing microheterogeneity by zone electrophoresis and chromatographic systems. Separation Science 9, 117-124, 1974.

Weiss, G. H., Catsimpoolas, N., Rodbard, D.: Transient state isoelectric focussing: Theory. Archives of Biophysics & Biochemistry.163, 106-112, 1974.

Correia, J. J., Johnson, M. L., Weiss, G. H., Yphantis, D. A.: Numerical study of the Johnston-Ogston effect in two component systems. Biophysical Chemistry (to appear).

Serial No. Z01 CT 00015-04 PSL
1. Physical Sciences Laboratory
2. Not Applicable
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Theory of the Helix-Coil Transformation of Polypeptides in Solution

Previous Serial Number: 5.2

Principal Investigator: James A. Ferretti, Ph.D.

Other Investigators: None

Cooperating Units: Robert L. Jernigan, Ph.D., Laboratory of Theoretical Biology, NCI

Man Years:

Total:	0.4
Professional:	0.4
Other:	0.0

Project Description:

The purpose of this project is to understand at the molecular level the nature and underlying mechanism of the helix-random coil transition in polypeptides. Relaxation rates for the transition have been obtained using ultrasonic attenuation and dielectric relaxation experiments. In terms of the theoretical model we have developed, it is possible to relate these measured relaxation rates to the molecular rate constants and equilibrium conformational statistics. The results are based upon a general description of the time rate of change of the conformational probabilities in the form of a set of coupled differential equations. We find that the effects of finite chain length are important and that these effects can persist to greater than 1,000 peptide units.

Keyword Descriptors: Helix-coil transformation, mean relaxation rate, conformational statistics, molecular rate constants.

Honors and Awards: None

Publications:

R. L. Jernigan and J. A. Ferretti: Mean Configurational Relaxation Rates in Finite Length Polypeptides. J. Chem. Phys., 62, 2519-2527, 1975.

Project No. Z01 CT 00016-02 PSL
1. Physical Sciences Laboratory
2. Not Applicable
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Rapid Scan Nuclear Magnetic Resonance Spectroscopy

Previous Serial Number:

Principal Investigator: James A. Ferretti, Ph.D.

Other Investigators: None

Cooperating Units: E. D. Becker, Ph.D., Laboratory of Chemical Physics, NIAMDD, Richard R. Ernst, Ph.D. Laboratorium fur Physikialische Chemie, Eidgenossische Technische Hochschule, Zurich, Switzerland, Raj K. Gupta, Institute for Cancer Research, Philadelphia, Pa., Thomas Clem, Biomedical Engineering Branch, DRS.

Man Years:

Total:	0.6
Professional:	0.6
Other:	0.0

Project Description:

The technique of rapidly scanning the magnetic field or the radio frequency to obtain NMR spectra has received further attention. The basic method consists of rapidly scanning a response, digitizing the analog data and storing the results in a Raytheon 704 computer. As long as the spin system can be considered as a linear and time-independent one, the response signals develop independently and without interference. The computer is then used to cross correlate the response signals either with a suitable reference response or with an appropriate analytical function. The result is an undistorted spectrum with considerably improved sensitivity. The principal effort during this fiscal year has been to demonstrate the advantages of the method and also to determine its limitations. We have demonstrated the ease with which a portion of the spectrum of a protein in water can be scanned without recording the HDO or H_2O peaks. This is a distinct advantage of the rapid scan method, since the pulse technique is severely limited due to the dynamic range problem. We have also developed a means using rapid scan to determine spin-lattice relaxation times. The approach, which is in some ways analogous to the saturation recovery method in pulse NMR is fairly general and good for both short and long times. Together with Professor Richard Ernst, I have investigated the effects of nonlinearity using rapid

scan on coupled spin systems. We find both experimentally and theoretically that for certain scan rates there are phase and intensity anomalies which appear when large flip angles are used to drive the spin system into a non-linear region.

Keyword Descriptors: Rapid scan, cross correlation, Nonlinear response

Honors and Awards: None

Publications:

Gupta, Raj K., Ferretti, James A., and Becker, Edwin D.: Spin-Lattice Relaxation Measurements Using Rapid Scan FT NMR. J. Magnetic Resonance, 16, 505-507, 1974.

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Project No. Z01 CT 00017-03 PSL
1. Physical Sciences Laboratory
2. Not Applicable
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Cellular Motility and Chemotaxis

Previous Serial Number: 5.4

Principal Investigator: Ralph Nossal, Ph.D.

Other Investigators: George H. Weiss, Ph.D.

Cooperating Units: Leonard D. Kohn, M.D., Yao T. Chang, M.D., Laboratory of Biochemical Pharmacology, NIAMDD.

Man Years:

Total:	0.8
Professional:	0.6
Other:	0.2

Project Description:

Primary among the objectives of this project is the elucidation of cellular mechanisms involved in chemoreception and cellular response, particularly regarding cell motility. Theories are constructed to related macroscopic mobility coefficients to microscopic response parameters and experiments are performed with both bacterial (E. Coli) and mammalian cells (leukocytes). New assay systems, involving laser light scattering and time-lapse cinemicrography are employed, and procedures are devised to isolate materials from cell surfaces for assay on reconstituted lipid bilayers.

One aspect of these studies relates to leukocyte migration as an assay for cellular immune sensitivity (MIF assay). In collaboration with Dr. L. D. Kohn of LBP/NIAMDD, we have modified migration inhibition assays and applied them to study autoimmunity in patients suffering from exophthalmic Graves' disease. A mathematical theory for the capillary MIF assay has been developed, with a view towards optimizing assay design.

The cellular mechanisms of the MIF assay are being investigated by cinemicrographic techniques which rely upon novel occupation number schemes for determining mobility parameters (in collaboration with Y. T. Chang, LPB/NIAMDD).

Cellular chemotaxis is implicated in inflammation and wound healing, and in the recognition of bacteria by leukocytes. It also may be related to tissue organization in multicellular organisms.

Keyword Descriptors: Chemotaxis, migration inhibition, cellular immunity, cell locomotion.

Honors and Awards: None

Publications:

Nossal, R., and Weiss, G. H.: A generalized Pearson random walk allowing for bias. J. Stat. Phys. 10, 245-253, 1974.

Nossal, R. and Weiss, G. H.: A descriptive theory of cell migration on surfaces. J. Theor. Biol. 47, 103-113, 1974.

Project No. Z01 CT 00018-03 PSL
1. Physical Sciences Laboratory
2. Not Applicable
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Measurement of van der Waals Forces

Principal Investigators: V. A. Parsegian, Ph.D., G. H. Weiss, Ph. D. and James E. Kiefer

Other Investigators: None

Cooperating Units: Arnold Shih, Ph.D., National Bureau of Standards, and Malcolm Shrader, Ph.D., Naval Weapons Research Laboratory.

Man Years:

Total:	0.8
Professional:	0.6
Other:	0.2

Project Description:

To continue to develop the theory and measurement of van der Waals electrodynamic forces to be useful in the study of biological organization.

Formulations of van der Waals forces have been extended to apply to the attraction of atoms or molecules with solid walls and to the attraction between curved parallel surfaces. We have continued to progress in developing methods for converting absorption spectra (from Oak Ridge National Laboratory) into intermolecular forces.

Measurements of forces attracting atoms or molecules in a beam to a planar surface have been carried out (at the National Bureau of Standards). Comparison with theoretical expressions developed in this lab are much better than theories previously available.

Wetting by water of clean surfaces seems to be compatible with our present understanding of van der Waals forces. We have collaborated successfully with Dr. Malcolm Schrader in making measurements of water adhesion. These measurements, contrary to earlier findings and earlier theories, suggest that conducting surfaces are a uniquely good surface for the adhesion of polar materials.

There are several parallels between the adhesion of cells to material substrates and that of liquids to solid bodies. The ability to analyze precise wetting experiments will strengthen our ability to look at cellular adhesion.

The measurement between beam particles and substrate are not directly biological. They are crucial to rigorous tests of the theoretical physical methods that we are using in a biological context where their accuracy cannot be verified very well.

Keyword Descriptors: van der Waals forces, theory; van der Waals, measurement; molecular beams, wetting of surfaces.

Publications:

Parsegian, V. A.: Formula for the electrodynamic interaction of point particles with a substrate. Molec. Phys. 27, 1503-1511, 1974.

Parsegian, V. A. and Weiss, G. H.: Electrodynamic interactions between curved parallel surfaces. J. Chem. Phys. 60, 5080-5085, 1974.

Shih, A. and Parsegian, V. A.: Van der Waals forces between heavy alkali atoms and gold surfaces: Comparison of measured and predicted values. Physical Review A (to appear).

Project No. Z01 CT 00019-07 PSL
1. Physical Sciences Laboratory
2. Not Applicable
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Physical Force Interactions Between Cell Membranes and Cell Membrane Analogues

Principal Investigator: V. A. Parsegian, Ph.D.

Other Investigators: None

Cooperating Units: D. Gingell, Ph.D., Middlesex Hospital Medical School, London, R. P. Rand, Ph. D., and D. M. LeNeveu, Ph.D., Brock University, St. Catherine's, Ontario.

Man Years:

Total:	0.4
Professional:	0.4
Other:	0.0

Project Description:

To measure, compute, and learn to modify forces between cell membranes.

We have succeeded in measuring the repulsion forces between membranes of the phospholipid lecithin. This has been possible by exerting an osmotic stress on a stack of membranes while doing x-ray diffraction to measure their spacing. Repulsion forces are mechanically large between these membranes and exceed two atmospheres even at 20 Angstrom separation. With the success of this method we are now introducing selected lipids bearing charge or sugars into the model membranes to measure systemic changes in membrane repulsion forces.

We have found that small sugar solutes in the medium between model membranes apparently modify the van der Waals attraction forces which create the lamellar array. This effect of solvent has been predicted by the general theory of forces but not been seen before.

Dr. D. Gingell has done two experiments that are a direct outgrowth of his work here in the DCRT. First, he has found red cell aggregation following precisely that predicted by modulating electric charge on the membrane surface. (His data were processed here at the DCRT during his visit last summer.) Second, he has succeeded in designing a substrate to which

cells may adhere which is at the same time an electrode to which attractive or repulsive potentials may be applied. He has demonstrated stable attraction of cell-to-substrate with an apparent gap between them. Modulation of the applied potential and observation of resultant cellular sticking or non-sticking will allow us to make quantitative estimates of cellular attraction forces.

We expect that the above measurements coupled with force computations will continue to give us a coherent physical understanding of cellular association in tissues. There is good evidence that aberrations in the electrostatic repulsion between cells are what create a failure to form good tissues.

Repulsion between membranes also affects cell fusion and vesicle fusion. Accurate measurements will be helpful in determining fusion mechanisms.

Keyword Descriptors: Cell membrane interaction, measurement, computation, electrostatic forces, electrodynamic forces.

Honors and Awards: None

Publications:

Parsegian, V. A. : Possible modulation of reactions on the cell surface by changes in electrostatic potential that accompany cell contact. Ann. N. Y. Acad. Sci. 238, 362-371, 1975.

Parsegian, V. A.: A physical approach to the study of cell membranes. Twelve Lectures to be published in the book based on the Simon Fraser University Summer School on Membranes, ed. K. Colbow, Alta Lake, B.C. Canada.

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Project No. Z01 CT 0020-07 PSL
1. Physical Sciences Laboratory
2. Not Applicable
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Influence of Electric Forces on the Organization of Proteins and Model Systems

Principal Investigators: V. A. Parsegian, Ph.D., Stephen L. Brenner, Ph.D., and R. J. Nossal, Ph.D.

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	1.5
Professional:	1.5
Other:	0.0

Project Description:

To learn how interactions between electrically charged bodies, particularly proteins, govern their mutual arrangement and perturb their surroundings.

We have developed an efficient way to formulate the electrostatic forces between charged particles in salt solution. This method has been applied to rod-like particles such as the Tobacco Mosaic virus and to spherical bodies.

We have derived a suggestion for the "anomalous" swelling pressure of the cornea. This pressure is seen to go down with increasing temperature while all previous theories predicted the reverse. Our suggestion includes direct measurements to test its validity.

The transparency of the cornea is highly sensitive to the amount of water it holds. Apparently a major force for its swelling to opacity is the electrostatic repulsion between its protein components. By learning to probe and possibly to modify the pressure for swelling we may have a better understanding for preventing unwanted swelling.

We have also applied the theory of attractive (electrodynamic) and repulsive (electrostatic) forces to the formation of ordered arrays of Tobacco Mosaic virus particles. Different causes suggest different relations between interval separation and medium salt concentration.

Keyword Descriptors: Electrostatic forces, corneal swelling, Tobacco Mosaic virus.

Honors and Awards: None

Publications:

Brenner, S. L. and Parsegian, V. A.: A physical method for deriving the electrostatic interaction between rod-like polyions at all mutual angles. Biophys. J. 14, 327-334, 1974.

Brenner, S. L. and Parsegian, V. A.: Suggested explanation for the anomalous temperature dependence of the corneal swelling pressure. Exptl. Eye Research (to appear).

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Project No. Z01 CT 00021-04 PSL
1. Physical Sciences Laboratory
2. Not Applicable
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Correlation Function Spectroscopy/Laser Light Scattering

Previous Serial Number: 5.6

Principal Investigator: Ralph Nossal, Ph.D.

Other Investigators: Stephen L. Brenner, Ph.D.

Cooperating Units: L. Kohn, M. D. Laboratory of Biochemical Pharmacology, MIAMDD, B. Berne, Columbia University, S.H. Chen, Massachusetts Institute of Technology

Man Years:

Total:	0.6
Professional:	0.6
Other:	0.0

Project Description:

A principal objective of this project is to develop laser inelastic light scattering techniques for performing measurements on biological cells and macromolecules. Theoretical analyses are performed in conjunction with various experimental studies: major emphasis is related towards problems of biological transport and cellular motility.

Previously, experimental work was performed in laboratories located at the Massachusetts Institute of Technology and Columbia University. However, we currently are constructing an inelastic light scattering spectrometer for use at NIH, to be located in facilities being made available to us by the Laboratory of Biophysical Chemistry, NIAMDD. The next phases of instrument development will involve design and construction of apparatus for detecting electrophoretic mobilities and also, instrumentation for performing fluorescence intensity fluctuation spectroscopy.

Laser inelastic light scattering techniques enable rapid and precise measurements of various physical parameters pertaining to biological molecules and cells. In principle, any process giving rise to refractive index fluctuations can be monitored; for example, concentration fluctuations can be used to determine diffusion coefficients of macromolecules, rate constants of bimolecular reactions, or swimming speed distributions of motile microorganisms.

Numerous applications structures larger than the wavelength of light can be envisioned. However, in this case new theories to relate observed spectra to underlying dielectric constant fluctuations must be provided. Thus, in the past year we have elucidated the effects of cell substructures on measurements of mobility coefficients, and also have provided a rubric for interpreting diffusion coefficient data for large anisotropic particles.

Keyword Descriptors: Lasers, light scattering, macromolecules, diffusion coefficients, motility, correlation functions.

Publications:

Boon, J.P., Nossal, R., and Chen, S.H.: Light scattering spectrum due to wiggling motions of bacteria. Biophys. J. 14: 847-864, 1974.

Berne, B., and Nossal, R.: Inelastic light scattering by large structured particles. Biophys. J. 14: 865-880, 1974.

Project No. Z01 CT 00022-08 PSL
1. Physical Sciences Laboratory
2. Not Applicable
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Consulting Services

Previous Serial Number: 5.8

Principal Investigator: George H. Weiss, Ph.D.

Other Investigators: Mildred L. McNeel

Cooperating Units: William F. Caveness, M.D., Laboratory of Experimental Neurology, NINDS, Eugene J. Fischmann, M.D., Freedmen's Hospital, Jay Herson, Ph.D., Howard University, Steven Weinstein, Ph.D., Howard University, Charles W. Boone, M.D., Viral Biology Branch, NCI, Steven Yeandle, Ph.D., Naval Medical Center.

Man Years:

Total:	1.6
Professional:	1.0
Other:	0.6

Project Description:

Members of the Physical Sciences Laboratory render assistance to other, primarily experimental scientists, in the areas of mathematics, statistics, theoretical physics and chemistry.

Progress in FY 1975: We have nearly completed a study of the effects of head injury on mortality in German veterans of World War I. The mortality rate and causes of death were correlated with severity of injury for varying numbers of head injured and uninjured controls from the same military units. The data indicate increasing mortality with increasing severity of injuries of different kinds, with an increase in the fraction of deaths due to cerebrovascular causes in the head injured. This work will shortly be written up and submitted for publication.

Considerable effort was made in assisting investigators at Freedmen's Hospital to determine the effectiveness of potential mapping in improving the performance of standard electrocardiography. For this purpose it was necessary to determine the best diagnostic variables from multilead data. So far we have considered only the QRS complex, and compared the time variation

of electrode potentials from different leads and at different times. Some tentative identifications of the most informative leads have been made using pattern recognition techniques. We have also examined the problem by means of discriminant analysis but this has proved to be less useful. Some techniques from signal processing appear to have some promise in this type of problem. More data is awaited to complete this study.

With Dr. C. W. Boone we have begun to develop some models to interpret experiments related to contact inhibition.

We have also developed mathematical theory to test different hypotheses about secondary reactions to visual stimuli in the eye, which have been studied experimentally by Dr. Steven Yeandle. We have found that several hypotheses are indistinguishable when the fraction of primary events that give rise to secondary responses are small.

Keyword Descriptors: Head injuries, mortality rates, cerebrovascular accidents, potential mapping in electrocardiography, pattern recognition.

Honors and Awards: None

Publications:

Weiss, G. H. and Yeandle, S.: Distribution of response times in visual sense cells after weak stimuli. J. Theoret. Biol. (to appear).

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Project No. Z01 CT 00023-08 PSL
1. Physical Sciences Laboratory
2. Not Applicable
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Miscellaneous Studies

Previous Serial Number: 5.9

Principal Investigators: George H. Weiss, Ph.D.

Other Investigators: James E. Kiefer

Cooperating Units: David G. Hoel, Ph.D., Biometry Branch, NIEHS, Menachem Dishon, Ph.D., Weizmann Institute of Science, Rehovot, Israel, Richard Simon, Division of Cancer Treatment, NCI, Dennis Blumenfeld, Ph.D., University of London, Donald R. McNeil, Ph.D., Princeton University, Robert J. Rubin, Ph.D., National Bureau of Standards.

Man Years:

Total:	0.8
Professional:	0.4
Others:	0.4

Project Description:

We have continued work on adaptive sampling in clinical trials, with the object of reducing either the expected number of patients in a clinical trial, the expected number of patients administered the poorer treatment during the course of a clinical trial, or the number of failures during the trial. Specifically, further applications of likelihood techniques for the stopping rules of sequential trials, as well as for adaptive sampling were made to the problem of choosing the better of a treatment compared to a control, where the new treatment can be as good as, or better than, the control. The likelihood sequential design was found to be the best of competing trial designs. Another topic that was investigated was the design of a clinical trial in which the maximum number of failures during the trial is fixed. Here we have showed that for many values of the probability of success, alternating allocation of patients to treatments is preferred to adaptive allocation, as suggested by Fushimi. Another topic investigated was the effect of minimizing the expected number of failures during the course of a clinical trial rather than the expected number of patients given the poorer treatment. Here it was found that this design criterion tended to favor alternating allocation as opposed to adaptive allocation in trial design. Finally we have investigated the effects

of covariates on clinical trial design, and found that they have a crucial importance when a trial is designed, and may altogether vitiate the use of adaptive allocation.

The extension of a singular perturbation technique developed for studying chromatographic systems, has been made to the solution of certain Fokker-Planck equations especially relevant to noise in lasers.

Together with Dr. R. J. Rubin we have developed the theory of ordered spans of random walks with relation to the configurations of polymer chains. Recent interest in such problems has been stimulated by the work of Stockmayer and Solč on the asymmetry of random walk models for polymer chains even when the step probabilities are isotropic. The ordered spans give another measure of this asymmetry which can persist to very large chain sizes.

We have continued a study of acoustic pollution from traffic by enumerating the effects of non-exponentially distributed headway spacings. These are shown to be of considerable importance in decreasing noise variance, which has been shown to be a critical factor in environmental impact.

Together with Professor D. R. McNeil we have developed a technique for estimating parameters in birth and death processes in large populations. These processes occur frequently in ecological and epidemiological models, and the technique that we have developed is expected to have wide application.

Keyword Descriptors: Clinical trials, adaptive sampling, sequential analysis, likelihood stopping, random walks, ordered spans, Fokker-Planck equations, singular perturbation, birth and death processes, estimation techniques.

Honors and Awards: None

Publications:

Hoel, D. G., Sobel, M., Weiss, G. H.: Comparison of methods for choosing the best binomial population with delayed observations. J. Stat. Comp. and Simul. (to appear).

Hoel, D. G., Sobel, M., Weiss, G. H.: A survey of adaptive sampling for clinical trials, in Advances in Biometry (to appear).

Kiefer, J. E., Weiss, G. H.: Truncated version of a play-the-winner rule for choosing the better of two binomial populations. J. Am. Stat. Assoc. 69, 807-809, 1974.

Simon, R., Weiss, G. H.: A class of adaptive sampling schemes for selecting the better of two binomial populations. J. Stat. Comp. and Simul. (to appear).

Hoel, D. G., Weiss, G. H.: A clinical trial design with a fixed maximum number of failures. Commun. in Stat. (to appear).

Hoel, D. G., Simon, R., Weiss, G. H.: Reexamination of the problem of choosing the better of two treatments in the context of clinical trials. Proc. Nat. Acad. Sci. (to appear).

Weiss, G. H., Dishon, M.: Application of a singular perturbation expansion to the solution of certain Fokker-Planck equations. J. Statist. Phys. (to appear).

Blumenfeld, D. E., Weiss, G. H.: Some radial and direction dependent models for densities of homes and workplaces. Transp. Res. 8, 149-155, 1974.

Blumenfeld, D. E., Shrager, R. I., Weiss, G. H.: Spatial distributions of homes for journeys to work by different modes of transport. Transp. Res. 9, 19-23. 1975.

Blumenfeld, D. E., Weiss, G. H.: Attenuation effects in the propagation of traffic noise. Transp. Res. (to appear).

Blumenfeld, D. E., Weiss, G. H.: Effects of headway distributions on second order properties of traffic noise. J. Sound and Vib. (to appear).

NATIONAL INSTITUTES OF HEALTH
DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

Summary of Branch Activities

1. DCRT

2. LABORATORY OF APPLIED STUDIES

3. Eugene K. Harris
Chief

During the past year, the Laboratory of Applied Studies (LAS) has strengthened those collaborative ties within NIH and extramurally which enable application of the mathematical and computing science methods developed by LAS staff.

For example, expertise in the numerical solution of partial differential equations under unusual boundary conditions was applied to the measurement of wall shear stress in model arteries as part of a cooperative study with NHLI and DRS (BEIB) scientists engaged in research on the development of atherosclerotic lesions at arterial branch points (Project No. 3.4). Similarly, continuing close collaboration among LAS, Nuclear Medicine and I/D clinical staff, particularly in NHLI, have produced several new applications of computer-based radionuclide scintigraphy with benefits to patient care and evaluation (Project No. 3.2). Two of these techniques, allowing high-resolution but non-invasive studies of dynamic changes in ventricular volume and myocardial contractility throughout the average cardiac cycle, have become important adjuncts to cardiac catheterization in patients with coronary artery disease and valvular diseases.

Another example is represented by the special skills in computer graphics which laboratory staff have applied to various projects in cooperation with NIH investigators. A noteworthy product of this work is the integrated plotting package, not initially developed at NIH but substantially improved here and modified for running on the NIH central computing system. One feature of this series of programs provides contour mapping of bivariate frequency distributions, particularly useful for epidemiologic investigations (e.g., Reference 13).

Finally, in other areas, such as the evaluation of computerized systems for interpretation of electrocardiograms (Project No. 3.1); the development of realistic models of transport of substrate through the microcirculation (Project No. 3.4); or the statistical analysis of serial blood chemistry studies in normal volunteers and patients (Project No. 3.6), the Laboratory has strengthened its collaboration with individuals and organizations outside the NIH actively working in these areas. For example, LAS staff members are currently serving as advisors to governmental agencies in this country and abroad on problems concerning the selection of ECG analysis programs and the data processing of time series of biochemical profiles in normal subjects.

As in past years, LAS staff participated in NIH educational programs. Dr. J. E. Fletcher, Head of the Applied Mathematics Section, is the current chairman of the FAES Department of Mathematics where he teaches many of the advanced applied mathematics courses. The course taught in FY 75 was Methods of Mathematical Physics I and II. Mr. J. D. Ashbrook conducts a regular course in computer graphics as part of the DCRT in hours training course program.

In July 1974 the Biomathematics and Statistics Section was detached from LAS to provide the leadership required for a new laboratory within DCRT (LSMM). Dr. James E. Mosimann, formerly head of this section, was designated chief of the new laboratory.

LAS reports published or "in press" during FY 75:

1. Agress, H., Jr., Levenson, S.M., Gelfand, M.J., Green, M.V., Bailey, J.J., and Johnston, G.S.: Application of computer-generated functional (parametric) maps in radionuclide renography. Proceedings of the Fifth Symposium on Sharing Computer Programs and Technology in Nuclear Medicine. U.S. Atomic Energy Commission Technical Information Center, Oakridge, Tennessee, 1975 (in press).

2. Ashbrook, J.D., Spector, A.A., Santos, E.C., and Fletcher, J.E.: Long chain fatty acid binding to human plasma albumin. Journal of Biological Chemistry, Vol. 250, No. 6, pp. 2333-2338, March 1975.

3. Ashbrook, J.D., and Sande, G.: A User's Guide to the Integrated Plotting Package. U.S. DHEW, PHS, NIH, DCRT, LAS., Wash., D.C., U.S. Govt. Print. Off., 1975, 120 pp.

4. Bailey, J.J., Itscoitz, S.B., Hirshfeld, J.W., Jr., Grauer, L.E., and Horton, M.R.: A method for evaluating computer programs for electrocardiographic interpretation. I. Application to the experimental IBM program of 1971. Circulation 50: 73, 1974.*

5. Bailey, J.J., Itscoitz, S.B., Grauer, L.E., Hirshfeld, J.W., Jr., and Horton, M.R.: A method for evaluating computer programs for electrocardiographic interpretation. II. Application to version D of the PHS program and the Mayo Clinic program of 1968. Circulation 50: 80, 1974.*

6. Bailey, J.J., Horton, M.R., and Itscoitz, S.B.: A method for evaluating computer programs for electrocardiographic interpretation. III. Reproducibility and the sources of program errors. Circulation 50: 88, 1974.*

7. Fletcher, J.E.: A Model Describing the Unsteady Transport of Substrate to Tissue from the Microcirculation. SIAM J. Applied Math., Vol. 29, No. 2, September 1975 (in press).

8. Fletcher, J.E.: Distributed Parameter Modeling of the Microcirculation. Systems Analysis of Biomedical Transport, edited by D.D. Reneau, Marcel Dekker, Inc., New York (in press).

9. Green, M.V., Agress, J., Jr., Brody, W.R., Pearlman, A.S., Itscoitz, S.B., and Johnston, G.S.: A comparison of high temporal resolution left ventricular volume curves before and after initial replacement. Proceedings of the Fifth Symposium on Sharing Computer Programs and Technology in Nuclear Medicine. U.S. Atomic Energy Commission Technical Information Center, Oak Ridge, Tennessee, 1975 (in press).

10. Green, M.V., Ostrow, H.G., Douglas, M.A., Myers, R.W., Bailey, J.J., and Johnston, G.S.: Scintigraphic cineangiography of the heart. Medinfo 1974, North Holland Publishing Company, Amsterdam, August 1974, pp. 827-830.

11. Green, M.V., Ostrow, H.G., Douglas, M.A., Myers, R.W., Scott, R.N., Bailey, J.J., and Johnston, G.S.: High temporal resolution ECG-gated scintigraphic angiocardiography. J. Nucl. Med. 16: 95, 1975

12. Harris, E.K.: Effects of intra- and interindividual variation on the appropriate use of normal ranges. Clin. Chem. 20: 1535, December 1974.

13. Hoffman, H.J., Stark, C.R., Lundin, F.E., Jr., and Ashbrook, J.D.: Analysis of birthweight, gestational age, and fetal viability, U.S. births, 1968. Obstetrical and Gynecological Survey, Vol. 29, No. 9, pp. 651-681, September 1974.

14. Horton, M.R., and Bailey, J.J.: Computer assisted electrocardiographic interpretation: I. Evaluation of computer processing. In Jenkin, M.A. (ed): Clinical Medicine and the Computer - Proceedings of the Fourth Annual Conference of the Society for Computer Medicine. Minneapolis, Minnesota, Society for Computer Medicine, Section 2.6, pp. 1-5, 1974.

15. Lutz, R.J., Cannon, J.N., Fletcher, J.E., and Fry, D.L.: The Measurement of Wall Shear Stress in Model Arteries by an Electrochemical Technique. Proceedings of ACEMB, October 1974.

16. Pottala, E.W. and Mortimer, J.A.: A hybrid compartmental model for the alligator purkinje cell. 1: Preferred somatopetal conduction of dendritic spikes and soma-axon interaction. J. Neurosci. Res. 1975 (in press).

17. Rinzel, J., and Rall, W.: Transient response in a dendritic neuron model for current injected at one branch. Biophys. J. 34, 1974.

18. Rinzel, J.: Voltage transients in neuronal dendritic trees. Federation Proc. 34: 1350-1356, 1975.

19. Rinzel, J: Spatial stability of traveling wave solutions of a nerve conduction equation. Biophys. J., 1975 (in press).

20. Simpson, R.B., Ashbrook, J.D., Santos, E.C., and Spector, A.A.: Partition of fatty acids, Journal of Lipid Research, Vol. 15, pp. 415-422, July 1974*.

*Reported in FY 74 as "in press".

Serial No. Z01 CT 00002-05 LAS
1. Laboratory of Applied Studies
2. Medical Applications Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Evaluation of Computer Systems for ECG Analysis

Previous Serial Number: 3.2

Principal Investigator: J. J. Bailey

Other Investigators: M. R. Horton, S. B. Itscoitz

Cooperating Units: Cardiology Branch, NHLI; ECG Laboratory, CC

Man Years:

Total: 1.3
Professional: 1.2
Others: 0.1

Project Description:

Objective:

To assess on a sound statistical and clinical basis, the usefulness of computer systems for ECG analysis.

Progress during FY 75:

This work begun in FY 70 has involved the study of various methods for ECG analysis, including the use of orthogonal transforms (Fourier, Hambly), use of vector loops, and use of computer programs to interpret resting ECGs. In FY 74 a clinical evaluation of three such programs was completed (publications 1-3).

In FY 75 an updated (improved) version of the IBM program was implemented and is now in daily use for routine ECGs from the Clinical Center. A 360 version of AVA 3.4 (Pipberger) program which uses Frank lead data was implemented and has been distributed to users in Europe and elsewhere in the U. S. Reproducibility of the AVA 3.4 program was tested by the previously reported method (publ. 3 & 4) and the results submitted for publication. A reliable method for acquiring ECG data on clinically documented cases from the Royal Glasgow Infirmary, Scotland has been achieved.

Proposed Course:

NHLI now has the capacity to provide good clinical documentation of cases through the use of cardiac catheter studies, echocardiography, radionuclide angio-cardiography, and myocardial scintigraphy. These cases will make excellent material with which the heuristic algorithms for the ECG diagnosis of chamber enlargement/overload in the IBM program can be tested and likewise also the multivariate statistical algorithms of the AVA 3.4 program. It is also proposed to compare the IBM program against the McFee lead program developed by the Royal Glasgow Infirmary using their clinically documented cases.

Keywords:

ECG analysis, heart disease, computer programs, clinical applications, clinical evaluations.

Publications:

1. Bailey, J.J., Itscoitz, S.B., Hirshfeld, J. W., Jr., Grauer, L.E., Horton, M.R.: A method for evaluating computer programs for electrocardiographic interpretation. I. Application to the experimental IBM program of 1971. Circulation 50: 73, 1974.*

2. Bailey, J.J., Itscoitz, S.B., Grauer, L.E., Hirshfeld, J.W.,Jr., Horton, M.R.: A method for evaluating computer programs for electrocardiographic interpretation. II. Application to version D of the PHS program and the Mayo Clinic program of 1968. Circulation 50: 80, 1974.*

3. Bailey, J.J., Horton, M.R., Itscoitz, S.B.: A method for evaluating computer programs for electrocardiographic interpretation. III. Reproducibility and the sources of program errors. Circulation 50: 88, 1974.*

4. Horton, M.R., and Bailey, J.J.: Computer assisted electrocardiographic interpretation: I. Evaluation of computer processing. In Jenkin, M.A. (ed): Clinical Medicine and the Computer - Proceedings of the Fourth Annual Conference of the Society for Computer Medicine. Minneapolis, Minnesota., Society for Computer Medicine, Section 2.6, pp. 1-5, 1974.

*Reported in FY 74 as "in press".

Serial No. Z01 CT 00003-04 LAS
1. Laboratory of Applied Studies
2. Medical Applications Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Computer Systems for Nuclear Medicine

Previous Serial Number: 3.2

Principal Investigators: J. J. Bailey, M. V. Green (NM/CC)

Other Investigators: H. Agress, Jr., M. A. Douglas,
H. G. Ostrow, S. L. Bacharach,
S. M. Levenson, B. R. Line, G. S. Johnston,
W. R. Brody, D. R. Redwood, S. B. Itscoitz

Cooperating Units: Nuclear Medicine Department, Clinical Center, NIH
Cardiology Branch, NHLI
Pulmonary Branch, NHLI
Surgical Neurology Branch, NINDS
Computer Systems Laboratory, DCRT

Man Years:

Total: 2.7
Professional: 2.6
Others: 0.1

Project Description:

Objectives:

To provide computer-based mathematical analysis in support of diagnostic activities in the Nuclear Medicine Department (NM) of the Clinical Center.

Progress during FY 75:

Since FY 72 LAS with support from CSL and in collaboration with the NM has accomplished the specification, selection, and acquisition of a minicomputer system which was mated to two gamma scintillation cameras in NM. Subsequently LAS programmers have developed and implemented extensive software (on both the NM minicomputer system and the PDP-10 facility in DCRT) which has found wide-ranging applications, including time function manipulation, curve fitting, and functional mapping for dynamic studies; orthogonal transforms for image restoration by deconvolution and for non-restorative image enhancements; and interpolation, expansion, and contraction of image arrays.

The most important clinical application developed in FY 74 and FY 75 is the computer-based ECG-gated technique of radionuclide angiocardiography (publications 1, 2, and 4). Because of its non-invasive, non-surgical nature (cf. cardiac catheterization) requiring no anesthesia and less radiation dose than a single chest Xray, this study can be repeated frequently or can be performed on patients too sick to undergo cardiac catheterization. Thus, this technique shows considerable promise as an addition to the diagnostic armamentarium of clinical cardiology.

Another important computer-based technique begun in FY 75 is ECG-gated myocardial scintigraphy during rest and stress using radionuclide labeled macroaggregated human serum albumin or albumin microspheres. This technique promises to help determine the pathophysiologic effect of anatomic lesions revealed by coronary angiography and thereby add considerably to the evaluation of patients who might be candidates for coronary artery surgery.

A third computer-based method involving functional (parametric) maps in radionuclide renography was begun in FY 73. In FY 74 and FY 75 this method was applied to 130 patients and was found to enhance the detection of functional abnormalities in more than one-third of the cases (publication 3).

The computer-based method for ventilation and perfusion scanning of the lungs was begun in FY 73. At that time it proved useful in following the changes in pulmonary dynamics in patients who underwent surgical repair of valvular heart disease. In FY 74 and FY 75 this method is being refined by the incorporation of volume gating.

During FY 75 the use of computer-based statistical studies of "flooded" gamma camera fields revealed non-uniformities in the camera response which, heretofore, had been unsuspected. The photomultipliers of the camera were re-tuned and this method is now being used weekly as a quality control measure for the gamma camera data.

In FY 75 computer-based methods for determining regional blood flow are being used to study the course of experimental cerebral infarction in monkeys.

Proposed Course:

The method for radionuclide angiocardiography will be validated using patient data from cardiac catheter laboratory and also experimental data in baboons with a surgically emplaced flowmeter about the ascending aorta. This method will also be used to detect regional abnormalities in left ventricular wall motion in patients with coronary heart disease. The method for myocardial scintigraphy will be used to assess coronary artery disease in

NHLI patients. The functional mapping of radionuclide renography will be added to the nuclear medicine armamentarium as a standard procedure. The method for ventilation/perfusion scanning of the lung will be used to study NHLI patients with a variety of pulmonary abnormalities and also patients from the D.C. Veterans Administration Hospital who have interstitial pulmonary fibrosis. Work on image enhancement through use of orthogonal transforms and other techniques and methods of pattern recognition in nuclear medicine will be extended.

Keywords:

radionuclide, radioisotope, nuclear medicine, scanning, scintiphotography, non-invasive techniques, computer analysis, coronary heart disease, myocardial infarct, left ventricular wall motion, ejection fraction, renography, renal function, functional mapping, pulmonary function, ventilation/perfusion, pulmonary disease, stroke, cerebral blood flow, iodohippuran-I 131, xenon-133, xenon-127, technecium-99m.

Publications:

1. Green, M.V., Ostrow, H.G., Douglas, M.A., Myers, R.W., Bailey, J.J., and Johnston, G.S.: Scintigraphic cineangiography of the heart. Medinfo 1974, North Holland Publishing Company, Amsterdam, August 1974, pp. 827-830.

2. Green, M.V., Ostrow, H.G., Douglas, M.A., Myers, R.W., Scott, R.N., Bailey, J.J., and Johnston, G.S.: High temporal resolution ECG-gated scintigraphic angiocardiography. J. Nucl. Med. 16: 95, 1975.

3. Agress, H., Jr., Levenson, S.M., Gelfand, M.J., Green, M.V., Bailey, J.J., and Johnston, G.S.: Application of computer-generated functional (parametric) maps in radionuclide renography. Proceedings of the Fifth Symposium on Sharing Computer Programs and Technology in Nuclear Medicine. U.S. Atomic Energy Commission Technical Information Center, Oak Ridge, Tennessee, 1975 (in press).

4. Green, M.V., Agress, J., Jr., Brody, W.R., Pearlman, A.S., Itscoitz, S.B., and Johnston, G.S.: A comparison of high temporal resolution left ventricular volume curves before and after initial replacement. Proceedings of the Fifth Symposium on Sharing Computer Programs and Technology in Nuclear Medicine. U.S. Atomic Energy Commission Technical Information Center, Oak Ridge, Tennessee, 1975 (in press).

Serial No. Z01 CT 00004-04 LAS
1. Laboratory of Applied Studies
2. Medical Applications Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Investigations of Physiologic Signals and Simulation Models by Distributed Hybrid Computing

Previous Serial Number: 3.6

Principal Investigators: Erik Pottala

Other Investigators: J. J. Bailey, J. B. Eisenberg, G. Wright, D. Humphrey, J. Mortimer

Cooperating Units: National Institute of Occupational Safety and Health; Emory University, Atlanta, Georgia; University of Minnesota, Minneapolis, Minnesota

Man Years:

Total: 1.9
Professional: 1.8
Others: 0.1

Project Description:

Objectives:

(1) To develop physiologic simulation models using distributed hybrid computing implemented on the LAS laboratory mini-computer with special purpose microprocessors:

(a) in neurophysiology to simulate neural networks and central nervous subsystems (e.g. cerebellum),

(b) in cardiovascular physiology to develop a global model of circulatory dynamics which can be easily modified to simulate pathophysiologic states (e.g. valvular disease).

(2) To develop the LAS mini-computer system as a research tool for handling physiologic data.

Progress during FY 75:

Neural network simulation employing physiologically realistic hardware neural models, which incorporate a distributed input system (analogous to a dendritic net) with simulated action potentials, has been pursued since FY 72. In FY 74 a neural hardware model interfaced with the mini-computer system was used to study a small neural net and show how an action potential can modify the shape and duration of post-synaptic potentials and their spatio-temporal interactions. This work with small neural nets and their reciprocal inhibition-excitation behavior has been extended to the study of the cerebellum (publ. 1).

Development of the LAS mini-computer system has continued. It has been interfaced with the Marquette tape drive (for routine ECGs from the Clinical Center); with the Honeywell 7600 analog tape transport; with a general purpose switch-filter network; with a real time spectral analyzer and ensemble averager; and with the neural control panel for the model work described above.

This system is capable of processing various analog (physiologic) signals. For example, in FY 74 and 75, electromyographic signals collected at the National Institute of Occupational Safety and Health from stressed subjects were analyzed by this system using the spectrum analyzer. The optimum ranges of power spectra for this study were determined by this analysis and the results are now being used to study muscle fatigue. Another example involves ECG data collected at the Royal Glasgow Infirmary (see 3.2). These data contain varying levels of 50 Hz. noise. With the aid of the LAS mini-computer system, the character of this noise was studied and an analog notch filter was designed. The effect of this filter on the data and ultimately upon the diagnostic statements of an ECG analysis program were greatly facilitated by means of the mini-computer system. The optimal parameters (attenuation and window size) of the filter could then be selected, in terms of a trade-off between noise suppression and artifact generation.

A general advantage of this system which has been demonstrated before in other studies (ECG and pressure from monkey preparations) is that an investigator

can automatically pre-process (edit, filter, and digitize) dynamic physiologic data so that optimal use of a large scale digital computer can be obtained.

Proposed Course:

The neurophysiological simulation work will be extended to larger nets of cerebellar cells and to other central nervous subsystems (e.g. walking reflexes). It is also proposed to build a global model of the cardiovascular system based on power conversion and distribution; data (e.g. time course of intraventricular pressure and volume) has already been collected, which can be used for testing sub-sections of the model. In the coming year the LAS mini-computer system will be upgraded with the addition of 16K core, a 1600 BPI magnetic tape drive, a MAP 100 array processor, a disk pack, and a grey-level CRT. It is anticipated that these improvements will allow speedy investigation of image processing schemes for nuclear medicine data (see 3.6).

Keywords:

neurophysiology, hybrid computer, simulation, cerebellum, cardiovascular models, signal analysis, electrocardiography, electromyography, image processing.

Publications:

1. Pottala, E.W., and Mortimer, J.A.: A hybrid compartmental model for the alligator purkinje cell. 1: Preferred somatopetal conduction of dendritic spikes and soma-axon interaction. J. Neurosci. Res. (in press) 1975.

Serial No. Z01 CT 00005-05 LAS
1. Laboratory of Applied Studies
2. Applied Mathematics Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Mathematical Modeling of Biological Processes

Previous Serial Number: 3.5

Principal Investigators: J. Fletcher, J. Rinzel (transferred to NIAMD 2/1/75)

Co-Investigators: R. Lutz, BEIB, DRS; W. Rall, MRB, NIAMD

Man Years: Professional 1.8

Project Descriptions:

Background and Objectives:

The primary responsibility of the Applied Mathematics Section is to provide DCRT and the NIH with high level mathematical competence for biomathematical modeling and data analysis. This competence includes both theoretical and applied techniques, as well as numerical computation methods. Each individual in the section has a primary specialty in computer science or mathematics, and in addition, each is a capable programmer.

Project Tasks during FY 75:

1) A Simulation Model for Substrate Supply in the Microcirculation:

During FY 75, a new mathematical formulation of substrate kinetics in capillary blood was discovered. This formulation resulted in some simplification of the model equations and permits the direct use of the substrate dissociation curve rather than its mathematical inverse which was used previously. In this form, the model suggested that substrate transfer to tissue was directly related to the slope of the dissociation curve rather than its coordinate position (P_{50} point) and subsequent modeling studies confirmed this conjecture. A number of simulations were completed relating the effects of substrate kinetics

to tissue supply, and the role of 2-3 DPG in modifying the oxygen-hemoglobin dissociation curve in humans was examined. The simulation results were presented at a recent international meeting, and a publication will appear in the proceedings.

2) Dynamic Behavior of Mass Transfer in Pulsating Laminar Tube Flow:

During FY 74, the collaboration of the Applied Mathematics Section was requested in a project directed toward the development and validation of an experimental technique for the measurement of mass transfer in tubes with pulsating flow. The ultimate objective was a technique for measuring shear stress in arteries and its possible relationship in the formation of sclerotic lesions at bifurcations. A brief literature survey revealed that the commonly used approximations were inappropriate for the full model equations, while most standard numerical methods were invalidated by the mathematical singularity induced by the leading edge of the imbedded electrode. During FY 75, a new formulation was developed which removed this singularity, thus posing the problem in a form more adaptable to numerical solution. A new numerical solution technique has been developed and is being tested for its validity. Some preliminary results have been presented at conferences and an application has been published. Further work in this area will center on validation of both experimental and theoretical results and the development of a valid error analysis.

3) Mathematical Description of Cellular Neuroelectric Signal Transmission:

The objectives of this study are to obtain biophysical understanding through mathematical modeling of integration in a model dendritic neuron and of impulse conduction along a model nerve axon. During FY 75, a simplified version of the FitzHugh-Nagumo nerve conduction model was used to study the phenomena of active axonal conduction. Though it too yields a nonlinear partial differential equation, its traveling wave solutions can be obtained explicitly. This permits a complete parametric description of its solutions, which model a simplified ideal nerve impulse, and periodic trains of pulses. The results suggest that, for steady repetitive firing. the propagation speed of a periodic train depends on firing frequency. Additional numerical calculations

are planned to further explore this dispersive aspect of nerve conduction.

As do other nerve conduction models, this simplified one has a multiplicity of traveling wave solutions. Such multiplicity is not found in experimental observations and has led several investigators to conjecture on the stability properties of these various waves. For the simple model, stability has been analyzed explicitly to verify the conjectures and to suggest which waves are likely to be observed. Two different stability notions are formulated: temporal stability, for perturbations generated at a single instant of time; and spatial stability, which may be continually applied in time, but spatially restricted to a fixed location. This is appropriate for many nerve signaling problems. Stability results for this simple model motivate their attempted extension to a general class of nerve conduction equations. Critical stability transition properties for these models have been analytically and parametrically examined. For periodic wave trains, maximum frequency was found to distinguish the transition from spatial stability to instability. A manuscript describing these results has been submitted.

Keywords:

applied mathematics, biomathematical modeling, numerical computation, simulation model, microcirculation, pulsating flow.

Publications:

1. Fletcher, J.E.: A model describing the unsteady transport of substrate to tissue from the microcirculation. SIAM. J. Applied Math., Vol. 29, No. 2, September 1975.

2. Lutz, R.J., Cannon, J.N., Fletcher, J.E., and Fry, D.L.: The measurement of wall shear stress in model arteries by an electrochemical technique. Proceedings of ACEMB, October 1974.

3. Fletcher, J.E.: Distributed parameter modeling of the microcirculation. Systems Analysis of Biomedical Transport, edited by D.D. Reneau, Marcel Dekker, Inc., New York (in press).

4. Rinzel, J.: Voltage transients in neuronal dendritic trees. Federation Proc. 34, 1350-1356, 1975.

5. Rinzel, J., and Rall, W.: Transient response in a dendritic neuron model for current injected at one branch. Biophys.J. 14, 759-790, 1974.

6. Rinzel, J.: Spatial stability of traveling wave solutions of a nerve conduction equation. Biophys. J. (in press).

DRG

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Serial No. Z01 CT 00006-05 LAS
1. Laboratory of Applied Studies
2. Applied Mathematics Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: General Mathematical and Computational Collaborative Efforts

Previous Serial Number: 3.5

Principal Investigators: J. Ashbrook, E. Hill, J. Fletcher

Co-Investigators: A. Spector, Univ. of Iowa
R. Shrager, DCRT; R. Feldmann, DCRT;
H. Hoffman, Biometry Branch, NICHD;
W. Sperry, CCB, DCRT

Man Years: Professional - 2.2

Project Description:

1) Modeling of Macromolecule-ligand Binding:

A study of the binding of physiologically important long-chain fatty acids to human plasma albumin has been completed and published. Further work in this area will concern displacement of albumin bound ligands by drugs or other competing compounds.

2) Low Weight for Age Study:

Computer software was completed for the generation of contour plots of collected data. The NICHD has employed this software for the construction of contour levels for bivariate distributions of birth weight and gestational age by race, sex and metropolitan status. Details of resulting studies are described in the reports of the Institutes concerned. Additional studies utilizing this software are currently being conducted by the Biometry and Epidemiology Branches, NICHD.

3) Computer Generated Graphics and Display Systems:

Several new post-processors have been added to the Integrated Plotting Package (IPP). This new software allows an IPP program to generate plots on any terminal in the Tektronix 4010 family of graphic displays, or

on a CalComp plotter attached to a remote job entry (RJE) workstation in addition to the previously supported plotting devices. Supporting software was rewritten in American National Standard (ANS) FORTRAN to preserve machine independence. The software has been distributed to other computer centers, and a user's guide is now in press. Additional research is being conducted in collaboration with CCB, DCRT in the general area of computer generated graphics and textual data representation.

4) Simulation of Body Fluid Balances:

This project involves the implementation of interactive digital computer models designed to help scientists study the interacting physiology of major body systems in health and disease. A model called MACPEE is being analyzed and implemented on DCRT's PDP-10 and IBM System 370 computers. MACPEE is a model of heart, circulation, body fluid compartments, kidneys, and various hormones. This model can be used to approximate most problems of renal disease, body fluid disturbance or complex interacting disorders such as nephrotic syndrome, heart failure, Addison's disease, etc.

5) Image Processing of Nuclear Medicine Data:

Algorithms are being developed to extract features, find edges, perform texture analysis, and find profiles of digitized radioisotope distribution patterns. These attributes will be used to classify images as either normal or abnormal using an adaptive supervisor. Discriminant analysis, classical pattern recognition techniques, and other optimization techniques are being used in developing such routines.

6) Energy Minimization of Protein Structures:

This project involves the integration of energy minimization techniques into the body of DCRT's molecular structure manipulation system. This involves determining the best methods for doing energy minimization and data structure manipulation with respect to protein structures. A group of computer programs that allow one to study the conformations of biological macromolecules is being analyzed and implemented on the PDP-10 computer system. The conformation is altered to minimize an empirical energy function by moving all atoms by the method of steepest descents. These techniques

are needed to refine coordinates obtained by X-Ray Crystallography and thus improve the techniques of stereochemistry.

Keywords:

mathematics, modeling, macromolecule-ligand binding, graphical displays, graphics, simulation, image processing, energy minimization, protein structures.

Publications:

1. Simpson, R.B., Ashbrook, J.D., Santos, E.C., and Spector, A.A.: Partition of fatty acids. Journal of Lipid Research, Vol. 15, pp. 415-422, July 1974.*

2. Hoffman, H.J., Stark, C.R., Lundin, F.E., Jr., and Ashbrook, J.D.: Analysis of birth weight, gestational age, and fetal viability, U.S. births, 1968. Obstetrical and Gynecological Survey, Vol. 29, No. 9, pp. 651-681, September 1974.

3. Ashbrook, J.D., Spector, A.A., Santos, E.C., and Fletcher, J.E.: Long chain fatty acid binding to human plasma albumin. Journal of Biological Chemistry, Vol. 250, No. 6, pp. 2333-2338, March 1975.

4. Ashbrook, J.D., and Sande, G.: A User's Guide to the Integrated Plotting Package. U.S. DHEW, PHS, NIH, DCRT, LAS. Wash., D.C., U.S. Govt. Print. Off., 1975, 120 pp.

*Reported in FY 74 as "in press".

Serial No. Z01 CT 00007-08 LAS
1. Laboratory of Applied Studies
2. Office of the Chief
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Statistical Research in Clinical Pathology

Previous Serial Number: 3.4

Principal Investigators: Eugene K. Harris, assisted by G. Shakarji, DMB, DCRT

Co-Investigators: M. Healy, Clinical Research Centre, Medical Research Council, England
S. Brown, Clinical Chemistry, Clinical Research Centre, England
D. S. Young, Clinical Chemistry Service, Clinical Center, NIH

May Years: Professional 0.5

Project Description:

Background:

The studies of variation in normal blood chemistries which form the background of this project have been amply discussed in earlier annual reports.

Progress during FY 74, 75:

This report covers two years because the principal investigator continued research in this area during assignment to the Clinical Research Centre near London in FY 74. During the past two years attention has focussed on the development of statistical theory to evaluate 1) the use of population-based normal ranges in assessing individual laboratory tests, and 2) use of previous measurements on the same individual to forecast and test a current measurement. These issues have particular significance for the interpretation of results from periodic health examinations of presumably normal individuals or from more intensive serial studies of patients in clinical trials. Two papers have resulted so far: one referenced below and a second just completed and submitted for publication (April, 1975). In addition, an extensive unpublished report was prepared on the use of

statistical methods in analyzing serial measurements on patients under intensive care following surgery, myocardial infarction, or other traumatic experience. Aims are rapid detection of eventual outcome.

To support this work, computing packages have been developed for the storage, updating, retrieval and statistical analysis of cumulative clinical data on individuals. A general description and full documentation of these programs is now in preparation. The storage, updating and retrieval programs have been in routine operation for the past 2 years in the Hypertension-Endocrine Laboratory of NHLI under Dr. F. C. Bartter, and now contain information on upwards of 100 patients. The full set of programs, including analysis routines, are expected to be used very shortly in the analysis of a serial study of normal volunteers designed in cooperation with the Clinical Chemistry Service of the Clinical Research Centre, Harrow (London), England and completed during FY 75. Data will be transmitted to NIH for analysis and a joint report prepared.

Plans for FY 76:

During the coming year, documentation of the computing programs mentioned above will be completed and included in a technical report for general distribution. Immediate application will be to the data from England cited above. Later, it is expected to apply these programs and supplemental theory to new data from normal subjects including baseline measurement series followed by single samples at periodic intervals. Cooperative efforts are also expected with the Clinical Chemistry Service of the Clinical Center in the application of various statistical monitoring and forecasting methods to the quality evaluation of new high-volume, multichannel autoanalyzer machines, possibly including a study of normal volunteers. Thus, FY 76 will see an emphasis on the application of theory developed during the preceding two years.

Keywords:

normal variations, inter-intra-individual variation, baseline reference values, normal ranges, clinical chemistry.

Publications:

1. Harris, E.K.: Effects of intra- and interindividual variation on the appropriate use of normal ranges. Clin. Chem., 20, 1535 (December, 1974).

July 1, 1974 through June 30, 1975

PHS-NIH

Division of Computer Research and Technology

Summary of Branch Activities DCRT

Data Management Branch

J. Emmett Ward
Branch Chief

I. SUMMARY

Providing practical solutions to complex research and administrative computer data processing problems is still the raison d'etre of the Data Management Branch (DMB).

Reasonable progress has been made in providing a useful Clinical Information Utility. This effort supports the Clinical Center's Office of Clinical and Management Systems by providing clinical investigators with diversified methods for reviewing and extracting clinical data from three available sources: Clinical Pathology Laboratory, Discharge Diagnosis and Census. The linkage, retrieval and security functions of this system are discussed under the Clinical Support Section's summary.

The impact at NIH of a new approach to systems development known as Data Base Management Systems (DBMS) has not been established at this time. IBM's Information Management System (IMS) is one of many such DBMS's currently marketed by software vendors. In a joint effort, the NCI and DMB have begun an evaluation of this system. A data base developed by Stanford Research Institute for an ongoing NCI study of potentially hazardous compounds was transferred to NIH during the year. DMB personnel adapted this data base to run under the IMS Interactive Query Facility and NCI is now testing the flexibility of this software to meet its needs. In an attempt to examine the full IMS utility, DMB is in the process of developing a Divisional Information System for Cancer Cause and Prevention.

A critical review of DMB applications software facilities resulted in a complete upgrade of the Recursive Macro Actuated Generator (RMAG) to its latest version RMAG21. This new facility handles all varieties of record formats, eliminates the need for intermediate reading of edit format data sets, provides automatic blocking and deblocking and enables parsing of input data in extremely flexible form. The overall impact of this effort is easier programming, shorter execution times and reduced costs. A complete rewrite and integration of all

of the existing generator programs using RMAG21 is currently in process and should be available for final testing by mid-fall 1975.

The IBM STATPAK software, a package of 40 on-line statistical routines, was recoded to FORTRAN IV from BASIC and implemented under the Time Sharing Option. Current usage of this package exceeds 175/week.

During the past year, development of a data management and statistics package (DMSP) was undertaken. This package will be used to solve a variety of problems including editing, consistency checking, updating , selection, transformation, recoding, and elementary statistics. It is desirable to consolidate the solutions to these problems into a single package in order to make the computer easier to use.

Both problem-oriented and procedure-oriented statements are available to the user of DMSP. Problems in data management and statistics are generally solved using the problem-oriented statements; but in cases where such statements are not adequate, it is possible to resort to the procedural statements, which are like those found in conventional programming languages. It is therefore possible to circumvent the limitations inherent in general systems which do not employ a procedural language, and it is also possible to provide unsophisticated users with easy-to-use problem-oriented statements not found in ordinary procedure-oriented languages.

A system has been completed to provide massive storage and retrieval of chemistry data for the Endocrinology Branch, NHLI. Complete demographic and the associated chemistry data on 75 patients have been stored on tape using this system. This data base will provide patient chemistry information for the NHLI staff. It will also provide data for statistical evaluations. Statistical analysis, to date, has included evaluations of time of blood as well as blood pressure data, and trend analysis to evaluate short-term effects on blood pressure of patients using certain drugs.

In collaboration with the NIAMDD Field Studies Section in Phoenix, Arizona, we are examining insulin responses in a relatively well-known Indian population. In another project Branch personnel are involved in orienting the research investigators in the NIAMD Field Studies Section in Phoenix, Arizona with statistical packages in DCRT, especially with the capabilities of the Statistical Analysis System. This orientation will provide them with tools to analyze large volumes of data representing relationships of insulin level to

oral glucose load in subjects with a wide spectrum of glucose tolerance among the Pima Indians (a group having an extremely high prevalence of diabetes). We have developed special procedures to insure the proper evaluation and execution of computer runs and to reduce computer run time on the projects.

In an effort to assist patients who have had laryngectomies the Veterans Administration is examining individual self concepts using Q-technique. A self assessment of definable personality traits is provided by each patient. Then evaluations of these data are performed. Evaluations have included correlations between "actual self-concept" and ideal self-concept; "actual self-concept" and "other" self-concept; evaluation of self-acceptance, independence, and good emotional control; and evaluation of self-rejection, dependence, poor emotional control, and withdrawal.

DMB has been working with the Laboratory of Statistical and Mathematical Methodology to evaluate and to detail test all options of the Statistical Analysis System (SAS) in order to determine the algorithmic validity of all features. Data Management Branch Staff was briefed on SAS capabilities and the use of this package is proving to be very valuable in editing and analyzing data.

In collaboration with Dr. Eugene Harris of the Laboratory of Applied Studies analysis software has been developed to assist him in evaluating intra-individual variations in serum blood constituents. Major portions of this package are complete. It has the capability to compute and plot tests for normality, test multivariate normality for selected combinations of tests, estimate average intra-individual variance, calculate pairwise correlations, calculate selected multivariate normal regions, and estimate purely physiologic variance.

A set of programs was modified and fully tested, on our system, to perform spectral analysis of digitized input data. These programs were written at Johns Hopkins University Applied Physics Laboratory. The programs compute three main functions: the power of spectral density data to decompose into different frequency components; autocorrelation to examine data periodicity; and stationarity and normality to determine the suitability of the data to be represented by spectral analysis alone.

The applications programming summary is as follows:

Documentation and Systems Support Section

1. In processing Case Reports new procedures to more closely control the editing and balancing of data using computer runs and AUTOTAB were introduced this year and personnel in

the OD/ORA Office were trained to use them effectively. For Fiscal Year 1973 approximately 50% of the 137 output reports were produced using generated programs. At the present time the OD/ORA Office is considering only producing about 25 general summary tables for this fiscal year and supplying detailed information by use of Query and AUTOTAB to those requesting such reports.

2. Continued our support for esoteric CICS programs in the ARMS Personnel System. Turned interactive retrieval programs over to SAB Staff.

3. Interfaced the Opportunity Skills System with ARMS to facilitate update and reduce manual effort.

4. Set up a system to verify Central Account Numbers for DRS via OFM CAN tables.

5. To support various DRS Branch activities, we are currently designing and developing systems for maintaining and controlling the 1) Glassware Billing System, 2) the Small Animal Billing System and 3) the Planning System.

6. Developed an NEI Information System for all extramural programs including contracts via the DRG IMPAC System and manually entered data of additional interest. System provides update, edit, report and query facilities.

7. Established an on-line consultant file for the NHLI, which provides update, edit and query capabilities to facilitate the selection of team members for such things as site visits.

8. Currently developing an inventory system for the NHLI to control approximately 25,000 "cell line" vials stored in six freezers at various locations within the Laboratory of Biochemical Genetics.

9. Produced a Data File of Soviet Cytologists and Geneticists for NIEHS.

10. Currently producing Machine Readable and Searchable indices of the PHS-149 series: "Survey of Compounds which have been tested for Carcinogenic Activity" for NCI.

11. Developed some fifty-one report programs which provide inventory and natural history data on primates (CEBUS monkeys) used in the NIMDS Herpes Study.

12. Currently designing a system to evaluate the Siperstein method of diagnosing diabetes. Current plan is to apply Siperstein's basement membrane theory to a known Pima Indian population and Caucasian normal control group. Drs. Siperstein and Williamson will provide input to the system in support of this NIAMD Field Studies Section evaluation.

13. Currently developing a system intended to correlate the incidence, morbidity and mortality of kidney and urinary tract disease with research need. The population being studied is the three armed services from January, 1971 through December, 1973.

14. Developed a Print Format Generator (PFG) for easy production of report programs from data layout sheet formats.

15. Case Data Preparation for NSF, OD/ORA.

16. KWIC Indices for the NIH Central Library, DRS/L.

17. NICHD Grant System.

18. Baltimore Cancer Research Center (BCRC) Study, NCI.

19. Lupus Study, NIAMD.

20. This section also supports Tablemaker and is responsible for reviewing all DMB documentation before it is released to NIH users.

Applied Systems Programming Sections

1. In support of the Type II Intervention Study for the Lipid Metabolism Branch, NHLI, continued our monitoring of all data base activities and provided several new reporting facilities.

2. Currently providing an interface between data base functions and the statistical segment for the Carcinogenesis Bioassay Data System.

3. Currently participating in a retrospective study of Cardiac Valve Replacements for the Clinical Surgery Branch, NHLI. The study involves the collection and analysis of various pre-and post-operative data on the more than one thousand patients who have had heart valves replaced at the NHLI.

4. Developed a completely new interactive system for the Emergency Virus Isolation Facility, NCI. All medical information on employees of the facility is now entered and retrieved in-house; this provides the facility with excellent security and privacy for all employee data.

5. Developed a computerized distribution list for the Grant and Contract Guide Distribution Center of DRG. The system creates, maintains, and selectively produces labels to be used in the distribution of the Grant and Contract Guide and/or any of its various supplements. Other NIH mailing list requirements have also been satisfied using this system.

6. Produced the 15 Federal Survey Tables depicting DHEW funding to institutions of higher education for Office of Resources Analysis, O.D.

7. Provided an indexed information system for the Research Analysis and Evaluation Branch, Division of Research Grants. The RAE branch has found that by indexing several different files, 1) Inventory of Clinical Trials; 2) Application for Grants; 3) NIH Grants Abstracts and 4) NIH Contracts Abstracts, with DMB's indexing programs and by searching the index files with DMB's index query program, they can very quickly satisfy questions relating to these data. Prior to the development of this technique data volume precluded quick access and retrieval.

8. Developed an NIH Central Registry of Biological Agents and Materials for the Environmental Services Branch, Division of Research Services. DMB is currently augmenting this ESB system to include carcinogenic chemicals in use at NIH.

9. Developed a pharmacy computer file system for the Clinical Center Pharmacy. The file contains drug product data on all drugs available through the Pharmacy.

10. Established a computerized data processing system for the Laboratory of Parasitic Diseases, NIAID. The system maintains all pertinent data on monkeys infected with malaria and mosquitos infected by feeding from the malaria infected monkeys. The study is intended to trace the life cycle of malaria.

11. Currently developing computerized grants information files for the Program Analysis and Evaluation Branch, Division of Cancer Grants, NCI.

12. Provided a Water Supply Systems Inventory facility for the Water Supply Branch, Environmental Protection Agency. This data processing system helps the EPA monitor the thousands

of water supply systems in the U.S. To date, there are approximately 46,000 water utilities on the master file. This accounts for approximately 138,000 water sources. The data source is a questionnaire distributed to each system. System data includes such things as treatment processes, capacities, sources, etc.

13. Implemented a system to produce the Journal of the National Cancer Institute (JNCI) for the Division of Cancer Cause and Prevention, NCI. The computerized system aids the Office of the Editor in Chief, JNCI in handling of data endemic to approximately 900 manuscripts per year submitted for publication in JNCI.

14. Provided programming support for the data collection and reporting segment of the Cigarette Condensate Study for the Etiology Branch, NCI.

15. Continued development of the complete inventory and retrieval system in support of the Institute of Laboratory Animal Resources (ILARS). This system is sponsored by the NCI.

16. Developed an International Activities and Personnel Monitoring System for Fogarty International Center.

Scientific Applications Section

1. In support of the Laboratory of Socio and Environmental Studies, NIMH, developed a generalized data management and statistical analysis system for psychological and physiological measures. Programs for handling heart rate and galvanic skin response are available, as is the ability to retrieve data from those measures using behavioral characteristics (or time) as the retrieval criteria. A statistical program produces summary statistics for single physiological measures and regression statistics for pairs of measures. During this fiscal year a program for identifying and flagging faulty data, programs which identify missing data and prevent erroneous data intervals from entering the statistical segment of the system, were developed. Future efforts include fine-tuning the user documentation and writing a routine for correcting of behavioral data.

2. Added nine new protocols to the Surgery Branch, NCI data files. Current plans call for retention of the operation data files and dropping the core and protocol data from the active system.

3. Currently developing a clinical patient followup file for the Surgery Branch. Using the DMB generators, programs were generated and modified for creating update transactions and for the update and edit functions. Retrieval programs and a print program which provides the physician with a summary of his patient's treatment history will be available soon. Plans for the future include changing the site and histology codes and the associated error checking routines when the new international cancer surgery coding scheme is available.

4. Continued support of the current awareness search for Clinical Biological Activities (CBAC). This service is still offered free of charge to all researchers at NIH and is run biweekly as tapes are received from Chemical Abstracts Service in Columbus, Ohio. Current plans are to drop retrospective searches in favor of timesharing systems. Programming effort to duplicate what is already offered by timesharing organizations precludes duplicate development. Use of timesharing services would also provide NIH reseachers access to CA Condensates, which reflects the entire 80 sections of CA, as well as easier, quicker access to CBAC.

   Completed first full year of support for current awareness search of Biosciences Information System (BIOSIS). Twice a month tapes are received from the Biological Abstracts Service and information is disseminated to the NIH community through the same vehicle as CBAC.

   Mr. Gillespie of the NIH Library has been the primary contact for NIH researchers wishing to search this data base; he submits their profiles to DMB for Current Awareness searching.

5. Continued support of the Survival System, which was originally developed to support the End Results in Cancer studies of NCI and now serves other NIH Institutes.

   During the year several new requests for copies of the system by organizations outside the NIH were satisfied.

   The next submission of data will involve changes in format and data code values making it necessary to modify the Survival System to reflect these changes.

6. Initiated work on the survival or life table analysis for the Cutting Oil Study. This system supports the efforts of the National Institute of Occupational Safety and Health. It is a study relating job type to mortality and morbidity of cutting oil workers. A data base has been established, and preliminary frequency tables have been produced.

7. Revised the programs which evaluate the daily scintillation counter output of radioimmunoassays for NICHD. Periodic revisions are necessary to keep pace with changing theory and methodology. In addition the plot portion of the system was replaced by a new printer plot capability.

8. Developed a cataloging system for sera and the multiple tests run on them for the Surgery Branch, NCI. Retrieval is possible by cancer site, histology, patient number and name. Time for collecting a representative batch of sera for desired lab tests has been cut from 14 hours to one hour.

9. Continued support of the Mass Spectral Retrieval System, in collaboration with Dr. Fales, Laboratory of Chemistry, NHLI.

   During FY 75, a new data file, which increased the number of spectra from 12,000 to 28,000 was put up despite severe interface problems between the system's two computers. A 17-tape file of spectra sorted by peak was also put up. The fiche generation program was updated and successfully run, a new option was added to the search, and a number of problems were uncovered and removed. A new data file which will raise the number of spectra to 35,000 is being worked on currently. When purified, subsets of the new file will be made available as the complete file is too large for present hardware. Maintenance documentation of the system is being completed.

10. Developed a program, which provides plots and quality control statistics for laboratory experiments having to do with radioimmunoassays, for the Reproduction Research Branch, NICHD.

    After a period of use in the lab, more tests will be added to the program.

11. In collaboration with Dr. Rodbard, Reproduction Research Branch, NICHD, modified a package of programs which do peak detection and non-linear curve-fitting analysis on chromatographic data. Several options for clumping and smoothing of data points have been added and a plot capability included in the package.

    Future plans for this package include the development of a preprocessor for deriving initial values from computer examination of data, a histogram to aid in making manual decisions on initial values, and addition of other equations, e.g., log-normal, to the curve-fitter program which now is used in the Gaussian mode.

12. Began development for the analysis phase of the Carcinogenesis Bioassay Data System. This involves data from ongoing bioassay experiments in mice. The immediate aim is to detect previously unidentified carcinogens. During the next fiscal year a statistical description program giving counts of animals with specific pathologies, and a program generating regular survival curves, Kaplan-Meier curves, and the Breslow statistic will be incorporated into a terminal-driven analysis system, which will build (in the conversational mode) parameter cards and JCL for batch runs.

13. Redesigned the format of the drug file for the Division of Cancer Treatment. This data set, which contains cost information on clinical trials and preclinical screening of drugs, required new variables and new codes for existing variables. A data edit and update program was generated and a report summarizing the input data was provided. Also to be completed are four other summary reports. Future plans include addition of data retrieval via a CRT.

14. Provided programs for performing analytic calculations on scintillation counter data and plotting the manipulated data for the Laboratory of Chemistry, NIAMD. Future plans include adding new input formats whenever new instruments are purchased, and adding more efficient correction equations as new types of experiments are undertaken.

15. Developed programs to provide summary statistics on Mirex pesticide residue potency and exposure time for the Department of Agriculture. It was also necessary to create a reformatted tape with generated fields. Statistical analysis of this data (e.g., regressions) is taking place at the Department of Agriculture and the EPA.

16. Provided Wylbur-oriented data collection and search procedure for Dr. Freese, NINDS, to allow him to access by computer a collection of about 10,000 paper and journal citations.

17. Assisted Dr. Reichert, Laboratory of Neurochemistry, NINDS, in developing a data file to best utilize DCRT computer facilities for data analysis of sound-induced epilepsy. Laboratory of Statistical and Mathematical Methodology, DCRT, is providing statistical advice.

18. Completed development of a data base of journal abstracts from the literature of gastroenterology. Reformat and print programs were written. The CRAC system was utilized for searching the text. This is a pilot project to determine the usefulness of computerizing this data base. A number of searches were run on the data base in order to

explore the completeness of the file and the utility of the search. This experience indicates that automatic searching would not be cost effective at this time, and that a manual search is adequate. Running the Concordance program on the data base to produce a KWIC index for manual searching is the direction currently being explored.

19. Provided analysis and statistical programming support for the Type II Coronary Intervention Study.

20. Converted five PL/I programs from F-level compiler to Optimiz-Optimizing compiler for NLM's Toxline Data Base. One program was incomplete and required that an additional module be written.

Clinical Support Section

THE INFORMATION SYSTEM

During the past year the Clinical Support Section, in collaboration with Dr. Sharma, NIAMDD, has developed new modules for a planning and forecasting system, and conceptually, has improved the structure and utility of the system. The new modules are defined as follows:

. PERSONNEL Module - This module permits the operator to retrieve user-selected information in the field of personnel for decision-making purposes. The selections are made using the output selection sub-module which permits the user to display all or specific parameters from the unit record.

. PROJECT Module - The PROJECT Module displays selected information from three major sources: allotment allowance registry, object classification data, and program and monetary data.

. TRACKING - In the planning area, a module was developed that permits the collection, processing, recording, and displaying of program information for administrative and management purposes. The TRACKING Module was developed using the following assumption: the planning phase goes through many stages, and managers would like to recall, manipulate, and display various changes, additions and modifications made to programs in the planning phase.

Functional descriptions of the older modules of this system are:

. PROJECTION - This module displays contract and grant information in a very special way: using a base year and a selection strategy, the module will project over a six-year period monetary requirements for the defined time period and area specified.

. RETRIEVAL - The RETRIEVAL Module displays contract and grant information in a matrix format. The basic information displayed may be characterized as a profile of grants and contracts in a selected area.

.SUPPORT Modules - These modules are simply support programs designed for system maintenance purposes.

Since this system was designed to be operated on-line and interactively, some work was done to improve the display of operational information. Each module has uniquely defined commands with positioning selection parameters for defining retrievals. These commands and selection parameters form sub-modules within each major module, and are used to extract subsets of a given data base for display.

A HELP Command was developed that permits the user to display information on how to operate a user-selected module or specific command within the selected module. This developmental work was done using BNF Notions not only for assisting the user, but to document the module.

THE CLINICAL CENTER PROJECT

The improvement of the availability of clinical data to the NIH research community has been our primary concern this past year. This task was done through the expansion of data coverage and the completion, of our initial concept of a Clinical Information Utility (CIU).

Presently, there are three clinical data sources: clinical pathology laboratory data, discharge diagnosis and census data. Although only two of these data sources are accessed using the CIU System, clinical pathology laboratory and discharge diagnosis data, techniques have been defined which permit the retrieval of census data within the CIU structure.

The Clinical Information Utility System is a special data base management system that accesses clinical data by patient hospital numbers, data coded elements or a logical expression of data coded elements. The access by patient hospital numbers is simply a direct procedure that permits the retrieval of all or subsets of patient data.

The most powerful accessing technique of clinical data is performed by defining a patient set using Boolean logic. This procedure allows the user to define a set of patients using data coded elements from clinical pathology laboratory data, discharge diagnosis or both. The data coded elements are laboratory test codes and ICDA codes.

The Boolean logic accessing technique is made possible by simply inverting the files on the data coded elements, i.e., the keys in the inverted files are the data coded element. The unit record, uniquely defined, contains all patients that have had a given test or all patients that were discharged and assigned a specific ICDA code.

The Boolean logic module uses RMAG, a data support system developed in the Data Management Branch. All of the Boolean operators can be used for defining a selection strategy.

The Privacy Bill requires all systems accessing Federal Data Bases to maintain a log-file. In this log-file, the systems must record the following information:

a) Who accessed the data?
b) When was the data accessed?
c) Why was the data accessed?
d) What data was retrieved?

This feature was defined and implemented this past year for recording the above information. The Privacy questions are answered by simply running an inquiry using IRS to retrieve the requested information from the log-file.

Administratively, CIU is operated by the Clinical Center Staff, OCAM'S. Access to the data base is approved by OCAM'S. This office will request answers to the questions previously stated on Privacy for recording into the log-file. Other information such as accounting and type of retrieval will be requested for the completion of access privileges.

The search parameters that are used for retrieval purposes are as follows:

a) patient hospital number
b) data coded elements
c) date or date range
d) test value or value range.

In general the types of retrievals that may be defined are : a) All data on specific tests for a list of patients; b) All data on for a list of patients; c) all discharge diagnoses on a list patients; and d) any combination of search parameters.

Software Support Section

As discussed in the Branch summary, RMAG21 has been developed this year and all of the DMB generators are being redesigned and implemented using this flexible software.

NATIONAL INSTITUTES OF HEALTH
DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

Summary of Branch Activities

1. DCRT

2. LABORATORY OF STATISTICAL AND MATHEMATICAL METHODOLOGY

3. James E. Mosimann
Chief

1. INTRODUCTION

In its initial year of activity, the Laboratory of Statistical and Mathematical Methodology (LSM) developed its role of service in statistics, mathematics, and computer science for the NIH community. First priority was given to the establishment of computational and consultative services available to any member of NIH. New program packages of statistical and mathematical routines were implemented, and an active program of consultation was initiated. The description of computational and consultative services is outlined in sections 2 and 3, respectively. Some consultative services resulted in close collaboration of LSM staff with the investigator, and joint publication of results occurred.

LSM's own research activity is indicated in section 4. This activity is essential, since a program of consultation and service like that of LSM requires highly skilled professionals in statistics, mathematics and computer science.

2. COMPUTATIONAL SERVICES OF LSM

An important part of LSM's activity is the implementation and maintenance of statistical and mathematical program packages for the NIH user community. These packages offer a variety of programs to the user.

In addition to those previously available, four packages have been newly installed on the IBM 370. These are: SAS, the Statistical Analysis System from North Carolina State; IMSL, the International Mathematical and Statistical Library; PSTAT, the Princeton Statistical Package; and BMDP, the new UCLA Biomed series of programs. Along with the old BMD series, which will still be offered, and the NIH program collection known as MSTAT1, a broad statistical and mathematical capability is now available to 370 users.

Each package has its own characteristics and advantages. Some attractive features of SAS are the ease of use, convenient analysis of subsets of a dataset, and simplicity in editing, modifying and transforming data. SAS and WYLBUR are particularly compatible since SAS statements are column-independent. SAS is usable by anyone willing to learn a few procedure statements. The IMSL library comprises about 400 mathematical and statistical routines. Unlike SAS,

the user writes his own main routine to call these. A strong point of this library is its use of up-to-date numerical algorithms. PSTAT, the Princeton statistical package, offers programs that will perform multivariate analyses on large databases involving many variables.

The use of LSM-supported statistical and mathematical packages at NIH is considerable. Routines of the BMD package had an average of over 600 user-accesses per month during the past year (low, 430; high, 890). The new BMDP series was implemented at the end of the fiscal year, and counts of its use are not yet available. SAS, a new package, has shown steady growth in use. Accesses for the last four months have climbed as follows: 220, 320, 480, 530. This system now has close to 200 users. As an example of a package used for specialized but essential purposes, PSTAT had an average of 10 accesses per month. Since IMSL is a subroutine library, counts are not available. The old math/stat library MSTAT1 had 900 accesses per month in the first half of the year. Unfortunately, comparable counts are not available for the second half of the year.

Important packages in the mathematical modeling area are MODELAIDE (S/370) and MLAB (PDP-10). Both packages receive wide use at NIH and elsewhere. Their authors are currently with LSM. Both the authors of MODELAIDE and MLAB are active in consultation and collaboration with NIH users. Both systems have been exported internationally and domestically to a variety of institutions. Most recently, the SUMEX computer project at the Stanford Medical School is providing MLAB to its users.

In the past year, a new MLAB manual (the 5th edition) has been prepared and is available. MLAB is promoted with demonstrations and courses. This system provides an interactive mathematical modeling capability with extensive graphical capability.

3. CONSULTATIVE SERVICES OF LSM

The consultative services of LSM range in subject and scope from answering a question about the job control language needed for a particular program package, to the development of statistical methods and models for data analysis for a particular experiment.

Specific consulting activity is defined as activity directly and consciously devoted to the needs of a specific user outside LSM. Hours devoted to direct consulting by LSM during the year are given below. Of course, other LSM activities underlie and support the direct consulting; for example, installation and maintenance of statistical packages requires considerable time which does not appear as direct consulting.

LSM averaged 550 hours per month of specific consulting out of 1600 total hours. All NIH institutes except NIGMS are represented in these hours. Eighty-five percent of LSM's specific consulting was directly to users outside DCRT. The remainder was also directed to users outside DCRT, but through the intermediary of non-LSM, DCRT staff.

Of the total hours, 20 percent involved largely mathematical or statistical advice with little computer use; 40 percent involved mathematical and statistical advice alongside considerable computer use; 40 percent involved mostly computation with little or no mathematical or statistical advice.

A major service of LSM consulting is responding to trouble-shooting questions rapidly and efficiently. Just over 50 percent of specific consulting activities involved sessions of one hour or less; and just over 80 percent, 4 hours or less. Availability of staff for the rapid resolution of user problems is a prime concern of LSM.

Of those jobs requiring more than four hours, many represent a sizeable effort on the part of LSM staff. The following list gives some indication of the variety of such projects.

1. J. Bieri and R. Evarts, LNE, NIAMD. Evaluation of the Vitamin E activity of gamma-tocopherol relative to alpha-tocopherol. Consultation was done on the analysis of experimental data to assess the relative potency of gamma-tocopherol as well as on the statistical principles underlying parallel line bioassays.

2. V. Bono, DE, NCI. Evaluation of chemotherapy drug assays. Computer models were developed and implemented for the analysis of cell DNA content, as revealed in histograms obtained from drug-treated tissue culture preparations. Therapeutic and non-therapeutic drug effects were contrasted.

3. A. Cheever, LPD, NIAID. Study of the effects of schistomiasis using autopsy data. A large file was organized. Numerous tables were produced. Discriminant and other analyses were performed. To date, association of egg and worms burden by anatomical site with pathological conditions have been studied.

4. B. Chock, LB, NHLI. Cascading enzyme systems. A system of cascading enzymes is simulated using MODELAIDE.

5. J. Folk and R. Chung, LB, NIDR. Activation and inhibition of clotting factor XIII. Mechanisms of action are being modeled.

6. M. Geier, LGCB, NIMH. Maintenance of data analysis software. Computer programs for evaluation and display of laboratory data were maintained, and user assistance provided as needed.

7. V. Geoffrey, IR, NINDS. Study of dystonia. Analysis of time intervals comprising sequences of speech, dystonia, speech, ... Calcomp programs were written for graphic display of the sequences over time. A large FORTRAN program generated tables of data cross-classified and grouped. Various descriptive statistics were generated by use of packaged programs.

8. V. Geoffrey, IR, NINDS. Parkinsonian patients. Accelerometer observations were made on speech sounds under two different treatments. The association of accelerometer variables with treatment was studied, assisted by Karen Pettigrew, NIMH. A package profile analysis, in conjunction with editing and other package programs was employed.

9. R. Ginsberg, EFS, NIAMD. Investigation of the effect of phenobarbital on biliary lipid metabolism in man. Biliary parameters were measured before and after administering the drug. Statistical tests of significance were performed to determine whether differences existed between the means of the biliary parameters before and after administration of phenobarbital.

10. R. Hamman, EFS, NIAMDD. Data on diabetes patients. Several days' study of BMDX76 (Survival Curve Program) to interpret options and output.

11. R. Hamman, EFS, NIAMDD. Time-in-study without a positive glucose tolerance test: subjects from a population with high incidence of diabetes. Age/sex/weight were cross-classified and compared. A FORTRAN program was devised.

12. R. Hendler, LB, NHLI. Oxidation of cytochromes. A paper has been completed using the non-linear fitting procedures of MLAB.

13. R. Hendler, LB, NHLI. Mathematical modeling. A paper on oxidation of cytochromes is now in print. Models for an improved multi-channel technique for resolving absorption data into chemical species are being considered. Also, models for DNA damage and repair are under discussion.

14. C. Hoover, DCBR, NIMH. Marital conflict in manic-depressive patients. The investigator is attempting to isolate factors in marital conflict which differentiate patients from their spouses or distinguish between diagnostic subclassifications of manic-depressive illness. Thus far, discriminant analysis has been the principal statistical method employed. A program has been written to evaluate discriminant functions calculated by the BMD series discriminant analysis program.

15. L. Keefer, CMT, NCI. Investigation of the hydrolysis of methyl (acetooxymethyl) nitrosamine (DMN-OAc) to the presumed carcinogenic metabolite of dimethylnitrosamine (DMN-OH). In order to determine the uniform consumption rate of the starting material and a uniform disappearance rate of the total nitrosamines, regression analyses were performed.

16. L. Kohn; R. Tate; L. Leive, LBP, NIAMD. Two counter scintillation. A mathematical solution for the optimum position of a discriminator between carbon and tritium channels was obtained.

17. L. Kvols, BC, NCI. Duration of remission and mortality data for Hodgkin's disease. Several analyses were made using the Breslow program.

18. C. Maloney, BOB, FDA. Pertussis potency tests. This project involves the development of statistical programs for use in the comprehensive examination of the potency and safety testing of pertussis vaccines by the Bureau of Biologics. Findings have led to innovations in testing procedures.

19. C. Maloney, BOB, FDA. Bioassay. This project involves evaluation of different computational methods in an effort to refine the assessment of biologics products. A bioassay program with a number computes either probits or logits with options for individual and/or pooled slopes, with or without conversion of, and a test for parallelism in relative potency has been written.

20. N. Matheson, EM, NLM. The impact of a one-year grants program on hospital library development. A master file was created, and programs to generate new variables were written. These were interfaced with the Statistical Analysis System (SAS) which was employed to calculate a large volume of descriptive statistics and tables. Ms. Matheson's report concluded that the grants program had had a statistically significant effect on the development of hospital libraries.

21. E. Mihalyi and D. Towne, LB, NHLI. Kinetics of Fibrinogen digestion. A fourth paper in a series on this topic has been completed. The analyses involved extensive use of MODELAIDE.

22. R. Peabody, DIR, CC. Interview scheduling. LSM has assumed the responsibility of preparing and running the interview scheduling system for the NIH Associate Program of the Clinical Center. This system, which schedules the applicants for interviews, prints acceptance letters, interview, applicant, and master schedules, is run each spring.

23. H. Pettigrew, B, NCI. Small-rodent carcinogen-bioassay experiments. The analyses employed survival curve methods. Modification of a previously existing Breslow program, and study of the literature on survival curves was performed.

24. W. Reichert, LNC, NINDS. Study of sound exposure and audiogenic seizure on cerebral ATPase activity in mice. Comparisons of enzyme activity in sound-exposed and control mice of two strains were made using analysis of variance and t-tests. Data were first standardized by litter. Reichert has finished a paper on this work.

25. D. Reiss, APB, NIMH. Multi-family group study. This study concerns disturbed adolescents and their families. There are four major types of data: "who-to-whom" speech data, cohesiveness questionnaire data, sociometry data, seating position data. Data for this study is voluminous. Although programs for each type of data are completed, maintenance and data processing does require considerable effort. Dr. Reiss is now with the Center for Family Research, George Washington University.

26. P. Savage, EFS, NIAMDD. Discriminant analysis of diabetes-related variables in patients with and without retinopathy.

27. P. Savage, LFS, NIAMDD. Multivariate observations on diabetes patients. Queries on mathematical models were handled and multiple and partial correlation and regressions were performed. Relevant literature was reviewed. Interpretation of SAS options and outputs in regression and correlation programs was given.

28. K. Smith, VR, DRS. Selection for body weight in mice. Statistical programs have been written for this study which are directed toward providing an objective evaluation of the effects upon genetic variation in inbred strains of mice.

29. G. Spellman, CP, CC. Effect on clotting of varying amounts of red cell protein. Extensive editing and package programs were used in conjunction with mathematical modeling by Karen Pettigrew, NIMH.

4. RESEARCH ACTIVITIES OF LSM

The LSM computational and consultative activities place highly qualified mathematicians, statisticians and computer scientists at the service of the biomedical community. LSM specialists must exhibit an up-to-date knowledge of their subject matter fields at the research level. Research activities within LSM in mathematics, statistics, or computer science (1) either spring directly from NIH problems which require new explorations in these fields or (2) contribute in a major way to the development of the staff member's excellence in the field for which he is responsible.

The LSM research effort averaged 500 hours per month. About 50 percent of these hours are in support of direct consulting activities. Individual projects follow.

Project No. Z01 CT 00008-01 LSM
1. Lab. of Stat. and Math. Methodology
2. Not Applicable
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Pattern Recognition

Previous Serial Number: None

Principal Investigator: Marvin B. Shapiro

Other Investigators: David Symmes (NICHHD)

Cooperating Units: None

Man Years:

Total:	0.5
Professional:	0.5
Others:	0.0

Project Description:

Objective:

The development of a set of pattern recognition computer programs for use in biomedical research.

Methods:

A variety of pattern recognition techniques are being implemented for the PDP-10 computer. These techniques include the computer learning machine, the minimal spanning tree algorithm, non-linear mapping methods, feature selection, and nearest neighbor analysis.

Major Findings:

(1) Both learning machine and cluster analysis techniques were applied to an analysis of monkey vocalization patterns. Results clearly showed that the patterns for each individual monkey clustered together and that patterns for a given monkey can be recognized as different from those of other monkeys.

(2) An algorithm was developed which considerably improved the efficiency of the nearest neighbor method, a widely used pattern classification technique.

(3) Learning machine and nearest neighbor classification techniques were applied to predicting the activity of cancer anti-tumor drugs based on substructural features. Using a training set of 138 drugs containing 421 different substructural features of three types - augmented atoms, ring structures, and paths between heteroatoms - a prediction rate of 80 - 90 percent was obtained on a test set of 24 drugs of unknown activity.

Significance to Biomedical Research:

The recently developed field of pattern recognition offers important new approaches to organizing and analyzing biomedical data. Especially important is its ability to find unexpected relations among data. To display multidimensional data, to analyze features in data are other important benefits.

Proposed Course:

The programs already developed plus a number of other important methods will be collected into a package designed for general use on the PDP-10 computer. A manual describing the package will be written and distributed.

Keywords:

pattern recognition, cluster analysis, learning machine, nearest neighbor classification, feature extraction

Honors or Awards: None

Publications:

Chu, K. C., Feldmann, R. J., Shapiro, M. B., Hazard, G. F., Geran, R. I.: Pattern Recognition and Structure-activity Relationship Studies. Computer-assisted Prediction of Antitumor Activity in Structurally Diverse Drugs in an Experimental Mouse Brain Tumor System. J. Med. Chem., June, 1975.

Project No. Z01 CT 00009-01 LSM
1. Lab. of Stat. and Math. Methodology
2. Not Applicable
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Research Topics in Computer Science

Previous Serial Number: None

Principal Investigator: Gary D. Knott

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	0.7
Professional:	0.5
Others:	0.2

Project Description:

The object of this project is to develop theoretical bases for new computer methods which will expand and improve its use in biomedical computation. The methods used are the application of known and the development of new pertinent theorems from combinatoric and other related mathematics. Research work in storage and retrieval algorithms and their efficiency has been the primary topic of concern. A Ph. D. thesis on deletion in binary storage trees has resulted from this research and is cited in the publications list below. This research will culminate in several further publications in the future. Other work concerns a numbering system for permutations of combinations cited below.

Research on Operating Systems Interprocess Communications has been done, resulting in a two-part publication on a proposal for such a facility in Operating Systems Review (cited below) and in the presentation of this work at the recent workshop on interprocess communications sponsored by SIGOPS and SIGCOMM of the ACM.

Optimal item orderings in split hashing schemes and certain interesting algebraic characterizations of fixed permutation open addressing methods are currently being studied.

These methods have and continue to improve the efficiency of computers in biomedicine and make new applications possible.

Keyword Descriptors:

computer science, storage and retrieval, operating systems

Honors and Awards: None

Publications:

Knott, Gary D.: "A Numbering System for Permutations of Combinations", CACM, to appear, 1975.

Knott, Gary D.: Deletion in Binary Storage Trees, Ph. D. thesis, Stanford University, Computer Science Department, 1975.

Knott, Gary D.: "A Proposal for Certain Process Management and Interprocess Communication Primitives, Part I", Op. Sys. Review, Vol. 8, No. 4, pp. 7-44, October 1974.

Knott, Gary D.: "A Proposal for Certain Process Management and Interprocess Communication Primitives, Part II," Op. Sys. Review, Vol. 9, No. 1, pp. 19-41, January 1975.

Project No. Z01 CT 00010-01 LSM
1. Lab. of Stat. and Math. Methodology
2. Not Applicable
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Nonlinear Equations

Previous Serial Number: None

Principal Investigator: Richard I. Shrager

Other Investigators: Gary D. Knott (LSM, DCRT)
Edward Hill (LAS, DCRT)
John E. Fletcher (LAS, DCRT)
J. Douglas Ashbrook (LAS, DCRT)

Cooperating Units: DCRT, Laboratory of Applied Studies

Man Years:

Total:	1.0
Professional:	1.0
Others:	0.0

Project Description:

Objective:

To develop methods for solving nonlinear equations frequently encountered at NIH.

Methods:

A continuing effort is made to create methods or extend existing methods to solve problems in a host of NIH applications, and to make those methods available in convenient computer programs or routines, such as MODELAIDE and MLAB.

Major Findings:

a) Marquardt's method for nonlinear least squares was extended to handle linear constraints.
b) A suitable error analysis was devised for constrained parameters.
c) A method for solving nonlinear stiff differential equations was adapted to computer from a Ph. D. thesis of Kai-Wen Tu.
d) Marquardt's method, see (a), is now being extended to norms other than least squares. Preliminary results are promising.

Significance to Biomedical Research:

These methods are now being applied to problems in human metabolism, cell growth, chemical kinetics, and spectral analysis (UV, IR, CD, ORD, NMR, ESR).

Proposed Course:

As the methods are proved in test and practice, they will be incorporated into easy-to-use systems like MLAB, and as a result, the systems themselves should evolve to do more useful work with both less human and less machine effort.

Keyword Descriptors:

nonlinear, parameter estimation, least squares, stiff differential equations, linear programming, quadratic programming, minimax approximation, error analysis

Honors and Awards: None

Publications:

R. I. Shrager: Constraint analysis in model building. Proceedings of the Fifth (1974) Annual Pittsburgh Conference on Modeling and Simulation, Part 2, 991-996, Instrument Soc. of America, 1975.

D. E. Blumenfeld, R. I. Shrager, G. H. Weiss: Spatial distributions of homes for journeys to work by different modes of transportation. Transportation Res., 9, 1, 19-23 (February 1975).

R. W. Hendler, D. W. Towne, R. I. Shrager: Redox properties of b-type cytochromes in Escherichia Coli and rat liver mitochondria and techniques for their analysis. Biochimica et Biophysica Acta, 376, 42-62, 1975.

I. G. Darvey, R. Shrager, L. D. Kohn: Integrated steady state rate equations and the determination of individual rate constants. J. Biol. Chem., (in press).

Project No. Z01 CT 00011-01 LSM
1. Lab. of Stat. and Math. Methodology
2. Not Applicable
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Discrete Mathematics and Applications

Previous Serial Number: None

Principal Investigator: George Hutchinson

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	0.5
Professional:	0.5
Others:	0.0

Project Description:

Objectives:

To make new mathematical methods, techniques and discoveries in discrete mathematics available and explore their application to biomathematics and computers.

Major Findings:

Advances were made in demonstration of recursive unsolvability of certain classes of problems concerning subspaces of a vector space. (In effect, no computer program can be written to solve this particular problem in a general way.) It was demonstrated that certain related classes of problems were solvable, and that the order relationships between arbitrarily many subspaces of a vector space can be reduced to their study between five subspaces.

Significance to Biomedical Research and the Program of the Division:

Contribution to mathematical research and constrains computer solutions to a wide class of applied biomathematical research.

Proposed Course:

An earlier study applying linear inequalities to chemical reaction systems will be revised for publication. Mathematical findings are now being edited and followup studies in preparation. Further development of chemical reaction system analysis will be considered, and new applications explored.

Keyword Descriptors:

linear algebra, modular lattices, linear inequalities, chemical diagrams

Honors and Awards: None

Publications:

Hutchinson, G.: On the representation of lattices by modules. Trans. Amer. Math. Soc. (In press).

DRG

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Project No. Z01 CT 00012-03 LSM
1. Lab. of Stat. and Math. Methodology
2. Not Applicable
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Visual and Biological Shape

Previous Serial Number: DCRT 1.1

Principal Investigator: Harry Blum

Other Investigators: Virgil Carlson (NIMH)
Brian Murphy (NIMH & U. of Md.)
Richard L. Webber (NIDR)

Cooperating Units: NIMH, Laboratory of Psychology and Psychopathology
NIDR, Clin. Invest. and Research Serv. Branch

Man Years:

Total:	0.6
Professional:	0.6
Others:	0.0

Project Description:

The overall objective of this project is to develop a formal descriptive language applicable to biological shapes and apply this language to the variety of problems arising in biology and medicine: taxonomy, neurobiology and organismic development. This would permit a better modeling, hence understanding of these processes and also allow for the automation of many shape processes now done by humans.

The method employed stems primarily from a new geometry conceived by the principal investigator. It is applied to a variety of problems, both to clarify the biological processes taking place and to develop the mathematics in biologically relevant directions. These have included cells and tissues from light microscopy, skeletal descriptions in growing organisms, chromosome description, visual psychophysics and visual neurophysiology.

A major accomplishment this year is the setting up of an experimental procedure for doing shape psychophysics on amorphous forms by humans. Other major accomplishments deal with theoretical developments to allow implementation of such a geometry on a computer. These are: (1) the development of a method for getting proper description on a computer without sacrificing the smoothness of the forms, (2) the extension of the method to forms that

are specified by gray scale pictures and (3) the extension of the methods to the description of 3-dimensional forms.

Anticipated work next year includes the continued experiments on visual psychophysics of amorphous forms, continued descriptive work on skeletal forms, continued implementation of the theory to computer implementation, and finishing of the application to the theory of shape processing in the vertebrate visual system.

Keyword Descriptors:

biological shape, biomathematics, geometry, taxonomy, developmental biology, visual psychology, visual physiology, nervous system models

Honors and Awards: None

Publications:

Blum, H.: A Geometry for Biology. In Gurel, O. (Ed.): Mathematical Analysis of Fundamental Biological Phenomena. Annals of the New York Academy of Sciences, Vol. 231, pp. 19-30,1974.

Project No. Z01 CT 00013-01 LSM
1. Lab. of Stat. and Math. Methodology
2. Not Applicable
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Multivariate Statistical Methods

Previous Serial Number: None

Principal Investigator: James E. Mosimann

Other Investigators: Cecelia B. Clark (Project Stride)

Cooperating Units: None

Man Years:

Total:	0.2
Professional:	0.2
Others:	0.0

Project Description:

The overall objective of this project is the study of multivariate statistical methods for the analysis of data which take the form of ratios or proportions. Included is a study of properties of the multivariate lognormal distribution in the analysis of ratios. This distribution has broad applicability to biomedical data at NIH.

Keyword Descriptors:

size variable, shape vector, multivariate lognormal distribution, gamma distribution, Dirichlet distribution, constrained variables

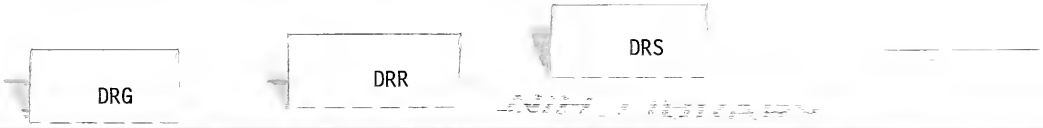
Honors and Awards: None

Publications:

Mosimann, J. E.: Statistical Problems of Size and Shape. I. Biological Applications and Basic Theorems. In Statistical Distributions in Scientific Work, Vol. 2, Model Building and Model Selection, G. P. Patil, S. Kotz, and J. K. Ord, eds. pp. 187-218, D. Reidel Publishing Company, Boston, Massachusetts, 1975.

Mosimann, J. E.: Statistical Problems of Size and Shape. II. Characterizations of the Lognormal, Gamma and Dirichlet Distributions. In Statistical Distributions in Scientific Work, Vol. 2, Model Building and Model Selection,

G. P. Patil, S. Kotz, and J. K. Ord, eds. pp. 219-240, D. Reidel Publishing Company, Boston, Massachusetts, 1975.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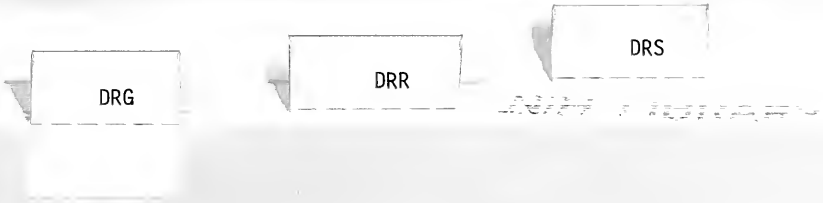
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CONTENTS

HIGHLIGHTS

The Division of Research Grants processed 30,167 applications for the FY 1975 councils. This represented a 19 percent increase over FY 1974 in applications processed and assigned and a 26 percent increase in competing applications reviewed.

Training programs have become increasingly complex with three different types of programs in operation--the traditional research training program, the research manpower program, and more recently the NRSA program. New application forms and revision of old ones have been necessitated and new guidelines developed.

There was a sharp increase in inquiries resulting from the NRSA program announced during the year.

The centralization of research grant application kits in control offices in grantee institutions has been generally accepted. Problems remain with NIH components supporting special programs under the research grants mechanism.

Eight conferences were held to review the status of research in population genetics, NMR resource facilities, nutrition intervention, bioinorganic chemistry, growth hormone and growth factors, behavioral toxicology, glycoprotein hormones, and epidemiology and biometry resources and needs.

The Grants Associates Board reviewed 43 candidates; 11 were recommended for the Program. By the end of the fiscal year, 8 GA's will be on board and 7 will have graduated.

A new system was developed to track applications involving human subjects.

Consolidation of various data-capture processes into a single system is presently under study.

Several data items in the IMPAC system were converted to conform with the new DFM accounting numbers.

An informational bulletin, "IMPAC Tech Notice" has been developed for issue as needed to keep users informed of current and proposed changes in the system.

Total redesign of the CRISP system was initiated.

A chart book, "NIH Extramural Trends FY 1967-1974" was prepared for administrative use. A series of overhead slides on key extramural trends was developed and presented in August 1974.

The Director attended several meetings during the year under review. He spoke at a workshop for new deans held by the Council of Graduate Schools of the United States in Gainesville, Florida, July 15-19, 1974; to the Association of Independent Research Institutes in Oklahoma City, Oklahoma, September 19-20, 1974; and at a workshop on sponsored research and training at the University of Florida, Gainesville, Florida, October 20-21, 1974.

The Director attended the meetings of the American Council on Education in San Diego, California, October 9-11, 1974; the Association of American Medical Colleges, Chicago, Illinois, November 11-14, 1974; the task force on biomedical sciences, Council of Graduate Schools, Phoenix, Arizona, December 4, 1974; the Western Association of Graduate Schools, Honolulu, Hawaii, March 3-6, 1975; and participated in a conference for science executives in Williamsburg, Virginia, December 8-13, 1974.

The Director is a member of the Coordinating Committee for Program Management.

The Deputy Director participated in the annual meeting of the Association of American Medical Colleges in Chicago, November 13, 1974; in a seminar sponsored by the Faculty of the University of Arkansas in December 1974, and met with graduate and research committees of the University. He also participated in a workshop on proposal development, sources of support, and budgeting at North Carolina State University, Raleigh, North Carolina, February 5-6, 1975; and visited Michael Reese Hospital, Chicago, Illinois, March 19, to consult with grantees.

The Deputy Director is Chairman of the Subgroup on Safeguarding Sensitive Statistical Data; the Coordinating Committee on Protection of Privacy; and the Manpower Utilization/Productivity Committee of ECEA.

The Deputy Director is a member of the Committee on Dissemination of Research Results; the Federal Information Processing Standards Task Group 15; the Grants Associates Board; the ECEA; and the ECEA Subcommittee on Training. He also attends meetings of the Collaborative Program Directors.

The Associate Director for Scientific Review acted as the moderator of the NIH Panel at the Federation of American Societies for Experimental Biology meeting in Atlantic City, April 14-18, 1975, and spoke at the Minority and Women's Opportunity and Resources Conference held at NIH on April 22-24, 1975. He also participated in a Conference for Federal Scientists and Science Executives sponsored by the Brookings Institute at Williamsburg, Virginia, March 9-14, 1975; and attended the Seminar for Executives on Legislative Operation held in Washington, D.C., June 11-13, 1975. The Associate Director is a member of the NIH Executive Committee for Extramural Affairs; the ECEA Subcommittee on Research; NIH Minority Coordinating Committee; Committee on Human Rights; Committee for Development of Peer Review Regulations; Action Committee on Review of R & D Contract Proposals; and the NIH Grants Peer Review Study Team. He is co-Chairman of the Executive Secretaries' Review

Activities Committee and Acting Executive Secretary of the Advisory Committee to the Director, NIH, on DNA Combinants. In his role as Acting Executive Secretary of the DNA Combinant Committee, the Associate Director was responsible for the organization and selection of the membership of this committee.

The Division's formal employee training program continued throughout the year to further the career needs of the staff. Eleven employees attended Federal City College under the Upward Mobility Program, and 27 signed up for the Staff Training Extramural Program (STEP). The Personnel Office received 647 applications for training courses, of which 408 were approved. Of these, 238 employees completed training programs. Ninety-two courses are still in progress. Fifty-six employees attended orientation sessions held throughout the Division during the year.

The Opportunity Program (TOP) Committee held a half-day orientation for employees to help them with problems and complaints. The Committee also assisted in arranging meetings between the Division's female staff members and the Federal Women's Coordinator who held three sessions during a day-long visit to the Westwood Building.

The Committee appointed a subcommittee to review the end results of training courses (especially those taken by minorities, women, and employees below GS 9)--whether or not the courses had a positive effect on employees' careers, and the reasons why they took courses if they did not apply for positions for which the training qualified them, or why they were not selected to fill such positions.

TOP Committee placed a box in the DRG Reference Room where employees could place comments and suggestions that would increase communication between the Committee and the staff.

New staff members are being approached informally by TOP Committee members to brief them on the Committee's role and to offer guidance or direction if needed.

The Committee is actively involved in the review and updating of the brochure, "DRG is People," to be used as a hand-out for new staff members.

The DRG-EEO Counselor participated in the NIH EEO Advisory Council functions and activities including bi-weekly council meetings, monthly Counselor Committee meetings, the annual 2-day NIH orientation for new EEO counselors, the Civil Service Commission 3-day on-site EEO Counselor Interagency Training Program, the NIH EEO Organizational Development Program, including Management by Objectives (2 planning sessions), and several of the NIH STEP Committee Continuing Education Program Modules.

The Counselor met with TOP Committee on a continuing basis, and attended the DRG Director's Staff Meetings and those of his ad hoc EEO program group. The Counselor participated with members of TOP Committee in a periodic 1-day orientation of DRG personnel and office functions, and was a speaker in three 1-day sessions of the DRG Employee Orientation Program, whereby 75 employees were informed of the EEO program. The Counselor also participated in several

Special Management Workshops and Sessions conducted by the NIH Supervisory and Management Development Branch.

The Counselor maintained a continuing open-door policy regarding opportunity for counseling on equal opportunity and discrimination procedures, and conducted several informal interviews and conferences with Division personnel regarding the new NIH Merit Promotion Plan, career ladder opportunities, training and participation in the Upward Mobility Program, and other training and education opportunities.

OFFICE OF GRANTS ASSOCIATES

The Grants Associates Program, unique to the Federal Government, is designed to train established biomedical and behavioral research scientists in health science administration. Since its inception in 1962, the Program has graduated 98 associates, 80 of whom remain in the Federal Government (77 of these are in the PHS). Fourteen others are no longer in Federal employment (although many of these had been in the Public Health Service after graduation from the Program); two others are deceased and two have retired.

Among the graduates are the Associate Director for Extramural Research and Training, and the Assistant to the Associate Director for Collaborative Research, Office of the Director, NIH, an NIH division director, an assistant NIH division director, institute associate directors of extramural programs, and several program directors and branch chiefs within the institutes.

Graduates hold positions in all the PHS agencies with the exception of the CDC and FDA. Within NIH, former associates hold positions within all the institutes (except the newly-established Institute on Aging) and in DRR and DRG. Among the graduates, 10 are women and 15 are members of minority groups.

A 3-day retreat was held this year to review the Program, its mission and the means toward its goals. Several recommendations resulted, some of which are being implemented; others are being processed or reconsidered. Among the recommendations is an emphasis on more formalized training, particularly in management. The varied courses offered in this area are selected by the Grants Associates in consultation with their preceptors to insure that they are appropriate to their training needs. Subsequently these courses are evaluated in terms of relevance to other GA's generally or selectively. These courses have included congressional operations for managers, management principles, program planning and evaluation, committee dynamics, management by objectives and public policy, and management of scientific research. Another recommendation is a more refined mission statement followed by clearer selection criteria. This will assist the Board in its selective process of inviting to the Program the most qualified from among the increasing number of applicants. Another recommendation is the expansion of GA assignments to NIH-wide task forces and to other Federal agencies such as OMB and NSF.

A new area of exploration, but related to the above, is the type of candidate who should enter the Program. Initially, the Program had been aimed at researchers with little, if any, administrative experience. The trend now is to allow into the Program scientists with varying degrees of administrative experience, not necessarily in Government. At present there is a mixture of both those with minimal and those with a fair degree of administrative experience. The rationale is that such a mixture would be advantageous to the GA's who learn a great deal from each other, and also that the person with a fair amount of experience in administration could transfer these skills to Federal administration, thus producing a stronger health scientist administrator. This kind of mixture resulted in an innovation being tried on one candidate, namely an abbreviated

GA program. The abbreviated period would be decided upon during the first few weeks between the associate and his or her preceptor (as opposed to the Board's approving a request during the 12-month training period for an associate to terminate early). Although this option has been available during the history of the Program, it has not been exercised. Should this prove successful, then it could be used again selectively.

The weekly seminars continue to be a blend of orientation to Public Health Service and examples of administration. This year they have included ethical issues: EEO, protection of human subjects, and concerns about conflict of interest.

In FY 1973, 500 inquiries were received about the program, and 557 in FY 1974. Up to 300* are anticipated in FY 1975, based on the expected increase in inquiries after the FASEB meetings held in April. Sixty-six people, including 8 females and 13 minorities, were interviewed at FASEB. The meetings are also expected to produce an influx of applications. Over 250* are expected by the end of this fiscal year compared with 298 received last fiscal year and 252 in FY 1973. Forty-three candidates will have reached Board review this fiscal year compared with 32 from over 250 applicants in each of FY 1973 and FY 1974. As of April 1975, 11 candidates were recommended to join the Program. By the end of this fiscal year, 4 of these will be on the Program, 3 others have firm EOD dates and 4 others have pending EOD dates. The Program has maintained from 8 to 10 associates at any given time. By the end of the fiscal year, the Program will have 8 associates on board and will have graduated 7. The 15 associates in the Program in fiscal year 1975 represent a variety of disciplines: one each in physical chemistry, genetics, experimental psychology, biochemistry, biophysics, microbiology and veterinary medicine, and molecular biophysics; and two each in physiology, organic chemistry, biology, and zoology. The range of disciplines does not affect the goal of the program to develop health scientist administrator generalists, but associates are encouraged to pursue their scientific interests on their own.

* The periodic recruitment advertisement in Science was not placed this year, hence these figures are not as high as in the past 2 years.

OFFICE OF GRANTS INQUIRIES

A sharp increase in routine mail and telephone requests for material resulted from the announcement of National Research Service Awards for individual and institutional postdoctoral fellows.

Amendments to the Freedom of Information Act and the advent of the Privacy Act have required staff attendance at meetings for interpretation of the Acts prerequisite to applying policy. The Office established the DRG Freedom of Information Index as an integral part of the overall NIH Index.

The centralization of grant application forms in control offices in grantee institutions has proved to be a speedier and less costly operation for the NIH than was the old method of mailing applications singly to investigators. Since the new system of bulk-mailing applications became effective in January 1974, complaints have been minor and, in the past 6 months, centralization of applications has been generally accepted by the grantee institutions. The problems now are created internally by NIH institutes that have special programs requiring inserts with application forms.

Restricted travel funds kept the Division exhibit in storage all year. The Grants Inquiries Officer accepted a local speaking engagement January 6, 1975, before campus representatives of the Associated Colleges of the Midwest and the Great Lakes Colleges Association.

A member of the staff was named by the Director as DRG's representative on the NIH Minority and Women's Resources Conference Committee.

A sound-on-slide series, "How a Research Grant is Made," was updated to show women and minority group members on the study sections.

OFFICE OF RESEARCH MANPOWER

During fiscal year 1974, the Office of Research Manpower (ORM) coordinated the reinstitution of training through the Research Manpower program. The National Research Service (NRS) Act of July 1974, however, rescinded these programs and all previous research training authority. Consequently, ORM has once again been involved in the many complexities associated with mounting new programs. For example, in cooperation with a committee of DRG and I/D representatives, the Office developed a new application form for the institutional NRS grant and expedited clearance of the form so that it would be available for the February 1975 application receipt date.

ORM also: prepared new program announcements on the individual and institutional NRS awards, working closely with each I/D on specified research areas considered to be in need of additional trained personnel; revised the individual fellowship application kit to reflect the NRS program, and obtained an extension on use of the application form and related materials until December 1975; and prepared the initial draft on the guidelines governing the NRS program. This document, which was issued in May 1975, reflects the official policy on the program.

Since applicants under the NRS program are subject to certain payback provisions, each applicant under the Research Manpower program was contacted to determine if he or she still wanted to be considered. The Chief, ORM, is serving on the PHS Task Force to implement the payback provisions. These provisions have been of considerable concern, and have caused innumerable discussions with applicants, academia, and NIH personnel.

Updated materials were also prepared for the Research Career Development Program: a) program announcement, b) extension on use of the application form, and c) a draft policy brochure for review by OERT.

The major areas in which the Office is now involved are:

1. developing a new continuation application form for the NRS institutional grant through a committee of DRG and institute representatives; and processing a request for extension of the old form for use under the old program; and,

2. preparing for clearance of a new application form for the individual NRS award. This form was being developed this time last year, but because of the change from the Research Manpower to the NRS program, the drafting committee had to be reconvened to adapt the form to the new program.

Routine operations of the Office included responding to numerous requests from within and outside NIH on status, statistics, and policy on the training programs.

Several tasks remain to be completed, including:

a. revision or extension before December 1975 of the RCDA application

forms, both new and continuation; the individual fellowship continuation application form; and the fellowship supplementary forms, such as the activation notice and termination notice;

b. revision of the Statement of Appointment Form to accommodate the NRS program, and

c. if the institutes consider it important enough, the Handbook for individual fellows will also need to be revised to accommodate the NRS program.

Problems encountered during the year under review are to a large part situational. The training programs have been in a constant state of change over the last 2 years. As a result of the changes, NIH has an old training program, a Research Manpower program, and an NRS program, and, as indicated above, NIH is in a period when all of the training forms are expiring and need to be revised or extended.

The individual NRS applications received under the May 1, 1974, receipt date were originally submitted under the Research Manpower program (F22) and had to be converted to NRS program. Although these applications were acted on at the November 1974 Council, no awards could be made until the final regulations governing the NRS program were published in the Federal Register. The regulations were published first as proposed rules on January 17, 1975, and then as final regulations on May 2, 1975.

ADMINISTRATIVE BRANCH

The DRG Budget Office has assisted in administering about $12.1 million for DRG operations: $9.8 million from the NIH Management Fund and $2.3 million from the institutes for the support of 47 Study Section Scientific Evaluation Grants. The $2.3 million was awarded among the study section chairmen; expenditures were monitored by a computer data base system which provides DRG management with up-to-date monthly costs analyses. For the first time, consultant costs were funded almost entirely from Scientific Evaluation Grants, saving time and effort in paying consultants.

The Budget Office, in conjunction with the Personnel Office, has assisted the Department in updating its personnel data system. This required many changes to the data in the Department's terminal data collection system (TDCS). The personnel data system is now being used for the official employment reports to the Civil Service Commission. Future plans are to merge the system with the payroll data system for pay purposes.

The Reference Room reorganized its card catalog system. All the books are now cataloged by subject, as well as title and author contributing to efficiency and savings in time. To correct a gap perceived in coverage of scientific areas, 84 new books and 43 new journals have been acquired. Reference Room personnel continue to provide a service to all Westwood employees.

The Travel Section continued providing information and assistance for DRG personnel and outside consultants traveling for the Government. During the past fiscal year, approximately 5,000 travel vouchers totaling over $2 million were processed and forwarded for payment for consultants who serve on the various study sections. Another $250,000 was spent to pay travel costs on approximately 800 vouchers for DRG travelers and other Government employees.

The Special Services Section continued to provide typing and clerical assistance to DRG and other institute/division staff. Four typists with magnetic card typewriters and one CRT unit completed about 2800 letters, 10,000 mailing labels, and 600 Summary Statements. The Section also typed 540 pages of draft and final copy for renewal of Study Section Charters, and several other documents during the period under review.

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

The DRG Mail Room received and processed approximately 30,000 grant applications of all types, and a large volume of supporting documents, letters and publications.

RESEARCH ANALYSIS AND EVALUATION BRANCH

The Research Analysis and Evaluation Branch continually provides support and answers to the Office of the Director, institutes, other Federal agencies, and interagency committees on a variety of questions and areas of the extramural activities of NIH. With the assistance of CRISP, IMPAC and the CSCS codes, the Branch has completed the following reports or assisted in their preparation:

- NIH budget analysis relating to competing and non-competing grants.
- Extramural funding in specified areas of hematology.
- Identification and analysis of extramural activities in basic, applied, clinical, development and control activities, research materials involved, and mechanisms of support of NIH extramural R&D.
- Inventory of clinical trials.
- NIH involvement in human fetal research, FY '72-74.
- Trends in priority scores assigned to traditional research projects.
- Summary and analysis of NIH support of research efforts on DNA hybrid molecules.
- Classification of NIH extramural research support primarily or partially concerned with nutrition.
- Extramural research activities in or related to social research and development.
- Estimate of NIH support of drug development.
- Research in chemistry and biochemistry supported by NIH contracts and grants.
- Research and research training programs which relate to maternal and child health.
- NIH and NIMH support of pediatric research FY '74.
- Follow-up studies on new principal investigators (first published in Science, July 20, 1973).
- Grants and contracts for animal production and facilities.
- FY '74 Matrix of scientific areas of research by institutes that provided support.

Many of the activities reported for prior fiscal years are updated periodically. Staff members are serving on the Federal Interagency Chemistry

Representatives, the NIH Library Committee, DRG Reference Room Advisory Committee, Training Opportunities Committee, and the Grants Associates Board. Nine of the twelve staff members undertook and completed work-related training during the year.

The Branch serves as the contact resource for several ongoing projects and programs, and prepared NIH coordinated responses for several issues raised during the year that spanned several institutes. The Branch continues to code research projects and grants by the Central Scientific Classification System. The Central Scientific Classification Code is presently under revision by the staff. The Branch assumed responsibility for the schedule of NIH Conferences.

At present the major thrust is on completing reports on the extramural programs in diabetes and toxicology, compiling data for the study and review of research and research training programs related to maternal and child health, updating periodical reports, improving the procedures for the broad scientific classification of NIH extramural research grants and contracts, and maintaining the files on the inventory of clinical trials.

REFERRAL BRANCH and SCIENTIFIC REVIEW BRANCH
(Formerly Research Grants Review Branch)

The number of applications assigned and processed by the Referral Branch and reviewed for scientific merit by the Scientific Review Branch in Fiscal Year 1975 far exceeded the previous record year, FY 1974. Competing and non-competing applications reached 30,167, up almost 19 percent from the previous year's total of 25,448. Competing applications assigned to initial review groups for review of technical merit as well as to awarding units rose to 20,618, up 26 percent from the previous year. Almost 79 percent of the research applications were assigned to NIH. During the year, the Scientific Review Branch provided the initial review for scientific merit for more than 90 percent of the NIH competing applications. A table showing the distribution of applications processed in fiscal year 1975 is appended to this report.

Early in the fiscal year, the Referral Branch and the Scientific Review Branch were established following a reorganization that abolished the Research Grants Review Branch and transferred its functions to the new branches. New responsibilities for referral and initial technical review of applications for fellowship and training programs were also assigned to the new branches.

The Referral Branch (1) receives and reviews applications for PHS research and training support to determine referral to the appropriate PHS health agency and to the appropriate NIH initial review group; (2) develops criteria for determining appropriate assignment of applications within the NIH by program area and by competencies of review groups; (3) proposes uniform instructions to applicants for proper preparation of applications and (4) extracts and records preliminary data from such applications and serves as information center for applications pending review.

The Scientific Review Branch (1) recommends policies and procedures governing technical review of applications; (2) administers the 52 study sections which provide scientific review of NIH research grant, fellowship, and research career development applications; (3) explains applications and interprets preliminary recommendations to the National Advisory Councils; (4) conducts the search for the most qualified and representative individuals to serve as members of initial review groups; (5) stimulates and coordinates the activities of NIH study sections or committees in surveys of research fields to determine current status of research and need for further development; and (6) coordinates scientific review activities with appropriate representatives of components of the NIH. On April 25, 1975, four new study sections were established in the Scientific Review Branch: Experimental Virology, Immunological Sciences, Molecular Cytology, and Pathobiological Chemistry.

A book, Invertebrate Immunity, to be published by Academic Press in June 1975, resulted from the conference on this subject conducted by the Tropical Medicine and Parasitology Study Section in April 1974.

"Computers in the Clinical Pathologic Laboratory: Chemistry and Image Processing" is the title of a paper written by Dr. Bernice S. Lipkin, a staff

member of the Scientific Review Branch. The paper is in press for the June 1975 issue of Annual Reviews of Biophysics and Bioengineering.

Dr. Thomas M. Tarpley, Jr., Scientific Review Branch, has prepared for presentation and/or publication several scientific papers this year:

(1) Wolf, R. O., Moss, M. E., and Tarpley, T. M.: Serum Salivary Isoamylases in Sjogren's Syndrome. IADR/AADR, April 1975. The paper has been submitted to the Annals of Internal Medicine.

(2) Cummings, Norman A. and Tarpley, T. M., Jr.: Salivary Gland Antigen and Radio-labeled Anti Salivary Duct Antibody in Sjogren's Syndrome. For the annual scientific meeting of the American Rheumatism Association to be held in New Orleans, June 1975.

(3) John E. Horton, D.M.D., Thomas M. Tarpley, Jr., D.D.S. and Larry D. Wood, D.V.M. "The Healing of Surgical Defects in Alveolar Bone Produced with Ultrasonic Instrumentation, Chisel, and Rotary Bur." Accepted for publication in Oral Surg., Oral Med., Oral Path., Vol. 39:4, April 1975, pp. 536-546.

(4) Dellon, A. Lee, M.D., Tarpley, Thomas M., Jr., D.D.S., M.S., and Chreten, Paul B., M.D.: Histologic Evaluation of Skin Grafts and Pedicle Flaps Placed Within the Oral Cavity in Humans. Submitted in April 1975 for presentation at the American Society of Oral Surgeons in September 1975.

In January 1975, Dr. Tarpley presented a lecture, "Non-Neoplastic Salivary Gland Swellings," to a group of oral pathologists participating in the U.S. Naval School Course in Oral Pathology. In March 1975, he presented "Non-Neoplastic Salivary Gland Sialandenopathies" in the annual Oral Pathology course at the Armed Forces Institute of Pathology.

As in previous years, but on a very limited scale, study sections conducted workshops and conferences to survey the status of research in their areas, enhance reviewer competence, and stimulate research in neglected areas. In all, eight conferences were held--two in September 1974, five in January 1975, and one in April 1975. Two have been planned for September 1975.

Both of the conferences in September 1974 were held in Bethesda. On September 18, a workshop, "Goals in Population Genetics with Emphasis on Human Populations," was sponsored by the Genetics Study Section. A small group of population geneticists met with members of the Genetics Study Section to review the research objectives and current trends in population genetic studies, with particular attention to what such studies hope to accomplish and to what extent present methodologies are adequate to achieve these goals. Research proposals in this field are exceptionally variable in quality. Furthermore, the problem of scientific evaluation of such applications is accentuated by lack of agreement among population geneticists on the attainable objectives of many types of studies. A main objective of the workshop therefore was to provide members of the Study Section with a broader understanding of the basis for the divergent

viewpoints held by experts, and their assessment of what current methodologies can be expected to achieve.

The discussion concentrated on three main questions in population genetics: 1) the study by population genetics methods of the etiology of human traits, including disease and dysfunction; 2) the study of genetics variation in natural populations of various organisms, including man; 3) the study of the genetics and culture of "primitive" human populations. It is planned to publish a summary of the discussion and information that emerged from this workshop in Genetics--the journal of the Genetics Society of America.

On September 25, 1974, a conference on "High Resolution Nuclear Magnetic Resonance Resource Facilities" was conducted by the Biophysics and Biophysical Chemistry B Study Section to survey existing facilities in the United States, their distribution and mode of operation, and to develop guidelines for optimal operation of such resources. A group of about 15 participants discussed high resolution NMR spectroscopy resources facilities, their basic components, current operations, and suggestions for improving them. Resource sharing and the levying of service charges were analyzed. Plans were described for developing ultrahigh frequency NMR spectrometers in the future. The group recommended establishment of an interagency (DRF-NSF) planning committee to inventory existing NMR facilities for biomedical research in the United States and to assess the need for additional resources. They also recommended that resource instruments displaced by more advanced spectrometers should be made available to other institutions where they could still give valuable service. An annual meeting of resource directors with NIH staff was recommended to exchange information on resource operation and service to the biomedical community.

The first January 1975 workshop "Current Activity and Areas of High Potential and Bioinorganic Chemistry," was conducted in New Orleans on January 6 and 7. At the sessions, which were sponsored by the Medicinal Chemistry B Study Section, the National Science Foundation, and the University of New Orleans, 26 scientists participated directly in the program and about 20 other persons attended. The primary purpose was to give the study section an overview of bioinorganic research areas most likely to be in the forefront of progress during the next decade and hence representing future heavy proposal activity for the study section. Areas covered included metal ion transport and storage, trace metals, toxic and carcinogenic metals, organometallic antitumor agents, nitrogen (and other small molecule) fixation, macromolecular probes and models, metalloproteins, and coenzymes. Results of the workshop are to be published informally by the National Science Foundation.

All of the other January workshops were held in Bethesda. Earliest of these was the January 10 workshop on "Growth Hormone and Growth Factors," sponsored by the Endocrinology Study Section and attended by about 35 persons. A variety of peptide factors that promote cell growth have recently been described, mostly in areas of investigation not traditionally associated with endocrinology. The discovery that a closely related factor is dependent upon hormone and may indeed mediate some of the actions of growth hormone has prompted an increasing number of investigators to explore the endocrinological implications of these new growth factors. The purpose of the meeting was to familiarize

members of the study section with this new body of information and its implications for understanding hormonal control of growth.

The morning session of the meeting was devoted to a discussion of growth hormone and a possible relationship of its biological actions to those of somatomedin, a growth dependent peptide that appears in the plasma several hours after injection of growth hormone. The afternoon session was devoted to a discussion of a series of other peptides that appear to be related both to somatomedin and to processes of growth. The general discussion provided a wealth of informational background for members of the study section to aid them in evaluating the increasing number of research proposals that deal with this new, important, and rapidly developing branch of endocrinology.

On January 15, a conference on "Evaluation of Large-Scale Nutrition Interventions," sponsored by the Nutrition Study Section, was attended by about 50 participants. Both in this country and throughout the world, large-scale nutrition interventions have been made and are being made without serious attempt to assess the benefits to the recipients. There is now a growing concern in both government and scientific circles about this deficiency. The New York Prenatal Project was presented as a point of departure for a discussion of the various aspects to be considered in planning, carrying out, and interpreting the results of nutrition interventions. Following a description of the prenatal project in New York City, discussions of various aspects were presented. Topics included study design, statistical evaluation, ethical considerations, and design comparisons with the Guatemala study.

A workshop on "Behavioral Toxicology," was held on January 16 under sponsorship of the Toxicology Study Section. Two main themes were discussed by the participants: (1) the current status of methods in behavioral toxicology, and (2) the problem of selection of appropriate animal tests for evaluation of hazards to humans. Five invited speakers covered a variety of methods and research results in their presentations on the following subjects: (1) the role of operant conditioning techniques in precise behavioral assessments, particularly where sensorimotor discrimination may be affected by toxic substances; examples of tests in animals and humans exposed to carbon disulphide were given; (2) methods of detection of reversible hyperkinesis in rats exposed to carbon monoxide as neonates; activity of permanent groups of animals monitored in a residential maze equipped with photocells was discussed; (3) importance of social behavior and development studies using the example of young rhesus monkeys given lead in their diet; such studies are of particular importance for comparisons with humans; (4) neurophysiological methods that can be used to detect toxic effects of compounds in animals; the visual system is particularly sensitive to some pesticides; and (5) tests in rodents that can be carried out throughout development when the animals are exposed to toxicants during gestation or early postnatal life. Sensitivity to low levels of toxicants occurs in swimming tests and open field activity.

In the discussion which followed, the participants discussed the problems of selection of appropriate tests for screening for hazards. It was generally agreed that the developing organism is more sensitive to behavioral alteration than the adult. The precise tests which are most useful are difficult to select, but sufficient knowledge is probably available to make a start. Publication of conference material is planned.

On January 16 and 17, the Reproductive Biology Study Section held a workshop on "The Glycoprotein Hormones and Their Receptors." About 100 persons attended this workshop at which 10 program participants presented the following topics: (1) the glycoprotein hormones, their origin, chemistry, use, and metabolism; (2) human follicular stimulating hormone, its subunits, and their structures; (3) immunologic relationships among the gonadotropins; (4) testicular and relevant receptors, and (5) clinical applications and comparison of these reactions in the human and sub-human primates.

A conference on "Matching Needs and Resources in Epidemiology and Biometry," was sponsored by the epidemiology and Disease Control Study Section, National Cancer Institute, National Heart and Lung Institute, Fogarty International Center, Epidemiology Section of the American Public Health Association, Epidemiology Program Directors of Schools of Public Health, Association of Teachers of Preventive Medicine, and the National Center for Health Statistics of the Health Resources Administration. About 60 people attended the conference, which was held in Los Angeles on April 7 and 8.

During its first decade, the Epidemiology and Disease Control Study Section has observed a dearth of productive epidemiologic research in all categorical areas. Two problems seem to characterize the rejected research proposals in most every instance: (1) they were presented by excellently trained clinicians who lacked epidemiologic concepts and methodological competence, and (2) they failed to involve trained and experienced epidemiologists and biometricians for the planning and ultimately the execution of the research. As the Study Section contemplated various approaches to the problem, it found its colleagues in other organizations were equally concerned. The result was a broadly-based sponsorship for the workshop including both the consumers and the producers of this specialty for biomedical research. The meeting was then to examine needs, problems, and approaches to their resolution. Its agenda was neither comprehensive nor conclusive.

Three of the principal position papers, therefore, provided insight and illustration of the dynamics of the problem from the viewpoint of the program areas of cancer, heart and lung, and infectious diseases. These presentations gave focus to requirements for epidemiologists and biometricians in comprehensive centers, intervention and control trials, specialized centers of research, clinical trials, surveillance and end results programs. Three other papers were then presented that dealt respectively with the research training opportunities in local, State, and Federal public health agencies; the current situation in schools of public health with regard to faculty, research personnel, and students; and the interrelationship of epidemiology with biometry, biostatistics, and health statistics. Each of the papers attempted to include hard data definitive of the problem area, and yet were thought-provoking regarding internal needs of the disciplines of epidemiology and biometry. Moreover, they provided substantive material for discussions, which carried to the second day in the deliberations of small working groups who were attempting to reach a consensus regarding needed follow-up. It is planned for the proceedings to be reported as part of the Fogarty International Center Series on Preventive Medicine.

September conferences in Bethesda are planned by the Medicinal Chemistry B and Tropical Medicine and Parasitology Study Sections. "Ionization, Chemical Ionization, and Field Desorption" is the subject of the conference being sponsored by Medicinal Chemistry B Study Section. "Intracellular Parasitism: Status, Concepts, and Speculations in Research on Leishmania and Trypanosoma Cruzi" is the subject of the second conference.

APPLICATIONS PROCESSED BY REFERRAL BRANCH, OADSR
Fiscal Year 1975: March 16, 1974 - March 15, 1975

COUNCIL		NOV 74	MARCH 75	JUNE 75	TOTAL FY 75
			COMPETING		
Types 1, 2, 3	NIH	3,831	3,865	3,987	11,683
	FDA	40	36	22	98
	HS	112	85	138	335
	OH	31	21	25	77
	ADAMHA	934	694	1,088	2,716
	Subtotal	4,948	4,701	5,260	14,909
Construction		0	0	6	6
PL 480		6	5	4	15
Training		87	869	349	1,305
Career Development		929	80	327	1,336
Fellowships		1,025	0	2,022	3,047
	Subtotal	2,047	954	2,708	5,709
TOTAL, COMPETING		6,995	5,655	7,968	20,618
			NON-COMPETING		
Type 5		3,085	2,655	2,751	8,491
Interim (Administrative)		350	287	265	902
Cross Fiscal		45	78	33	156
TOTAL, NON-COMPETING		3,480	3,020	3,049	9,549
			TOTAL		
COMPETING		6,995	5,655	7,968	20,618
NON-COMPETING		3,480	3,020	3,049	9,549
GRAND TOTAL		10,475	8,675	11,017	30,167

STATISTICS AND ANALYSIS BRANCH

Fiscal year 1975 was characterized by increased demands on the Statistics and Analysis Branch for information services and data processing support. During the year, the Branch provided review and award support services for a record breaking number of competing applications. Similar increases occurred in virtually every other measure of existing SAB operations.

In addition to these increases in routine activities, the SAB met demands for such new services as the development and operation of a system of tracking applications involving human subjects through the review and award process. Another major new project is the Manpower Report which collects information on personnel paid under research grants and contracts.

To meet these and other demands the Branch is continuing to seek out, particularly through application of the latest technology, ways and means by which productivity can be improved. There is, for example, a study currently under way which will consolidate the various data-capture processes into one single method with a significant improvement expected in the utilization of resources.

The Branch, in collaboration with the American Association of Medical Colleges (AAMC), presented to medical school representatives at the November 1974 AAMC meeting in Chicago a proposed system for a medical school/NIH interface on extramural information. Following this presentation, eight schools have participated in a pilot study of such an interface system. A meeting with the participating medical schools, as well as the AAMC, to evaluate the system is planned for June 1975.

Management support and employee interest in training and development for better job performance and career development purposes continued to remain high with 73 Branch employees participating in 55 different training courses and seminars. In addition, a number of courses were applied for but were oversubscribed; employees will pursue this training as spaces become available. A wide spectrum of training was covered including computer-related training, administrative and managerial, communications and office skills, EEO and management sciences. Special training programs in which Branch employees were involved included the Upward Mobility College and attendant workshops and seminars, the STEP Continuing Education Program, the NIH Manager Development Program, the Federal Executive Institute, and the Symposium on the Freedom of Information Act. The three Student Trainees recruited under the Federal Junior Fellowship Program in 1973 continued their third year of training. Also, during FY 1975 the Branch acquired a trainee under the Project Stride Program.

1. Office of Systems Planning. The Office of Systems Planning in collaboration with the other Sections of the Branch, continued its activities for expansion of the NIH extramural central data system and for the design and implementation of new applications. Systems design and procedural development connected with the entry into the system of new accounting numbers established by the Division of Financial Management (DFM), establishment of a human subjects

tracking system, a link with DFM to permit balancing of contract and interagency and intraagency agreement information contained in the IMPAC system, and the processing of Core Center applications for the National Institute of General Medical Sciences were undertaken. These projects are discussed in detail in the individual section reports that follow.

2. Data Processing Section

Document and Entity Numbers. The Section converted several data items in the IMPAC System this year to conform to the following new Division of Financial Management (DFM) accounting numbers:

> Document Number - This number replaces the Transaction Number on PHS extramural grant award statements and approval lists. It is used by DFM as the obligation number in the NIH Central Accounting System and the DHEW Federal Assistance Financing System. The new Document Number will assure consistency in the assignment of obligation numbers in various DHEW systems. It contains several characters of the grant number permitting each number to be cross-referenced to its related grant.
>
> Entity Number - This number replaces the PHS Account Number on PHS extramural grant award statements and approval lists. It is used by the DFM as the payee number in the NIH Central Accounting System and DHEW Federal Assistance Financing System. The DHEW Central Registry office is responsible for establishing standarized codes to uniquely identify all entities dealing with the Department. An entity is broadly defined as an individual or organization or as a segment, division, school, or component of the organization. The standard organization code is derived from the Internal Revenue Service Employer Identification Number (EIN) with the Social Security Number (SSN) assigned as the standard code for individuals. Use of codes became mandatory for all agencies on July 1, 1974, for any award to entities included in the Central Registry System.

Core Center Grants. DRG agreed to assign and review Core Center applications for NIGMS beginning with the June 1975 review cycle. Data relating to these applications were available in the IMPAC pending file in April. The procedures established for processing these applications provided for recording the full range of Initial Review Group, National Advisory Council, and Awarding Unit actions for both the Core Center and the related individual projects.

Human Subjects Tracking System. A computerized tracking system has been installed in the Section to identify projects involving human subjects. The system was implemented in May 1975 for applications assigned for September review by DRG Study Sections. The system documents the fact that review of questions involving human subjects has taken place, decisions reached, and problems resolved in the following manner:

- At the time a pending application is received, an entry is made in the IMPAC computer record indicating whether human subjects are involved in the proposed project.

- If human subjects are involved, the Study Section will determine whether there is adequate protection or if possible risks exist. This distinction will also be recorded in the IMPAC computer record.

- In the case of possible risks, awarding unit staff are responsible for resolving the problem and issuing a Grant/Application Change Notice to that effect.

No award statements will be produced by the IMPAC System until all possible risks have been resolved by the appropriate awarding unit.

Contracts. A link between the Division of Financial Management's Central Accounting System and the IMPAC System, similar to the grant link between the two systems, is being developed for research contracts and interagency and intraagency agreements. Under this system, DFM will provide SAB monthly tapes on these contracts and agreements containing dollars encumbered, entity number, object class codes, and document numbers to permit reconciliation between the NIH Central Accounting System and the IMPAC contract files. The system will be fully operational in fiscal year 1976 and will provide increased control over data in the contract file.

Approval Lists. The Section has assumed additional operating responsibilities associated with a system being programmed to provide the Division of Financial Management with IMPAC grant-award data on magnetic tape. This system will result in major procedural changes in the grant award process. Under the new procedures, the awarding units will forward the original signed grant-award statements and approval lists directly to the Data Processing Section Control Point. On receipt, the staff will update a special IMPAC file, and, from this file, will create an encumbrance transaction tape for DFM. DPS will then forward the signed approval lists to DFM. Once operational, considerable manpower and time savings will be realized in DFM because they will no longer have to keypunch approval lists.

IMPAC Tech Notice. DPS has developed a new informational bulletin called "IMPAC Tech Notice" to notify users of the IMPAC system of current and proposed changes in the system. It will be issued on an "as needed" and not periodic basis.

System for Computer Retrieval of Information of Scientific Projects (CRISP). A total redesign of the CRISP system has been initiated to permit the generation of an increasing number of reports, to improve the accuracy and contents of these reports, to provide more flexibility in reporting, and to reduce operational costs. All aspects of the system's maintenance and reporting procedures have been considered, data collection methods have been reexamined, and input formats have been simplified and combined as appropriate. Record contents have been altered, internal coding of data changed, and the number of on-line files and records have been reduced to speed procession and facilitate use of the system.

Expansion of Record. IMPAC Master File records have been expanded from 1138 to 1378 bytes. This expansion will allow for future development as follows:

- Expansion of research contract records to include the collection and maintenance of certain data from the Request for Proposal (RFP) form. Commitment information on incrementally funded contracts will also be added.

- Development of a telecommunications system which will permit awarding units to have direct access to the IMPAC System's files and produce grant award notices via remote terminals.

- Expansion of IMPAC records to identify grants awarded under Public Law 93-348, National Research Act. One of the conditions of the National Research Service Award Program is that no trainee will be appointed unless he or she has signed and submitted a statement of intent to meet the service or payback provisions required under this law. It is expected that the IMPAC System will be used to monitor this compliance.

3. Research Documentation Section (RDS). The Section maintains a computerized disk storage and retrieval system, CRISP (Computer Retrieval of Information on Scientific Projects) containing scientific data on the research grants and contracts supported by the Public Health Service. Through this medium, RDS functions to service ad hoc and recurring requests for scientific information from Government administrators, scientists, and information personnel for purposes such as analysis and evaluation of research programs, specific scientific areas, and preparation of reports. In similar fashion, the Section responds to inquiries from grantee and non-grantee institutions and scientists, the news media, and other non-Government individuals engaged in, concerned with, or reporting on medical research.

RDS publishes annually as a "spin off" of the CRISP file:

1. The Research Grants Index, prepared in two volumes. Volume I is a scientific subject index with associated project numbers and titles. Volume II contains three sections (a) project identification data (b) research contract identification data and (c) project investigator information.

2. The Medical and Health Related Sciences Thesaurus, the vocabulary authority list of subject headings used by the RDS Indexing Staff in indexing the research projects.

CRISP 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 Boolean search logic. Select queries for providing individual institutes with tapes or hard copy of their projects by subject, project (sub-project) number or investigator, and individual institute listing or projects with indexing terms (Scientific Profiles) can be provided. Query capability limiting subject searches or Scientific Profiles to certain program (R, M, N, P, S) or IPF Codes is available.

A specially designed CRISP subroutine provides for furnishing grantee institutions or NIH institutes possessing appropriate computer capabilities with specially formatted tapes with which they can search the scientific subject content of their own research grant and contract records. This subroutine called CESI (CRISP Extract System for Institutions/Institutes) is updated monthly and can furnish select tapes on an ad hoc or recurring basis.

In addition, performing subject searches and producing Scientific Profiles or Investigator Listings on subprojects of program projects, center and other large grants is a unique feature of the CRISP System.

New features of the CRISP system include: (1) the CESI System described above; (2) a narrative file termed CRISP File 5 (Format F) which offers the capability of furnishing research grant and contract narratives in response to grant or subject queries, and provides users with summaries of project objectives in addition to previously existing formats describing fiscal or subject heading information; and (3) Principal Investigator Indexer Records (computer printouts of individual project Scientific Profiles) which have been modified to eliminate the need of typing address labels. The innovations described above have been made possible largely through the efforts of the SAB System Planning and Data Processing Groups.

Research Grants Index. Linotron tapes for the fully automated printing of this two-volume set were submitted to the Government Printing Office in January for publication (DHEW Publication No. (NIH) 75-200) in May 1975.

Medical and Health Related Sciences Thesaurus. In addition to its in-house use, the revised edition (DHEW Publication No. (NIH) 75-199) was distributed on a request basis to research analysts, information specialists and other individuals who have responsibility for scientific communication systems.

CRISP Services. In addition to responding to hundreds of requests on a wide range of subjects, the Section (1) prepared Linotron tapes used in the creation of extract Indexes for three institutes; (2) provided Scientific Profile data reports and/or CESI tapes for numerous Grantee Institutions; and (3) furnished NIH-wide scientific area data to responsible institutes.

In attempts to improve SAB personnel utilization, RDS Technical Information Specialists have assumed responsiblity for professional editing operations involving thousands of approved research project applications during the current fiscal year. This activity was formerly conducted by other members of the SAB staff.

Intramural research projects. Efforts are well underway to develop a system for incorporating the keyword indexing of individual intramural research project reports into the CRISP System. This will allow for uniform reporting of intramural research using the full capacity of Boolean logic heretofore available only on queries for information on extramural research.

Training. A total of 11 employees participated in NIH training programs. The courses included WYLBUR, CPS, System/370, Mag Card, IRS Query, STEP Module 6, Supervision, and Science, Technology & Government. In addition, one employee continued in Upward Mobility College.

4. Reports, Analysis, and Presentations Section. The primary function of the Section is to satisfy the information requirements of NIH and PHS centralized extramural activities. In fulfilling this function, the Section utilizes the IMPAC system as well as other data sources. Its responsibilities include: design, maintenance, and operation of computer reporting systems; training and technical assistance in data retrieval; planning and coordination of NIH responses to annual surveys covering Federal obligations for R & D; preparation of formal publications such as the PHS "Blue Books" and the NIH Basic Data Book; statistical analysis to compile and present visual materials dealing with extramural trends or other topics; and the development and implementation of special evaluation projects. This Section also works closely with the Data Processing Section in maintaining and extending the IMPAC system, and has direct responsibility for establishing institution classifications and related computer files, as well as ensuring the accuracy of selected key data items for publications or reports.

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

(1) Public Health Service Grants and Awards, Part VI, FY 1973 Health Services and Mental Health Administration. (DHEW Publication No. (NIH) 74-500).

(2) Public Health Service Grants and Awards, Part I, FY 1974 and FY 1973/1974. Research Grants. (DHEW Publication No. (NIH) 75-494).

(3) Public Health Service Grants and Awards, Part III, FY 1974 and FY 1973/1974. Research and Development Contracts. (DHEW Publication No. (NIH) 75-496).

(4) Public Health Service Grants and Awards, Part IV, FY 1974 and FY 1973/1974. Health Planning and Health Services Grants. (DHEW Publication No. (NIH) 75-497).

Data for the pocket reference book, Basic Data Relating to the NIH-1975, were compiled in cooperation with the NIH Office of Program Planning and Evaluation. This publication presents information on the programs and resources of the NIH.

Special Statistical Presentations. The Section compiled and analyzed extramural program statistics for fiscal year 1967-1974, and participated with the Chief, Statistics and Analysis Branch, in developing a set of overhead projection slides illustrating key extramural trends. These slides were presented formally to the Director, NIH, and other officials in August 1974, and subsequently to various additional audiences. The data were also issued, with an accompanying analysis, in a chart-book entitled NIH Extramural Trends, Fiscal Years 1967-1974 prepared for administrative use.

Reporting Activities. There are several major reporting activities which are recurring or cyclical and 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 along with estimated obligations for the next 2 fiscal 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 summarizes 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 nonprofit organizations, with an individual report for each health professional school. In addition, data by field of science grouping and program are also requested for institutions of higher education.

The Section assisted other PHS agencies by compiling their CASE Reports for those programs that are 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 versus 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 Division of Financial Management, the institutes/divisions, and the Office of Research Manpower, DRG.

The Section supplies material each month for the NIH Management Data Book, published by the Associate Director for Administration to provide top management with a comprehensive view of the resources, status, and trends of major programs and operations.

Inquiries. The Section responds to hundreds of requests for information each month from Federal agencies, NIH officials, other Government and non-Government organizations. These requests are primarily for statistical and analytical information concerning the NIH extramural programs and characteristics of grantee institutions contained in the IMPAC system. The response to these

inquiries frequently requires analysis and compilation of historical data covering several years, design of special computer reporting files, providing consultation services to requesters concerning available data, and assisting in developing specifications for the output. The Section is responsible for supplying magnetic tape extracts from the IMPAC system to several institutes and outside organizations for special research projects, or as inputs to existing management information systems.

The Section has devoted considerable effort to the development of shelf, or reference listings, unpublished reports, and microfiche, to answer routine inquiries covering support to individual investigators or specific institutions. The Inquiry and Reporting System (a computer software facility) is the primary method for data extraction, manipulation, and hard-copy presentation requested. More than 9,000 queries were processed by the Section during fiscal year 1975.

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 fiscal year 1974, over 1,000 new institutions were added to the IPF. The IPF now contains about 21,500 records on institutions participating in NIH programs, as well as the programs of other agencies of the Public Health Service.

Annual Manpower Report. The Section participated in planning and designing the annual report form for personnel working on NIH research grants. This report will supply needed information on the manpower used in the performance of biomedical research funded by NIH. It will build upon and supplement the data from the 1970 manpower sample survey conducted by the Section. The initial distribution of the form to principal investigators and program directors was made in December 1973.

The Section has coordinated responses to grantee correspondence concerning completion of the form, and also has helped to solve processing and systems design problems. A computer file containing data for fiscal year 1973 grants was developed by the Section during fiscal year 1975.

Research Grant Expenditures. A computerized data base of the Report of Expenditures (ROEs) for fiscal year 1972 NIH research grants was established. The data base combines, with pertinent data from the IMPAC file, information reported to NIH on the ROE form by grantees. Data input and table programming were performed by a contractor funded under the NIH Health Evaluation Program.

Retrieval Methodology. Two basic IMPAC Inquiry and Reporting System (IRS) courses were offered by the Section. A total of 45 persons attended these courses. IRS is the primary instrument for extracting and reporting IMPAC data.

About eight 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 was continued as an informal, technical series 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 60 copies of each issue are distributed to DRG and institute/division personnel responsible for compiling IMPAC data.

Graphic Arts. Approximately 3,000 pieces of graphic art work and photographics were completed by the Illustrator in fiscal year 1975. This is a considerable increase over the 1,100 pieces of work completed in fiscal year 1974. The bulk of this work included: cover designs, charts, certificates, slides, signs, visuals, special exhibits, and illustrations for flyers and handbooks. Other major assignments involved the development and preparation of slides for various statistical presentations by the Director, NIH, and other officials. The Illustrator was also responsible for the artistic preparation and assembly of the chartbook entitled Extramural Trends, Fiscal Years 1967-1974.


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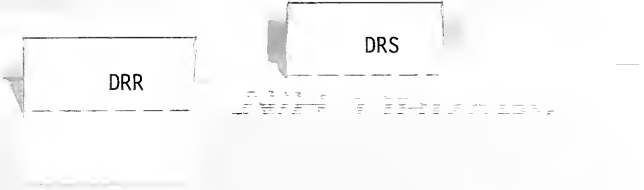
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ANNUAL REPORT

FISCAL YEAR 1975
(July 1, 1974-June 30, 1975)

DIVISION OF RESEARCH RESOURCES

National Institutes of Health
Bethesda, Maryland 20014

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REPORT OF THE DIRECTOR

Dr. Thomas G. Bowery

Report of the Division Director

Fiscal Year 1975 has been a significant year for the Division of Research Resources (DRR). The DRR Self-study, initiated over a year and one-half ago, has resulted in the formulation of a contemporary goal for the Division--

> TO IDENTIFY AND MEET THE RESEARCH RESOURCE NEEDS
> AND OPPORTUNITIES OF THE NIH.

This concept was affirmed by the Director, NIH, in October 1974, in a statement to the Director, DRR--

> "The functions of the Division of Research Resources have a particular relationship to the totality of the NIH mission in contradistinction to the more segmented relationships of the categorical Institutes. Thus the programs of DRR have a special relationship to the concerns of the Office of the Director, NIH.
>
> "As NIH examines its ever changing responsibilities in the support of biomedical research, it is appropriate that the critical question of its role in providing research resources should be studied."

Therefore, the Division has been actively involved this year in determining whether the contemporary goal can better serve the total NIH, whether necessary DRR/Institute interfaces can be established and maintained, and whether the DRR can realign its internal and external resources to accomplish the new goal. A series of meetings have been held with the top program staff of five of the Institutes (NIAID, NICHD, NINCDS, NIDR, and NHLI) to portray our contemporary goal, display the extent and impact of DRR resources on each of the Institutes' programs, and explore further mutual programmatic opportunities. We plan to hold similar interface sessions with the remaining Institutes in the near future.

With respect to internal realignment so as ". . . to better utilize management resources and assure coordination of programs" as directed by the Office of the Director, NIH, four internal work groups have been established to examine the several essential functional areas of the Division:

> Resource Development
> Grants and Contracts Management
> Technical Merit Review
> Program Data and Information Management.

These work groups have submitted recommendations and it is anticipated that implementation of several new systems will begin within the next few months following a submission of an organizational plan to the OD, NIH.

Additionally, the Director, NIH, has charged the Division with undertaking an examination of the scientific missions of the various program components of the Division. A Request for Proposal for such an evaluation has been issued and a contract will be signed by the end of this fiscal year. We anticipate that the mission study will take place over the next fifteen months. The study hopefully will provide the Director, NIH; the Director, DRR; and the National Advisory Research Resources Council information necessary in determining how effective the Division's programs are in relation to the NIH mission and what, if any, program changes are called for.

The Division looks forward to Fiscal Year 1976 as an opportunity for strengthening the role of the DRR within the National Institutes of Health.

REPORT OF THE ASSISTANT DIRECTOR

Dr. James F. O'Donnell

Report of the Assistant Director

As detailed within the accompanying pages of this report, Fiscal Year 1975 has been a highly significant year for program accomplishments in the Division of Research Resources. These accomplishments were met, in no small measure, by the conscientious efforts of all members of the Division. Critical staffing problems remain and have been exacerbated by the loss of several key Health Scientist-Administrators and the absence of four support personnel who were on maternity leave. Dr. Benjamin Alexander, Acting Chief of the General Research Support Branch, left to become President of Chicago State University in July, and in November, Dr. William Raub, Chief of the Biotechnology Resources Branch, left the Division to become the Associate Director of the National Eye Institute. In June, Dr. William Goodwin, Director of the Primate Research Centers Program of the Animal Resources Branch, retired from the Commissioned Officers Corps of the U.S. Public Health Service.

The loss of these key staff members combined with increases in project site visiting activities has resulted in less than optimal amounts of time available for strategic program planning and program evaluation.

Fiscal Year 1975 marked a milestone for the Division in relation to the National Advisory Research Resources Council. This was the first time in over four years that the Council was at full strength. This should now provide us with the necessary advisory function we seek as we move forward to implementing our contemporary goal.

Critical program decisions face the Division in this coming year attendant with the severity of fiscal constraints which may be imposed. Unless the Congress restores funds to the General Research Support Grant Program, this program will be terminated in Fiscal Year 1975. Decisions will have to be made concerning the number and location of General Clinical Research Centers across the Nation which will have to be phased out unless significant budgetary increases are provided. This crisis has occurred chiefly because of the rapid inflationary spiral in hospitalization costs which have occurred in the past few years. The supply of nonhuman primates for biomedical research investigators, and the costs necessary to maintain the physical facilities of the seven primate centers are major problems affecting the Animal Resources Branch programs. Both additional staff and fiscal resources are necessary for the Biotechnology Resources Branch to optimally extend the resource sharing concept. Additional fiscal resources are also essential if the Minority Biomedical Support Program is to be extended beyond the limited communities it is now serving. The American Indian community is one which the program is especially anxious to have as participants in this program.

Internal reorganization of the Division with the anticipated better utilization of our scarce personnel resources and a participative "governance" process will hopefully provide us with the ability to meet the programmatic challenges of Fiscal Year 1976.

DRR BRANCH REPORTS

Fiscal Year 1975 Annual Report
Animal Resources Branch
Division of Research Resources

INTRODUCTION

The overall objective of the Animal Resources Branch (ARB) 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 Sciences Program, and Research Contracts.

PRIMATE RESEARCH CENTERS PROGRAM

The Primate Research Centers were established with Federal funds in the early 1960's to provide special research environments for the use of primates in many important areas of biomedical research. The seven centers, operated by Federal grant funds, continue to provide national and international leadership in biomedical primatology. During this year, significant research contributions were made in numerous areas including carcinogenesis, kidney diseases, drug addiction, and infant respiratory diseases.

The core grant support provided by this program permitted the 152 core staff scientists to conduct research on a total of 111 grants and contracts with a total funding of $6.6 million. In addition, the 432 collaborative scientists from a number of universities utilized the facilities to conduct research on 127 grants and contracts with a total funding of $11.0 million. The Centers also provided the research environment for 163 graduate students to undertake their thesis research. The program provided salary support for 170 doctoral level staff and 706 technical and administrative personnel.

During this year, the problem of obtaining sufficient primates for research purposes reached a critical stage; therefore, it became necessary to significantly increase the domestic production of the primate species commonly used in the research programs. The Centers have provided the necessary basic knowledge required in the establishment of large primate breeding programs and are developing plans to expand their breeding programs in order to become self-sufficient in the production of primates for their own needs. They are currently producing approximately 50 percent of their annual requirements for experimental primates with a total of 1055 infant primates being produced during this year. The missions and examples of research accomplishments at each of the Centers are as follows:

OREGON PRIMATE RESEARCH CENTER

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

Effects of Development and Early Nutrition on Brain Composition:

In all species, aging is accompanied by a sequence of changes in the composition of the different parts of the central nervous system. During the period of most rapid change, a given area is usually susceptible to various insults, including nutritional deprivation. The rhesus monkey has been used for a correlative biochemical, histological and behavioral study of the effects of maternal and infant protein malnutrition on the development of the young. It was found that protein malnutrition during early development reduced the size of the brain, particularly the brain stem.

DELTA PRIMATE RESEARCH CENTER

The primary mission of this Center is infectious disease research and an example of their research activities is as follows:

Potential Developments of a Vaccine for Chickenpox:

There were 121,985 cases of chickenpox in the United States during 1974 and 90 percent of these occurred in children under 10 years of age. Currently, there is no effective vaccine available as a suitable animal host for the development and testing of a vaccine has not been identified. A recent outbreak of a disease among a colony of monkeys at this Center has been identified as being caused by a virus almost identical to the chickenpox virus (varicella) in man. It is believed that the monkey will serve as a model for the development and testing of vaccines against this human disease. In addition, it will provide an opportunity to study the manner in which this virus can remain dormant in human tissue and then reactivate years later to cause diseases like zoster and shingles.

YERKES PRIMATE RESEARCH CENTER

The missions of this Center are neural and behavioral research and the study of neoplastic diseases. This Center has the largest colony of great apes available anywhere in the world for biomedical research. The following is an example of their research:

Development of a Remotely-Controlled Injection and Blood Withdrawal System:

In a number of research and clinical problem areas, there are needs for assessing variations in blood constituents in unanesthetized, ambulatory animals. Scientists at this Center have designed an instrument that can be worn by humans and primates that is remotely controlled through a radio link. This device enables them to withdraw blood samples through an indwelling catheter, flushing the catheter between samples to achieve separation. Telemetry is incorporated into the design of the instrument so that the temporal sequence of events is signalled to the investigator without any cue to the subject. The infusion capabilities of the device enables the investigators to inject, intravenously, biologically active substances and to then measure their subsequent blood levels or effects. This device is now being used in research on alterations in endocrine

activity that are induced as consequences of stimulation of the central nervous system and in response to the stress of social environments.

WASHINGTON PRIMATE RESEARCH CENTER

The mission of this Center is research in neurophysiology relating to the cardiovascular system and the support of an extensive collaborative research program involving a number of scientists in many disciplines. The following is an example of the research conducted at this Center:

Sudden Infant Death Syndrome:

This research using infant monkeys is directed toward identifying factors which may be involved in human crib deaths. These studies are focused on observations made by pathologists and others who have done extensive autopsy studies on crib death babies. Baby monkeys can be brought to the point of death by stimulating the nerves controlling the muscles of the larynx. In addition, the reflex pathways which serve to protect the larynx and the balance of the airways can be stimulated in a manner which results in death of the infant monkey. This result cannot be obtained in adult monkeys. This would indicate that the upper airways of infants can be thrown into a spasm which impairs respiration and other vital functions. These investigations also suggest that infant monkeys are sensitive to reduced oxygen in the air, and breathing a low-oxygen mixture alters their sensitivity to other stimulation. This indicates that changes in the composition of the air breathed by human infants can produce adverse effects upon the respiratory system. These studies are important for the identification and investigation of factors which could not otherwise be evaluated in human infants as potential contributors to crib death.

WISCONSIN PRIMATE RESEARCH CENTER

Neural and behavioral sciences and reproductive biology are the basic missions of this Center. An example of their research accomplishments is as follows:

Primate Ecology

A new program in primate ecology was established during this year and is the only activity of this nature in the Primate Research Centers Program. A senior investigator will undertake extensive field studies in Cameroon on a number of African primate species. These studies concern the conservation of some of Africa's endangered species and the determination of whether the more common species of African primates can play a greater role as subjects in future biomedical research. The latter goal is especially important due to the reduced imports of primates from India and other countries.

NEW ENGLAND PRIMATE RESEARCH CENTER

The core staff of this Center is conducting research in areas of infectious diseases and primate pathology. In addition, a number of collaborative

scientists from several institutions conduct a major portion of their research activities at this Center. The following is an example of the research activities undertaken at this Center.

New Technique for the Identification of Microfilaria:

A technique has been developed which allows precise identification of circulating parasite larvae in peripheral blood. Identification of these parasites, heretofore, was exceedingly difficult and, in some cases, impossible. The method utilizes the location of the enzyme, acid phosphatase, within the parasite. This method has been used to identify two filarial parasites of humans which were almost impossible to tell apart with other techniques. Their differentiation is important as one causes disease and the other does not.

CALIFORNIA PRIMATE RESEARCH CENTER

The mission of this Center is in the area of infectious diseases and environmental health sciences, and one of their research accomplishments is as follows:

Effects of Ozone on Pulmonary Function:

In these studies, monkeys were exposed to 0.2, 0.35, 0.5, and 0.8 ppm of ozone for 8 hours per day on 7 consecutive days. These concentrations of ozone range down to the oxidant level not uncommon in regions severely affected by air pollution. Lesions were produced in lungs of all experimental monkeys with more severe lesions caused by the higher concentrations of ozone. Most of the damage occurred in the respiratory bronchioles; the response being characterized by hyperplasia and hypertrophy of nonciliated bronchiolar epithelial cells. Large conducting airways were also affected, but in a more random pattern. The similarities in the morphology of distal airways in man and the monkey, and the localization of the ozone-induced lesions in the respiratory bronchioles of the latter, make the monkey particularly useful for studies concerning the long-term relationships between air pollution and respiratory diseases in man.

LABORATORY ANIMAL SCIENCES PROGRAM

The Laboratory Animal Sciences Program (LASP) assists institutions in developing and improving animal resources for biomedical research and training through the award of research and resource grants. Currently active program areas include support for 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; 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; reference and information centers dealing with selected problems; and training of specialists in the field of laboratory animal medicine. The program awarded funds totaling $7.782 million in fiscal year 1975,

which supported 88 discrete animal research and resources projects, 5 training programs, 6 fellowship awards, and 10 contracts.

ANIMAL MODELS AND SPECIAL COLONIES

The major objectives of this program area are (1) to define, characterize and exploit the relevant biological attributes of selected animals which display potential for use in several areas of biomedical research; (2) to establish, improve or expand special colonies of well characterized animals which are of proven value for specialized areas of biomedical research, but which are not generally available from other sources; and (3) to preserve unique and valuable stocks and strains of animals which may otherwise be lost due to particular circumstances.

Support for projects related to the establishment of special animal colonies and animal model development has remained rather static during the past several years. Twenty-one projects in these categories were supported during FY 1975 (approximate total of $1.267 million), as compared to 22 projects supported during FY 1974 (approximately $1.250 million) and 20 projects supported during FY 1973 ($1.141 million).

The majority of the currently active projects in these categories are related to vertebrate species (e.g., rats, mice, guinea pigs, hamsters, dogs, rabbits, nonhuman primates, armadillos, degus, etc.). One of the projects very recently funded relates to the investigation of systems for the laboratory culture and maintenance of sea urchins. Support has also been provided for model development and/or special resources of several species of invertebrate animals, e.g., rare species of Drosophilia and Xyleborus (wood-boring beetle). Two contracts were awarded during the past year for development of laboratory mariculture techniques to rear and maintain species of Aplysia (sea-hare) and two related species of marine gastropods (i.e., Hermissenda and Pleurobranchaea). Both studies have reported good progress to date. If successful, methodology will become available for the cultivation and rearing of these marine invertebrate species in any laboratory, thus precluding problems of uncertain health status and seasonal availability from their native marine habitats which currently confront researchers.

Projects devoted to the definition, characterization and development of new types of animal models have generally been limited to those species or strains which evidence good potential for use in several disciplines or disease categories. Full exploitation of the potential usefulness of such animals normally requires the efforts of investigators in several disciplinary areas over an extended time period.

Examples of model development projects currently supported by the LASP include:

1. Studies at Washington State University on inherited neurological types of diseases including leukodystrophy, an autosomal recessive trait in cats; progressive myoclonic epilepsy (La Fora's Disease)

in dogs; Ehlers-Danlos syndrome, an autosomal dominant disorder in dogs and mink; a lower motor neuron disease in dogs; and a lysosomal disorder of cats similar to the mucolipidoses of children.

2. The characterization of eight strains of germfree mice and three strains of germfree rats for use in several research areas, including gerontology, cancer therapy and environmental pollutants at the Lobund Laboratory, Notre Dame University.

3. The biological characterization and development of 10 new inbred lines of Syrian hamsters which were derived from the first animals to be brought to the United States from their native source in Syria since 1930. These new inbred lines have good potential as appropriate models for many areas of health-related research, including studies of viruses, aging, hibernation, dental caries, transplantation, tumor induction, myopathy, etc.

4. A colony of PBB/Ld mice at the University of Alabama Medical Center which have high concentrations of plasma cholesterol and triglycerides are being characterized and developed as a potential model of familial hyperlipoproteinemia, Type IV (Fredrickson). This inbred mouse strain also shows considerable promise as a model of obesity and dental caries.

5. A colony of squirrel monkeys at the Bowman Gray School of Medicine which are being studied as potential models of cholelithiasis, chronic glomerulonephritis and the nephrotic syndrome, and lactose intolerance.

Examples of ongoing projects which provide support for the maintenance of special colonies and serve as institutional and/or national resources include:

1. A colony of genetically obese rats (Harriet G. Bird Foundation, Stow, Massachusetts) which serves as a resource for many investigators in nutritional and metabolic research.

2. A resource of gnotobiotic mice, rats, guinea pigs and rabbits which is being made available from the Lobund Laboratory of Notre Dame University to the biomedical community for studies including cancer induction and chemotherapy, immunosuppression, and bone marrow transplantation.

3. A colony comprised of highly inbred lines of rabbits at the University of Illinois College of Medicine which are utilized as models for studies of transplantation, immune response and cancer immunotherapy.

4. A colony of nine-banded armadillos at the Gulf South Research Institute, New Iberia, Louisiana, which has contributed significantly to recent breakthroughs in the use of this animal as a model for studies on human lepromatous leprosy and production of purified leprosy antigen for prognostic skin testing of human

lepers.

5. A colony of inbred strains and mutant-bearing stocks of rabbits at the Jackson Laboratory, Bar Harbor, Maine, which are made widely available to investigators of important human disease conditions including ataxia, epilepsy, buphthalmia, lymphosarcoma, hemolytic anemia, renal cysts and mandibular prognathism.

6. A resource colony of degus (a South American rodent) at the University of Vermont which is useful for research in immunology and development of eye cataracts.

7. A resource of rare Drosophila species at the University of Texas which is made available to investigators in research areas such as cytogenetics, biochemical genetics, behavior, evolution and taxonomy.

During FY 1975, 14 of these special colony resources provided support for 70 NIH-funded research projects with a total funded value of $5,331,000 and 130 biomedical research projects which received funding from other sources (total research funding value of $3,400,000).

Only one institutional nonhuman primate resource received support during FY 1975. Support for this area has gradually diminished over the past several years due to a general LASP policy that well established primate resources should become financially self-sufficient through charges to users for their maintenance operation. However, the initial establishment of primate resources at institutions for interdepartmental usage is of proven value and remains as an eligible area in the Program. The LASP has continued to assess its possible role in the support of areas which are experiencing critical shortages of experimental animals. For example, the acknowledged national shortage of frogs from their native habitats prompted the organization of a conference on this subject under LASP auspices in March, 1975. The future role of the LASP in supporting studies to alleviate the shortage of frog resources for biomedical researchers is currently under active consideration.

INSTITUTIONAL ANIMAL RESOURCE IMPROVEMENTS

Upgrading of existing animal facilities and development of new centralized animal resource programs has continued to be the most active program area. Requests in this area usually include animal cages to meet current regulations, general sanitation equipment such as cage washers, renovation of animal facilities, and addition of trained professional and technical personnel. The projects are supported for one to three years after which time the applicant institution is expected to take over complete financial responsibility for its basic animal resource. The amount of funded research involving the use of animals and the sources of funding are important factors in establishing funding priorities. The Program Analysis Branch has identified 1433 projects ($90 million current annual funding) involving the use of animals which are supported by NIH at those institutions with currently active resource improvement projects.

Institutional improvement projects have been supported since the inception of the Laboratory Animal Sciences Program; however, they received increased emphasis beginning in FY 1972 when Congress appropriated an additional $1.5 million. These funds were added to the regular budget to help research institutions achieve compliance with the Animal Welfare Act of 1970 (P.L. 91-579). The NIH policy on "Care and Treatment of Laboratory Animals" (issued June 14, 1971) and the subsequent DHEW policy on "Animal Welfare" (issued May 14, 1973) also contributed to the overall response in this area. The following figures demonstrate progression of support:

	FY 1971	FY 1972	FY 1973	FY 1974	FY 1975
No. of Improvement Projects	14	24	28	46	38
Dollars Awarded (in $1,000's)	673	2,169	2,318	3,217	2,582
Percentage of LASP Budget	11%	35%	37%	55%	42%

The number of new applications for developing institutional animal resource programs has continued at approximately the same level as last year (FY 74 - 19, FY 75 - 21). Seventeen projects were recommended for approval and 15 of these were funded. In addition, 4 of 7 projects from previous years were supported making a total of 19 new projects ($2,143,950). The three projects dating back nearly two years will be administratively withdrawn. Thus, the large backlog of unfunded projects in this area which developed over a period of several years has been reduced to two projects.

DIAGNOSTIC LABORATORIES

The objectives of these laboratories is to provide for improved animal health programs through investigation of naturally occurring laboratory animal disease, to support indepth studies resulting in new information on disease processes and their etiology, to aid in the elucidation of new laboratory animal models of human disease, and to develop resources, including tissues, slides, photographs, etc., for research and training in laboratory animal medicine and comparative pathology. There are 13 programs which are currently being supported ($1.217 million - 20% of LASP budget). A shortage of appropriately trained specialists (veterinary pathologists and microbiologists) has been a limiting factor, precluding any rapid establishment of new programs. However, two new laboratories were funded during FY 1975. Special attention is being given to laboratories which have the potential of serving more than one institution in the same metropolitan area. Unfortunately, several proposals of this type were not approved due to weaknesses in the projected staffing and basic animal care program of the participating institutions.

By undergirding an institution's animal health program, the laboratories make a direct contribution to approximately 885 NIH supported research projects using animals with total funding of nearly $56 million. In addition to the service aspects of diagnosis, the laboratories have been productive in terms of new information and techniques. In-depth studies of laboratory animal disease problems resulted in over 70 publications and presentations during the past year. The value of routine surveillance

activities continues to be demonstrated. Various suppliers of rats were evaluated for the incidence of respiratory pathogens at one institution. Providing this information to investigators coupled with changes in the sources of supply resulted in a much lower incidence of disease in rat colonies. Early recognition of Tyzzer's disease in newly received rabbits resulted in modifications in quarantine procedures and control of this potentially serious problem. One laboratory has continued its close association with a major amphibian facility. Various disease problems have been investigated and a number of publications have resulted. The importance of diet as a source of aerobic gram negative bacteria isolated from cloacal contents was established. These bacteria originated in arthropods being fed as live food. A serious disease problem was reported in one group of Rana pipiens due to naturally occurring infection with a pigmented fungus. The fungus was transmitted experimentally to healthy Rana pipiens, demonstrating a potentially serious clinical problem in laboratory housed frogs. Several laboratories have been investigating regional enteritis, a well known enzootic disease of hamsters. One laboratory was able, for the first time, to establish conditions for the experimental induction of this disease. Future studies to elucidate the etiology and pathogensis will be pursued under a recently funded research grant. A laboratory in Florida receives specimens from a number of exotic species including reptiles and marine mammals. It was noted that the BSP clearance time for healthy indigo snakes was 45-50 hours as compared to times of 30 minutes in rat snakes. This study shows promise in providing an important model for liver function studies. Another potential model for retinitis pigmentosa in humans was discovered following routine screening of an inbred colony of rats. The condition was found in 100% of the rats and was characterized as a slow, progressive degeneration of photoreceptor cells.

RESEARCH PROJECTS

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

	FY 71	FY 72	FY 73	FY 74	FY 75
Number of Projects	4	6	8	10	9
Awarded (in thousands)	403	449	593	591	490
Percentage of Total $	9%	7%	10%	10%	8%

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. For example, currently active projects include studies of sialodacryoadenitis in the laboratory rat, definition of environmental conditions for laboratory animals, development of a vaccine to control feline viral rhinotracheitis, and diagnosis and control of mammalian encephalitozoonosis. Work during the past year on the latter project has resulted in the development of a new serologic test (complement fixation) for experimentally and spontaneously

infected rabbits. The advantage of the complement fixation test is that it is more quantitative than the immunfluorescence test and is applicable to a variety of antigenic fractions. A study currently in progress is comparing the sensitivity of skin tests and serological tests. Comparative studies from human material resulted in the observation that two spontaneous human cases of microsporidosis were due to microsporida belonging to the genus Nosema rather than to the mammalian genus Encephalitozoon. These observations suggest that more emphasis should be given to using immunologically incompetent animals in the safety testing of insect Nosema intended for use as biological pesticides and for distribution into the environment. It is possible that the important human pathogen is the genus Nosema rather than Encephalitozoon as previously assumed.

REFERENCE CENTERS AND INFORMATION PROJECTS

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

1. A Simian Virus Reference Laboratory at the Southwest Foundation for Research and Education, San Antonio, Texas. The Laboratory 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, 48 laboratories submitted nearly 2400 specimens for antibody surveys or virus isolation and identification.

2. The Registry of Comparative Pathology, located at the Armed Forces Institute of Pathology (AFIP). 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" has been prepared for sale. Three fasciles covering 45 models have been published so far and a fourth containing 15 additional animal models plus an index is planned for 1975. An annual short course (3 days) in Comparative Pathology was offered for the second time this May.

3. The Laboratory Primate Newsletter, which now has a mailing list of about 1,700 individuals and organizations. 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

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.

The Animal Resources Branch has supported training programs in laboratory animal medicine since 1967. Seven programs and approximately 20 trainees were supported during the current fiscal year. 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. In addition to the training grant mechanism, the Branch supports training through the award of individual postdoctoral fellowships (six currently active Fellows). In some cases, these individuals have enrolled in ARB training programs. Approximately half of the individuals seek more specialized research training. These fellows have engaged in in-depth studies in a discipline or specialty such as surgery, pathology, virology or physiology, through which they can contribute to research animal resources.

Currently available figures indicate that 110 trainees and fellows have completed training since the inception of training grants and fellowships in laboratory animal science and medicine. Forty (40) of these are employed by medical schools and 50 by other academic, research or governmental organizations. The majority (62) are functioning as directors or staff members of a vivarium; 41 are engaged in research or are obtaining additional training; and 7 are engaged in public health and other activities. Retention in the field of laboratory animal medicine has been excellent, emphasizing the career orientation provided by the training and the continuing need and opportunities available for such individuals.

The attraction of well qualified and motivated individuals to the field of laboratory animal medicine has been a continuing problem, particularly over the past several years. In an effort to help this situation, the Branch, this year, has encouraged existing training programs and diagnostic resources to employ veterinary students during their summer break. It is hoped that this work experience will result in greater knowledge and interest in the field. Development of a "pool" of such individuals for future postdoctoral training should result in long term benefits to the field. Reaction during the first year is highly encouraging as some 41 students inquired about opportunities and approximately 20 will be employed at 11 different institutions.

In the fall of 1974, a new National Research Service Award Program was announced. This program replaces all previous training authorities which terminated July 12, 1974 with the passage of the National Research Service Awards Act (Public Law 93-348). As currently active training programs reach the end of their project period, they will have to compete under the provisions of the new authority. The main changes in the new authority are a requirement for recipients (institutional or individual fellows) of NRS Awards to engage in biomedical research or teaching for a period equal to their period of support and a limitation of 25% of the total award for other than trainee costs (institutional programs). Two programs submitted institutional applications for the June Council competition. Additional receipt dates have not been announced and the future of institutional programs supported by NIH is somewhat uncertain since the authority resulting from PL 93-348 was limited to one year. Additional questions to be resolved include the desirability of limiting the proportion of funds awarded to institutional programs compared to individual fellowship awards and the manpower requirements in various research fields that would justify federal training support. The changes and uncertainties surrounding the training programs have made it difficult for them to plan programs and attract well qualified students. If this continues, it will adversely affect research animal resources.

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. Research contract funds for ARB in FY 1975 were about $1,300,000, including $300,000 transferred from The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) for support of the Caribbean Primate Center. Ten projects were supported. These contract projects are in the following area:

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 animals models and genetic stocks and a field survey on the abundance and distribution of primates of biomedical interest in selected areas in South America. A special activity, completed this year, has been a survey and analysis of use of primates for research and a study to provide information for planning numbers and species of primates which should be bred in this

country. The final report has been received and it will be very useful in planning primate supply programs.

AMERICAN ASSOCIATION FOR ACCREDITATION OF LABORATORY ANIMAL CARE (AAALAC)

The Animal Resources Branch is providing, through a small contract, partial support for site visits that are conducted as part of the AAALAC accreditation program. 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.

MARICULTURE OF MARINE INVERTEBRATES

The Animal Resources Branch has awarded two complementary contracts for laboratory breeding and rearing of Aplysia and related species. These marine mollusks are used in a variety of biomedical studies and are becoming increasingly difficult to obtain from nature (the principal supplier now "rations" the animals to researchers). It is felt that, with two or three years' effort, it is feasible to establish laboratory culture of these species, thereby assuring a supply of high quality animals. Both contractors, Pacific Biomarine Inc. and The University of Hawaii, are making good progress toward this goal.

CARIBBEAN PRIMATE CENTER

This primate resource is being supported by funds transferred from NINCDS 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 relationships and has the potential to be an important breeding center. The breeding potential is, in part, being realized as the Bureau of Biologics, FDA, awarded a contract which supports production of 500 rhesus monkeys per year, and additional animals are being bred under contract from NINCDS.

RHESUS MONKEY BREEDING

The Animal Resources Branch has awarded three contracts for the domestic production of rhesus monkeys. This is part of an effort to assure a supply of primates for essential biomedical activities in the face of drastically curtailed importation of wild caught animals. When they come into full production in three to four years, these colonies are expected to produce about one-third of the rhesus monkeys required for NIH extramural programs. The oldest and largest of these three colonies is the Charles River Breeding Laboratories in the Florida Keys. This free ranging island colony currently has 800 breeding animals and about 125 infants were born this year. The colony is targeted for 1500 breeders producing 1000 animals annually. The second colony is the Hazelton Laboratories colony in Texas. The breeders of this colony are housed in corn crib structures. It presently has 300 breeding animals and is targeted to have 900 breeders producing 500 offspring annually. The third colony is the Litton-Bionetics colony in South Carolina. This colony is housed

in sheltered outdoor runs. It currently has 260 of an anticipated 620 breeders which will produce 400 animals annually. About 50 babies were born this year.

SQUIRREL MONKEY BREEDING

Late in the fiscal year, the Animal Resources Branch awarded two contracts for domestic breeding of squirrel monkeys. Next to the rhesus, squirrel monkeys are the most commonly used primate in biomedical activities. The prime sources of these animals, Peru and Colombia, have virtually stopped exportation of them in the past year. Animals can still be obtained from Guyana and Bolivia but these sources are not secure. The ARB contract projects are expected to produce 400 squirrel monkeys annually.

ADMINISTRATION

Primate supply problems continued to be a focus of administrative activity in Fiscal Year 1975. Bans on exporting of animals from Brazil, Colombia, and Peru continued in effect. Late in the fiscal year, we were informed that the Government of India was reducing the quota for export of rhesus monkeys from 30,000 to 20,000 annually. Other nations are considering restriction of primate exports, and chimpanzees will probably be placed on the endangered species list. All this has made development of plans for domestic production, agreements with foreign governments for primate supply, and conservation of use of primates of critical importance. In order to co-ordinate various primate supply activities, the Assistant Secretary for Health has appointed a Primate Steering Committee with NIH as the lead agency. This Committee will also co-ordinate with other government agencies that use primates. The Committee was fortunate to obtain the services of Dr. Benjamin Blood to provide staff leadership. The Animal Resources Branch is providing office space and secretarial assistance to Dr. Blood, and is in the forefront of domestic breeding and conservation of use programs.

Another administrative activity has been the establishment of a Research Career Development Award (RCDA) program. The Branch received approval to announce such a program in January, 1975, and the first applications were received on May 1, 1975. The RCDA provides salary support for individuals that have had at least three years post doctoral experience and have demonstrated potential for development into creative independent investigators. The purpose is to increase the number of first rate investigators who have, as their career goal, research on laboratory animal resource problems.

TABLE I - Primate Research Centers Program Applications, FY 1975

Type	Number Received	Amount Requested[1]	Number Approved	Amount Approved[1]	Number Funded	Amount Funded[2]
New	-	-	-	-	-	-
Renewal	1	1,727,156	1	1,504,552	1	1,452,228
Supplemental	-	-	-	-	-	-
Continuation	6	12,876,984	6	11,404,435	6	9,693,772
Totals	7	14,604,140	7	12,908,987	7	11,146,000

1/ Direct Costs Only
2/ Includes Indirect Costs

TABLE II - Laboratory Animal Sciences Program Applications, FY 1975

Type	Number Received	Amount Requested[1]	Number Approved	Amount Approved[1]	Number Funded	Amount Funded[2]
New	45	4,053,288	28	2,314,848	27	2,836,766[3]
Renewal	8	1,099,216	5	329,476	5	438,795
Supplemental	9	201,372	8	188,357	8	240,847
Continuation	48	2,705,679	48	2,004,424	47	2,665,236
Totals	110	8,059,555	89	4,837,105	88	6,180,844

1/ Direct Costs Only
2/ Includes Indirect Costs
3/ Includes 5 Prior Year Approvals at $451,199

TABLE III - Training Grant Applications in Laboratory Animal Medicine, FY 1975

Type	Number Received	Amount Requested[1]	Number Approved	Amount Approved[1]	Number Funded	Amount Funded[2]
New	2	163,523	2	95,406	2	103,038
Renewal	-	-	-	-	-	-
Supplemental	-	-	-	-	-	-
Continuation	4	313,092	4	247,153	4	256,621
Totals	6	476,615	6	342,559	6	359,659

1/ Direct Costs Only
2/ Includes Indirect Costs

TABLE IV - Fellowship Applications in Laboratory Animal Science, FY 1975

Type	Number Received	Number Approved	Number Funded	Amount Funded
New	5	3	1	27,738
Renewal	-	-	-	-
Supplemental	-	-	-	-
Continuation	5	5	5	21,111
Totals	10	8	6	48,849

TABLE V - Laboratory Animal Sciences Program Resource and Research Grants, Project Distribution, FY 1975

Type	Number Received	Amount Requested[1/]	Number Approved	Amount Approved[1/]	Number Funded	Amount Funded[2/&3/]
Basic Improvement	42	3,188,025	37	2,145,733	38	2,581,834
Special Colonies and Models	26	1,645,629	22	1,095,217	21	1,267,019
Primate Resources	1	22,195	1	11,098	2	118,615
Resource Research	17	1,265,469	10	380,496	9	490,115
Diagnostic Labs	18	1,559,287	13	851,322	13	1,216,661
Reference & Info.	6	378,951	6	353,239	5	506,600
Totals	110	8,059,555	89	4,837,105	88	6,180,844

1/ Direct Costs Only
2/ Includes Indirect Costs
3/ Includes Prior Year Approvals

TABLE VI - Laboratory Animal Sciences Program, Research Utilization of Selected Animal Resource Colonies, FY 1975

No. of Colonies	No. of NIH Grants	Dollar Amt. of NIH Grants in $1,000's	No. Other Projects	Dollar Amt. Other Projects in $1,000's
14	70	$5,331	130	$3,400

Fiscal Year 1975 Annual Report
Biotechnology Resources Branch
Division of Research Resources

The Biotechnology Resource is a vehicle through which the physical sciences, mathematics, and engineering are interfaced to biology and medicine. Such a resource combines expensive equipment, complex methodologies, and scarce expertise to facilitate the solution of important medical problems. A continuous effort to meet program goals is maintained within each resource by (1) providing services to the biomedical research community; (2) engaging in collaborative research arrangements with appropriate scientists; (3) engaging in core research and development designed to provide new technological opportunities for the research community and/or increase the usefulness of existing technology; and (4) providing training opportunities to the user community so that they can better understand the technology and apply it more effectively to their own research problems.

During the past few years it has become increasingly apparent that even some of the most distinguished biomedical research institutions throughout the country are unable to provide their member scientists with either up-to-date, health-relevant, research tools or the opportunity to collaborate with innovative experts at the technology/medicine interface. Accordingly, a concerted effort in Biotechnology Resource Sharing was initiated and promoted during FY 1974 and will continue for the foreseeable future. The objective is to effect a more nearly equitable distribution of highly specialized research support capabilities in the nation, including especially those institutions having limited biotechnology capabilities but strong biomedical research programs and compelling biotechnology needs.

STATE OF THE PROGRAM

BASIC DATA

The variety of supported Biotechnology Resources and the diversity of assistance they provide the research community are shown by the following classification of the 47 grants and five contracts active during FY 1975.

- 17 computer resource grants
- 17 biomolecular characterization resource grants
- 1 resource-related project in biomolecular characterization
- 6 biomedical image and image processing resource grants
- 1 resource-related project in biomedical image and image processing
- 5 biomedical engineering and other resource grants
- 1 electron microscopy services contract
- 4 clinical research data management and analysis developmental contracts

The aggregate annual expenditure level for these activities is approximately $12 million. A listing of the BRB sponsored activities active during FY 1975 is given in Table I. A brief description of each Resource's capabilities, highlighted with an example of its application, is included in Table IIa-d. The interaction of the Biotechnology Resources Program with other NIH programs is shown in Table III.

It is particularly interesting to view the Biotechnology Resources Program in historical perspective. In 1967, for example, 61 resources were supported 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

Both the numbers and the substantive nature of each type of resource have 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 had only one resource of this type in 1975. Whereas in 1967 the average annual award for a computer resource was about $174,000, it was approximately $346,000 in 1975. There seems to be little doubt that the ever more sophisticated computational needs of biomedical scientists are requiring 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, such as the study of metabolic errors in infants. 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.

BIOTECHNOLOGY RESOURCE SHARING

The succeeding sections will describe representative biotechnology resource activities in several areas. It is obvious that these biomedical research activities are of great value to their respective research communities. It is also apparent that these research communities are especially fortunate in having these excellent opportunities immediately available.

Because these highly specialized resources are both expensive and dependent on critical assemblies of scarce talent, only a few medical research centers having needs for them can be accommodated by the BRB, using traditional program support mechanisms, within present and foreseeable funding constraints.

TABLE I

BRB-Sponsored Activities During FY 1975
Active as of May 31, 1975

NUMBER	PRINCIPAL INVESTIGATOR INSTITUTION	TITLE	FY 1975	CUMULATIVE AWARDS
RR-3-14	Wilfrid J. Dixon, Ph.D. University of California Los Angeles, California	Health Sciences Computer Resource	$1,452,285	$19,509,928
RR-7-12	Earl H. Wood, M.D. Mayo Foundation Rochester, Minnesota	Computer Processing in Biomedical Systems	222,326	4,544,848
RR-12-13	Homer R. Warner, M.D. University of Utah Salt Lake City, Utah	Biomedical Engineering Resource	160,123	2,651,066
RR-15-13	Martin Pring, Ph.D. University of Pennsylvania Philadelphia, Pennsylvania	Medical School Computer Facility	195,417	3,603,134
RR-249-10	William S. Rhode, Ph.D. University of Wisconsin Madison, Wisconsin	Support of Laboratory Computer Resources	238,891	2,248,607
RR-259-09	Allan H. Levy, M.D. Baylor College of Medicine Houston, Texas	Computational Research Center Program	25,000	2,259,581

RR-267-10	Eugene Ackerman, Ph.D. University of Minnesota Minneapolis, Minnesota	Health Computer Resource	145,288	2,801,234
RR-273-10	Richard Abrams, Ph.D. University of Pittsburgh, Pittsburgh, Pennsylvania	Mass Spectrometric Facility for Biomedical Studies	67,666	510,711
RR-276-10	Ivan R. Neilsen, Ph.D. Loma Linda University Loma Linda, California	Development of Biomedical Computation Facility	206,184	1,166,412
RR-291-09	Jack Lubowsky, Ph.D. SUNY - Downstate Medical Center, Brooklyn, N.W.	Biomathematical Computer Research Center	a/	1,408,892
RR-292-10	Axel A. Bothner-By, Ph.D. Mellon-Pittsburgh-Carnegie Corporation, Pittsburgh, Pennsylvania	NMR Facility for Biomedical Studies	110,920	1,223,225
RR-317-08	Klaus Biemann, Ph.D. Massachusetts Institute of Technology, Cambridge, Massachusetts	Mass Spectrometry Facility for Biomedical Research	187,277	1,633,789
RR-326-09	Howard Moraff, Ph.D. Cornell University Ithaca, New York	Computer Research Resources	35,567	623,614
RR-330-08	David Rosenthal, Ph.D. Research Triangle Institute Research Triangle Park North Carolina	Mass Spectrometry Center for Research Triangle Region	131,498	836,800

RR-355-08S1	Martin F. Semmelhack, Ph.D. Cornell University Ithaca, New York	High Resolution Mass Spectrometer Facility	43,290	570,972
RR-356-08S1	Seymour R. Lipsky, M.D. Yale University, New Haven, Connecticut	Continuation of Physical Sciences Instrument Facility	112,511	1,419,366
RR-374-08	Theodore H. Kehl, Ph.D. University of Washington Seattle, Washington	Support for Physiology and Biophysics Computer	176,735	1,060,567
RR-396-08	Jerome R. Cox, Jr., Sc.D. Washington University St. Louis, Missouri	A Resource for Biomedical Computing	1,195,100	9,721,729
RR-442-06	Cyrus Levinthal, Ph.D. Columbia University New York, New York	Computer Resource for Image Processing and Displays	239,410	1,278,573
RR-443-06	Robert Nathan, Ph.D. California Institute of Technology, Pasadena, California	A Computer Resource for Pictorial Data Processing	a/	3,153,897
RR-480-07	Charles C. Sweeley, Ph.D. Michigan State University East Lansing, Michigan	Support of Michigan State Mass Spectrometer Facility	101,278	625,126
RR-542-05	George McDonald, Ph.D. University of Pennsylvania Philadelphia, Pennsylvania	Middle Atlantic Regional NMR Facility	72,339	631,864

RR-570-05	Hans Ris, Ph.D. University of Wisconsin Madison, Wisconsin	Electron Microscope Facility for Biomedical Research	88,339	1,012,244
RR-574-04	David M. Grant, Ph.D. University of Utah Salt Lake City, Utah	Regional Research Facility in NMR	146,447	526,523
RR-576-04	John Patterson, Ph.D. Pennsylvania State University, Hershey, Pennsylvania	Biomedical Computing Resource	43,729	467,351
RR-578-05A1	Robert Langridge, Ph.D. Princeton University Princeton, New Jersey	Special Research Resource for Biomolecular Graphics	223,937	1,009,678
RR-592-05	Keith R. Porter, Ph.D. University of Colorado Boulder, Colorado	High Voltage Electron Microscopy of Biological Systems	191,683	1,304,937
RR-612-05A1	Carl Djerassi, Ph.D. Stanford University Stanford, California	Resource Related Research Computers and Chemistry	a/	1,314,215
RR-636-03	Arthur P. Grollman, M.D. Albert Einstein College of Medicine, Bronx, New York	Biotechnology Resource for NMR Studies of Biomolecules	57,138	326,310

RR-639-02	Jay A. Glasel, Ph.D. University of Connecticut Hartford, Connecticut	A New England Area NMR Research Resource	77,889	240,111
RR-643-04	Saul Amarel, Sc.D. Rutgers University New Brunswick, N. J.	Biotechnology Resource Computers in Biomedicine	395,244	985,941
RR-657-01A1	Alfred P. Wolf, Ph.D. Associated Universitites Brookhaven National Lab., Upton, New York	A Program in Support of Nuclear Medicine	a/	237,960
RR-665-02	Rodger L. Foltz, Ph.D. Battelle Memorial Inst. Columbus, Ohio	Regional Medical Mass Spectrometry Resource	68,408	155,484
RR-679-03	Clifford A. Barger, M.D. Harvard Medical School Boston, Massachusetts	Biotechnology Resource in Electronprobe Microanalysis	184,323	481,399
RR-708-01	Nathan O. Kaplan, Ph.D. University of California at San Diego La Jolla, California	Special Resource for NMR and Mass Spectrometry	a/	306,081
RR-711-02S1	Oleg Jardetzky, M.D. Stanford University School of Medicine Stanford, California	High Frequency NMR Biotechnology Resource	14,186	202,665

RR-711-03	Oleg Jardetzky, M.D. Stanford University School of Medicine Stanford, California	High Frequency NMR Biotechnology Resource	104,010	306,675
RR-715-03	Elliott N. Shaw, Ph.D. Associated Universitites Inc., Upton, New York	Electron Microscope Facility	62,974	225,214
RR-716-07	Harold W. Shipton, C. Eng. University of Iowa, Iowa City, Iowa	A Bioengineering Resource Facility	a/	247,931
RR-719-02	A.L. Burlingame, Ph.D. University of California Berkeley, California	Biomedical, Clinical Mass Spectrometry Resource	144,370	333,573
RR-754-01	Donald P. Parsons, M.D. Roswell Park Memorial Inst., Buffalo, New York	Emulsions & Image Intensifier for the HVEM	a/	128,153
RR-757-03	Joseph Kraut, Ph.D. University of California La Jolla, California	Implementation of a Laboratory Automation System	160,832	482,871
RR-759-02	Milton Helpern, M.D. New York University New York, New York	The Institute of Forensic Medicine as a Research Resource	29,105	110,604
RR-785-02	Joshua Lederberg, Ph.D. Stanford University Stanford, California	Stanford University Medical Experimental Computing Facility (SUMEX)	619,435	1,946,061

RR-798-01	Martin Saunders, Ph.D. Yale University New Haven, Connecticut	Southern New England High Field NMR Facility	a/	305,816
RR-857-01A1	Wen H. Ko, Ph.D. Case Western Reserve University, Cleveland, Ohio	Biomedical Electronics Resource	a/	433,318
RR-862-02	Frank H. Field, Ph.D. Rockefeller University New York, New York	A Mass Spectrometric Biotechnology Resource	85,922	166,356
RR-898-01	James D. Foley, Ph.D. University of North Carolina Chapel Hill, North Carolina	Interactive Graphics for Molecular Studies	a/	125,000

BRB-SPONSORED CONTRACTS

NIH-70-4136	Robert M. Fisher, Ph.D. U.S. Steel Engineers and Consultants, Inc., A Subsidiary of the U.S. Steel Corporation Pittsburgh, Pennsylvania	Access Health Scientists to the high voltage electron mic roscope located in the Edgar E. Bain Laboratory for Fundamental Research, Monroeville, Pennsylvania	a/	215,000
NIH-72-2098	Arthur W. Nunnery M.D. University of Oklahoma Oklahoma City, Oklahoma	Development of a Clinical Research Data Management and Analysis Role for Computers	25,748	119,509

NIH-72-2102	T. G. Christopher, M.D. University of Washington Seattle, Washington	Development of a Clinical Research Data Management and Analysis Role for Computers	69,058	114,203
NIH-72-2104	H. K. Thompson, Jr., M.D. Baylor College of Medicine Houston, Texas	"	65,583	185,119
NIH-72-2106	Gabriel F. Groner, Ph.D. The RAND Corporation Santa Monica, California	"	371,784	778,235

a/ Active during FY 1975 but received no FY 1975 funds.

Table IIa

Resource Characterizations

Computers

Grant No.	Capability	Illustrative Applications
RR-03-14	Batch processing, timeshare, and graphics	Biostatistical research; modelling cell cycle dynamics
RR-07-12	Image Processing and analysis	Non-invasive monitoring of cardiac function via roentgen video densitometry
RR-15-13	Time sharing and batch processing	Biochemical kinetics modelling
RR-249-10	Stand-alone minicomputers	On-line real-time control of neurophysiology experiments
RR-259-09	Batch processing and tele-processing	Patient record management
RR-267-10	Batch processing and time-sharing	EKG analysis
RR-276-10	Dedicated systems and time-sharing	Computer assisted pulmonary function testing
RR-291-09	Batch processing or dedicated digital analog system	Biomathematical modelling
RR-326-09	On-line interactive laboratory computing	Acquisition and processing of neurophysiology data
RR-374-08	Experiments hardwired to resource computers plus time-sharing	On-line control and analysis of physiology experiments
RR-396-08	Dedicated computers and macromodule systems	Cardiac rhythm monitoring; biomolecular modelling

Computers (continued)

Grant No.	Capability	Illustrative Applications
RR-576-04	Remote job entry to institution's computers; stand-alone minicomputer	On-line real-time control of biomolecular characterization devices
RR-578-05	Stand alone medium computer and graphics	Biomolecular modelling and computer-assisted design of organic systhesis
RR-643-04	Access to timesharing systems	Application of artificial intelligence to clinical decision making
RR-757-03	Computer-based automated laboratory systems	Image processing, on-line acquisition and processing of X-ray crystallography data
RR-785-02	Remote access through computer networks	Applications of artificial intelligence in biology and medicine
RR-898-01	Interactive graphics and modelling	Displaying and manipulating molecular models.

Table IIb

Resource Characterizations

Biomolecular Characterization

Grant No.	Capability	Illustrative Applications
RR-273-10	Gas chromatography/low resolution, mass spectrometry/gas flow proportional counter	Metabolic profiles
RR-292-10	High-frequency NMR, Multinuclear capability	Structure and function of hemoglobins and other molecules
RR-317-08	Mass spectrometry-High resolution, gas chromatography/ mass spectrometry, chemical ionization	Drug identification, structure determination of unknown biomaterials
RR-330-08	Mass spectrometry-High resolution, gas chromatography/ mass spectrometry	Structure determination of potential anti-tumor drugs
RR-355-08S1	Mass spectrometry - High resolution, gas chromatography/ low resolution	Structure determination of antibiotics
RR-356-08S1	Mass spectrometry - High resolution, low resolution, NMR - Carbon-13, Proton, High performance chromatography	Separation and detection of mucleosides
RR-480-07	Mass spectrometry - High resolution, gas chromatography/ mass spectrometry, field desorption mass spectrometry	Structure determination. Lipids of biomedical importance
RR-542-05	High-frequency NMR	Enzyme/substrate interaction mechanisms
RR-574-04	NMR-multinuclear capability	Carbon-13 labeled macromolecules
RR-612-05A1	Resource related research Mass Spectrometry	Application of artificial intelligence to mass spectrometry

Biomolecular Characterization (continued)

Grant No.	Capability	Illustrative Applications
RR-636-03	NMR-multinuclear capability	Structure and function of peptide hormones
RR-639-02	NMR-Proton, Carbon-13	Carbon-13 studies of nucleoside bases
RR-665-02	Mass spectrometry - high resolution, gas chromatography/ low resolution, chemical ionization	Structure identification of natural products
RR-708-01	Mass spectrometry, gas chromatography/low resolution, NMR-220MH_z	Metabolic studies, structure and function of biomolecules using stable isotopes
RR-711-02S1 -03	NMR - 360MH_z	Structure and function of macromolecules
RR-719-02	Mass spectrometry - high resolution, gas chromatography/high resolution, low resolution	Application of mass spectrometric techniques to clinical problems
RR-798-01	NMR - 270MH_z; Proton, carbon-13; deuterium; swept and fourier transform modes	Membrane structure, drug and hormone action, immune responses, carcinogenic activity
RR-862-02	Mass spectrometry-chemical ionization	Application of mass spectrometry to medical problems

Table IIc

Resource Characterizations

Biomedical Image and Image Processing

Grant No.	Capability	Illustrative Applications
RR-442-06	Image processing and displays	Neuroanatomical modelling
RR-443-06	Image processing	Electronmicrographs and medical images
RR-570-05	One-million volt electron microscope	Structure and function of chromosomes
RR-592-05	One-million volt electron microscope	Structure and function of the nucleolus
RR-679-03	Electron Microprobe	Histochemistry - quantitative analysis of renal cell composition
RR-715-03	Scanning electron microscope	Under development
RR-754-01	Image processing	More sensitive systems for recording images in the high voltage electron microscope

Table IId

Resource Characterizations

Biomedical Engineering and Others

Grant No.	Capability	Illustrative Applications
RR-12-13	Activities hardwired to resource computer	Patient monitoring; medical record management
RR-657-01A1	Production of radiochemicals that incorporate short-lived radionuclides	Nuclear medicine
RR-716-07	On-line real-time integration methods; on-line real-time display	Interfacing of laboratory instruments to computers; acquisition of electrophysiological and other biological data under computer control
RR-759-02	Serology, toxicology, histology	Forensic pathology
RR-857-01A1	Microelectronics fabrication, packaging, and evaluation capabilities	Microelectronics devices for biological and clinical research

Table III

Number & Dollar Amount, by NIH Institute, of Projects Receiving Technological Support from a Sample of 30 of the 47 Biotechnology Resources

Active During FY 1974

Institute	Number of Projects	Dollar Value of Project (in millions)
Allergy and Infectious Diseases	26	1.5
Arthritis, Metabolism and Digestive Diseases	57	4
Cancer	64	9.7
Child Health and Human Development	45	2.8
Dental Research	4	.1
Environmental Health Sciences	6	.4
Eye	7	.6
General Medical Sciences	140	7.9
Heart and Lung	226	8.5
Neurological and Communicative Disorders and Stroke	59	5
	634	40.5

Projected Totals for all 47 Active Grants

Number = 993

Value = $64 million

Moreover, these specialized resources usually must have great capacity in order to function effectively. At the same time such great capacity may exceed the needs of a single institution, yet could be of even greater value with specific supplementation.

The logical solution to these problems of high costs, scarce talents, needs for broad and versatile resource support, and inter-institutional collaboration, lies in linking and sharing resources.

Because of the varied natures of sharable resources, specific appropriate administrative arrangements are needed. Some biotechnology resources, such as computers which can be linked by telecommunication networks, are readily adapted to the shared mode. Others, e.g., the HVEM resources, presently require that the investigator and the problem be brought to the resource facility, under suitable arrangements assuring effective management, participation of qualified researchers, needed training, and ongoing evaluation of effectiveness as a shared resource.

Assembly of related but dissimilar biotechnology resources into shared networks offers the advantage of pooling diverse talents and instrument capabilities to produce levels of capability superior to those of any component.

The pooling effect has special benefits for those investigators and institutions with potential, but who for lack of opportunity have inadequate training and experience in the exacting skilled fields encompassed. Sharing of resources therefore offers opportunities for disadvantaged institutions and isolated investigators. However, the linking of institutions and investigators of grossly dissimilar levels of sophistication poses new problems of program management to assure equitable involvement of the "have" and "have not" components in shared resource systems. Both the review and the ongoing management by NIH staff must enter a new dimension.

The benefits of shared biotechnology resources are obvious. These include: (1) the support of a larger and more varied body of investigators and problems, (2) fuller utilization of expensive instrumentation, (3) increased collaboration between investigators in different institutions who have research interests in common, and (4) the increase in numbers and quality of researchers and institutions able to benefit from sophisticated biotechnology approaches to their biomedical activities.

Although shared biotechnology resource programs are still in comparative infancy, the potential for expansion is impressive. The experience gained in developing and managing these arrays may well establish patterns of wide applicability in biomedical research.

COMPUTER RESOURCES

CLINICAL DECISION MAKING IN GLAUCOMA

Research on the management of medical knowledge relevant to glaucoma diagnosis and therapy at Rutgers University and Mt. Sinai School of Medicine is now making

clinically significant contributions. A conceptual model of how this knowledge is organized for computer-based problem solving is an iceberg: the visible portion is the set of observed signs and symptoms; at the water line are descriptions of disease states appropriate to the specific patient; and under the water are found the detailed normal and pathophysiological models containing most of what is known about glaucoma-related ocular mechanisms and functions. This system is designed to trap inconsistent observations, to be restructured and rebased from new knowledge acquired from the experts in glaucoma as they interact with the system, to provide the rationale for each action recommended, to simulate how each of several glaucoma experts would handle a difficult case, and to provide advice on diagnosis and therapy through the stages of glaucoma. Linkages between experts at different institutions and the Rutgers group are being developed to broaden and deepen this effort and its impact.

At present the system contains about 80 causal states associated with glaucoma. This number seems to be approaching the optimum for an effective yet efficient clinical consultation tool for those dealing with this disease. Future work will strengthen the linkages between the disease state and the pathophysiological models and explore how knowledge of the disease and computer-predicted consequences of candidate therapeutic actions can be organized and presented in the most compact but comprehensive form.

SUMEX-AIM

During FY 1974 the BRB awarded funds for the creation of SUMEX, Stanford University Medical Experimental facility. This resource is the first and only such installation expressly devoted to research on Artificial Intelligence in Medicine (AIM). The SUMEX computer has 50 per cent of its capacity devoted to AIM activities within the Stanford University Medical School and the remaining 50 per cent of the capacity allocated to AIM activities throughout the country via computer networks. The initial SUMEX/AIM community included mass spectrometry data interpretation studies at Stanford, the glaucoma activity at Rutgers University, and X-ray crystallography studies at the University of California at San Diego. National solicitation to identify additional qualified participants began in FY 1975 and is currently well underway.

The intellectual ties among the SUMEX-AIM participants are expected to serve as a key element of the shared resource function. Benefits should accrue through exchange of ideas and techniques, and these interactions should lead to further strengthening biomedical research through collaboration both within the artificial intelligence community and between the computer scientists and their medical research counterparts.

AIM WORKSHOPS

Health researchers outside the SUMEX-AIM activity have expressed interest in learning more about these advanced computing techniques and their potential biomedical application. As a result, a series of AIM workshops are planned. These workshops are to be an arena where biomedical scientists with significant health research problems can interact with advanced computer scientists who

are stimulated by the methodological challenges of the biomedical milieu. The Biotechnology Resource at Rutgers University will be the focus for these workshop activities. The first workshops were held at Rutgers University June 14-17, 1975.

CANDIDATE NEW TOOLS FOR PROGRAM MANAGEMENT

There have been many subjective indicators over the years suggesting that the BRB Program best serves the biomedical research community by encouraging the development and use of specialized computer resources rather than general-purpose ones. Therefore, it is important to assess the relative costs of specialization and generality. Measures of total costs to create both generalized and specialized computer centers have, interestingly enough, shown little difference; and, in most cases, those computer systems especially developed for the research community are more vigorously utilized 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.

Utilization of computer system capacity can be evaluated effectively by various metrics. The computer systems supported by the BRB Program have in common the mission to diffuse technology into health research. The proposed selection of talent and equipment to do this is reviewed prior to the initiation of each resource. The progress of the resource in serving qualified investigators can be examined by observing the ratio between this utilization and the size of the systems and applications programming staff. It is important that both systems and applications work be included in this analysis, for the more effectively the systems programmers bend the machine to serve man, the less need there is to provide applications programming support to the user community. After a resource has achieved mature and stable capabilities, strong effort is required to maintain a competitive edge with the constantly emerging new computer technology. The BRB diffusion metric (user hours/computer programming FTEs) is sensitive to these variations and strengths.

Cost measures also are central to this analysis. BRB interests in cost measures stem from the programmatic goal of having biomedical computer technology contribute optimally within the funds available. The strategy has been to create and nurture resources and then to 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 highly successful and moderately successful 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 1968-1974.

BRB Dollars Per Computer Production Hour	1968	1969	1970	1971	1972	1973	1974
	$91/hr.	$70/hr.	$72/hr.	$52/hr.	$32/hr.	$27/hr.	$20/hr.

WORKSHOP ADMINISTRATIVE ASSISTANCE

Workshops and related activities represent a potentially indispensable mechanism to facilitate both the planning and communication activities associated with resource sharing. By assembling scientists in groups of various sizes, NIH staff can simultaneously encourage the interchange of ideas and draw upon expert technical advise. Moreover, by having individual scientists visit shared biotechnology resources, use the capabilities offered on research problems of their choice, and furnish a written report on the experience, NIH staff can build the kind of data base the workshop participants will need for their efforts to be most effective. A continuing workshop series could be the principal forum through which NIH staff and the biomedical research community jointly bring about successful sharing of highly specialized biotechnology research resources. The BRB is initiating a contract to provide administrative assistance for these activities.

CLINFO

The CLINFO project is a scientific inquiry sponsored by the BRB and General Clinical Research Centers Branch. It is aimed at identifying and characterizing the information analytic tasks and the information flows in human clinical investigation and at developing methods for facilitating these tasks and flows. The first phase of the inquiry gathered information about and characterized the investigative processes, identified potential roles of computer technology in facilitating clinical research, and identified existing and potential systems to fill these roles.

CLINFO is currently being effected by a consortium comprised of clinical contractors at Baylor College of Medicine, the University of Oklahoma, and the University of Washington, information scientists at The Rand Corporation, and staff members of DRR. The clinical contractors have been contributing knowledge about clinical research, the information scientists have been contributing experience in computer technology and knowledge of information science, and DRR staff members have been providing overall direction.

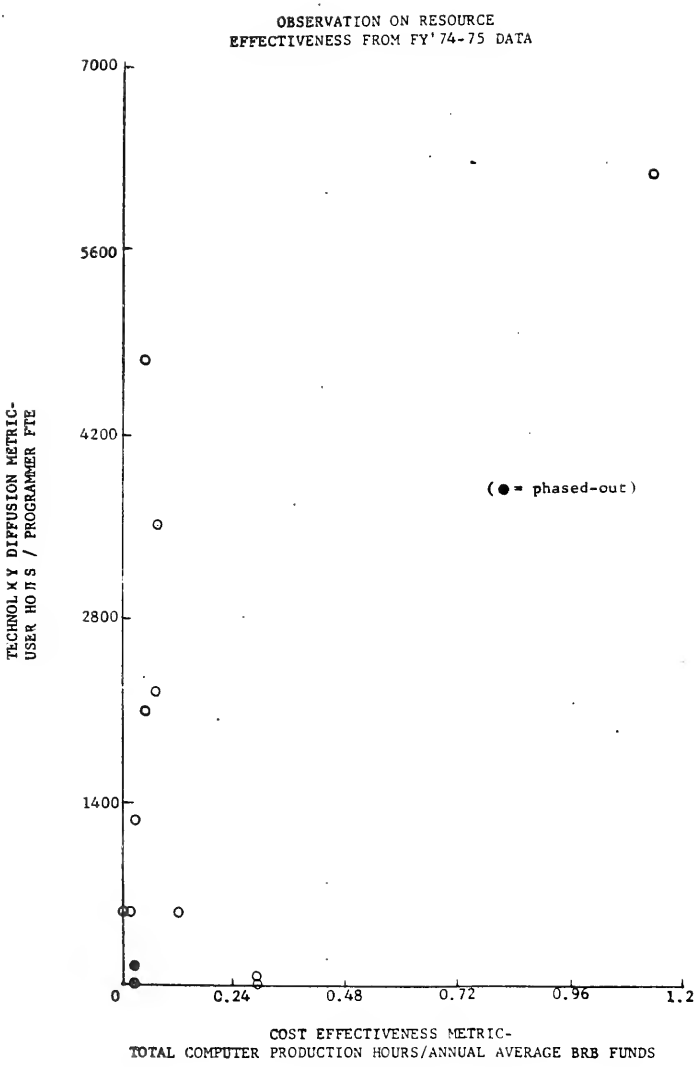
OBSERVATION ON RESOURCE
EFFECTIVENESS FROM FY'74-75 DATA
7000
5600
4200
2800
1400
0
0.24
0.48
0.72
0.96
1.2
(● = phased-out)
TECHNOLOGY DIFFUSION METRIC-
USER HOSTS / PROGRAMMER FTE
COST EFFECTIVENESS METRIC-
TOTAL COMPUTER PRODUCTION HOURS/ANNUAL AVERAGE BRB FUNDS

FIGURE I

The CLINFO project has thus far

- broadly characterized clinical research activities,
- identified research data management and analysis as major problems in clinical research,
- shown (through an extensive survey of clinical investigators) that these problems are widespread, and
- examined a number of existing systems that might alleviate these problems.

The present goal is to increase the quality and effectiveness of clinical research by developing an economical, readily accessible, widely usable computer system that, together with specially trained personnel, will help clinical investigators to collect, organize, store, retrieve, and analyze their research data. Past attempts to develop useful computer systems have often failed because development projects have been uncoordinated and inadequately staffed, because they have not had an adequate understanding of the hardware, software, and personnel requirements, and because they have not adequately tested the systems with a variety of users in a variety of situations. Plans for the next phase include a well staffed, well tested, evolutionary approach which will

- implement an initial prototype system;
- install copies of this system at the three clinical-investigator contractors' institutions where they will be used by several investigators during the course of their execution of approved protocols;
- investigate the use of the prototypes, and (as unobtrusively as possible) modify the systems functional characteristics to maximize their acceptability and utility to a broad variety of users;
- estimate the benefits and operating costs of the prototypes; and
- test the conclusions reached by installing a stable version of the system at and providing personnel to an additional clinical research center where there is no CLINFO contractor and by (passively) observing its use there.

Thus in the next two years the project is to develop a prototype clinical research data management and analysis system and test it with several clinical investigators at each of four sites, including one where there is no CLINFO contractor. The expected results are

- a tested, practical system which can continue to operate at the four sites and which can be duplicated and further distributed in a straightforward fashion;
- documentation of the requirements for, and benefits of, a system designed to have wide applicability;
- knowledge about how to introduce such systems into new institutions, how to promote their use, and how to assist and educate their users;
- information about the requirements for both on-site and centralized personnel to perform these functions;

- a dispersed, trained group of such personnel; and
- a number of newly uncovered problems whose solution could benefit clinical research.

BIOMOLECULAR CHARACTERIZATION RESOURCES

During FY 1975 the Biomolecular Characterization Resources Program encompassed a broad range of capabilities within the areas of mass spectrometry and nuclear magnetic resonance spectroscopy. As illustrated in Table IIb, each Resource is a unique complement to the total program.

For example, a significant impact has been made in the area of clinical mass spectrometry through the Biomolecular Characterization Resources Program. Although the technology has not reached the status of a routinely usable tool for the clinical chemistry laboratory, sufficient experience was gained during FY 1975 to encourage continued emphasis in this area.

At the Michigan State University Mass Spectrometry Facility computer-based techniques have been developed in combination with gas chromatography/mass spectrometry to allow rapid simultaneous identification and quantification of a large number of compounds in urine or other biological fluids as an aid to disease diagnosis and metabolic studies.

A unique and powerful tool, a combined gas chromatograph/mass spectrometer/gas flow proportional counter system, has been developed at the University of Pittsburgh's Mass Spectrometric Facility for Biomedical Research. This instrument makes it possible to separate the components present in an extract of cells or growth medium, identify them, quantitate each component, and assay their isotope content. From such information an accurate metabolic profile can be determined. The system is being applied to a model study designed to diagnose muscular dystrophy at the embryonic level. The availability of such prenatal information would be invaluable in helping to make a decision whether or not to terminate a pregnancy.

In the area of nuclear magnetic resonance spectroscopy, a 360 MH_z instrument, funded jointly with the National Science Foundation, was acquired by the High Frequency NMR Biotechnology Resource at the Stanford University Medical School and in the near future will be widely available to scientists with appropriate problems. A 270 MH_z instrument was recently installed at Yale University. This spectrometer has proton, carbon-13, and deuterium capabilities and will be available to scientists in the Eastern part of the United States.

As part of the BRB commitment to resource sharing, steps have been initiated to develop a coordinated national effort in mass spectrometry and nuclear magnetic resonance spectroscopy. Each center is being encouraged to specialize according to expertise, primary fields of interest and experience, and hardware capability to maximize its effectiveness and impact on important medical problems. The BRB has undertaken the development of a Resource Directory for distribution to NIH grantees and contractors to aid them in identifying sources of highly specialized analytical support available through the program.

HIGH VOLTAGE ELECTRON MICROSCOPY RESOURCES

The High Voltage Electron Microscopy Resources at the University of Wisconsin and the University of Colorado -- and the contract with U.S. Steel Corporation to purchase time on their one-million volt electron microscope -- are another part of the shared resources program in BRB. These resources are national in scope and are available to qualified biomedical investigators throughout the country. Administrative mechanisms have been established to insure that the community of potential users outside the resources' institutions know about the installations and of their opportunity to make application for their use. An ad hoc advisory group to BRB assists in the review of applications for beam time from these scientists, and BRB staff informs these applicants of the results of the review.

During the past year approximately 55 per cent of the microscopes' operating time at the Universities of Colorado and Wisconsin HVEM Resources was allocated to off-campus users. Time purchased by the BRB on the U.S. Steel million volt microscope is used completely by outside scientists. About 70 scientists used the microscopes in a wide variety of investigations.

Considerable progress has been made in the Resources in developing applications of HVEM in biomedical research. The greater penetration and higher resolution gained by the use of the HVEM presents some important advantages to electron microscopists. Small cellular structures such as chromatin fibers, microtubules, microfilaments, and ribosomes are seen with clarity in thick sections at 1000 kv with spatial relationships between structures preserved. The ability to observe whole cells is proving important in studying the interaction of virus and cell. The probability of finding virus particles suspected to be present in small numbers is greatly enhanced when viewing thick sections and whole cells in the HVEM. Using thick sections for autoradiography experiments shortens the exposure times by a factor of 10 to 20. Grain densities that take months to form in the thin sections required in 100 kv microscopes are obtained in two to three days with thicker sections in the 1000 kv instrument. The reconstruction of three-dimensional structure and organization of intracellular systems from stereo images of thick sections in the HVEM is proving to be more accurate and less tedious than has been possible using serial thin sections. The ease with which thick sections can be cut and handled is another practical advantage of high voltage electron microscopy.

BIOMEDICAL ENGINEERING RESOURCES

A biotechnology resource specializing in microelectronics for health research was funded last year. This resource is based upon an established program at Case Western Reserve University focused on strengthening biomedical engineering capabilities; the goal of the new resource is to interact with health scientists in ways that lead to new and improved capabilities of general applicability to health research and patient care. The role of the biomedical engineer in this setting is to reduce the research overhead of medical scientists by providing ways to gain information which is attainable only with microelectronics techniques.

This resource, through its past experience and present capabilities, provides a base to develop telemetry devices which can be

- implanted in the human body to study stress and strain of orthopedic appliances,
- implanted to monitor intercranial pressure, cerebral spinal fluid pressure, and pO_2 of neurosurgical patients and hydrocephalic children, and
- implanted for chronic monitoring of a patient's condition after organ transplant or other critical surgical procedures;

and implant stimulation devices which can effect

- pain suppression by stimulation in spinal cord or periphery,
- blood pressure control of hypertensive patients, and
- control of central nervous system functions.

Using the above devices, systems may be developed to operate an internal signal to control and study the regulation of body functions. Ameliorative steps such as providing a bypass for a damaged neural network is possible with a system of implanted sensors and stimulators.

The collaboration activities of this resource in the past have been with single collaborators on each research area. Extension to other collaborators is desirable to test the efficacy of the ideas in a number of research environments; it is important that the commonality of research needs met by the engineering product be determined and the number of sites for its potential diffusion be multiplied.

The opportunity to examine the processes of pursuing these goals through the resource mechanism is offered in this activity. Two measures of progress can be identified. Early in the resource's life progress may be measured by the strength and geographical range of the resource's collaborative activities. Later, successes may be evaluated in terms of the range and value of the resource's services that are subscribed to by outside users and the appearance and national diffusion of its "finished products" in the commercial marketplace.

"INTERFACE" RESOURCES

In order to make the benefits of highly specialized and expensive biotechnology research resources more widely available to potential health researchers, the sharing of these resources is being encouraged and supported. This sharing makes possible the broader availability of specialized abilities between resources, permits concentration on individual problem areas, and most importantly, brings new investigators and institutions into the national array of biotechnology research activities.

An "interface" resource is designed to make the capabilities of nationally shareable resources available to local or special groups of the biomedical research community. An "interface" resource would need to meet the following criteria:

1. The activity must emphasize a dynamically evolving health-relevant technology such as computer mass spectrometer capabilities, biomedical engineering capabilities, and molecular modelling capabilities. The Resource Director will participate in technical innovation to upgrade capabilities of the resource which he uses.

2. The service and collaborative capabilities rendered by the "interface" resource staff must exceed those which are exploited by a single user.

3. The operating costs of the "interface" resource (i.e., expenditures for personnel, supplies, travel, communications) must be at a level which cannot be justified by a single research effort.

An example of "interface" resources is found at Rutgers University where that resource's staff collaborate and provide service for glaucoma investigators at Mt. Sinai Medical School in New York, Washington University, and Johns Hopkins through the capabilities of the BRB supported computer resource at Stanford University.

Such sharing results in a more equitable distribution and effective use of limited resource support funds and in the inclusion in the national program of promising talented individuals in institutions now isolated from the capabilities of expensive and specialized equipment developed for biomedical research.

RESOURCE SHARING - SUMMARY

The following table displays and summarizes the nature, status, and projected future of shared resource programs. Shared biotechnology resources must meet the present four essential criteria for BRB resources and in addition must include inter-institutional collaboration in research, policy, and management activities. Presently active BRB shared resources are described above. Shared BRB resources under development or planning are listed in Table IV. Potential sharing of resources need not be limited to biotechnology.

In the development and on-going management of shared resources several considerations must be kept in mind in addition to those that pertain to traditional research resource support programs. The preparation by applicants of requests for support of shared resources will need consultation and advice by staff to ensure that plans for inter-institutional sharing are described clearly. The peer merit review of proposals must include, in addition to the traditional considerations, evaluation of the need for and the feasibility of the proposed sharing arrangements.

The management of NIH-supported shared resources must take into account the increased complexity of multi-institutional relationships, geographical separation, and unequal sophistication of participants. This management must be a partnership among components, including an on-going role for the staff of the supporting agency.

TABLE IV

SHARED BIOTECHNOLOGY RESOURCES UNDER DEVELOPMENT OR CONSIDERATION

Biomolecular characterization resources

- High resolution mass spectroscopy
- Nuclear magnetic resonance spectroscopy
- X-ray crystallography
- Activation analysis

Biomedical computer specialized resources

- Modeling of biological processes
- Molecular modeling
- Image processing
- Biomedical graphics
- Biostatistics
- Chemical-biological information-handling

Electron probe resources

Biomedical engineering resources

- Diffusible products -- computer, instruments, and sensors
- Programmed console for radiation therapy
- Clinical monitoring systems

The management must provide for

- equitable responsibilities and opportunities for all participants -- both suppliers and users of services,
- justified expansion of opportunities -- including training for inexperienced candidates needing to participate,
- equitable funding support among components,
- appropriate participation by funding agency, and
- on-going inter-institution management ("interface" resource).

In planning and setting up national networks of shared resources, the need for subsequent evaluation of effectiveness must be recognized. This evaluation can be done most dependably if incorporated into the original design, so that records will reflect the basis for and consequences of decisions made. It will then be possible to make comparative measurements of relative effectiveness in terms of program and costs.

These considerations hopefully will evolve into an agenda for action insofar as further biotechnology resource sharing is concerned. But meaningful action on the agenda will take place only if both the letter and spirit of these concepts are embraced by leaders in the biomedical research community. BRB staff and advisors look forward to playing at least a small role in catalyzing the testing and elaboration of these concepts in the real world of biomedical science. There is little doubt that the key contributions of biotechnology resources toward fulfilling the NIH mission will be even more visible in the future than they have been in the past.

"PROPHET encourages the investigator to ask more searching questions of (his) data, and to look at it from perspectives he ordinarily would not explore...."

-- PROPHET user working in human clinical investigation

PROPHET "...permits ideas and research to continually and daily be redirected in the most promising directions. Notions that would have been too extravagant to pursue, in terms of the investigator's time, can now be taken up and rapidly settled."

-- PROPHET user working in molecular biology

"Bill, the ?*!*? thing really works.... We now can do data analysis so much faster, the difference is not just quantitative, it's qualitative! We never were able to test so many hypotheses before."

-- PROPHET user working in neuropharmacology

BACKGROUND

Better understanding of the interrelationships between chemical substances and living systems is of critical importance to almost every area of biology and medicine. Whether the focus is drug development and evaluation, endocrine function, toxic compounds present in the environment, or antigen-antibody interactions--to name only the more prominent examples--, significant advances invariably depend upon the acquisition of detailed new knowledge about how specific molecules affect and are affected by life processes. Nowhere are insights into molecular mechanisms more actively sought or more urgently needed. Nowhere is there research more relevant to the cure and prevention of disease in humans and animals and to the improvement of the quality of life. It hardly is surprising that chemical/biological interactions are featured among the research activities of every one of the National Institutes of Health (NIH) and the Institutes comprising the Alcoholism, Drug Abuse, and Mental Health Administration (ADAMHA).

The Chemical/Biological Information-Handling (CBIH) Program has a special mission with respect to the rest of the NIH and to ADAMHA. The CBIH Program (a) designs and develops computer-based information-handling tools for the study of chemical/biological interactions; (b) makes these tools available to the national scientific community in an easy-to-use and highly reliable form; and (c) collaborates with the users of these tools not only to refine

and extend them but also to understand better the investigative process itself. Throughout this work, emphasis is placed on discovering where and how computer technology and information science can help scientists learn to predict how chemical substances and living systems will interact under various circumstances. In this way, the CBIH Program strives to be a resource for many other programs throughout NIH and ADAMHA, undertaking technological innovations that no one Institute generally could justify doing alone and sharing the results wherever they are needed.

All of the activities of the CBIH Program involve a specialized computer resource called the PROPHET System. PROPHET is accessible from essentially anywhere in the Nation by means of digital telecommunications facilities and is capable of serving several users simultaneously. It features tools for data management, data analysis, and molecular modelling via the medium of an English-like command language and an interactive graphical display. PROPHET is the most nearly comprehensive array of information-handling tools for the study of chemical/biological interactions ever to be integrated into a single system and made available to laboratory and clinical scientists in national competition. The evaluation and refinement of the PROPHET System is the means by which the CBIH Program carries out its mission.

Substantial documentation exists regarding PROPHET and its research uses. The features of the System are explained in detail in several manuals (1,2). The principal characteristics of PROPHET's architecture have been reviewed from several perspectives (3,4,5). There are accounts of specific research projects involving PROPHET (6,7,8,9), as well as a discussion of issues associated with the management and administration of the resource (10).

The paragraphs which follow summarize the progress of the CBIH Program and its PROPHET System during Fiscal Year 1975.

PARTICIPANTS IN THE PROPHET PROJECT

The continuing maturation of the PROPHET project and its ever-broadening impact upon biomedical research reflects a successful blending of the talents of many individuals. The bulk of the responsibility for the development and operation of the PROPHET System rests with two NIH contractors: Bolt Beranek and Newman Inc. (BBN) of Cambridge, Mass. and First Data Coproration (FDC) of Waltham, Mass. BBN is the focus for improvements to and maintenance of the PROPHET software, as well as being the principal point of contact with the PROPHET users. FDC houses and manages the PROPHET System computer facility (a Digital Equipment Corporation PDP-10) and arranges for the digital telecommunication services that make PROPHET accessible nationwide. Both of these contractor organizations have distinguished themselves and the project by exhibiting high technical competence and professionalism in carrying out their assigned tasks.

The CBIH Program staff and contractors receive invaluable assistance in the planning, execution, and evaluation of PROPHET System activities from the Chemical/Biological Information-Handling (CBIH) Review Committee (see Table I). This group, a formally chartered DHEW advisory body, participates in four

basic ways. First, the Committee reviews position papers, draft Requests for Proposals, and other documents which deal with proposed PROPHET System activities. Second, the Committee assists the CBIH Program Director in the technical evaluation of the performance of the contractors. Third, the Committee reviews research prospectuses submitted by individuals or groups who wish to use the PROPHET System in their research and advises the CBIH Program Director as to the appropriate allocation of PROPHET System services. Fourth, the Committee, augmented by ad hoc consultants having special expertise in selected subject matter areas, helps NIH staff determine the relative technical merits of contract proposals submitted in response to CBIH Program solicitations. The PROPHET project is fortunate to have the counsel and critique of this able and dedicated group of men and women.

The third and final group of participants in the PROPHET project--the user community--in many ways is the most important. It is these scientists to whom everyone else in the project frequently turns for evaluation of present PROPHET System capabilities and for suggestions about new ones. It is these scientists through whom the significance of PROPHET is being made ever more visible in the milieu of laboratory and clinical investigation. It is these scientists and their applications of the technology, not the technology per se, that produces the benefits to society that taxpayers expect and deserve.

The list of institutions presently having access to the PROPHET System is shown in Table II. At each location there is available either a graphic display terminal, a teletypewriter terminal, or both. The last four user sites listed began receiving PROPHET services during Fiscal Year 1975. There also was an increase in the number of users associated with each of the five installations established prior to Fiscal Year 1975.

The growth in both number of user installations and number of users per site is gratifying. It demonstrates that the results of years of system design and technological development are indeed being delivered to qualified scientists in laboratory and clinical environments essentially irrespective of their geographical location or institutional affiliation. It also insures that, in evaluating and refining the PROPHET System, CBIH Program staff and advisors are able to draw upon a considerable breadth and depth of expertise "at the bench" and "in the clinic"--i.e., at the business end of biomedical inquiry. It is doubtful that anyone has ever been in a better position to blend the perspectives of computer scientists and biomedical scientists in producing powerful yet easy to use tools for the study of chemical/biological interactions.

RESEARCH APPLICATIONS OF THE PROPHET SYSTEM

The research uses of PROPHET are many and varied, reflecting the neterogeneity of studies involving chemical/biological interactions. PROPHET users range from molecular biologists and quantum pharmacologists concerned with the fine details of biomolecular mechanisms to epidemiologists and social scientists dealing with the use of alcohol and other drugs of abuse. The applications of the System range from (a) management of empirical data gathered in the laboratory and clinic through (b) statistical analyses and pharmacokinetic modelling to (c) the construction and manipulation of molecular models.

Tables III.A - III.H summarize the research uses of the PROPHET System during Fiscal Year 1975. In general, each table deals with one user installation. The principal exception is Table III.F which involves the collaboration of investigators at three sites. Additional discussion of this collaborative activity is given below.

The format of the tables hopefully is self-explanatory. For the most part, the individuals identified are affiliated with the institution housing the PROPHET terminal. There are a few exceptions (e.g., scientists located at neighboring institutions), but these other institutions are not included explicitly in the interest of keeping the tabulations simple. The use of the phrase "same as number " under the heading "sponsor(s)" signifies not only the same funding source but also the same grant or contract award.

AN APPLICATION OF THE PROPHET SYSTEM IN IMMUNOCHEMISTRY

While Tables III.A - III.H give one some feeling as to the scope of PROPHET System uses, they necessarily are too brief to impart much about any one individual research project in terms of its significance, its intellectual excitement, or the ways in which PROPHET facilitates its progress. Accordingly, this section is devoted to a discussion in some detail of one investigation which made extensive use of PROPHET during Fiscal Year 1975. Perhaps this illustration will help the reader to appreciate how PROPHET functions as a national research resource.

1. The Problem

This example deals with the research of E. A. Kabat and T. T. Wu of Columbia University and Northwestern University, respectively. Their joint investigations, which have been in progress for several years, are designed to elucidate the molecular bases of antibody specificity. Thus, the work is relevant to essentially any area of biology and medicine where an organism's immune system may play a role in combating (or, in some cases, causing) disease or dysfunction. Among the questions these investigators are concerned with are the following: (a) What structural features enable antibodies to be so incredibly specific in their associations with antigens, in some cases exhibiting an ability to distinguish one optical isomer from another? (b) What significance should be attributed to the fact that all immunoglobulin molecules have many structural features in common, irrespective of the antigen against which they are directed or the animal species from which they are obtained? (c) In view of the absence of detailed x-ray crystallographic findings as to the three-dimensional structure of immunoglobulin molecules, to what extent can one use knowledge of the primary structure of these proteins (i.e., the linear sequence of amino acids which comprise the polypeptide chains) to make predictions about an antibody's molecular conformation?

Use of the PROPHET System to study these and related questions began during Dr. Kabat's tenure as a Fogarty Scholar in residence at the NIH. Dr. Wu was provided access to PROPHET from his laboratories at Northwestern University as soon as the feasibility of this application was established. Because of the breadth and complexity of this effort, Dr. H. Bilofsky of BBN works closely

with Drs. Kabat and Wu, providing consultation in the use of PROPHET, developing selected application programs, and participating in the mathematical and statistical analyses of the immunoglobulin sequence data which Dr. Wu amasses from the scientific literature.

2. Predicting Polypeptide Conformation

One major aspect of this research effort involves the development of techniques for predicting how polypeptide chains fold up. The objective is a method whereby one need know only the sequence of the amino acids which comprise a given polypeptide to identify where there are alpha helices, beta sheets, beta bends, and other secondary and tertiary structural characteristics of these molecules (11). The need for such a method, of course, is not limited to immunochemistry. Knowledge about the mechanisms of polypeptide folding is relevant, for example, to enzymology, to endocrinology, and to the studies of biological membranes; and investigators throughout the world are attempting to develop predictive methodologies (12). The need for predictive methods in this field is especially acute, for there are formidable problems involved in attempting to determine the three-dimensional structure of polypeptides directly via x-ray crystallography.

Kabat and Wu approach the chain folding problem as follows. They focus on the tripeptide as their basic unit of interest. Using data on the few proteins whose three-dimensional structures have been solved x-ray crystallographically, they determine how frequently certain types of theoretically possible structural characteristics actually occur in nature. Concentrating on the first and third amino acids in each tripeptide and allowing the middle one to be any one of the 20 normally found in proteins, they prepare a "20 by 20 table" (13). This specialized matrix serves to abstract selected features of the proteins whose three-dimensional structures are known and to represent the result in terms of amino acid pairs (i.e., the first and third members of each possible tripeptide). For example, the 20 by 20 table reveals how frequently the sequence glycine-x-alanine occurs (where x is any amino acid) and how frequently this sequence occurs in an alpha helix, a beta sheet, etc. Kabat and Wu use this specialized matrix to classify certain tripeptides as helix-permissive, helix-breaking, sheet-breaking, etc.; and, armed with this classification, they then attempt to infer secondary structural characteristics of individual unknown polypeptides from their primary structures.

The methodology described above can be extended further where sequence data on a homologous series of polypeptides is available (e.g., the cytochromes, the neurohypophyseal hormones, immunoglobulins, etc.). In these cases, evolutionary mechanisms have allowed changes to occur in the amino acid composition of some parts of the molecule while simultaneously preserving the overall three-dimensional shape (which presumably is indispensable to the molecule's normal function). Where data on a homologous series is available, Drs. Kabat and Wu have developed an algorithm for selecting values of phi and psi, the pair of rotation angles commonly associated with each juncture in a polypeptide backbone (14). Given these phi-psi estimates and assuming the peptide bond to be planar, one then can build a three-dimensional model of the backbone of the class of polypeptides.

The PROPHET System facilitates this work in several major ways. They are described sequentially below.

a. Preparing the 20 by 20 tables. The first step in preparing a 20 by 20 table is to get into useful form selected data on the proteins whose structures have been solved x-ray crystallographically (approximately 20 proteins at this writing). This is accomplished by preparing a standard PROPHET TABLE for each protein using the MAKE TABLE command. Column 1 is designated to include amino acid residue names in standard 3-letter code, is named "residue," and is defined to be of data type "text." Columns 2 and 3 are designated to include the values of phi and psi, respectively, are named accordingly, and are defined to be of data type "number." The appropriate text and numeric values then are entered either row by row from the keyboard in response to prompting by PROPHET or in bulk if already available to PROPHET in machine manipulable form. The command

MAKE TABLE PAPAIN.

for example, invokes a dialogue which eventually results in a 212 row by 3 column tabulation of the backbone structure of this proteolytic enzyme.

Once the protein backbone data are in this form, they can be manipulated with PROPHET's wide array of TABLE-handling commands. One such use is the preparation of a classical Ramachandran plot for the protein (11). This is essentially a scattergram of phi (x-axis) plotted against psi (y-axis), and it can be used to characterize a protein with respect to its secondary structural characteristics. That is, one can determine at a glance if large numbers of phi-psi pairs fall within the alpha helical domain (just below and to the left of center), the beta sheet domain (upper left), etc. If, for instance, one wished to generate a Ramachandran plot for papain and to manipulate it subsequently under the name of PAPAINPLOT, this could be accomplished by giving the command

MAKE GRAPH PAPAINPLOT FROM PAPAIN AS PHI VS PSI

and then following it with the command

DISPLAY PAPAINPLOT.

Alternatively, one could invoke a small PL/PROPHET procedure written by Bilofsky to produce the plot with an overlay of the specific boundaries Kabat and Wu elect to use in determining whether or not a given value for a phi-psi pair falls with the alpha helical domain or the beta sheet domain. Whichever way PROPHET is used to prepare the plot, a task which may require an hour or more by hand is accomplished in less than a minute.

Using some or all of the protein TABLEs, the user also can invoke another PL/PROPHET procedure to prepare the 20 by 20 table. The result is a 20 by 20 PROPHET TABLE, where each cell corresponds to a different amino acid pair (the first and last members of a tripeptide), where each column is of data type "fixed array," and where each cell contains an array of 6 numbers. The

six numbers indicate the number of times this tripeptide sequence was found (1) in the alpha helical domain, (2) in the beta sheet domain, (3) outside of either domain, (4) the frequency with which four successive values occurred in the helical domain, (5) the frequency with which three successive residues occurred in the beta sheet domain, and (6) the frequency of a beta bend involving the middle amino acid. Because PROPHET reduces the time required to prepare this matrix from many days to a few hours, it not only can be more readily updated as new published protein structure solutions become available but also can be prepared in a variety of forms for the purpose of comparative evaluation--e.g., using only proteins which are rich in alpha helix, using different definitions of what constitutes the alpha helical and beta sheet domains, etc. Hypotheses which once were impractical to test now can be addressed quite readily.

b. Predicting secondary structural features. The PROPHET version of the 20 by 20 table can be used via a PL/PROPHET procedure to predict the secondary structural characteristics of polypeptide chains. To do this one creates a PROPHET TABLE for the "unknown" polypeptide using a pre-existing empty template TABLE. The residue names (in standard three-letter code) are put into the cells of column 1; the other columns are left blank. Then one gives the command

```
CALL METHOD1
```

to invoke a procedure which, after prompting the user for specific items of information (e.g., the name of the TABLE containing the sequence data on the "unknown"), uses the summary data on the tripeptides to identify each residue as to whether or not it is helix-breaking or sheet-breaking. As an option one may also compute the probability of a beta bend occurring at each residue position. The procedure records its results by automatically filling in, where appropriate, cells in the empty columns of the TABLE.

Through the medium of another PL/PROPHET procedure called DAYSEARCH, METHOD1 also can be applied quickly and easily to polypeptide sequences in the file recorded and maintained by Dayhoff et al (15). The magnetic tape version of this file has been purchased and implemented on the PROPHET computer. The command

```
CALL DAYSEARCH
```

allows the user to interactively review the directory of sequences recorded in the file and select one or various combinations for inspection. Optionally, the user may specify that one or more selected sequences are to be read out of the file in the form of a PROPHET TABLE all ready for use with the METHOD1 procedure. Thus, by "gluing together" some standard top-level PROPHET TABLE-handling functions with a few custom built PL/PROPHET procedures, it was possible to build an easy-to-use subsystem for evaluating successive versions of METHOD1 against the extensive collection of sequences which Dayhoff et al glean from the scientific literature.

c. Constructing models of polypeptide backbones. In those cases where homologous series of polypeptide sequences are available for use in estimating phi-psi angle values (see above), additional PROPHET capabilities are exploited. Wu has written a FORTRAN program embodying the angle selection algorithm. Not only can this program be run on the PROPHET computer; there also exists a standard interfacing procedure whereby this FORTRAN program can be made to appear to the user as if it were an integral part of PROPHET. This is an excellent example of PROPHET's ability to absorb and integrate procedures that technically exist outside of it.

One of the direct benefits of this integration is that the results produced by the "extra-PROPHET" procedure can be manipulated subsequently within the mainstream of top-level PROPHET functions. This is especially important in Wu's work, for the output of his program (estimates for phi-psi angle pairs), once recorded in PROPHET as part of an instance of the data type MOLECULE, can be operated on by PROPHET MOLECULE-handling commands to produce displayable and manipulable models of the polypeptide backbone. This opportunity to manipulate the computational results interactively in graphical form makes the continuing evaluation and refinement of the structure prediction algorithm much more efficient and effective than was previously the case when only manual methods or batch processing computing facilities were used.

3. Tabulation and Analysis of Immunoglobulin Sequences

The other principal area of interest to Kabat and Wu is the study of variations in the amino acid composition of immunoglobulin molecules. The existence of constant regions and variable regions in both the light chains and the heavy chains of immunoglobulins has stimulated considerable research regarding their significance, the underlying genetic mechanisms, etc. It seems clear that the key to antibody specificity is to be found in this area.

Several years ago, Kabat and Wu developed a statistic with which to characterize immunoglobulin variability (16). For any given collection of variable region sequences (e.g., human heavy chains), they arrange the sequences for maximum homology and then compute for each position in the chain a variability index. This index is defined as

$$\text{variability}_i = \frac{n_i}{f_i}$$

where n_i is the number of different amino acids observed to occur at position i and f_i is the frequency of the most common amino acid at that position (i.e., the number of times the most common amino acid occurs divided by the total number of sequences examined). With this statistic an invariant position has a value of 1; were all 20 amino acids to occur randomly at a position, the upper bound would be 400. This statistic has proved extremely useful in establishing the existence of discrete regions of hypervariability in both light and heavy immunoglobulin chains. And this type of analysis has received added impetus in recent years by preliminary x-ray crystallographic evidence which suggests that these hypervariable regions play a principal role in the formation of an antibody's active site.

While conceptually and arithmetically simple, both tabulation and analysis of immunoglobulin sequences are tedious, error-prone tasks. In the absence of convenient information-handling tools, only a small subset of all the interesting hypotheses can be tested. Research options are seriously constrained by the sheer volume of data and the multitude of calculations.

The PROPHET System has been used successfully to ease these constraints. Published immunoglobulin sequences and the associated literature references are recorded in PROPHET TABLES by Wu on a continuing basis. PROPHET's interactive mode and editing facilities do much to minimize transcription errors. Moreover, the data are immediately available to the other participants in the study, even though they are widely separated geographically from one another.

Once available in the form of TABLES, the sequence data can be subjected to analyses in a very convenient way. The calculation of the variability indices is carried out via a PL/PROPHET procedure called VARIAB; this procedure records its results by adding several new columns to each TABLE it operates upon, the last column containing the values of the variability statistic described above. A graphical representation of the variability then can be obtained by calling the PL/PROPHET procedure VARGRAPH. Once again, the combination of standard top-level PROPHET functions and a few custom-built PL/PROPHET procedures has done much to remove an information-handling bottleneck previously faced by Kabat and Wu and exposed to their creative energies targets that could not realistically be explored before.

Within recent months this work has progressed to the point where virtually all of the immunoglobulin sequences that have appeared in refereed scientific journals have been recorded in PROPHET and enriched with calculated variability values, variability plots, etc. Thus, this unique data base has the potential of being a valuable resource in its own right; access to the collection no doubt could facilitate the work of many other investigators studying antibody structure and function. In recognition of this, arrangements now are being formulated whereby Kabat, Wu, and Bilofsky will undertake not only to maintain and update this data base as part of their continuing research but also to produce low cost printed versions of this collection in a form that will make broad distribution possible. The power of PROPHET and its ease of use are responsible in large measure for a data compilation of this magnitude being amassed and distributed as a by-product of a single research project.

NEW PROPHET SYSTEM FEATURES

Just as PROPHET alters the research milieu and investigative opportunities of its users, so users' experiences cause PROPHET to change and grow. The users have, in fact, become a principal source of ideas for new and improved PROPHET features. This section highlights the major new capabilities which were introduced into service during Fiscal Year 1975.

1. Tools for Data Analysis

Since the introduction of PROPHET services three years ago, there has been a steady growth in the statistical functions available to PROPHET users.

These PROPHET procedures generally are based upon and incorporate code from programs made available by the UCLA Health Sciences Computer Facility and other leading centers of biostatistical research. PROPHET's design allows for an essentially open-ended accretion of such programs and their graceful integration into the System, with users' requirements being the major determinant of the pace and course of this growth. Among the results of recent activities are procedures for probit analysis and chi-square analysis and the elaboration of the collection of procedures for analysis of variance (2).

Other broadly useful tools for data analysis are developed from time to time by individual PROPHET users and made public via the PROPHET public procedure exchange. During Fiscal Year 1975, for example, Dr. Carl Johnson of Mt. Sinai School of Medicine prepared and made available a number of programs for analysis of kinetic data emphasizing Michaelis-Menton kinetics and other methods useful in interpreting dose-response curves.

In a related but more nearly comprehensive vein, PROPHET System contractors introduced MLAB into PROPHET within the past few months. MLAB (Modelling Laboratory) is a program developed at the NIH's Division of Computer Research and Technology for use in a wide array of situations where mathematical functions need to be fit to experimental data. MLAB can be invoked by the users either directly or through the medium of special PL/PROPHET functions which not only make it easier to use but also return its output as PROPHET-manipulable variables. MLAB can be used to fit functions of almost arbitrary complexity-i.e., combinations of powers, exponentials, logarithms, and trigonometric and hyperbolic expressions.

2. Molecule-Handling Tools

Fiscal Year 1975 marked the addition of several new PROPHET features in the area of molecular modelling. As a result of collaboration between PROPHET users at the Medical Foundation of Buffalo and BBN staff, a procedure was developed whereby an instance of a PROPHET data type MOLECULE can be created directly from x-ray crystallography results. That is, using the measured atomic coordinates for all three dimensions and knowing the connectivity among the atoms, one can create MOLECULE variables in the standard PROPHET form and thereby take advantage of the wide array of pre-existing functions for manipulating such variables. Before this development, instances of MOLECULE variables could be created only one way--by sketching a two-dimensional structural diagram with the stylus and tablet in response to prompting associated with the MAKE MOLECULE command. Moreover, the only three-dimensional molecular models previously available for manipulation were those that had been derived from a representation of atomic connectivity using the COMPUTE MODEL command. Users now have two ways to create MOLECULE variables and, when the crystallorgraphy data exists, can work with "observed" structure as well as "estimated" structure.

The PROPHET users at the Medical Foundation of Buffalo also were instrumental in enriching the System's capabilities for molecular display. With the assistance of BBN staff, they modified and introduced the ORTEP program for producing perspective drawings of three-dimensional molecular models. This program was developed at the Oak Ridge National Laboratory about a decade ago

and is widely used in a variety of forms throughout the chemical research community, usually with computer driven plotters. Its accessibility via a simple procedure call now lets PROPHET users choose, for any given three-dimensional molecular model, whether they wish to visualize a stick figure or an ORTEP perspective drawing on their display terminal.

There also was a major upgrading in the power of the COMPUTE MODEL command. In collaboration with Dr. W. Todd Wipke and his associates at Princeton University, PROPHET was fitted out with Dr. Wipke's procedure for building plausible three-dimensional molecular models for cyclic compounds of almost arbitrary complexity. Previously, the PROPHET System had relied exclusively on a "ring library" for such computations and consequently could construct models of only those cyclic compounds whose ring constituents were represented in the library in terms of their three-dimensional atomic coordinates. BBN staff now are collaborating with PROPHET users in order to establish better the limitations of the Wipke algorithm in this implementation and to determine how best to combine it with the "ring dictionary" approach.

3. Remote Terminals

The Tektronix 4010 graphic display terminal was added to PROPHET's line of remote access devices during the past year. This terminal is based on essentially the same storage tube technology as the Computek 400 terminals originally used with PROPHET and is fully compatible with them. The new terminal and Tektronix's nationwide array of field service installations should give PROPHET users and contractors alike greater flexibility with respect to maintenance of the devices in the field. In addition, the Tektronix 4010 terminal is an important step toward the large screen storage tube devices that recently have become commercially available.

There also was some emphasis during Fiscal Year 1975 on improving "teletype" access to PROPHET. Originally, use of PROPHET via teletypewriter devices was restricted to programmers at BBN. While almost all PROPHET features can, in fact, be exercised from a typewriter terminal, the task often is complex or tedious or both. In the early years of the PROPHET project (when all involved were uncertain as to just how "friendly" PROPHET had to be to attract computer-naive users), access by PROPHET users was limited to display devices.

Within the last eighteen months or so, it has become clear that this proscription regarding low-performance terminal devices can be relaxed somewhat. User groups whose activities involve principally numeric and textual data (and not, say, molecular models) have found that PROPHET's TABLE-handling functions and computational capabilities are quite satisfactorily exercised from a teletypewriter device. This being the case, a number of improvements have been made (especially in the area of tabular and graphic output) to facilitate such use. Given the significantly lower cost and easier field maintenance of these devices (when compared with a graphic terminal), the goals of the PROPHET project are well served by making selective use of teletypewriter terminals as a principal access medium.

4. Dial-Up Telecommunications for Graphic Terminals

During Fiscal Year 1975, dial-up access to PROPHET for users with graphic terminals became a realistic alternative to use of dedicated telephone lines. Two events brought this about: (a) the emergence during the last few years of telephone modems capable of transmitting 120 characters per second over a switched network and (b) the recent introduction of new telephone company tariffs which make the use of INWATS lines more attractive economically than had previously been the case. Several PROPHET terminal sites are or soon will be serviced via a dial-up arrangement. The additional flexibility afforded by dial-up access should become increasingly important as the PROPHET user community grows in the years ahead.

5. Tools for Self Instruction

As the PROPHET user community expands, so does the importance of maintaining good communications between and among the participants in the project. This is especially true insofar as instruction in the use of PROPHET is concerned. While every effort is made to keep the User Manual and Public Procedures Manual accurate and clear and while a small cadre of BBN staff are available to users on a regular basis both via telephone and in person, this of course does not guarantee that every PROPHET user fully understands the strengths and limitations of the tools at his or her disposal. Even in those several cases where a user group has one or more resident experts in the use of PROPHET, it is quite possible that individual users are not receiving all the assistance they should. If PROPHET were a static system, this would be problem enough. But the steady accretion of new functions only heightens the possibility that an inexperienced user will miss something of importance or fail to notice that a previously absent feature now exists.

In recognition of the above, BBN staff have developed and introduced into service some tools for preparing on-line self instructional materials. One of these tools allows a user to "record" an actual PROPHET session; that is, it produces a script of both user commands and System responses in a special format. This script then can be "played back" via another command at a subsequent time, thereby allowing the user to proceed step-by-step through simulated recreation of the original session. The user is required to depress the GO key after each command appearing in the script in order to have some control over the rate of the presentation and to acquire some feeling of participation. Since the "play back" is in reality only the read-out of a disc file, the computational resources required in this step are almost trivial. Only when the session actually is being "recorded" is PROPHET being exercised and making appreciable demands on the computer hardware. And then the demands are essentially identical to those associated with normal System use.

The strengths and limits of these programs for building self-instruction materials now are being assessed. BBN staff have prepared a number of scripts covering basic PROPHET operations such as making TABLES, GRAPHS, and MOLECULES. Some PROPHET users are studying the possibility that self-instruction scripts will be valuable as a medium for explaining how to use various public procedures and public data bases they have in preparation.

ADMINISTRATIVE CONSIDERATIONS

Research resources have unique problems and special opportunities. Resources may be involved in important ways with a wide array of categorical disease problems, but they rarely receive the benefits of being identified with any one of them. Resources may be key ingredients in achieving Federal health objectives, but the significance of their contributions frequently may be overshadowed by issues more obviously aligned to the medical problems themselves. Resources may succeed in opening up new opportunities for biomedical scientists, but judgments as to the value of the resources' accomplishments necessarily must wait until users have demonstrated that those opportunities are both wanted and needed. Like the rest of the Division of Research Resources, the CBIH Program must deal with and accommodate to these facts throughout its management and administrative activities.

In the case of the PROPHET System, the mission of the resource is inextricably linked to the missions of the categorical disease programs elsewhere in NIH and ADAMHA. Computer tools for studying chemical/biological interactions have little value if they are designed and tested outside the mainstream of high quality biomedical science. And the significance of even the most exquisitely crafted tools generally will go unappreciated unless their use is directed by a prepared mind. The CBIH Program therefore places a premium on establishing meaningful ties to other Federal program activities in which chemical/biological interactions are being investigated and where modern information-handling technology is not at hand.

The PROPHET System has special attributes as a research resource. First, it came into being as a result of a specific Federal initiative and is sponsored via the contract mechanism; most research resources are initiated by their host institutions in response to Federal program guidelines and are funded via the grant mechanism. Second, the continuing development and operation of the PROPHET System involve the efforts of several contractors, with coordination and overall direction being furnished by CBIH Program staff; most research resources involve only a single award and staff of the awardee provide the direction. Third, the PROPHET System is a nationally shared research resource; most research resources have a much more restricted geographic impact. Fourth, services of the PROPHET System are allocated on a national basis with the aid of a peer review mechanism; most research resources have considerably less formal procedures for this. Fifth, PROPHET users directly reimburse the CBIH Program for a portion of the costs associated with the services they receive; the majority of research resources furnish their services at no cost to the users. Because of these and other attributes, the PROPHET System may well become a paradigm for other specialized research resources in the future.

PLANS

The CBIH Program plans to continue the evaluation and refinement of the PROPHET System. Additional high quality users will be selected and their needs will be addressed along with those of the present users. Efforts will

be made to expand not only the physical capacity of the resource but also the array of powerful tools it contains. Special emphasis will be placed on pharmacokinetics, molecular modelling, and archival management. The prospects for further successful interaction with important research projects seem excellent.

Table 1. Chemical/Biological Information-Handling Review Committee
Fiscal Year 1975

CHAIRMAN

Amarel, Saul
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Department of Computer Science
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Med. University of South Carolina
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EXECUTIVE SECRETARY

Raub, William F.
Program Director
Chemical/Biological Information-Handling Program
Division of Research Resources
National Institutes of Health, PHS
Bethesda, Maryland 20014

Table II. Prophet User Groups as of June 1975

1. Department of Pharmacology
   School of Medicine
   University of Pittsburgh
   Pittsburgh, Pennsylvania

2. Harvard University General Clinical Research Center
   Beth Israel Hospital
   Boston, Massachusetts

3. Department of Pharmacology
   Mount Sinai School of Medicine
   New York, New York

4. Molecular Biophysics Department
   Medical Foundation of Buffalo
   Buffalo, New York

5. Research Institute on Alcoholism
   New York State Department of Mental Hygiene
   Buffalo, New York

6. Technological Institute
   Northwestern University
   Evanston, Illinois

7. Harborview Medical Center
   University of Washington
   Seattle, Washington

8. Biology Department
   Yale University
   New Haven, Connecticut

9. Division of Research Resources
   National Institutes of Health
   Bethesda, Maryland

Table III.A. Applications of the Prophet System at the School of Medicine, University of Pittsburgh, Pittsburgh, Pa.

	Project	Investigator(s)	Sponsor(s)
1.	Drug interactions through depot formation	J. Anderson	Medical Alumni Association, University of Pittsburgh
2.	Study of phenotypic resistance to tetracycline	R. Connamacher	--
3.	Hypertension screening protocol	C. Corder	--
4.	Pharmacokinetics of bethanidine	C. Corder	--
5.	Kinetics of pyruvate kinase	L. Decker	--
6.	Discharge patterns in neuron populations of primate somato-sensory cortex	G. Werner	Alfred P. Sloan Foundation; National Science Foundation
7.	Hallucinogenic drug action on the somatosensory system	G. Werner	National Institute of Mental Health
8.	Kinetics of anticoagulant effects of warfarin in rats	G. Werner	--
9.	Pharmacodynamics of d-tubo-curarine in humans	L. Wingard	--

Table III.B. Applications of the Prophet System at Beth Israel Hospital, Boston, Mass.

	Project	Investigator(s)	Sponsor(s)
1.	Error analyses of amino acid determinations	R. Auty B. Ransil	General Research Support Program, Division of Research Resources, NIH
2.	Analysis of electrolyte interferences in pooled plasma by the method of additions	R. Auty B. Ransil	Same as #1.
3.	Analysis of ultracentrifuge sedimentation rates	R. Auty M. Lanner	Same as #1.
4.	Non-pharmacological approach to hypertension, anxiety, cardiac arrythmias, headache, and drug abuse in post-myocardial infarction patients	H. Benson	National Institute of Mental Health; National Heart and Lung Institute; Hoffman-La-Roche; General Clinical Research Center Program; Division of Research Resources, NIH; General Service Foundation of St. Paul, Minnesota
5.	Study of oral protein sparing in human subjects	G. Blackburn	MIT Center for Nutritional Research; General Clinical Research Center Program, Division of Research Resources, NIH
6.	Analysis of nutritional status of hospitalized patients	G. Blackburn	National Institute of General Medical Sciences; National Institute of Arthritis, Metabolic and Digestive Diseases
7.	Determination of optimal hyperalimentation infusion rates	G. Blackburn	Deaconess Hospital Nutrition Support Service; Same as #6.
8.	Metabolic response to severe trauma	G. Blackburn	Same as #7.
9.	Response of QT interval of the electrocardiogram to exercise	H. Hartley	National Heart and Lung Institute

10.	Prevalence of premature ventricular contraction induced by exercise	H. Hartley	Same as #9.
11.	Effect of relaxation technique on O_2-uptake during exercise	H. Hartley	Same as #9.
12.	Effect of acute ozone exposure on pulmonary host defense mechanisms	G. Huber	Tobacco Companies Grant #49906
13.	Effect of acute and chronic smoking on pulmonary host defense mechanisms	G. Huber	Same as #12.
14.	Airway mechanics and relation to smoking artificial tobacco (Celanese)	G. Huber	Celanese Corporation of America
15.	Subject variability of 24-hour urinary creatinines	B. Ransil D. Greenblatt	--
16.	Pharmacological behavior of librium	B. Ransil D. Greenblatt	--
17.	Debug of progesterone and aldosterone assay for programmable calculators	B. Ransil	Same as #1.
18.	Effects of sodium salicylate in acute Chagasic myocarditis in mice	B. Ransil F. Duncanson	National Heart and Lung
19.	Systolic time intervals during submaximal and maximal exercise in man	B. Ransil J. Maher G. Beller H. Hartley	U.S. Army Research Institute of Environmental Medicine
20.	Left ventricular ejection time by densitrometry	B. Ransil R. Chiriffee J. Foerster O. Bing	Same as #1.
21.	Cardiopulmonary resuscitation on medical and surgical wards	B. Ransil A. Goldberg A. Ramirez	--
22.	Insulin clearance in pre- and post-nephrectomized subjects	B. Ransil	--
23.	The electron charge density basis of chemical reactivity and biological activity	B. Ransil	--

24.	Kinetics of K^+ clearance in perfused rat kidney	B. Ransil P. Silva	National Institute of Arthritis, Metabolic, and Digestive Diseases
25.	Evaluation of the relationship between emotional stress and ischemic heart disease with the quiz-electrocardiogram technique	F. Schiffer	National Heart and Lung Institute
26.	Transport of potassium and sodium by the isolated perfused kidney	P. Silva R. Solomon A. Besarab	Same as #24.
27.	Potassium adaptation and Na-K-ATPase activity in the mucosa of the colon	P. Silva R. Solomon A. Besarab	Same as #24.
28.	Thiocyanate inhibition of ATPase and its relationship to anion transport	P. Silva R. Solomon A. Besarab	Same as #24.
29.	Metabolic adjustment of the kidney involved in the adaptation to potassium loading	P. Silva R. Solomon A. Besarab	Same as #24.
30.	Role of Na-K-ATPase in renal function and relation to respiratory rate	P. Silva R. Solomon A. Besarab	Same as #24.
31.	Role of platelets in maintenance of endothelial integrity	P. Silva R. Solomon A. Besarab	National Heart and Lung Institute

Table III.C. Application of the Prophet System at Mount Sinai School of Medicine, New York, N. Y.

	Project	Investigator(s)	Sponsor(s)
1.	Derivation of quantitative structure-activity relationships for tryptamines on the LSD-receptor of the rat fundus	C. Johnson	National Institute of Mental Health
2.	Analysis of relationships between peptide hormone conformation and pharmacological activity	S. Kang	Same as #1.
3.	Response of Renshaw cells to multiple input; changes with chronic spinal section and chronic drug administration	S. Goldfarb	National Institute of Neurological Diseases and Stroke
4.	Relationships between spatial preferences and d-amphetamine effects on timing behavior in rats	S. Glick	National Institute of Mental Health

Table III.D. Applications of the Prophet System at the Medical Foundation of Buffalo, Buffalo, N. Y.

	Project	Investigator(s)	Sponsor(s)
1.	Dissemination of molecular data for biomedical use	W. Duax V. Cody C. Weeks	National Library of Medicine
2.	Molecular structures of steroids	W. Duax C. Weeks R. Rohrer	National Cancer Institute
3.	Ultrastructure of the antihypertensive prostaglandins	H. Hauptman G. DeTitta	National Heart and Lung Institute
4.	Cancer of the thyroid and its hormonal identity	E. Volpert	National Cancer Institute
5.	Molecular structures of thyroactive compounds	V. Cody	Julia R. and Estelle L. Foundation of Buffalo; National Institute of Arthritis, Metabolic and Digestive Diseases

Table III.E. Applications of the Prophet System at the Research Institute on Alcoholism, Buffalo, N. Y.

	Project	Investigator(s)	Sponsor(s)
1.	Analysis of subjectively perceived effects of alcohol-barbiturate combinations by means of drug discrimination procedures	J. York	New York State Department of Mental Hygiene
2.	Fetal alcohol syndrome: epidemiological study	M. Russell	Same as #1.
3.	Effects of ethanol and barbiturates on membranes and membrane-bound enzymes from drinking and non-drinking mice	D. Lin	Same as #1; National Council on Alcoholism
4.	Effects of acute and chronic administration of ethanol on muscle afferent activity	D. Greenhouse	Same as #1; National Institute of General Medical Sciences
5.	Survey of teenage drinking patterns	G. Barnes	Same as #1.
6.	Alcohol ingestion in lactating rats: effects on offspring	E. Abel	Same as #1; United Way of Erie County
7.	Evaluation of the Erie County, N.Y. Driving While Intoxicated Program	F. Hooper	Same as #1.
8.	Correlates of alcohol-related drinking behavior in twins	F. Hooper	Same as #1.
9.	Evaluation of model sobering-up stations in New York State	R. Cabral	Same as #1.
10.	Alcohol-induced biochemical changes in the central nervous system	A. Chan	Same as #1.

Table III.F. Applications of the Prophet System at the National Institutes of Health; Northwestern University, Evanston, Ill., and Bolt, Beranek, and Newman, Inc., Cambridge, Mass.

	Project	Investigator(s)	Sponsor(s)
1.	Prediction of polypeptide conformation	E. Kabat T. Wu H. Bilofsky	National Cancer Institute; National Institute of Allergy and Infectious Diseases; National Science Foundation
2.	Tabulation and analysis of immunoglobulin sequence data	E. Kabat T. Wu H. Bilofsky	Same as #1.

Table III.G. Applications of the Prophet System at the Biology Department, Yale University, New Haven, Connecticut

	Project	Investigator(s)	Sponsor(s)
1.	Growth control by membrane matrix matching lipids	B. Stowe M. Dotts	--

Table III.H. Applications of the Prophet System at Harborview Medical Center, University of Washington, Seattle, Wash.

	Project	Investigator(s)	Sponsor(s)
1.	Central nervous system regulation of fuel mobilization and storage	C. Goodner	National Institute of Arthritis, Metabolic and Digestive Diseases
2.	Studies of thyroid hormone metabolism	W. Green	National Institute of Arthritis, Metabolic and Digestive Diseases
3.	Platelet mechanisms in disease	L. Harker S. Slichter	National Heart and Lung Institute
4.	Thrombopoiesis	L. Harker W. von Behrens	Same as #3.
5.	Community blood resource center	L. Harker W. von Behrens	Same as #3.
6.	Coronary thrombosis	L. Harker	Boehringer Ingelheim

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Fiscal Year 1975
Annual Report
General Clinical Research Centers Branch
Division of Research Resources

I. Introduction and Goals of the Program

In 1959, Congress expressed the view that the Nation should receive the benefits of basic research as rapidly as these became available. Passage of P.L. 86-798 established the legislative basis for the General Clinical Research Centers (GCRC) Program, and in 1960 Congress appropriated $3 million for its establishment. The GCRCs were designed as loci for clinical investigation; they were created to supplement ongoing medical research in universities and hospitals.

The GCRC Program has 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 an 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 general research unit effectively meets the needs of many investigators studying a variety of disease problems in a most effective and economic fashion.

The primary goal of the GCRC Program is the establishment of a resource for clinical investigation to:

> Increase the knowledge of human physiology and pathophysiology by the investigation of the epidemiology, etiology, progression, prevention, control and cure of human disease by studies in man;
>
> Provide an optimal setting for controlled studies by clinical investigators supported through NIH and other research support programs;
>
> Encourage and foster disciplinary interaction;
>
> Contribute to the maintenance of a national core of qualified clinical investigators, and
>
> Develop technological and therapeutic advances in the expeditious translation of basic biological knowledge into effective patient care.

A GCRC is defined as "a distinct organizational and physical entity providing a continuing resource for clinical research efforts, including the necessary laboratory and supporting services." Specifically, a GCRC is a re-

source to a medical institution permitting quality clinical investigation. The research conducted in the GCRC derives its support from various Institutes of the NIH as well as from numerous foundations and philanthropic organizations. Funds for the GCRC Program are intended primarily for the establishment and maintenance of the separate discrete units in which clinical research is to be done.

A GCRC consists of four to thirty beds, the average being eleven. Usually a GCRC contains bedrooms, treatment rooms, a core laboratory, diet kitchen, patients' lounge, nurses' station, and conference room. Centers can usually accommodate both adults and children, but about one-fifth of the GCRCs are entirely pediatric. Several GCRCs specialize in areas involving premature infants, maternal-child, or acute surgical problems.

Over 13,000 individuals are involved with GCRCs. GCRC grants provide salary support for staff, numbering approximately 1,800. Currently, the Program consists of 84 GCRCs, plus an outpatient GCRC, a special surgical unit, and pays 76 percent of the extramural research patient care cost funded by NIH.

Within the GCRCs, senior scientists, research fellows, and house staff are exposed to increasingly sophisticated methods and concepts of clinical research. Such training is essential for the continued development of competent investigators and improved medical care. An additional benefit of these GCRCs is that future medical practitioners develop knowledge that facilitates critical evaluation of new medical discoveries with which they will be confronted in their careers. In addition, the GCRCs assist in the training of large numbers of paramedical personnel.

Information concerning the research done in the GCRCs is distributed to the medical community in a variety of ways. For example, in fiscal year 1973 there were a total of 2,360 publications and 1175 abstracts (see table 1) which appeared in scientific books or journals.

Table 1
Center Publications

Year	Publications	Abstracts
1969	2,077	931
1970	2,341	996
1971	2,229[1/]	991
1972	2,462[2/]	994
1973	2,360[3/]	1175

1/ Includes 246 publications involving outpatients
2/ Includes 411 publications involving outpatients
3/ Includes 549 publications involving outpatients

The GCRC Branch has also been active in anticipating the needs of the GCRCs and has continued to evaluate and develop resources which facilitate clinical investigation. The following is a list of major program modifications and in-

novations of the past seven years:

..Outpatient Program
..Service Patient Policy
..Third Party Credits
..Clinical Research in Surgery
..Discrete Unit Costing
..Contribution papers (Atherosclerosis, Growth and Development, Drug Abuse, Narcotic Addiction, Diabetes, Sickle Cell Anemia, Cancer, Transplantation, Bed Occupancy)
..Annual Ranking Procedures for GCRCs
..Resource-Related Research Grants
..Clinical Associate Program
..Mixed Centers

The GCRC Branch staff is continuing to evaluate its Program and to modify procedures where appropriate. The following areas are being studied:

1. Occupancy

   GCRC Branch staff is preparing a manual so that all GCRCs can report their occupancy rates by using identical formulae.

2. Physicians' Fees

   A position paper is being written on whether to allow physicians' fees for certain types of patients admitted to the GCRCs. This practice is not currently allowable.

3. Clinical Mass Spectrometry Resources (CLINSPEC)

   The field of mass spectrometry is being surveyed to determine applications to clinical research problems. The potential for a mass spectrometry resource program in clinical research in collaboration with the Biotechnology Resources Branch of the Division of Research Resources, is being explored. A two-day workshop was held in May 1975 to determine the feasibility of supporting this instrumentation as a resource to the GCRCs. Topics were developed to provide data and to assist in making programmatic decisions with regard to this instrumentation.

4. Funding Sources for Clinical Investigators

   A pilot study is being done to determine the efficiency of proposed reporting procedures so that all supporting sources (e.g., NIH research project grants, philanthropic donations, foundation grants, etc.) can accurately be tabulated and analyzed.

5. NIH Clinical Research Coordinating Committee

With representation from each of the Institutes at the NIH, this Committee has held six meetings since September 10, 1974 to inform itself of the clinical research activities at the NIH. The Committee is exploring several methods of coordinating the clinical research supported by each Institute. The Chief, GCRC Branch, is the Executive Secretary of the Committee.

6. Program Directors' Meeting

A national meeting of GCRC Program Directors is being planned. It is anticipated that not only will the GCRC Branch benefit by a discussion of Program needs and trends, but the Program Directors will also benefit by interchanging ideas and solutions in administrative or scientific problem areas. In addition, better communication in terms of coordinating the research of identical clinical problems is expected to occur.

7. CLINFO

CLINFO is a collaborative scientific inquiry sponsored by the GCRC Branch and the Biotechnology Resources Branch. It is aimed at: 1) identifying and characterizing the intellectual tasks and flows of information occurring in clinical investigation, and 2) developing methods for facilitating these tasks and flows. The project was conceived because significant problems exist in the clinical investigative process which could be met by better information systems. Contracts have been awarded to develop a stand-alone minicomputer which will be designed, tested, and installed initially at selected GCRCs.

8. National Association of Research Nurses and Dieticians

The GCRC Branch has been working with the research nurses and dieticians of the Nation to encourage collaboration and to foster exchange of information. This past year, with GCRC Branch encouragement, a national meeting of the research nurses and dieticians was held, at which time scientific papers were presented and workshops were held in several scientific, nursing, dietary or administrative areas. Also at this meeting, the research nurses and dieticians agreed to meet every other year at seven regional workshops and to hold a national meeting during the year when no regional meetings take place. The GCRC Branch is continuing to encourage the research nurses and dieticians to involve themselves more intimately with GCRC programs.

9. Core Laboratory Evaluation

The GCRC Branch is in the process of demonstrating the rationale and utility of the core laboratories within GCRCs. This study has a second purpose, and that is to determine the feasibility of a collaborative exchange of technology and samples between GCRCs. Thus, the establishment of geographical core laboratories in certain areas might help to standardize testing, reduce the number of laboratories doing similar tests, and increase scientific productivity of core laboratories.

10. Principal Users of GCRCs

A review of the use of GCRCs by Program Directors and Principal Investigators in terms of their patient-day involvement indicated that a few Centers appear to be dominated by their Program Director's or Principal Investigator's interest or projects. While many such studies are sound and of good quality, the GCRC Branch is reviewing such situations to insure that the GCRC is indeed a general institutional research facility available to all qualified investigators at the institution.

II. Training

Within the GCRCs, 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. Moreover, the GCRCs are the primary hospital facility in which nurses, dieticians, and laboratory technicians gain practical experience in newly developed patient care techniques, generally resulting in better quality of hospital care. Table II shows the numbers of individuals receiving training in the GCRC during the past five years.

Table II

Number and Types of Training in GCRCs, 1969-1973

	1969	1970	1971	1972	1973
Medical Students	2939	3065	2872	3152	2780
Interns	1019	911	921	873	733
Residents	1870	1751	1646	1745	1466
Fellows	1340	1321	1169	1281	1212
Dietary Interns	422	487	578	460	600
Student Nurses	1066	1089	914	944	799

III. Fiscal Summary

The GCRC Program grew at an almost constant rate between 1960 and 1967. In the past few years, however, rising costs and fiscal constraints have prevented expansion and have forced support for fewer Centers and a decreasing number of beds.

GCRCs exist in about two-thirds of the teaching medical institutions in this Nation. A number of such institutions with great potential do not have a Center. Table III depicits the Program history since 1968. The Program has operated effectively despite sharp inflationary rises and modest budget increases through a number of adjustments, such as termination of a number of GCRCs, reducing the number of beds supported, savings realized through new discrete costing procedures, service patient policy, and some research done on an outpatient rather than an inpatient basis.

Table III

GCRC Program, FY 1968-1975

Fiscal Year	Medical Schools with a GCRC	Number of Centers	Funded Beds	Patient Days	Full-Time Equivalent Positions Funded	Apportionment (in thousands)
1968	62	91	1051	260,696		30,443
1969	64	93	1023	245,943	2,297	35,004
1970	64	93	940	231,020	1,920	35,004
1971	56	82	881	218,716	1,885	38,004
1972	58	84	907	220,490	1,801	42,181
1973	59	83	893	204,993	1,790	41,300
1974	62	87	888	238,560	1,812	42,320
1975	61	84	827	212,831	1,722	42,300

Despite budgetary constraints, the Program continues to support the best available resources for clinical research. More than half of all hospital beds in the Nation, specialized for research on humans, are supported by this Program.

During 1967-75, a dynamic exchange of beds and GCRCs occurred within the Program. In 1967, 1,131 beds were approved in 91 Centers. In subsequent scientific reviews, 23 Centers with 192 beds were disapproved and NIH support terminated. An additional 251 beds, on the basis of limited scientific productivity in 46 Centers, were eliminated with corresponding staff reductions. During this same period, 12 new Centers and six reapproved Centers (with revised applications of higher scientific merit) for a total of 161 beds were funded. In addition, six of the new Centers given two-year renewals worked to revise their program to compete successfully with programs of high scientific merit. The net result has been a substantial improvement in the overall scientific quality of the Program and the funded beds now correspond closely with the bed needs of investigators holding NIH-sponsored grants and contracts. Despite these reductions and modest increases in appropriated and apportioned funds, rising costs have outstripped available funds. This differential has been met in part through appropriate collections from third party carriers, and in part by encouraging investigators to carry out some of their activities through less expensive outpatient protocols whenever feasible. Table IV shows the history of service patient credits that have been credited to the GCRC Program since 1972.

Table IV
Service Patient Savings
to the GCRC Program

FY	Credits
1972	$3,350,927
1973	3,418,216
1974	4,100,000(est.)

Table V shows the increase in outpatient visits since the outpatient program was initiated in 1970.

Table V
Summary of Outpatient Visits, 1970-1974

FY	Outpatient Visits
1970	1,175
1971	13,426
1972	24,658
1973	36,309
1974	48,845

Figure I presents the National Advisory Research Resource Council's ceilings, gross Program expenditures, service patient credits, plus appropriations since 1967.

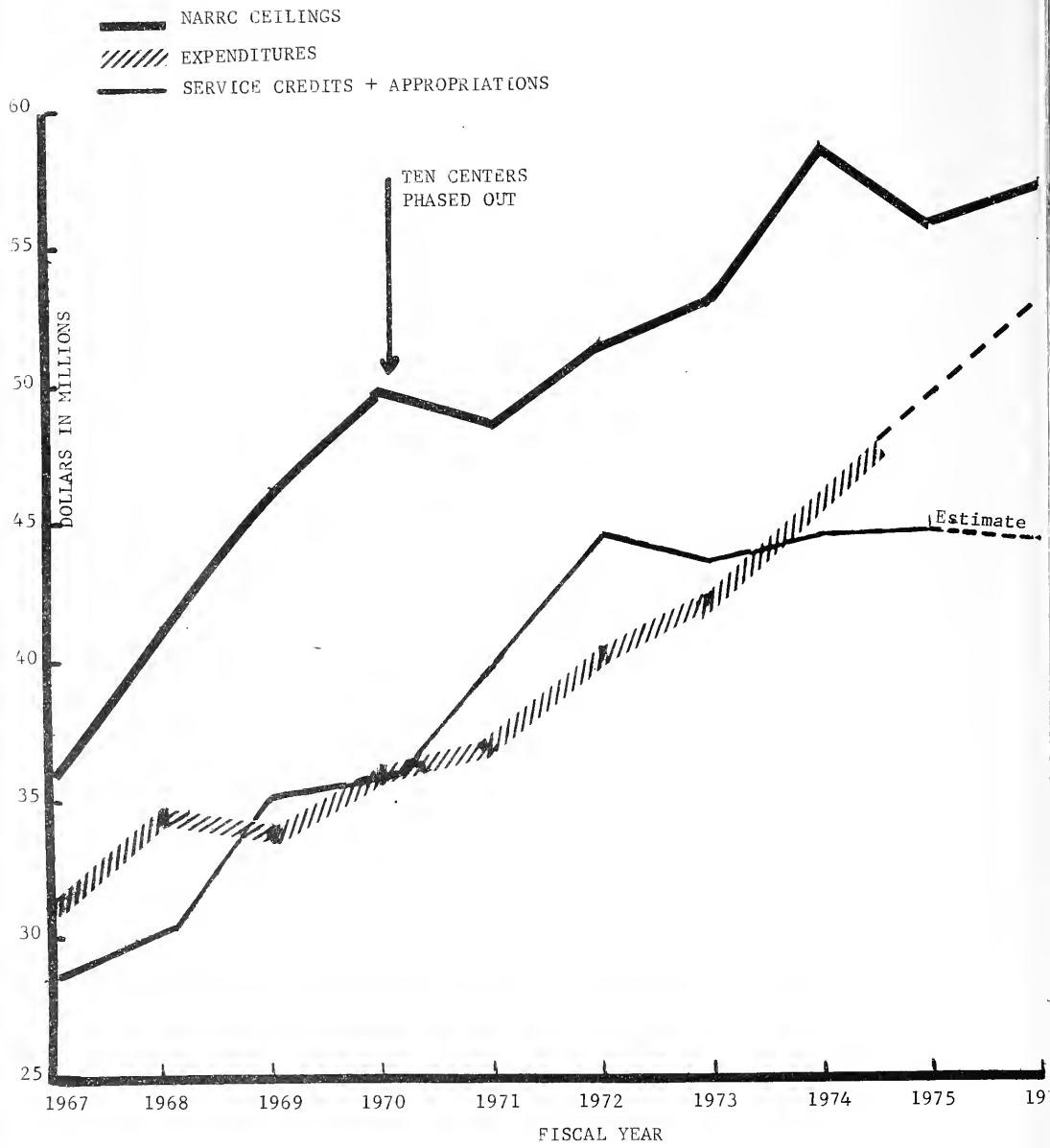
Table VI presents the cost increases for beds and personnel position in the GCRC Program, FY 1968-1976.

Table VI
Cost Increase for Beds and Personnel
Positions in the GCRC Program
FY 1968 thru FY 1976

FY	Percent Increase Cost/Position/Year	Percent Increase Over Previous Year	Cost/Patient Day	Percent Increase Over Previous Year
1968	$ 8,170		$127.89	
1969	8,335	2.02	135.53	6.27
1970	9,244	10.91	148.78	9.78
1971	10,228	10.64	156.67	5.30
1972	10,985	7.40	165.10	5.38
1973	11,746	6.92	182.89	10.77
1974	12,755	8.59	194.72	6.47
1975	13,763	7.90	209.35	7.51
1976	15,139 est.	10.00 est.	230.29 est.	10.00 est.

GENERAL CLINICAL RESEARCH CENTERS
FY 1967 - FY 1976
(Dollars in Millions)

FIGURE 1



IV. Research Highlights

Rheumatic Heart Disease

Rheumatic heart disease commonly involves the mitral valve, resulting in inadequate valve closure (mitral insufficiency). The severity generally increases with age. In adults, replacement of the diseased valve with an artificial valve is the treatment of choice; in children, management has often consisted of continued medical treatment or artificial valve replacement. At one GCRC, an operation known as "annuloplasty," which consists of surgically making the base of the leaky valve narrower, has been found to result in marked clinical improvement in 11 children with mitral insufficiency. Leaking of the valve almost disappeared, and abnormal blood pressure in the heart returned to normal. These findings suggest that annuloplasty in childhood is corrective and may help avoid future valve replacement in adult life.

Excessive Scar Tissue

During the normal healing process following an infection or injury, scar tissue forms around the injured structure. When this occurs around the urethra, the tube carrying urine away from the bladder, the patient experiences pain, bleeding, and difficulty urinating. A drug called B-aminopropionitrite fumarate can cause a marked decrease in the amount of scar tissue which forms in patients operated on for relief of a narrowing of the urethra. As a result, it is possible that relief can be offered not only to patients with disabling urinary symptoms as a result of scar tissue formation around the urethra, but also in other human ailments caused by formation of scar tissue. These include adhesions after abdominal surgery, scarring of the liver from hepatitis or alcohol, scars in the esophagus from chemicals, and heart valves scarred from rheumatic fever.

Paget's Disease

Nearly 5% of the U.S. population over the age of 40 is affected by Paget's disease of bone. In many patients, this disease is painful and produces crippling deformities. Until recently, no effective treatment has been available, but work performed over the past two years at a GCRC and elsewhere has readied a new and promising drug, disodium etidronate, for clinical use in Paget's disease. Its effectiveness and safety have been documented by careful clinical and laboratory investigations, and the precise doses and amount of time required to see a response have been worked out.

Parkinson's Disease

The treatment of Parkinson's disease was revolutionized about seven years ago by the introduction of L-dopa, an amino acid which calms the tremor and improves the mobility of Parkinson patients, usually sparing them from surgery. Much of the work in developing L-dopa was performed on a GCRC. Work has continued to combat the increasingly common problems with L-dopa: the recurrence

of uncontrollable movements and long-term resistance to the drug. On this GCRC new drugs have been tested which are modifications of L-dopa designed specifically to improve its potency. One drug, Piribedil, has been found to be particularly beneficial to many patients. By use of such a drug, the extraordinary but often temporary benefits of L-dopa may be extended into permanent control of Parkinsonism.

Childhood Hypertension

Although much is known about hypertension (high blood pressure) in adult life, little is known about childhood hypertension and its course through adolescence. The causes of childhood hypertension are particularly mysterious. Recently, investigators at a GCRC have discovered several forms of hypertension caused by adrenal hormones, including one caused by a hormone which was previously unknown. By understanding the underlying hormonal causes of high blood pressure in these patients, investigators have been able to design treatment which can reverse the hypertension. This has profound implications in the prevention of adult hypertension, a leading public health problem.

Growth Hormone Deficiency

Growth hormone deficiency causes dwarfism. Treatment with human growth hormone accelerates growth so that dwarfed children can achieve socially acceptable heights. Yet only a small fraction of the children with growth hormone deficiency can be treated because of the scarcity of human growth hormone which is obtained from human pituitary glands. However, recent results on a GCRC indicate that the metabolic response to recently modified fractions of bovine growth hormone is similar to that of human growth hormone. This could mean a great relief to families who now often learn that although human growth hormone is a successful means of treatment, inadequate supplies may prevent their children from receiving it.

Thyroid Cancer

Patients with cancer of the thyroid gland have a much greater chance of survival when this disease is diagnosed at an early stage. A GCRC is currently refining a new diagnostic test with the capability of detecting this disease before the thyroid becomes sufficiently large to be recognized clinically. Investigators there have discovered that a protein of the thyroid gland, thyroglobulin, occurs in the blood in high concentration in patients with cancer of the thyroid, thus permitting early diagnosis. This unique diagnostic test may prove to be of considerable value in the early treatment and subsequent cure of this lethal disease.

Gallstones

Gallstones are a common health problem in the United States with an estimated 10 percent occurrence in this population. Other countries,such as Japan, have a very low incidence of gallstones. Because these stones are composed primarily of cholesterol and because of the disparity in the incidence from

country to country, the possibility exists that gallstone formation is related to dietary cholesterol content. One GCRC has demonstrated that high dietary cholesterol can alter the composition of bile, making it more likely to precipitate cholesterol and form stones. This suggests that gallstone formation can be retarded or prevented by dietary measures. Preventive measures are very important because once stones have formed they must either be removed surgically or dissolved medically, a very slow process.

Studies of Patients with Defective Defense Mechanisms

Over 100 children and adults with a variety of immunodeficiency syndromes resulting in frequent severe infections have been studied and treated in one GCRC.

These patients provided the opportunity to develop a number of laboratory tests which should be useful to others. A potent antigen (bacteriophage ØX 174) accurately measures the ability of patients to make antibody and identifies those patients who may benefit from gamma globulin injections. In addition, this antigen permits the diagnosis of infantile X-linked agammaglobulinemia during the newborn period before clinical symptoms and life-threatening infections develop. Recently a World Health Organization Committee recommended this antigen as a standard for diagnosis and classification of immune deficiency syndromes. This GCRC, with support from the National Foundation, assists other Centers in the United States and abroad by performing the assay.

In addition, a simple and accurate microtest to detect chronic granulomatous disease (an illness in which white blood cells cannot kill certain bacteria, resulting in life-threatening infections) and to identify symptom-free carrier females of this inherited disease has been devised. The test requires only one drop of blood and large numbers of patients can be screened. Six new cases have been detected and extensive studies at a GCRC provided important and valuable information about normal and affected white blood cells.

The treatment of immunodeficient patients is complicated and often unsatisfactory. During the past year pilot studies in 14 patients have been done using a new, modified gamma globulin preparation which can be given by the intravenous instead of the intramusclar route, causing less pain, insuring better absorption and allowing the infusion of larger doses at regular intervals.

Arterial and Venous Angiotensin II, Plasma Renin Activity, and Aldosterone in Mild Hypertension

High blood pressure affects about one of ten American adults. Untreated, it plays significant roles in the genesis of heart disease, stroke, kidney failure, and eye disease. Adequate treatment, leading to the prevention of these important complications, hinges upon a thorough knowledge of the underlying mechanisms of its development. The cause of the vast majority of cases, the category of so-called "essential hypertension," is undetermined. An understanding of a well-known kidney and adrenal gland hormonal complex, the renin-angiotensin-aldosterone system, is helping to shed light on the mechanisms

which lead to the generation of essential hypertension and which at the same time give rise to a scientific basis for appropriate treatment.

Studies presently conducted in an outpatient GCRC are showing that marked suppression of the renin-angiotensin - aldosterone system occurs in mild hypertension prior to the initiation of therapy, as evidenced by the finding of subnormal concentrations of plasma renin activity, arterial and venous angiotensin II, and aldosterone. Both renin and aldosterone levels consistently and progressively decrease as the levels of blood pressure increase in this group of patients. The findings are most pronounced in blacks, who are known to develop hypertension more frequently and of generally greater severity than whites.

In contrast to previous interpretations that hypertension associated with low plasma renin activity suggests a special subgroup of these patients with a different and less ominous prognosis, the current studies indicate that renin and aldosterone supression represents a sequence of events in the evolution of hypertensive disease. Complete understanding of such hormonal suppression will likely pave the way for appropriate treatment and avoidance of morbid complications of this highly prevalent disease state.

Evaluation of Influenza A Georgia 65-1 (E) Virus in Normal Adults

The aim of this research is to develop improved vaccination materials against pandemic influenza. Current influenza vaccination which uses killed influenza virus offers only incomplete protection against pandemic influenza. Using recently developed methods which can combine various strains of viruses, investigators at the NIH have recombined an influenza virus strain which stops growth at normal body temperature of the "wild type" virus. In preliminary tests such a strain provokes a very mild respiratory infection, but provides substantial protection against wild type (epidemic) virus. During the past 9 months such a hybrid live virus vaccine has been administered to 31 volunteers in one GCRC. The vaccine induced complete resistance to influenzal disease produced by challenge with virulent wild type virus. Work is now being done to confirm the efficacy and safety of a newer live virus vaccine which may provide broad protection against recent virus mutations.

Intractable Diarrhea of Infancy

Most infants and children with diarrhea recover spontaneously after an illness of three to five days duration. Intractable diarrhea of infancy is a term used to describe a diarrheal syndrome occurring in the first two months of life and associated with a prolonged course of weeks to months with a mortality of up to 80%. The cause of this syndrome is unknown and it has remained refractory to the usual treatment for diarrhea and dehydration. Development of total parenteral nutrition therapy, which allows feeding by vein of all essential protein, calories and vitamins, has resulted in survival of these infants and allowed study of the causes of the syndrome.

Bile acid malabsorption as a cause of diarrhea in the adult has been well documented. Bile acids are cholesterol derivatives which are excreted from the liver in bile and which function as detergents to allow dietary fat to be made

water miscible so that it can be digested and then absorbed. After this function is performed in the upper small intestine, bile acids are reabsorbed in the lower small intestine (terminal ileum) and conserved to be recycled and utilized again.

Bile acid diarrhea results from loss of the terminal ileum from disease or surgery so that bile acids enter the large intestine (colon). Here they induce secretion of water and electrolytes with resultant severe watery diarrhea. One GCRC is studying bile acid kinetics in children with intractable diarrhea of various types. Labeled bile acid was administered by mouth to 15 infants with diarrhea of various types. The two patients with the "intractable diarrhea syndrome" were found to have markedly increased excretion of bile acid similiar in magnitude to that of four infants with the short gut syndrome resulting from surgical resection in which the terminal ileum had been removed. Infants with steatorrhea (failure to absorb fat) and self-limited diarrhea had no increased bile acid loss. This study documents bile acid malabsorption as one factor in the causation of intractable diarrhea in infancy. Rational treatment in infants with intractable diarrhea with bile acid-sequestering resin is suggested by the results. Further studies to determine the value of such treatment are in progress. Without the GCRC such a study, which involves careful collection of stool and urine specimen in infants who simultaneously require total parenteral nutrition to maintain life, would not be possible.

Obesity

Obesity and its attendant diseases such as diabetes, atherosclerosis, and hypertension represents one of the major health hazards in this country. In addition to the physical disability attributable to obesity, the mental anguish of these obese patients is noteworthy in that they must live in a culture that places great emphasis upon slimness and physical attractiveness.

All currently available modalites of weight control have failed. However, a relatively new procedure has appeared. This is the intestinal bypass whereby 90% of the small intestine is bypassed from the normal passage of food. Studies begun in the one GCRC are attempting to define some of the basic metabolic abnormalities which lead to body weights of from 300 to 850 pounds.

Surgical technique was carefully controlled and to date there has been but a single operative death (from a pulmonary embolus) in 160 operations. This means that one can operate upon and care for massively obese patients with a high degree of safety whereas previously they were denied surgical therapy of serious lesions because of obesity alone.

Present studies are confined to two separate aspects of obesity; first, the obese state *per se* and, secondly, a careful follow-up of the patients who have undergone intestinal bypass surgery at this institution.

Studies performed in the obese state have demonstrated that a percentage of obese individuals require a tremendous protein intake (3 to 5 times normal) to be in proper nitrogen balance. This means that the patient must consume a high number of calories to provide his body with its nitrogen requirements. This is

one of the first metabolic clues to the etiology of the insatiable appetites of some of these individuals.

Intestinal bypass surgery for obesity is still experimental because relatively little is known about the long-term safety of having undergone the procedure. All patients operated upon at this GCRC must agree to return to the GCRC at intervals for a period of five years. During these visits many tests are performed, but the most important one may be a liver biopsy, where changes are being seen that are indistinguishable from alcoholic cirrhosis in some patients. These changes are quite serious.

Radiation Therapy

From about 1930 to 1958, radiation therapy was commonly employed for a variety of benign conditions in children, principally for enlargement of tonsils, adenoids and thymus glands. About 1951, it became apparent that at least some of the patients who had been exposed to head and neck radiation were developing abnormalities, including malignancies, of the thyroid gland. More recent studies suggest that there is a latent period which may extend beyond 20 years following radiation to the head and neck before clinically evident thyroid malignancies are detected. Because of the widespread use of head and neck radiation and the uncertainty of the incidence and mechanisms of related disorders, the endocrinology group along with radiation biologists and immunologists of a GCRC began a large scale screening program for individuals who had received such radiation. Thus far 1,100 patients have been studied. Several broad conclusions can be formulated. About 20% of the irradiated subjects had developed some thyroid abnormality. About 250 patients had thyroid scans to detect nodules; however, this technique was not found to be superior to a careful physical examination. The patient's blood was also assayed for thyroid stimulating hormone (TSH) and for the two circulating thyroid hormones. Thyroid antibodies were also measured along with skin tests for various fungi, to assess whether any abnormalities of the immune system had developed as a result of the head and neck radiation. There are some investigations which suggest that this may occur. Of the 110 patients who were found to have discrete thyroid nodules, thus far, 42 have undergone surgery. Of these, 25% have been found to be malignant. Some of the patients who presently do not have nodules may ultimately develop nodules, some of which may be cancerous. Since growth of thyroid malignancies is supported by TSH , efforts are now underway to examine whether patients taking thyroid replacement therapy will be protected from developing thyroid malignancy. To answer this question, one group of patients has voluntarily agreed to take thyroid replacement therapy to suppress TSH, amd another group no therapy. These patients will be followed on a yearly basis. Attempts are also underway to correlate the dose of the head and neck radiation with the likelihood of developing thyroid abnormalities.

Damage to Red Blood Cells Caused by Artificial Heart Valves

Cardiologists have studied patients with hemolytic anemia following the insertion of a heart valve prosthesis. It is believed that the hemolytic anemia is due to trauma to the red cells based on physical contact with the prosthetic valves. The early model prostheses, particularly for the aortic valve, were especially likely to produce hemolysis. Change to clothcovered prostheses has distinctly decreased the magnitude of the problem of hemolytic anemia. However, it does persist. It has been found that in patients with either the original or the improved clothcovered prosthesis that when the heart rate is slowed with propranolol, there is increased red cell survival as demonstrated by slower turnover of isotope labeled red cells.

Medullary Carcinoma of the Thyroid Syndrome

One type of cancer of the thyroid, medullary carcinoma, is a familial disease frequently associated with pheochromocytoma, a tumor of the adrenal glands. One large family with several members having medullary carcinoma has been located. Genetically, half of the members of this family are at risk for developing this cancer in their lifetime. Investigators at a GCRC have developed a test which enables them to identify this disease before it has become clinically detectable. Thus, when identified, these individuals can have their thyroid removed before the cancer has metastasized and become life-threatening.

Renal Transplantation

Renal transplantation is now an accepted form of therapy for chronic renal failure. Despite the apparent success, a number of problems remain which can best be thoroughly examined and solved in a GCRC environment.

Approximately 45 percent of renal transplants from cadaver donors are unsuccessful and a second or even a third transplant (retransplant) is often necessary if the patient is to avoid chronic dialysis for the remainder of his life. Cadaver kidney retransplants have successfully supported patients for more than nine years, but they have been most successful when the cause of failure of the first transplant was either technical,or chronic rejection. When the loss of the first transplant was due to a high state of immunization manifested by early rejection of the transplant or the presence of cytotoxic antibodies in the recipient, the success rate of retransplantation has been poor. After prolonged study of the problem, two discoveries have been made which now make it possible to perform retransplantations successfully in these high risk patients. The first observation was that the withdrawal of immunosuppressive therapy prior to the removal of the previous transplant seriously prejudices the outcome of a subsequent transplant. The second discovery was the development of a kidney cell crossmatch which supplements the standard lymphocyte crossmatch. This technique helps to avoid both the hyperacute and chronic types of rejection due to antibodies which were frequent causes of failure in this group of patients. It is now possible to perform retransplants in this high risk group of patients with the same degree of success that is achieved in recipients of first cadaver kidneys.

Treatment of Acute Leukemia by Marrow Transplantation from Identical Twins

Leukemia is a cancer originating in the bone marrow. It interferes with production of red blood cells, white blood cells,and platelets,with resultant anemia, susceptibility to infections,and bleeding. Although acute leukemia of childhood is increasingly responsive to chemotherapy, more than half such children and virtually all adults with acute leukemia ultimately die with recurrent disease despite chemotherapy. Such refractory leukemia might still be susceptible to vigorous doses of drugs or total body irradiation; however, this treatment also destroys all normal marrow elements and is therefore itself lethal. Therefore, it has been proposed that patients with resistant leukemia might be treated with extraordinarily large doses of drugs and total body irradiation if they could thereafter receive a transplant of bone marrow from a normal donor.

The rare leukemia patient who has a normal, genetically identical twin presents the opportunity to attempt such an approach under conditions in which the transplanted marrow is not foreign to the host and will not be rejected. Accordingly, patients with end-stage leukemia resistant to conventional therapy have been admitted to a GCRC and treated by a combination of drugs, a supralethal dose of total body irradiation,and transplantation of marrow from a normal genetically identical twin. The marrow was obtained by multiple needle aspirations from the donor's pelvic bones under spinal anesthesia and was infused intravenously into the patient. The procedure required only one day's hospitalization and was associated with no complications to the normal donor. The normal marrow usually established itself and produced normal marrow elements within two to three weeks.

The principal problems encountered have been persistence of leukemia despite the radical therapy and several instances of major or fatal infections. However, a large majority of patients exhibited disappearance of leukemia and went into complete remission. Although leukemia recurred in three to seven months in several patients, seven patients thus treated (about one-third of the total) are free of disease and leading normal lives without any additional treatment or hospitalization at seven to fifty-two months after the transplant.

The importance of these results, made possible by access to a GCRC, is not only the good health and survival of these unique patients but also the opportunity to obtain information which will permit applications of this approach more effectively to the treatment of leukemia patients who do not have genetically identical twins, and conceivably to patients who have other kinds of malignancies. Thus, the twin marrow transplant program provides important information relevant to the rather large ongoing study involving treatment of leukemia by marrow transplants from non-twin siblings.

Renal Failure

Chronic renal failure is a major medical problem in the U.S.A. The financial problem associated with maintaining patients lacking kidney function is one which is growing and will continue to grow as long as an effective, but expen-

sive, life-supporting technique is available. Dialysis is such a technique. A patient who is committed to dialysis in most cases can look forward to a long life, but there is usually no hope of terminating this treatment. The rate of successful kidney transplantation is 50 - 75% over the first few post-operative years. The patients frequently remain on high doses of immunosuppressive drugs, and the entire transplant procedure cannot be considered as a totally satisfactory answer to renal failure. It has been the aim of one GCRC to develop inexpensive, but effective, techniques of prolonging useful life in uremic patients without resorting to dialysis. If each patient can be maintained for one to five years in a comparatively comfortable and active state before being required to go into dialysis, the savings in physical and emotional trauma, as well as money, will be considerable.

Advantage has been taken of reports that oxidized starch when taken orally will absorb various uremic toxins. Patients can be maintained in relatively good health without dialysis, with only minimal renal function, if they ingest the starch product. The scope of this study has been enlarged and investigators are looking at the effects of charcoal and charcoal-oxidized starch mixture on the metabolism and general condition of moderately uremic individuals. Balance studies are necessary to determine the objective effects of the intestinal absorbents. These studies measure the entire input and output of a large number of nutrients and excretion products. Only in a GCRC can such balance studies be performed.

As of now, investigators have studied a large number of patients on starch alone and have reported this to the American Society for Artificial Internal Organs. Initial studies have established that ingested, oxidized starch lowers such parameters of uremia as elevated blood urea nitrogen. Indeed, some return towards a more normal nitrogen metabolism was noted. In addition, the patients reported a reversal of many of the clinical signs of uremia, such as nausea, drowsiness and lethargy. Control studies with unoxidized starch, as placebo, indicates that these results could be attributed to ingestion of the specific sorbent.

Renal Disease in Children

Renal disease among young children is in many way more devasting than in adults. Because children's bones are forming, the ill effects of acid-base dysfunction and disordered calcium and phosphorus metabolism in children with poor kidney function are magnified. In fact, the syndrome of "renal rickets" is well recognized by pediatricians. Vitamin D is metabolized by both the liver and kidney before it achieves maximum effectiveness. Patients with renal disease may, therefore, suffer the extra burden of an inability to produce potent vitamin D metabolites.

Investigators are currently testing the effects of synthetically produced vitamin D metabolites on a group of young children with renal failure in order to determine if the ravages of renal rickets can be ameliorated, permitting normal development. The patients are brought in on total calcium balance, a procedure only possible in the GCRC and,after proper trial periods, they are

treated with vitamin D metabolites. Initial studies on eight patients have been most promising. A return towards normal serum calcium and a trend towards positive calcium balance have been noted in all.

Dietary Treatment of Renal Failure

Approximately 30,000 patients die each year in the U.S.A. of renal failure. More than half of these patients could be helped by hemodialysis, an artificial means of removing waste from the blood normally removed by the kidneys when they are functioning properly. There are between 10,000 and 15,000 patients receiving hemodialysis. Any type of therapy that reduces the need for this costly form of treatment would represent a major contribution toward effective treatment for all who are in need of it.

Work supported by the Inpatient and Outpatient GCRC at one institution has shown that the provision of a dietary supplement in the form of keto acids, building blocks which the body can use to make needed protein, decreases the work required of the kidney. These substances can serve as building blocks for protein and under these conditions there is a marked reduction in the quantity of waste products from the diet requiring excretion by the kidney.

Use of the treatment program in chronic uremic patients significantly prolonged the ability of their markedly diseased kidneys to get rid of the daily waste products, thereby prolonging the time before they require treatment by hemodialysis.

Since this treatment markedly reduces the rate of waste material accumulation from dietary intake, it offers the potential for reducing the frequency of dialysis in patients who are already on dialysis. If this treatment regimen can be shown to be practically applicable to large numbers of patients on hemodialysis, it will thus permit existing dialysis facilities to treat a greater number of patients and will also improve the quality of life for the patient on dialysis since he will be required to spend less time on the hemodialysis machine.

Premature Infants

The seriously ill premature and neonate are in a very critical situation due to rapid and profound changes in basic physiological and biochemical parameters as they attempt to adapt to extrauterine life. Because of this, they must be closely monitored and repeated blood tests are frequently necessary. Despite the fact that only small quantities of blood are necessary for various tests, the infant requires frequent replenishment of its rapidly dwindling blood volume. In the past, each time an infant required a small transfusion (10-30 ml), a complete 500 ml unit of whole blood was utilized, thereby contaminating the remaining 450+ ml and rendering it unsuitable for further use. Therefore, various methods of blood transfusions have been developed throughout the country to make a more efficient use of donated blood.

One of the techniques utilized in the nurseries is to establish a walking donor blood program wherein hospital-based donors are used to donate small quantities of blood to needy infants. A "stable" of donors is screened periodically to check blood type and antibody formation, to detect whether or not the donor has developed antigen for hepatitis virus, and antibodies to various viral illnesses and syphilis. These donors are then assigned on a randomized basis to neonates who need repeated transfusions. A GCRC was one of the first in the United States to develop such a program, and the only unit to evaluate the efficiency and potential dangers and complications of such a program.

V. Future Objectives and Trends

The President's Budget request for FY 1976 proposed $41.6 million for the GCRC Program. This compares with $42.2 million appropriated in FY 1972 and an appropriation level of $42.3 million for 1975. The history of appropriations, service patient credits, Council recommendations, and expenditures can be seen in Figure 1 (see page 90).

During the early 1970s, several factors combined to cushion the impact of the rapidly escalating cost on the GCRC Program budget. These included the phasing out of support to ten Centers in 1969. Also, in 1970, a policy of charging "hospital sick" patients on the GCRCs was instituted, which was successful in reducing Program-wide costs by nearly 10%. Additional measures included a research out-patient policy implemented in 1970 which decreased hospitalization expenditures and has reduced the bed requirements and hospitalization costs in many Centers; and a discrete unit costing method by which the Program essentially rents hospital space for research. The latter has helped hold down facility costs and has resulted in a better management of ancillary services purchased by the unit.

Between 1970 and 1973, the Program was able to accumulate a substantial potential balance in various grant accounts. This is shown in Figure 1, where available funds appropriated plus service patient credits exceeded expenditures. It should be noted that these potential balances do not materialize until the grant account is closed, a process which is totally dependent on the availability of finalized hospitalization rates. Moreover, these balances are currently being rapidly consumed by an expenditure level which exceeds available funds, a situation not unlike that occuring in 1969. It is projected that an estimated $3.5 million remaining in these accounts will become available during FY 1976, thus exhausting the savings accumulated between 1970 and 1973.

Further substantial savings have been achieved by a 25% decrease in the number of personnel supported, from 2,297 positions in 1969 to a current level of 1,722 positions. The number of supported beds has been similarly decreased from 1,051 in 1968 to 827 in 1975. During this same period, the cost per position and cost per patient day have nearly doubled (see Table VI on page 89)

It is now apparent that with the continuing cost escalation, without concomitant budget increases, further substantial reduction in GCRC resources must now be undertaken and further reductions in number of extramural dedicated research beds will occur. Efforts to recover third party payments for both research and nonresearch patients will be intensified. However, after all possible steps to conserve Program funds have been taken, it is estimated that support for 8 to 12 Centers will have to be phased out during FY 1976 and FY 1977 to establish a balance between expenditures and available funds.

Fiscal Year 1975
Annual Report
General Research Support Branch
Division of Research Resources

The General Research Support Branch in FY 1975 administered the General Research Support Grant, the Biomedical Sciences Support Grant, the Health Sciences Advancement Award, and the Minority Biomedical Support programs.

GENERAL RESEARCH SUPPORT GRANT AND BIOMEDICAL SCIENCES SUPPORT GRANT PROGRAMS

The General Research Support Grant (GRSG) program was authorized by Public Law 86-798 which was approved September 15, 1960, and the first awards were made in FY 1962. Recipients of GRSGs are 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 general program objective is to strengthen, to balance, and to stabilize Public Health Service supported biomedical and behavioral research programs by providing flexible institutional funds on a formula basis to non-Federal public and non-profit private health professional schools, universities, hospitals, research organizations and other institutions actively engaged in biomedical and behavioral research. These funds are to complement and to enhance the effectiveness and efficiency of biomedical and behavioral research in those institutions. The most distinguishing feature of the program is the opportunity provided for grantee institutions to exercise on-site judgment regarding emphasis, specific direction and content of activities supported, thus enabling the institution to respond quickly and effectively to emerging opportunities and unpredictable requirements, to enhance creativity, to encourage innovation, to provide for pilot studies and to improve research resources, both physical and human.

This program thus recognizes the need to share resources and to respond to opportunities that develop during the course of active, diverse biomedical and behavioral research programs and to contribute to the stability of the national research effort.

Grants from this program are intended to support primarily those biomedical and behavioral research activities not readily or normally supported by PHS categorical research grant programs. Examples of areas of emphasis are:

- Pilot projects
- Initial investigations in new fields and in fields new to the investigator

- Unanticpated opportunities and requirements
- New and more effective patterns of use of resources within and without the grantee institution
- Central shared resources
- Enhancement of investigator's biomedical research skills
- Expansion of research capabilities through improved research opportunities for minorities and women
- Animal welfare improvement

Fiscal and Administrative Considerations

Tables I and II show how GRSG and BSSG funds were used in FY 1973.

TABLE I

FY 1973 Expenditure of General Research Support Grant Funds by Activity

	Number	Dollars (in thousands)	% of Total Dollars
RESEARCH PROJECTS	5,706		
New Pilot Proj.	1,118	$ 2,887	10.4
Cont. Pilot Proj.	1,244	3,005	10.9
New Reg. Res. Proj.	824	3,438	12.4
Cont. Reg. Res. Proj.	2,520	10,050	36.3
CENTRAL RESOURCES			
Animal Facilities		1,461	5.3
Computer Facility		680	2.5
General Use Equip.		990	3.6
Instrument Shop		398	1.4
Central Lab. Facility		1,265	4.6
Photog. and Med. Arts		206	0.7
Other		1,260	4.6
RESEARCH TRAINING		1,165	4.2
OTHER ACTIVITIES		852	3.1
Total		$27,657	100.0

TABLE II

FY 1973 Expenditure of Biomedical Sciences Support Grant Funds by Activity

	Number	Dollars (in thousands)	% of Total Dollars
RESEARCH PROJECTS	1,846		
New Pilot Proj.	425	$ 601	13.5
Cont. Pilot Proj.	404	542	12.5
New Reg. Res. Proj.	393	779	17.6
Cont. Reg. Res. Proj.	624	1,102	24.9
CENTRAL RESOURCES			
Animal Facilities		126	2.9
Computer Facility		38	0.8
General Use Equip.		364	8.2
Instrument Shop		11	0.2
Central Lab. Facility		385	8.7
Photog. and Med. Arts		6	0.1
Other		98	2.2
RESEARCH TRAINING		217	4.9
OTHER ACTIVITIES		154	3.5
Total		$4,423	100.0

Tables III and IV show for the GRSG and BSSG programs respectively, (1) the trend in allowable research grants awarded by PHS 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.

It can be seen from these data that there has been a steady upward trend in entitlement for the GRSG/BSSG programs. The GRSG entitlement base has increased seven fold since the start of the program in FY 1962, while the amount of money made available for the program in FY 1975 is less than twice the amount awarded in FY 1962. In FY 1962 GRSG grantees received 18.48¢ for each dollar of entitlement. This figure dropped to a new low of 4.91¢ in FY 1975. The same trends are reflected in the BSSG program data. In FY 1975 a new low of 2.86¢ was paid for each dollar of BSSG entitlement.

TABLE III

GENERAL RESEARCH SUPPORT GRANT PROGRAM
Trends in PHS Research Grant Awards
(Entitlements) 1/ and in General Research Support Grant Funds, FY 1962-1975

Fiscal Year	PHS 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	46,277,000	8.00
1974	667,165,273	38,242,000	5.73
1975	756,111,529	37,116,205	4.91

1/ Previous fiscal year research grant awards received from the PHS by GRSG awardees.

TABLE IV

BIOMEDICAL SCIENCES SUPPORT GRANT PROGRAM
Trends in PHS Research Grant Awards
(Entitlements) and in BSSG Funds, FY 1966-1975 1/

Fiscal Year	PHS 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	7,223,000	4.49
1974	174,303,033	6,007,000	3.45
1975	199,865,557	5,714,795	2.86

1/ Previous fiscal year research grant awards received from the PHS by BSSG awardees.

P.L. 86-798 states that up to 15 percent of the amount provided for research grants for any fiscal year to the National Institutes of Health may be used for the General Research Support program. Reports of appropriation hearings in both Houses of Congress have repeatedly affirmed the congressional intent that ultimately the 15 percent level be made available, but this goal has never been reached. As shown in Table V, a high of 8.3 percent was reached in FY 1969. Since then the level has declined to 3.7 percent in FY 1975.

TABLE V

GENERAL RESEARCH SUPPORT PROGRAM
(Dollars in Thousands)

	Funds Available for NIH Research Grants 1/	If 15% were made available for GRS Program	Amount made available for GRS Program 2/	Percent of available GRS funds to total
1966	$ 604,377	$ 90,657	$45,200	7.5
1967	681,197	102,180	51,700	7.6
1968	727,366	109,105	59,700	8.2
1969	729,230	109,385	60,700	8.3
1970	744,061	111,609	57,677	7.8
1971	765,510	114,827	54,200	7.1
1972	901,119	135,168	55,212	6.1
1973	820,913 1/	123,137	60,700 2/	7.3
1974	1,091,795	163,769	45,149 3/	4.1
1975	1,142,782	171,417	42,957	3.7

1/ Thru 1972 includes NIMH
2/ Includes 33.5 million impounded funds
3/ Excludes Minority Biomedical Support program funds

Tables VI, VII, and VIII summarize the distribution of GRSG and BSSG awards by categories of institution, size of award, range and average size of award, and amounts of funds awarded each year for Fiscal Years 1968 through 1975. The average size of awards has declined steadily over this period in parallel with a decline in the total amounts of funds awarded, and modest increase in number of grantees.

TABLE VI

GENERAL RESEARCH SUPPORT GRANT PROGRAM

Number of Grantees by Type for the General Research Support Grant Program FY 1968 - 1975

Type of Grantee Inst.	FY 1968	FY 1969	FY 1970	FY 1971	FY 1972	FY 1973	Revised FY 1974	FY 1975
Medicine	95	99	100	100	101	104	104	107
Dentistry	49	49	49	33	34	34	33	34
Osteopathy	5	5	5	0	0	0	0	1
Pub. Health	12	12	12	12	12	12	12	12
Pharmacy	10	12	15	15	16	14	12	17
Vet. Med.	15	17	17	17	16	15	14	15
Nursing	0	0	0	2	4	3	4	5
Allied Health	0	0	0	0	0	1	1	1
Hospitals	71	75	79	76	79	71	66	71
Health Dept.	3	3	3	2	2	2	2	2
Res. Inst.	51	58	64	69	75	71	70	75
TOTAL	311	330	344	326	339	327	318	340

TABLE VII

GENERAL RESEARCH SUPPORT GRANT PROGRAM

Distribution of General Research Support Grants by Size of Awards and Funds Awarded for Fiscal Years 1968 Through 1975

Size of Grant (in thousands)	Number of Institutions							
	FY 1968	FY 1969	FY 1970	FY 1971	FY 1972	FY 1973	FY 1974	FY 1975
Under - $ 30.0	27	30	49	34	46	17	29	54
$ 30 - 49.9	54	46	47	51	54	67	63	57
50 - 99.9	74	80	85	77	78	69	71	73
100 - 149.9	41	49	41	50	36	41	47	54
150 - 199.9	40	36	34	36	45	41	48	45
200 - 249.9	21	21	26	25	26	36	22	20
250 - 299.9	19	29	31	25	21	19	38	37
300 - 349.9	13	12	8	8	10	12	--	--
350 - 399.9	13	9	23	20	23	25	--	--
400 - 449.9	9	18	--	--	--	--	--	--
450 - 499.9	--	--	--	--	--	--	--	--
500 - 599.9	--	--	--	--	--	--	--	--
TOTAL	311	330	344	326	339	327	318	340

Grant Range (All Inst.)	Amounts (In Thousands)							
	FY 1968	FY 1969	FY 1970	FY 1971	FY 1972	FY 1973	FY 1974	FY 1975
Low	13	12	5	11	12	11	16	15
High	424	429	396	383	367	359	280	255
Average	155	146	133	133	130	141	120	109

Total General Research Support Grant Funds Awarded (In Millions)

	FY 1968	FY 1969	FY 1970	FY 1971	FY 1972	FY 1973	FY 1974	FY 1975
Total Funds Awarded	$48.2	$48.2	$45.8	$43.4	$44.3	$46.2	$38.2	$37.2

TABLE VIII

BIOMEDICAL SCIENCES SUPPORT GRANT PROGRAM

Distribution of Biomedical Sciences Support Grants by Size of Awards and Funds Awarded for Fiscal Years 1968 Through 1975

Size of Grants (In thousands)	Number of Institutions FY 1968	FY 1969	FY 1970	FY 1971	FY 1972	FY 1973	FY 1974	FY 1975
Under - $ 30.0	--	1	8	8	14	7	16	27
$ 30 -- 49.9	27	36	35	36	36	38	42	55
50 - 99.9	60	59	59	57	59	53	45	34
100 - 149.9	11	11	9	9	5	11	1	2
150 - 199.9	3	2	2	1	2	2	4	3
200 - 249.9	1	1	--	1	1	2	--	--
Total No. of Grants	102	110	113	112	117	113	108	121

Grant Range (All Inst.)	Amounts (In Thousands) FY 1968	FY 1969	FY 1970	FY 1971	FY 1972	FY 1973	FY 1974	FY 1975
Low	$ 36	$ 29	$ 15	$ 12	$ 15	$ 27	$ 23	$ 19
High	219	220	199	210	212	221	187	165
Average	74	68	63	61	59	63	56	47

Total Biomedical Sciences Support Grant Funds Awarded (In Millions)

	FY 1968	FY 1969	FY 1970	FY 1971	FY 1972	FY 1973	FY 1974	FY 1975
Total Funds Awarded	$7.5	$7.5	$7.1	$6.7	$6.9	$7.2	$6.0	$5.7

Program Funding

The FY 1973 appropriation for the GRSG/BSSG programs was $53.5 million. Of this amount, $33,576 million was impounded, and then released in FY 1974. The President's budget for FY 1974 called for $9,500,000, but the final allocation was $44,232,000. The President's budget for FY 1975 requested no funds for the GRSG/BSSG program. However, $43,000,000 was appropriated for the programs in FY 1975.

The FY 1975 DHEW Appropriation Bill allocated $43,000,000 to the GRSG/BSSG program. The administration proposed a deferral/rescission action for the entire $43,000,000, but the proposed rescission was not accepted by the Congress. FY 1975 GRSG awards were not made until March, three months later than usual, because it was necessary to know the outcome of the rescission request. The President's budget for FY 1976 again shows no funding for the GRSG/BSSG program. Grantee institutions have been unable to plan their research programs effectively in the face of these uncertainties. Expenditures of grant funds have been delayed and reduced because of reduced and delayed funding, and uncertainty of future funding.

Program Plans

The Subcommittee on Appropriations for Labor, and Health, Education and Welfare, of the House of Representatives, stated during the Fiscal Year 1975 appropriations hearings, H. R. Report No. 93-1140, pages 45-46, that changed circumstances and the passage of time, while not diminishing the need for General Research Support, may have modified the program function and need, and therefore directed that NIH reconsider the General Research Support formulas and guidelines with a view to revising eligibility, and allocation and usage of the grants. The Senate Appropriations Subcommittee endorsed the request and asked that consideration be given also to support of small institutions (Senate Report No. 93-1146, page 67).

In response to these congressional directives, extensive study was made of General Research Support program needs and desired changes by program staff and program advisory groups, and public comment was received on proposed changes. These actions culminated in recommendations for program modification that were forwarded through the echelons of DHEW to each congressional appropriations committee. The major changes that were recommended are:

1. Merge the General Research Support Grant (GRSG) and Biomedical Sciences Support Grant (BSSG) programs into a single program, a Biomedical Research Support (BRS) Grant program.

2. Establish a level of $200,000 in PHS research grants as the criterion of eligibility for each institution. Current regulations require $200,000 in NIH and NIMH research grants for BSSG awards and $100,000 for GRSG awards.

3. Establish a new formula for the merged program with a maximum award of $300,000.

4. Limit to $500,000 the credit permitted for any one allowable PHS grant to which the formula is applied.

5. Support of research salaries of tenured faculty would be permitted only on a short-term basis provided it can be justified.

6. Supplementation of ongoing PHS research project grants would be permitted only for unexpected or emergency needs.

7. Alterations and renovations of research facilities could be charged to the grant not to exceed 20 percent of the BRSG award for the current year, or $40,000, whichever amount is smaller.

8. Require each grantee to establish mechanisms acceptable to the NIH to assure: broadly-based review for advice on the use of the grant funds; wide dissemination within the grantee institution of information about the availability of grant funds and accomplishments of the grant; and policies and procedures for strong programmatic and fiscal accountability.

9. Conduct periodic on-site evaluations to assess program performance, and to re-evaluate program goals.

A Biomedical Research Development Grant (BRDG) program was also proposed as a companion program to the Biomedical Research Support Grant (BRSG) program to assist eligible institutions to establish specific capabilities for the conduct of biomedical and behavioral research.

The purpose of the Biomedical Research Development Grant program would be to enhance the achievement of the Federal commitment to discovery of new knowledge necessary for better health through research contributions from a broader array of institutions. The program is intended for those institutions that currently have limited involvement in biomedical and behavioral research, but possess the necessary potential and can justify such research advancement in terms of the national interest and the NIH mission.

Eligible institutions would be those which receive less than $200,000 of direct and indirect costs annually in PHS biomedical and behavioral research grant support as required for the proposed BRSG program.

Biomedical Research Development Grants would be awarded on the basis of detailed applications that describe institutional objectives for development of biomedical and behavioral research capability, existing strengths and weaknesses, and plans to achieve the objectives.

Up to 10 percent of the funds appropriated and apportioned each year for the Biomedical Research Support Grant program (formerly the General Research Support Grant and Biomedical Sciences Support Grant programs), would be designated for support of the Biomedical Research Development Grant program.

Although the Administration's FY 1976 budget message requested no funds for GRSG/BSSG, because other biomedical research programs were judged to have a

higher priority, it is prudent to continue work on issues that confront the GRSG/BSSG program because the details of the 1976 appropriation that ultimately will be enacted cannot be foreseen. If funding is forthcoming for FY 1976, it is planned to make program modifications as stated above.

HEALTH SCIENCES ADVANCEMENT AWARD PROGRAM

During FY 1975 the following grantees completed their Health Sciences Advancement Award program:

University of Kansas
Duke University
Washington University

The Health Sciences Advancement Award program is now terminated. A total of $26,250,000 was awarded to eleven institutions during the nine years that the program was in operation. The following is a summary of these awards:

Institution	Total Awarded	Inclusive Dates of Support
University of Virginia	$ 2,199,571	6/1/66-12/31/71
Cornell University	1,780,233	6/1/66-12/31/71
Purdue University	2,542,352	6/29/67-12/31/72
University of Oregon	2,097,200	6/29/67-12/31/73
Vanderbilt University	2,491,265	6/29/67-6/30/73
University of Colorado	2,654,802	6/29/67-12/31/72
Washington University	2,731,258	6/29/67-6/30/75
Rice University	2,130,074	6/19/68-5/31/74
University of Calif. at Davis	2,468,767	6/19/68-3/31/74
University of Kansas	2,638,288	6/1/69-5/31/75
Duke University	2,516,190	6/1/69-5/31/75

Evaluation of this program is desirable; however, this cannot be undertaken with the present staffing.

A. Introduction

1. Historical

The Minority Biomedical Support (MBS) Program was deemed necessary in order that ethnic minorities may have equality of opportunity to participate in biomedical research. The Division of Research Resources launched this program in 1971 and made the first awards in June of 1972. Accordingly, the program is intended to encourage increased involvement of ethnic minority students and faculty in the biomedical sciences and in health professions so that the nation can benefit from this untapped resource.

2. Goals of the Program

The most important of all research resources are people. Minorities, a large segment of the talent in this country, have been an untapped resource for enhancing biomedical research. The NIH has elected to tap this resource through the MBS Program.

The program goals are: to increase the numbers of ethnic minority faculty, students and investigators in the biomedical sciences and to broaden the opportunities for research and research participation by ethnic minorities. The MBS Program is the NIH's major effort in providing opportunities for minorities to participate in biomedical research. This is a recognition that minority biomedical investigators can make a significant contribution to furthering the mission of the NIH and should be provided that opportunity.

B. Program Highlights

The MBS Program is an entirely new program to the NIH and thus has been experimental and changing in nature. It is unique in that it is centered in institutions that generally have not been NIH grantees and have had minimal biomedical research involvement. It is also unique in that one of the main elements of the program is undergraduate research participation. Undergraduate students are intimately involved in biomedical research with faculty at the grantee institutions and participate in all aspects of the projects including publishing and presenting papers at scientific meetings.

1. The Xavier MBS Symposium

Xavier University in New Orleans, through their MBS grant, conducts an annual symposium where MBS participants present papers on their research. There has been a tremendous increase in the number of participants attending and the number of papers presented since the first symposium was held in 1973. The following table indicates the growth.

TABLE I

	1973	1974	1975
Numbers attending	250	470	900
Papers presented	76	165	280

The quality of the papers has improved to a point that in 1975 they were comparable to those presented at most other scientific meetings. (According to comments of NIH staff and members of the General Research Support Program Advisory Committee (GRSPAC) who were in attendance in 1975.)

2. Funding of MBS Projects by NCI and NHLI

During the latter part of FY 74 and FY 75, staff of the MBS Program and of the National Heart and Lung Institute (NHLI) met several times to negotiate an agreement whereby the Division of Lung Diseases would fund those MBS projects that were deemed appropriate for the mission of the Division of Lung Diseases, NHLI, and which had been reviewed and approved by the General Research Support Program Advisory Committee, National Advisory Research Resources Council, and the National Advisory Heart and Lung Council. The NHLI invited MBS program directors to come or send a representative to a meeting at NIH where the programs of the Division of Lung Diseases were described. Minority institutions were encouraged to submit projects through the MBS Program for funding by NHLI. Several were submitted but none were approved. However, the NHLI did identify two ongoing projects which they wished to fund. Subsequently, the other Divisions of NHLI agreed to follow the agreement between MBS and the Division of Lung Diseases. In summary, the NHLI has funded three MBS projects totaling about $113,696 in FY 75. A formal agreement was signed to the effect and the NHLI will continue its efforts to identify other projects and encourage MBS grantees to submit new projects for review.

A second agreement was also made with the National Cancer Institute (NCI) whereby six cancer-related research projects were approved for funding by the National Cancer Board in their March 1975 meeting.

A list of the projects funded by each institute follows:

TABLE II

NHLI Funding Agreement

	FY 75	FY 76	FY 77	FY 78
Charles R. Drew Post Graduate Medical School Dr. Niden	35,419	24,113 1/	23,652 1/	
New Mexico State University Dr. Bernstein	53,490	23,621 1/	24,054 1/	
Tuskegee Institute Dr. Dixon	24,787	26,341 1/	26,612 1/	10,997 1/

NCI Funding Agreement

Texas Southern University				
Dr. Session	96,510	98,102		
Dr. Guilford	24,675	24,765		
Tennessee State University Dr. Hogg		62,886		
Norfolk State College Dr. Bempong	43,145	49,091		
Catholic University of Puerto Rico Dr. Correa	25,415	37,099		
Charles R. Drew Post Graduate Medical School Dr. Alfred	38,523	43,341		

1/ Indirect costs not included

3. Expansion of Eligibility

On December 30, 1974, the proposed regulations for the MBS Program were published in the Federal Register. The regulations extended the eligibility to institutions other than the traditional minority institutions. Eligibility was extended to: (1) four-year institutions with significant but not necessarily over 50 percent minority enrollment, provided they have a history of encouragement and assistance to minorities, (2) two-year colleges with 50 percent minority enrollment, and (3) American Indian Tribal Councils ... (see regulations.)

These regulations were promulgated to provide opportunities to the numerous minority students who are not enrolled in the traditional minority institutions but are also in need of the same opportunities. This was deemed necessary to provide a program balance by geography and different ethnic minorities. Comments on the proposed regulations were received and final amended regulations were submitted for publication.

4. Other Program Related Activity

Several presentations about the MBS Program were presented at the request of outside groups. In September 1974, the University of Connecticut and Chicago State University requested that an MBS staff member be present at a meeting in which these two institutions would discuss a cooperative plan for minority research participation. MBS grantees are now involved with the University of Connecticut in research participation at Storrs, Connecticut. The effort is jointly financed by MBS grant funds at the MBS grantee institutions and by the University of Connecticut. An exchange of faculty has been planned.

The American Biophysical Society invited the Acting Director, MBS Program, to participate in a symposium at their annual meeting in Philadelphia. The presentation described the MBS Program and its impact in the minority institutions. A presentation was also made to a meeting of representatives from the American Association of State Colleges and Universities at their request.

A request was received from Radio Station WGMS in Washington to discuss the MBS Program and the role of minorities in the sciences. A taped interview was prepared for broadcast in several local stations throughout the country.

In April the MBS Program staff participated in planning and carrying out the NIH Minority and Women's Conference in Bethesda.

C. Program Status

1. Numbers of Minorities Participating in the MBS Program

As shown in Table III, there has been a marked increase in minority participation in biomedical research through the MBS Program. The increase is attributed to support of released time to faculty and financial support to students who collaborate with the faculty in biomedical research projects. Other support such as equipment, travel, supplies, and consultants has also made it possible for minority faculty and students at grantee institutions to carry out biomedical research.

TABLE III

	1972	1973	1974	1975
No. faculty	199	358	499	589
No. undergraduates	288	643	906	1,008
No. graduates	44	94	143	184
No. postdoctorals	1	--	2	3
Total participants	532	1,095	1,550	1,784
Total support	2,000,000	5,000,000	8,000,000 1/	7,662,964*
Total No. of grantees	38	51	66	74

1/ Includes $1 million impounded FY 73 funds

As was the case in FY 74, this year there were several supplemental applications received. Program balance and limited funds and disapprovals placed constraints on the number that would be funded.

An indication of the types of applications funded is illustrated in Table IV.

TABLE IV

MBS Awards FY 1975

	No.	Amount
Type 1	7	$1,182,446
Type 2	-	--
Type 3	5	356,289
Type 5	56	6,124,229
TOTAL	68	$7,662,964*

* Includes $341,964 from NCI and NHLI for support of individual projects in those areas related to NCI and NHLI and $57,000 derived from reprogrammed funds

2. Policy and Procedural Changes

In reviewing applications, experience dictated a change in requirements for project descriptions. Staff revised the format for submitted research project protocols to conform to the format used by the Division of Research Grants. This resulted in better project descriptions that have been easier to review and consequently improved the track record of approved projects.

A new policy in program management was instituted to deal with emerging problems where investigators were leaving the institution and the grantees were requesting approval for substituting new investigators. Any new project investigator must now submit a complete application for peer review through the MBS Program prior to becoming eligible to participate in an ongoing program where funds have become available through attrition or other means.

Review procedures will involve rating of individual projects as to scientific merit and ability to meet MBS goals. This will be done during the site visit or by the primary reviewers prior to being considered by the GRSPAC.

A revision of the MBS Policy and Information Statement was initiated and is being continued. Much of the revision will relate to the published regulations and the present considerations on evaluation and renewals by the GRSPAC.

D. Program Evaluation

During FY 1975 a concerted effort was made by staff to make detailed reviews of progress reports in order to set up a scheme for evaluating the program. In cooperation with MBS staff, the Program Analysis Branch developed data collection forms to reflect the information needs for an evaluation and the capturable data from progress reports. A trial run with a sample of grants was made as a test of the efficacy of the data collection sheets. The system is now being implemented for capture of data from FY 74 progress reports.

Staff and members of the advisory committee developed a document listing data and information that would be useful in evaluating the program. These items were developed specifically to determine whether specific goals are being met by the program. A final document will be developed in early FY 76. The plan is to have it ready by the fall of 1976.

E. Future Plans and Perspectives

During the April meeting of the advisory committee, a discussion document on policies and criteria for renewal applications was considered and recommendations made. The committee recommended criteria to be used in evaluating the ongoing grants and in reviewing renewal applications. The recommendations included a need for continuing the program at some

of the present institutions after the end of the present five-year project period.

Criteria for the MBS Program evaluation will be developed early in FY 76. Policies and guidelines for renewal applications will be readied for anticipated applications in the fall of 1976.

In the future the MBS applicants will be required to use the NIH 398 forms for submitting applications. An addendum to the instructions for completing the NIH 398 form will be readied for next fall. A deadline of October has been specified by OMB.

During FY 1976, a revised policy and information booklet will be completed. This will have to incorporate the published regulations, evaluation criteria, and criteria and policy on renewal applications.

Expanded interfacing and cooperative agreements with other Institutes besides NCI and NHLI will be explored as well as increasing the activity with NCI and NHLI using a consultant slot from NCI for programming cancer-related projects.

Expected increased interaction with other categorical institutes will require that MBS staff become acquainted with their programs and policies. Priority in training requests will be given to this aspect of staff enrichment.

A major effort will be made to program applications from the new eligible institutions in order to achieve a better program balance.

It is expected that budget constraints will limit the opportunities to expand the program to those institutions that have become eligible with the new regulations. The requested budget for FY 1976 is $7,165,000. This level will be just enough to fund our ongoing commitments. Unless the appropriation is larger than the requested amount, the only source of funds for the new eligibles would be from funds released as a result of projects funded by NCI and NHLI.

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The Program Analysis Branch is responsible for assessing the Division's data requirements and structuring an appropriate Division-wide data base to support decision making in the various program areas. This includes application of system analysis and design, maintenance of data in systems and employment of appropriate systems to produce reports, records, graphics and statistics for purposes of planning, developing and assessing programs. During the past year, PAB has expended a major effort to meet the Division's requirements for an integrated information management sytem as indicated by the following progress.

1. A system for the expansion of data collection on the Minority Biomedical Support Program has been developed, tested, approved and implemented. Procedures have been established for capturing the scientific research projects, trainee and personnel-support data, and a fact sheet of useful items has been prepared.

2. The Biotechnology Resources data system was expanded to collect the expenditures data from the Report of Expenditures instead of the Progress Report.

3. The General Clinical Research Centers data items on the master file were reviewed and revised to include newly identified items as well as to purge certain non-used data elements. Programs have been written to produce several reports previously prepared by hand, i.e., ROE worksheet, Budget worksheet.

4. The Animal Resources Branch with PAB assistance has developed, reviewed and adopted a research project summary report for the Primate Centers as well as the Laboratory Animal Sciences Program, where appropriate and with modifications for various types of resources. Although the Primate Centers data is being received, procedures for editing have to be developed before collection begins. Also data collection from the Report of Expenditures have been implemented.

Over a 3-4 month period, PAB worked closely with Program Staff and review committee members for the General Research Support (GRS) program to provide data for a number of revisions in the GRS procedure for determining awards. PAB adapted several computer 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 GRS and BSS programs. The package of various analyses showing the possible effects of program changes was presented to the review committee and to the advisory council.

The PAB continues to meet with the General Clinical Research Centers Branch

in developing criteria for the acquisition of appropriate data to be used in assessing scientific programs. A great deal of data was provided and data programming changes made to assist the program in responding to the concerns of the House of Representatives Appropriation's Subcommittee in the occupancy rates for the program.

This year PAB has worked on an entirely new and more compact version of data to be published as "Division of Research Resources Handbook." This will be a compendium of current and historical data on the awards of the Division and its five programs. It presents a brief description of the goals, objectives and general activities of the Division's programs with graphs and tables to reflect the magnitude, scientific and technical diversity, geographical coverage and general vitality of the offered programs. This publication constitutes a merger and revision of two previous publications--the "Research Resources Grants" booklet and the "Handbook for the National Advisory Research Resources Council."

Other products derived from the computer based system includes the General Research Support Expenditures Booklet which shows the expenditures 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. A similar publication produced in PAB is the Biomedical Sciences Support Program Expenditures Booklet.

For some time PAB staff has participated in the ECEA Subcommittee study of center grants and program projects. A sampling strategy and several study techniques were developed, described and incorporated into a final report submitted to the OAERT, OD, NIH.

As DRR requirements for a mission evaluation study began to develop, PAB became involved in computer processing and analysis of sets of questions which described the general and specific objectives of the study. PAB developed a taxonomy for the questions and participated in the development of the RFP.

Requests which come to DRR for information or support of large fields of research are usually handled centrally in PAB. This year a number of these were processed for such subject areas as genetics, nutrition, population research, heart and lung disease, digestive diseases, eye research, clinical research, and others.

The Branch has responded to a large number of inquiries for data which are located and maintained by DRG. PAB has written queries to obtain on a regular basis such information as active NIH/ADAMHA research grant support at selected institutions, grants with $10,000 or more awarded for Hospitalization, and NIH grant support in schools of veterinary medicine. The CRISP files were assessed to obtain information on grants using primates. Application and award data is obtained from DRG's IMPAC system and prepared in a booklet form for each round of the National Advisory Research Resources Council.

The above exemplify some of the Program Analysis Branch's 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 and/or develop systems or revised procedures. Future plans include:

1. Examining the specific output requirements of program and committee staff.

2. Establishing a procedure to analyze and link DRR resource user's to other components of NIH.

3. Educating staff as to what data is available, where and under what constraints.

4. Reviewing and evaluating the PROPHETØØ system as an element in the Division's Integrated Information Management System.

Operating in close cooperation with Xavier University of New Orleans which provided pictures and background, the Office produced a news story, with photos, on the 3d Annual Xavier Minority Biomedical Support Symposium. These went to a representative minority press list throughout the United States.

Earlier in the year, feature news stories on the Minority Biomedical Support program were written and placed in Lab Animal, Laboratory Management, Bioscience, and American Druggist.

An Office-generated MBS feature also appeared in Vogue Magazine, and United Press International carried a MBS-related news story, headlined "Alligator Tongue Oil May Aid Arthritis Sufferers." This story was widely carried. Placements included the Miami Herald; the Camden Courier; Cleveland Press; Amarillo, Texas, Globe Times; Science Digest; the Providence Journal; and the New Orleans Times-Picayune.

FASEB's Federation Proceedings ran an Office-written two-page spread on the 2d Annual Symposium which dealt in-depth with its varied activities.

During the year, a news release on new MBS grants appeared in the Birmingham Times. It proclaimed "Black Alabama Schools Get HEW Grants." Similar local angles based on an Office story appeared in the Harlingen, Texas, Valley Star, the McAllen, Texas, Valley Monitor, and the Miami, Fla., Times, plus numerous other papers.

The Message Magazine carried several references to the MBS program as part of a major article on "Outstanding Black Scientists." It was reprinted for distribution

The Office arranged for the publication of a full-page treatment on the Minority Biomedical Support program in the "Letters" section of Science Magazine. This insertion included correspondence from Dr. Thomas G. Bowery and also Dr. Joe Johnson, MBS program director at Atlanta University.

In the audiovisual arena, the Office produced approximately 200 slides for the Division's "interfacing" presentations with other institutes. The slides were carefully designed to convey maximum information about DRR's programs. Assistance with the structure, design, and delivery of the program presentations was provided. In addition, the Office produced color prints of the slides for the Director to present to the home Institute, and black and white (and color) prints for interested Institute viewers. As the year ended, the DRR "interfacing show" had been seen by the top staff of NHLI, NIAID, NICHD, NIDR, and NINDS. Plans were being made to continue the series in the fall.

An editorial sparked by the Office in Lab Animal plugged DRR's "Cost Analysis and Rate Setting Manual for Animal Resource Facilities." The magazine wrote: "The problem is that (with few exceptions) cost accounting is a low priority item in most laboratory animal facilities. To its credit, the National Institutes of Health's Division of Research Resources has recognized this

fact. Even more to its credit, DRR has done something about it. . . Single copies of this manual may be obtained free of charge from Animal Resources Branch, Division of Research Resources. . . We strongly recommend that every laboratory animal facility director avail himself of this offer."

The Office made arrangements for the placement and editing of an article in Lab Animal on the Primate Information Center at the Washington Primate Research Center. Authored by Maryeva Terry, the piece, titled "An Information Resource for the Biomedical Primatologist," gave worldwide publicity to this unique resource. In addition, the Office wrote a Primate Information Center article for NIH News and Features and the NIH Record.

A picture of a Japanese macaque standing erect on a pole at the Oregon Primate Center went out over the United Press Wire; it appeared on the front page of the Washington Star-News, in numerous other papers, and in Bioscience.

A copy of the Office-produced "UCLA Health Sciences Computing Facility" booklet was sent to each of the 1,076 persons on the Association for Computing Machinery's SIGBIO mailing list, together with a letter. The Information Officer bylined an article in the Federation Proceedings on the facility; the NIH Record ran a center spread with 12 pictures; the NIH News and Features ran a UCLA Health Sciences Computing Facility story with pictures; the NIH Search for Health sent a four-part series on the UCLA Center to over 500 newspapers.

A one-minute television spot on good laboratory animal care, which the Office of Science and Health Reports had helped to develop in conjunction with the American Association for Laboratory Animal Science, was given by AALAS members to 58 television stations across the United States. It appeared on KDKA-TV, Pittsburgh; KMBA-TV, Raleigh; WMBA-TV, Kansas City; WKBW, Buffalo; WCTV, Tallahassee; as well as other stations. It will be sent to another 125 stations throughout the U.S. this summer.

Requests for Division booklets continued to be strong, with the majority of requestors interested in our clinical research center booklets: "Research Advances in Human Transplantation" and "How Children Grow." Over 21,450 publications were distributed by the Office during the fiscal year. They were mailed as a result of 4,875 individual requests. Among these were 43 requests from Congressmen for almost 1,400 booklets. Bulk requests for "How Children Grow" included: 60 copies for in-service training of parent education staff members in the Sacramento School District; 25 copies for the Family Nurse Practitioner Program at the University of North Carolina; and 50 copies to elementary and special education teachers at Illinois State University. About 4,000 copies of "How Children Grow" were distributed at the NIH Open House.

An Office photo featuring Trick and Treat, a pair of baby orangutans cared for by the Wisconsin Primate Center, was carried over the United Press International wire; the duo also appeared in Lab Animal and were featured on the cover of the spring 1975 issue of ILAR News.

A primate breeding story, datelined Fredrick, Md., quoted the Animal Resources Program Chief, Dr. Charles McPherson. The AP story said: "American scientists, facing a monkey shortage, have embarked on a plan to make the U.S. self-sufficient in the production of non-human primates for laboratory experimentation." A domestic breeding contracts story was placed in Federation Proceedings, and the shortage of primates for biomedical research was front page material in the NSMR Bulletin.

For the Animal Resources Program, the Office produced a beautiful new exhibit pegged to the "Laboratory Animal Care" educational series. Using a "LAC = Better Staff Skills" theme, the new exhibit featured a filmstrip projector and "listening island" for interested professionals to view the series. The new show was exhibited by the Office and Animal Resources staffers at the American Association for Laboratory Animal Sciences Convention in Cincinnati, and the Federation meetings in Atlantic City.

Additional promotion for the "Laboratory Animal Care" educational series included a cover article, written and photographed by the Office for Lab Animal Magazine. Featured on the cover was Dr. Joseph Spinelli, creator of the series, who was interviewed and photographed by the Office in California. The long interview, titled "A New Audiovisual Program for Supervisor and Technician Training," was reprinted for distribution at the new exhibit. While on assignment, the Office staffers photographed animal caretakers at the California Primate Research Center. This photo, together with a promotional article, appeared in the Federation Proceedings, News and Features from NIH, and the NSMR Bulletin, among other publications.

While on assignment in California, the Office photographed Dr. Joshua Lederberg, Nobel Laureate, and helped plan the dedication of the Stanford University Experimental Computer (SUMEX), funded by the Biotechnology Resources Program. The Office cooperated with the Stanford News Bureau on the dedication story. The photo of Lederberg and our news feature appeared in Medical Group News, Laboratory Management, NIH News and Features, and the NSMR Bulletin.

An Office-created article together with photo of an infant with Menkes Kinky Hair Syndrome, told the story of the treatment of the boy's defect with copper at a clinical research center. It appeared in the Medical Tribune, the NIH Record, and News and Features from NIH.

Late in the year, the Office worked with Dr. Charles McPherson in the development of a bylined article on laboratory animal diagnostic laboratories, exclusively for Lab Animal. The Office arranged for placement and supplied camera-ready art from the "Do We Care?" flyer to be used on the front cover. Also appearing in this issue was an article promoted by the Office on sea hare mariculture by Dr. Michael G. Hadfield of the Kewalo Marine Laboratory in Hawaii.

The Office was responsible for radio interviews of DRR personnel on three occasions during the year. Dr. William Goodwin was interviewed by Fred Fiske on Station WWDC for his Empathy Program. (Washington Metropolitan Area). Both Dr. Thomas G. Bowery and Dr. Ciriaco Gonzales were separately interviewed

by June Carter Perry on WGMS for her Heritage Program. This program was aired in Washington D.C., New York, Chicago, Los Angeles, San Francisco, Fort Lauderdale, Boston, and Memphis.

As the year drew to a close, the Office had made arrangements for the complete July issue of the Federation Proceedings to be devoted to research activities at Division-supported Primate Research Centers. The Information Officer and the Primate Centers Chief authored the introductory article. Along with the special issue, a press briefing will be held, a trade press story written on one article, and a news release completed on another paper.

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

DIVISION OF RESEARCH SERVICES

Report of Program Activities
July 1, 1974 through June 30, 1975

CONTENTS

NATIONAL INSTITUTES OF HEALTH

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

Report of Program Activities
July 1, 1974, through June 30, 1975

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 functional areas: Biomedical Engineering and Instrumentation, Environmental Health and Safety, 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:

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. Surveillance of biohazards, control of radioactive materials and maintenance of health and safety programs.
5. Library and bibliographic services.
6. Foreign language translation.
7. Still photography and motion picture production.
8. Graphics arts services and exhibits design.
9. Medical illustration and model making.
10. Animal production, procurement, conditioning and holding.
11. Animal health services.
12. Experimental surgery and related activities.
13. The production of tissue cultures, microbiologic medias and animal biologics.
14. Central processing and sterile preparation of laboratory glassware.

C. Program Progress and Accomplishments

1. Biomedical Engineering and Instrumentation

Fiscal Year 1975 emphasized the refinement and extension of techniques innovated in previous years. Engineering design together with novel fabrication processes provided NIH with instrumental methods of unprecedented versatility. The ability of the Branch to promptly respond to intramural research demands was hampered by staff curtailments and associated personnel constraints; the quality of BEIB contributions, however, was not compromised.

Mathematically based systems modeling and prediction, verified for animals were successfully applied to human toxicology and therapy. Cytokinetic, pharmacokinetic, and pharmacodynamic bases for cancer chemotherapy were placed in quantitative perspective and used to explore alternative routes of drug administration, e.g., intrathecal and intraperitoneal, to seek optimal regimens. New methods for quantitative detection of trace metals in biological fluids were developed to better characterize environmental, diagnostic and therapeutic exposure of man to metallic ions.

Significant advances were achieved in ultrasonic imaging of structure and function in the cardiovascular system together with improved techniques for non-invasive blood flow measurement of unprecedented accuracy and precision. Ultrasonic methods were extended to ophthalmological scanning for diagnostic and therapeutic purposes. Quantitative measurements of cortical metabolism via televised fluoroscopy opened new avenues for the investigation of CNS physiology.

An important breakthrough was achieved by the completion of a microelectrode positioner that enables long term stable recordings of action potentials from a single neuron in the exposed pulsating cortex of animals and humans. A comprehensive set of instruments for ophthalmological surgery, including remotely controlled surgical tools, syringes, fluid exchangers and retinal suturing devices were provided to extend the capabilities of the eye surgeon and make his task easier.

2. Environmental Health and Safety Program

a. Office of the Associate Director for Environmental Health and Safety

The transfer of the Radiation Safety Section, Department of Nuclear Medicine, Clinical Center, to the Division of Research Services as the Radiation Safety Program, took place on July 1, 1974. On the same date, the Safety Management Program transferred to DRS. On December 23, 1974, the Associate Director was appointed and given responsibility for the development of a well-integrated, comprehensive and centralized environmental health and safety program. Further progress toward centralization of functions was made on March 1, 1975, when the responsibilities for implementation of the National Environmental Policy Act (NEPA) were assigned to the Associate Director.

b. Environmental Services Branch

Sixteen EPA effluent guidelines and several non-DHEW environmental impact statements were reviewed for the Office of the Assistant Secretary for Health, DHEW. Staff assistance was provided to the Division of Engineering Services in preparing the environmental assessment of the NIH Master Plan involving approximately sixteen construction projects.

Staff assistance was provided to the Assistant Director for Administration, NIH, in the Generic Analysis of all NIH programs. Staff also served on a task force of the Assistant Secretary for Health, DHEW, to develop proposed Departmental regulations and procedures for implementation of NEPA.

The national concern for employee health and safety was reflected in the ESB workload. Thirty-two employee requests were investigated concerning suspected hazards in their work places and three extensive surveys were conducted for requested Environmental Differential Pay. Three formal OSHA complaints were also reviewed and 108 other laboratory surveillance visits directly related to employee health were made.

c. Radiation Safety Program

The Nuclear Regulatory Commission issued seven licenses to NIH for the use of radionuclides. Possession of these licenses has greatly reduced the detailed problems of isotope procurement, but carries strict responsibilities governing use and ultimate disposal.

License renewals and amendments were obtained to permit the installation of two irradiators at the Clinical Center, one of 2400 curie capacity, the other of 500 curie.

Radioactive waste volume increased by 31% for the reporting period. Improvements in the waste handling area consisted of equipping the waste compactor with a HEPA filter to prevent radioactive aerosols from escaping into the work environment, and of installing a ventilated hood for the storage of volatile radioactive wastes.

Laboratory surveillance was maintained at a high level and carried out in the nearly 1500 areas where radioactive materials are being used. Strong emphasis was placed on the control of airborn radioactive substances. The number of air samples taken increased by 271% over the previous fiscal year. Investigation and remedial action took place where contamination was found.

The Radiation Safety Program continued to provide training in the safe handling of radioactive materials. Over 850 individuals attended training courses, most of them the one-day course entitled, "Radiation Safety in the Laboratory."

d. Safety Management Program

Accident investigations were conducted on a continuing basis by safety specialists. The NIH accident and injury reporting system continued during the reporting period to function on a recognized better level than most DHEW agencies. The close coordination of this activity with the Employee Health Service and other branches kept reporting close to 100%. Wherever necessary, remedial action was taken and recommendations were given. Fire prevention continued to be of major concern. A report, "NIH Fire Safety Posture", was completed. In it, each building on the NIH Bethesda location is described and discussed with regard to fire safety. The report provides a basis for eliminating fire hazards and for up-grading NIH facilities to prevent losses from fire.

There was a wide range of training activities throughout the year. An important part is the new employee orientation for Clinical Center and ADA personnel.

3. Library Branch

The Library Advisory Committee met three times during the year. Dr. Philip McMaster, NIAID, was appointed Chairman in February replacing Dr. John S. Finlayson, BB, who had served in that capacity for several years. At the same time the Committee was enlarged to 17 members with representation from all I/D's.

On February 24, the Supreme Court, by a tie vote four to four, with Justice Blackmun disqualifying himself, affirmed without opinion the U.S. Court of Claims decision in the case of Williams and Wilkins vs. the U.S. that large-scale unauthorized photocopying and free distribution of copyrighted medical journal articles by NLM and the NIH Library are not copyright infringements.

Effective November 1, the Technical Services Section was reorganized into two units, the Monographs Processing Unit and the Journals Processing Unit replacing the Acquisitions and the Cataloging Units.

The Library became a member of the Ohio College Library Center's shared cataloging automated network system through the Federal Library Experiment in Cooperative Cataloging.

A nonprint collection was organized. Current audiocassettes, tapes and slides were added to previous microform holdings and are available for use in the Library or for loan. Newly acquired nonprint items are included in the monthly memorandum of additions to the Library.

4. Medical Arts and Photography Branch

Demands for MAPB services increased approximately 25 percent in FY 1975. Physical consolidation of the graphics activities has satisfied the need for complete unity in graphics and statistical art preparation. With new equipment and wider use of contract service, delivering finished work has accelerated. Delivery of scientific photography has been reduced from 15 days to seven. Work has been done to establish graphic standards for statistical materials produced by the Branch. This is a forerunner of a continued drive to establish a unified visual communications system for the NIH.

5. Veterinary Resources Branch

VRB service functions continued to increase to meet demands of expanding intramural BID programs, although Branch personnel ceilings have been reduced 18 percent over the last seven years. Increased service with decreased personnel was accomplished by extensive use of overtime, improved animal production methods, automated processing of glassware and production of media, limited use of temporary positions, and contracting.

The VRB rodent breeding colonies were designated as a World Health Organization collaborating center in recognition of their importance as an international genetic repository. A committee of the National Research Council reviewed this effort and recommended that it be removed from the Service and Supply Fund and be given separate funding. More breeding nuclei

were provided this year to start new colonies outside NIH than have been requested in previous years. VRB colonies now serve as the genetic base for most NCI contract programs as well as the Frederick Cancer Research Center. The Catalogue of NIH Rodents was distributed internationally to over 1,000 researchers and specialists in fields of laboratory animal science. Twelve new rodent strains were added to the collection.

Open or complete disclosure formula rations for laboratory animal feeds developed by VRB permit competitive bidding for feed contracts, thereby reducing prices. Savings this year from conversion to open formula rations are estimated to be over $100,000 compared to the estimated costs of closed formula rations purchased under noncompetitive contracts.

Pathogen-free rabbit and guinea pig colonies were successfully initiated this year. Nucleus colonies of guinea pigs were hysterectomy derived and extablished in the barrier in a clean, conventional area. An autoclavable diet for guinea pigs was successfully tested. Hysterectomy derivations were completed to establish all VRB rabbit strains in a new nonbarrier facility. They were foster nursed by SPF Edgewood Arsenal rabbits.

The Perrine Primate Center, established by DRS in FY 1974, is now stocked with 350 rhesus breeders and 75 squirrel monkeys. Two contracts were awarded in June 1974 for additional rhesus monkey breeding colonies. By FY 1978, these three DRS breeding operations are expected to supply 1,000 rhesus and 100 squirrel monkeys annually for intramural research.

Tissue culture and media production increased 7 percent. Blood agar plates were issued at a 7 percent increase also. Glassware issues increased slightly over last year, as did the use of disposable supplies. Surgical facilities were relocated from Building 28 to Building 14E, increasing capacity for surgical procedures.

D. Division Management

1. Personnel Appointments

Mr. Levi C. Carter and Mrs. Rebecca Wilner were appointed during the year as the Division's Executive Officer and Personnel Officer, respectively.

2. Equal Employment Opportunity

The Division's EEO Office and the Human Relations Committee (HRC) worked together to plan the second in a series of EEO Seminars around the theme "Think People." The success of the two sessions demonstrated the need to increase awareness of all DRS employees to the problems and frustrations experienced by employees and management alike.

The Division Human Relations Committee continued to keep the Director advised and aware of employee concerns. A compilation of these efforts was issued in an HRC report to all employees detailing the more significant actions initiated by the committee. The HRC also began holding its meetings in the various Branches and areas of DRS to afford a greater number of employees an opportunity to communicate their concerns to the committee.

In this regard also, suggestion boxes were installed in each Branch so that employees could relate concerns and problems to the committee and the EEO Office.

3. Employee Development

The Division's Training Office held interviews with all employees, GS-9 and below (and equivalents), to gather necessary data for formulating career development plans. This activity was coordinated with the Guidance and Counseling Branch, Division of Personnel Management.

Nineteen employees participated in the NIH Executive Development Program, coordinated by the Executive Management and Development Branch, DPM. These individuals, GS-12 and above (and their equivalents), completed individual development plans and remain active members in the program to develop managerial skills in executives.

Employee training activities were designed to meet individual as well as Division needs. Several female employees participated in programs designed for women in or aspiring to administrative/managerial/supervisory positions.

A well-balanced, incremental supervisors' training program was initiated within the Division. The DRS Supervisory Training Program, divided into modules, affords supervisors an opportunity to attend sessions to enhance their management skills and knowledge. More than 200 supervisors participated and have indicated approval of the program. Their evaluations led to constructive revisions and additions to the overall program.

4. Management Analysis Projects

The Management Analysis staff conducted a work improvement study of the Glassware Unit, VRB, to increase efficiency of the glassware processing system. Final recommendations centered on the redistribution of current manpower, installation of new automated systems, and modifications of current processing procedures. A work measurement study project quantified the time required to perform all end-product tasks during glassware processing. The data will establish more equitable rates for glassware sold under the Service and Supply Fund.

To increase effectiveness of the Small Animal and Glassware Billing Systems, the staff redesigned systems to include special reports for each group concerned with the sale of commodities from these activities. The new systems incorporate an improved distribution technique to automatically address each report system with the name and location of the individual receiving it. A variable message facility was also provided for the activity manager to communicate in written form with each customer of his service.

The Management Analysis staff provided consultative services to the Library Branch in acquiring an Automatic Circulation Control System. Through the efforts of the Management Analysis Office, the Division of Computer Research and Technology agreed to play a major role in acquisition, modification, and installation of a computerized Circulation Control System currently being run by the University of South Carolina.

5. Contracting and Materiel Management

More administrative time and attention were given to contracting operations because of the increased emphasis on securing outside services precipitated by the continued reduction in manpower over a period of years. For instance, operation of the NIH Perrine Primate Center was converted from an inhouse activity to contract because of staff shortages. Increased use of contracts for art and photography services has stimulated development of graphic standards for use by contractors. The Division Director's role as Chairman of the Primate Steering Committee broadened the Division's responsibility for such matters as establishment of a contract with the Pan American Health Organization for the development of New World monkey breeding stations in Latin America. Partial support for a international meeting on the primate resources also was provided to PAHO.

Contract support was given to the National Academy of Sciences for establishment of a committee on veterinary medicine. Increased emphasis was placed on the use of contracts for surveillance of laboratories, laboratory hoods and other equipment used in radiation, biohazard, and chemical carcinogenic activities. A new chemical waste disposal/recycling contract was awarded and attention was given to the possibility of contracting for total radioactive waste handling program.

The Division Administrative and Management Analysis Offices were contacts with the NIH Materiel Management System study group, primarily because of the existing BEIB computerized inventory system. The proposed computerized ordering receiving and inventory system appears to have high potential for benefiting NIH, if properly coordinated with all users of the system.

E. Visual Communications Projects

The Visual Communications Project Officer provided consultation and advice on a wide variety of visual and editorial design projects. Included were scientific papers, slides and exhibits by investigators from DRS and other BID's, development of various training materials, and presentations on program and administrative matters.

Consultation was provided regarding the sound and visual presentation capabilities of alterations to Jack Masur Auditorium in the Clinical Center.

Continuing design and editorial assistance was provided the NCI in development of a series of slide/tape biohazard control and safety training packages. An additional presentation titled, "Hazard Control in the Animal Laboratory", was completed and released through the National Audio-Visual Center. Two additional scripts and story boards were assessed and edited; "Safety Standards for Research in Cancer" and "Assessment of Risk in the Cancer Virus Lab."

Editorial and format design assistance was provided for the "NIH Biohazards Safety Guide." It was released in loose leaf form for NIH laboratory use and in bound form for sale by the Superintendent of Documents, GPO.

A series of carcinogen warning symbols was developed for review and possible

use in research labortories.

More material was added to a centralized file of original slides of DRS subjects. Slides were made available to a number of BID's for use in lectures and publications.

The Visual Communications Project Officer continued to lecture on effective communication techniques to NIH and NIH-related audiences. He served as Division contact for Freedom of Information Act affairs and also continued to coordinate and edit DRS scientific documents, reports, news stories, press releases, publications, and visual materials. Liaison was maintained with the NIH/OD, other BID's on reporting and informational matters, and representation was maintained with public interest groups such as the American Science Film Association and American Medical Writers Association. He also served on the science jury for CINE film awards and selection of U.S. motion pictures for use overseas.

A project which began 26 years ago at the time of the PHS Donora (Pa.) smog disaster study was completed as a visual comparison of conditions in pictures and sketches made from identical locations at Donora in 1949 and 1975. It was presented at the annual American Industrial Hygiene Conference.

DIVISION OF RESEARCH SERVICES

Summary of Branch Activities July 1, 1974, through June 30, 1975

BIOMEDICAL ENGINEERING AND INSTRUMENTATION BRANCH Dr. Lester Goodman, Chief

I. SUMMARY

Fiscal Year 1975 emphasized the refinement and extension of techniques innovated in previous years. Engineering design together with novel fabrication processes provided NIH with instrumental methods of unprecedented versatility. The ability of the Branch to promptly respond to intramural research demands was hampered by staff curtailments and associated personnel constraints; the quality of BEIB contributions, however, was not compromised.

Mathematically based systems modeling and prediction, verified for animals, were successfully applied to human toxicology and therapy. Cytokinetic, pharmacokinetic, and pharmacodynamic bases for cancer chemotherapy were placed in quantitative perspective and used to explore alternative routes of drug administration, e.g., intrathecal and intraperitoneal, to seek optimal regimens. New methods for quantitative detection of trace metals in biological fluids were developed to better characterize environmental, diagnostic and therapeutic exposure of man to metallic ions. More reliable quantification of the interaction of polymeric materials with intracorporeal media enabled improved implant devices. Fluid mechanic analysis and physical models were effective in better explicating atherogenesis.

Significant advances were achieved in ultrasonic imaging of structure and function in the cardiovascular system together with improved techniques for non-invasive blood flow measurement of unprecedented accuracy and precision. Ultrasonic methods were extended to ophthalmological scanning for diagnostic and therapeutic purposes. Quantitative measurements of cortical metabolism via televised fluoroscopy opened new avenues for the investigation of CNS physiology. The patient electrical safety program was extended, better codified and advanced; versatile, new test apparatus was constructed and applied. NIH was provided with a variety of new systems for cell separation, biochemical analyses via NMR and calorimetry. Real-time physiological monitoring and display for surgery and patient care were improved significantly by innovative electronic and video methods.

Mechanization and automation of routine procedures provided for more economic utilization of manpower, dollars and materials especially in the area of processing samples for physical and chemical analysis. Devices were introduced to better protect personnel from the hazards associated with radioisotope administration. Substantial progress was attained and fresh directions of investigation established via new concepts and instrumentation for defining the electrical, chemical and physical concomitants of muscle contraction and nerve conduction in normal and traumatized tissues. An important breakthrough was achieved by the completion of a microelectrode positioner that enables long term stable recordings of action potentials

from a single neuron in the exposed pulsating cortex of animals and humans. A comprehensive set of instruments for ophthalmological surgery, including remotely controlled surgical tools, syringes, fluid exchangers and retinal suturing devices were provided to extend the capabilities of the eye surgeon and make his task easier.

The Scientific Equipment Rental Program continued to expand; it has been enthusiastically accepted and widely used by the NIH intramural research community as a reliable economic resource.

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. BEIB activities, therefore, are identified with many of the individual programs that constitute the intramural research effort. The overall Branch program is best described as the coordinated effort of its operating elements.

1. Instrument Fabrication

Production, modification, and design of biomedical 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 the 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

Backlogs increased markedly over the year due to reductions in manpower. Although quality was maintained, delays in responding to typical requests for fabrication increased to more than two months; patient care related projects continued to receive first priority. Substantial overtime enabled the section to complete 3600 jobs valued at $900,000 compared with 3800 jobs valued at $850,000 in FY 1974.

b. Systems Maintenance Section

First priority attention to patient care related requests and emergency demands, coupled with virtually complete elimination of preventive maintenance due to a shortage of personnel, increased response time for typical demands to an excessive two weeks; two days is considered reasonable. Greater use of overtime and more direct production by supervisory technicians enabled the section to perform 10,200 jobs at a cost of $1,100,000 compared with 9,500 and $1,000,000 respectively in FY 1974.

The Scientific Equipment Rental Program continued to expand over the year as summarized below:

	July 1, 1974	July 1, 1975	Percent Increase
Number of pool items	423	550	23
Dollar value	$478,000	$700,000	42
Number of items on rental	194	240	24
Utilization rate	46%	46%	0

	FY 1974	FY 1975	Percent Increas
Gross revenue	$65,000	$102,000	57
New equipment investment	$17,500	$ 43,000	146

Full realization of the potential value of this program to the NIH continues to be impeded by constraints on personnel and space.

c. Supply Unit

The effort was made, throughout the year, to achieve greater economy by consolidating inventories in terms of capital investment and number of items carried. A comparison with FY 1974 operations shows a change in number of transactions processed from 21,000 to 22,000 with the value of goods sold increasing from $373,000 to $440,000 in FY 1975.

2. Engineering and Applied Sciences

a. Chemical Engineering

Substantial progress was achieved in applying chemical reaction engineering to problems of drug, metabolic and environmental contaminant distribution in the body. Principles established in animals were demonstrated applicable to humans for both toxic effects and optimal therapeutic protocols. A pharmacokinetic model, originally developed on the basis of extensive studies in mice, was used successfully to predict priming doses and infusion rates necessary to achieve arbitrary plasma concentrations of methotrexate in individual patients. The dynamics of plasma concentration following infusion was investigated to provide safer and more reliable "rescue" therapy following large methotrexate dosage. Cytokinetic, pharmacokinetic, and pharmacodynamic bases of resistance to anti-cancer drug therapy were explored, and several pharmacokinetic factors placed in quantitative perspective. Alternate routes of drug administration, e.g., intrathecal and intraperitoneal, were studied to exploit possible therapeutic advantage and avoid toxic consequences.

Environmental, diagnostic and therapeutic exposure of humans to metallic ions and complexes requires more sensitive and reliable methodology for analysis and characterization. Flameless atomic absorption spectrophotometry was applied to quantitative trace analysis of platinum in biological fluids and tissues. Other elements measured in biological or biomedical materials by this technique include calcium, magnesium, silicon, copper, and iron; gallium is under investigation. An instrument was developed for electronic control of the furnace temperature program to enhance sensitivity and enable analysis of materials with different combustion characteristics.

Both our understanding of biomaterials and ability to design prosthetic devices were advanced. A study to elucidate the kinetic and thermodynamic mechanisms associated with phthalate plasticizers from vinyl plastics revealed that desorption rate into a pseudoserum was independent of flow rate but strongly dependent upon lipid concentration in the serum. Studies which explored the effect of antineoplastic drugs on wound strength have significant potential bearing on the conduct of early chemotherapy following surgery. The application of segmented polyurethane to biomedicine, pioneered by one of our staff, was advanced by numerous applications at NIH and elsewhere to heart assist devices, cannulas, heart valves, and other devices. Of particular relevance are ventricular-aortic bypasses and composite heart valves developed at NIH which have been successful in animal studies.

Shear stress distributions in costs of canine aortas were studied by electrochemical instrumentation in steady and pulsatile flow. Regions of high shear were shown to exist at flow divider tips and other sites of developing velocity profiles especially in the presence of intricate three-dimensional geometry, flow branching, separation and reversal during pulsations. Regions of high shear and regions of disturbed flow correlate with anatomical localization of atherosclerotic plaque.

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

b. Electrical and Electronic Engineering

BEIB completed a substantial number of new designs for electrical and electronic apparatus for the NIH research programs; projects deserving special mention are summarized as follows:

Progress in clinical instrumentation was marked by further developments in two dimensional dynamic ultrasonic displays of physiological structures. Ultrasonic scanning was effectively extended to improve the quality of ophthalmological examinations and significant improvements were attained in measurements of blood flow rates. Others include: A new method for quantifying cortical metabolism as function of position via low light level TV fluoroscopy; a laser powered ophthalmological drill; electronic monitoring of culture growth; and several systems for multiplexing various modes of clinical information onto video displays.

In the field of laboratory instrumentation, noteworthy advances were made in cell separation technology; rapid-scan Fourier transform NMR; dual thermistor differential micro-calorimetry.

The patient electrical safety program was highlighted by the development of "second generation" test apparatus, new methods for scheduling and recording inspections, and more extensive consultation regarding equipment purchases.

c. Mechanical Engineering

Continued close collaboration with research and applications program principals throughout the NIH resulted in substantial developments in several areas. Mechanization and automation of routine laboratory procedures were extended and improved; large-scale media preparation operations and glassware processing were made more economical in terms of manpower and costs thus permitting reallocation of resources to more productive and challenging assignments.

Substantial advances were achieved in fundamental and applied research on concomitants of CNS trauma, particularly in examination of the relationship of electrical conduction in nerve fibers with mechanical shock; protection to clinical personnel handling radioactive material; new visual acuity tests; processing of electrophoretic preparations; combining the advantages of visual microscopy with those of electron microscopy; application of fluidic logic and control to the programming of reagent inputs to a rapid reaction stop-flow calorimeter.

A new family of instruments for use in eye surgery was generated. These include special surgical knives, a vitreous humor extractor, a unique foot control, a syringe drive, a sub-retinal fluid drainer, and new retinal suturing techniques. Two new devices for placement of electrodes in brain of man and of test animals are undergoing tests. Each of these advances the state of the art in specific areas.

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

d. Florence Agreement

BEIB is responsible for implementing NIH commitments related to the "Florence Agreement." Duties involve review of applications for duty-free entry of foreign manufactured scientific apparatus acquired by domestic nonprofit institutions, assessment of the suitability of equipment cited for intended applications, investigation of availability of domestically produced scientific equivalents, recommendations to the U.S. Department of Commerce for approval, disapproval, or resubmission; and providing pertinent technical advice to requesting agencies and the Department of Commerce. The Branch Chief serves as Chairman of the NIH Florence Agreement Committee which includes a number of NIH professionals who are expert in particular categories of instrumentation. The Executive Secretary, who must be thoroughly knowledgeable in modern scientific equipment, has become recognized as a reliable source of expert guidance, especially in the areas of transmission and scanning electron microscopy. Activities for FY 1975 are summarized as follows:

Number of applications received by NIH	610
Referred to other agencies	100
Processed by NIH	510
Processed independently by the Executive Secretary	480
Processed with help of other Committee members	30
Recommendations for approval	340
Recommendations for disapproval	30
Recommendations for resubmission	140

3. Technical Advances

A CHIN ACTUATED REMOTE CONTROLLER manipulates a viewing microscope in three axes to enable full use of a surgeon's hands for ophthalmological procedures.

CONCOMITANTS OF NERVE TRAUMA are derived with a new apparatus that monitors compound action potential changes resulting from applied dynamic mechanical stresses.

A FLUIDIC LOGIC CONTROLLED SYSTEM transfers precise volumes of reagents within a chemical analyzer to improve the quality of kinetic reaction studies.

NMR SPECTROMETRY VIA RAPID SCAN FT TECHNIQUES is enhanced by automatic sequencing of fixed frequency pre-scan irradiation, homogeneity spoiling, and broad band rapid scan processes.

SCANNING ELECTRON MICROSCOPE VERSATILITY is substantially expanded with externally controlled accessories which provide three axis sample manipulation and direct optical viewing.

BACTERIAL GROWTH IN BLOOD CULTURE bottles is monitored more accurately and conveniently by measuring minute electrical impedance changes.

ELECTROPHORESIS GEL DESTAINING is accelerated by circulation of buffer through a charcoal bed.

AORTIC BALL VALVE PROSTHESIS INTEGRITY is non-invasively assessed with a coordianted radioisotopic and microphonic signal detection and data processing system.

RADIOACTIVE SERUM INFECTION with markedly improved safety is achieved with a novel tantalum-stainless steel syringe shield.

SYNCHRONOUS VIDEO DISPLAY of images and temporal signals substantially expedites interpretation and evaluation of cardiodynamic phenomena.

A VERSATILE TIME CODED DATA PLAYBACK TECHNIQUE using low speed magnetic tape recording is useful in epilepsy studies.

LOCALIZED QUANTITATIVE MEASUREMENT OF CORTICAL FLUORESCENCE, flow rate and oxygenation of blood adds new dimensions to the understanding of central nervous system metabolism.

A SYSTEM FOR IN VITRO STUDY OF CARDIAC MUSCLE HYPERTROPHY controls local ambient temperature and partial pressures of O_2 and CO_2, supplies periodic isometric clamping and electrical stimulation, and optically determines muscle growth rate.

CONTAINERS UP TO ONE LITER ARE AUTOMATICALLY LABELED with pressure sensitive printed tags at a rate of 110 per minute in a mechanized glassware processing apparatus.

A MULTIPLEXED VIDEO MONITOR AND TAPE RECORDING SYSTEM helps to define the relationship between evoked pupillary response and CNS disorders.

A PROGRAMMABLE EXTERNAL CARDIAC PACEMAKER changes heart rate in prescribed temporal patterns as an aid to therapy.

AN INFANT HEAD MOTION MONITOR extends the versatility of a system used to study mother-infant behavior interactions.

A SELF CONTAINED PORTABLE VISUAL ACUITY TESTER implements the "illiterate E" test randomly to eliminate the effect of patient anticipation.

4. Training

An effective professional and technical program was essential in maintaining high quality support and service. Fifty-seven employees participated in

116 academic, administrative, and technical courses. Thirteen (123 man-days) undertook formal university education and training courses. Thirteen (52 man-days) received specialized training on scientific equipment at manufacturers' facilities and at the NIH. Thirty-eight (165 man-days) attended various administrative, clerical, technical and scientific courses and training seminars. One employee attended Basic Adult Education at NIH sponsored by the Montgomery County School System and three employees were enrolled in the Upward Mobility College taking a total of 25 quarters of college-level courses.

D. Program Plans

Fiscal 1975 was distinguished by the refinement and extension of concepts, methods and devices conceived in previous years. Several promising new avenues of investigation were opened in fundamental research and engineering applications. The expectation of constraints on personnel and materiel for the coming year requires careful consideration of priorities and utilization of available resources. Modified methods for maximally satisfying the needs of the NIH program including, perhaps, more extensive use of contractors is anticipated. Reorientation of duties and functions within the Branch must be explored.

1. Considerable emphasis will be placed on innovating, improving and extending engineering applications for the benefit of research and clinical practice, especially in the areas of:

a. Optimization of chemotherapeutic processes.

b. Detection and analysis of trace elements and their role in toxicology, diagnosis, and treatment.

c. Elucidation of the interaction between implanted artificial devices and the living environment.

d. Improved non-invasive physiological measurements and anatomical imaging.

e. Explication of the chemical, electrical and mechanical concomitants of physiological phenomena associated with muscle, nerve, and blood.

f. Automated materiel and information processing systems.

g. Apparatus and methods for protection of personnel from hazards in laboratories and clinics.

2. Expansion of the Scientific Equipment Rental Program and increased operational efficiency.

3. More extensive use of private sector capabilities for procurement of services via contract.

4. Incorporation of Branch financial management functions within the forthcoming NIH Material Management and Common Accounting Systems to improve responsiveness and economy of operations.

E. Publications and Patents

1. Publications

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Project No. ZO1 RS 00001-07 BEI

1. Biomedical Engineering and Instrumentation Branch
2. Chemical Engineering Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Pharmacokinetics

Previous Serial Number: DRS-BEIB-1

Principal Investigator: Robert L. Dedrick

Other Investigators: Daniel S. Zaharko, Richard A. Bender, Anthony M. Guarino, Robert J. Lutz, André F. LeRoy, Kenneth B. Bischoff, Marshall Anderson, Bruce Chabner, W. Archie Bleyer

Cooperating Units: LCHPH-NCI, LT-NCI, PB-NIEHS, AK-CU Program NIAMDD, University of Washington, M-NCI

Man Years:

Total:	3.0
Professional:	2.0
Other:	1.0

Project Description:

Objectives: Improve and extend mathematical models for the distribution and disposition of drugs, environmental contaminants and endogenous metabolites in animals 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 pharmacodynamics, provide a basis for optimization of cancer chemotherapy and chronic hemodialysis.

(4) Enable rational transfer of *in vitro* thermodynamic and kinetic data to *in vivo* cases.

(5) Predict effective dose schedules of anti-cancer drugs in individual patients.

Methods Employed: Mathematical models are developed from 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) Methotrexate distribution in spontaneous canine lymphosarcoma has been modeled as a saturable transport process with strong intracellular binding to dihydrofolate reductase and weak binding to cell membranes or extracellular tumor components.

(2) A pharmacokinetic model, originally developed on the basis of extensive studies in mice, has been used successfully to predict methotrexate priming doses and infusion rates required to achieve selected plasma concentrations in individual patients.

(3) Tumor perfusion, membrane transport, intracellular enzyme levels and enzyme synthesis rate have been illustrated and placed in quantitative perspective by a discussion of the pharmacokinetics and pharmacodynamics of methotrexate. This provides an operational basis for examination of drug resistance.

(4) Filterability of platinum administered as cis-dichlorodiammine platinum (II) decreases during incubation with dog plasma in vitro. This appears to correlate with a decrease in kidney clearance in vivo and suggests that one or more chemical reactions occur which may influence distribution, disposition, and biological effect.

Significance: Drugs and other chemicals are tested for effect in animals, and the extrapolation to man is a subject of serious concern. At issue are both the risk associated with environmental contaminants and optimization of therapy.

Proposed Course: Continued pharmacokinetic modeling with particular attention to pharmacodynamic and cytokinetic events. Increased clinical emphasis through support of high-dose methotrexate protocols and other attempts to overcome drug resistance.

Keyword Descriptors: Pharmacokinetics, methotrexate, polychlorinated biphenyls, mathematical modeling, drug resistance, cancer chemotherapy, cis-dichlorodiammine platinum (II).

Honors and Awards: Food, Pharmaceutical and Bioengineering Division Award of American Institute of Chemical Engineers to R.L. Dedrick.

Publications:

Teorell, T., Dedrick, R.L. and Condliff, P.G. (Eds.): Pharmacology and Pharmacokinetics. New York, Plenum Press, 1974, 388 pp.

Dedrick, R.L.: Animal Scale-Up. In Teorell, T., Dedrick, R.L. and Condliffe, P.G. (Eds.): Pharmacology and Pharmacokinetics, New York, Plenum Press, 1974, pp. 117-144.

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Bischoff, K.B.: Pharmacokinetics and Cancer Chemotherapy. In Teorell, T., Dedrick, R.L. and Condliffe, P.G. (Eds.): Pharmacology and Pharmacokinetics, New York, Plenum Press, 1974, pp. 351-366.

_____: Some Fundamental Considerations in Applications of Pharmacokinetics to Cancer Chemotherapy. Cancer Chemotherapy Rep. (In Press).

Project No. Z01 RS 00002-10 BEI

1. Biomedical Engineering and Instrumentation Branch
2. Chemical Engineering Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Implant Device Development

Previous Serial Number: DRS-BEIB-4

Principal Investigator: John W. Boretos

Other Investigators: William S. Pierce, Robert Poirier, James W. Prescott, C. Kollarits, M. Fisherman, John W. Brown, Robert Baier, Robert L. Dedrick, Robert J. Lutz

Cooperating Units: SB-NHLI, GD-NICHD, Pennsylvania State University, CB-NEI, Calspan Corp.

Man Years:

Total:	1.8
Professional:	1.5
Others:	0.3

Project Description:

Objectives: Elucidate the interaction of polymers used for specific implants with the physiological environment; explore specially prepared polymers and design features with respect to their suitability and performance in a variety of contexts.

Methods Employed: Basic polymer composition is carefully controlled and modification of cross-linking systems is employed. Rheological properties are studied as a function of cross-linking. Implants are examined after removal for lipid absorption, protein deposition, changes in surface-free energy, and alteration of physical properties. Observations include SEM, infrared spectroscopy, contact angle measurements, energy dispersive x-ray analysis and atomic absorption spectroscopy. Flow characteristics and pressure gradients across heart valve implants are studied in vitro in test apparatus.

Major Findings: Ten heart assist devices with segmented polyurethane blood contacting surfaces were implanted in calves for up to 35 weeks. No lipid absorption was observed; physical strength remained stable; surfaces developed a biocompatible layer of protein. Six additional assist devices have been implanted with similar results; two total heart implants have been achieved.

A series of ventricular-aortic by-pass devices functioned satisfactorily for periods up to 17 weeks in dogs with negligible blood damage. Clinical trials are now being planned.

Six segmented polyurethane covered polypropylene poppets housed in standard "Starr-Edwards 3M" cages have been implanted in calves. One was electively removed after one year; no obvious physical or chemical changes occurred and there was no evidence of injury to the animal.

Significance: Physiologically compatible polymers with enduring strength are needed for such applications as heart valves, heart assist devices, vascular implants, and subcutaneous uses.

Proposed Course: (1) Extend experimental studies to further characterize the surface and bulk properties of polyether urethanes and more specifically determine its interactions with blood and subcutaneous tissue.

(2) Study new designs of tricuspid heart valves for acute and chronic use.

(3) Study new designs of drains to be used in the eye to treat glaucoma.

Keyword Descriptors: Polymers, implants, heart valves, heart pumps, glaucoma drains.

Honors and Awards: None

Publications:

Boretos, J.W., Pierce, W.S., Baier, R.E., LeRoy, A.F., and Donachy, H.J.: Surface and Bulk Characteristics of a Polyether Urethane for Artificial Heart. J. Biomed. Mater. Res. (in press).

Boretos, J.W. and Brown, J.W.: Materials and Design Characteristics for Improved Apical Aortic Anastomosis. In 1974 ASME Advances in Bioengineering. Brighton, J.A. and Goldstein, S.R. (eds.) American Society of Mechanical Engineers.

Boretos, J.W.: Silicones. In Polymers in Medicine and Surgery, Proceedings of a Symposium, 1974, Morristown, New Jersey. Kronenthal, D. and Oser, Z. (eds.), Plenum Polymer and Science Technology Series, Plenum Press (in press).

Boretos, J.W.: Polymer Considerations for Electronic Implants. In Ray, C.D. (ed.) Medical Engineering, Year Book Medical Publishers, Inc., Chicago, IL, 1974, pp 1120-1123.

Boretos, J.W.: Machining of Plastics. In Ray, C.D. (ed.), Medical Engineering, Year Book Medical Publishers, Inc., Chicago, IL, 1974, pp. 1173-1181.

Project No. Z01 RS 00003-03 BEI

1. Biomedical Engineering and Instrumentation Branch
2. Chemical Engineering Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Trace Element Analysis in Biological Materials

Previous Serial Number: DRS-BEIB-2

Principal Investigators: André F. LeRoy

Other Investigators: H.M. Olson, A.M. Guarino, R.L. Dedrick, C. Litterst, T.E. Gram, G.P. Canellos

Cooperating Units: LT-NCI, M-NCI

Man Years:

Total:	2.0
Professional:	1.6
Others:	0.4

Project Description:

Objectives: Enhance analysis and identification of metal complexes in biological materials. Improve analytical methods with detection limits on the order of nanograms to picograms in milligram samples. Emphasize analysis of platinum, gallium, calcium and magnesium compounds as they relate to diagnosis and chemotherapy.

Methods Employed: Flameless atomic absorption spectrophotometry for analysis of specific elements. Chemical agents are used to promote release of elements from the biological matrix more smoothly and completely. Solvent extraction may be very useful for many applications. Electronic control of the temperature program for combustion allows materials with different combustion characteristics to be analyzed.

Electrophoresis to fractionate proteins with subsequent determination of metal species among fractions. In some cases, ultrafiltration is required to concentrate proteins enough to permit detection of metals.

Major Findings: Sensitivity of platinum determination is approximately one nanogram. Urine and plasma samples from dogs treated with cis-dichlorodiammine platinum have been directly analyzed as a function of time. More than half of platinum administered appears in the urine within about two hours; the remainder is released in the urine much more slowly. Samples of various tissues from treated dogs have been analyzed after acid digestion. The results indicate that loss of platinum taken up in tissue is very slow.

Direct analysis of gallium has given erratic results to date.

Significance: Quantitation, identification and characterization of metal species at trace levels in biological tissue is important in biochemical research and environmental toxicology. Characterization of such compounds in tissues and body fluids can help identify drug action and suggest other potentially useful compounds. Methods under development offer an alternative to administering radiolabeled substances to human subjects.

Proposed Course: Extend applicability of direct combustion techniques to more tissue types by use of suitable time-timperature relationships; try to minimize need for pretreatment. Complete analyses required for pharmacokinetic modeling. Perform referee analyses for metals using neutron activation analysis where applicable. Improve analysis for gallium.

Keyword Descriptors: Trace-element analysis, biological tissues and fluids, atomic absorption spectrophotometry.

Honors and Awards: None

Publications:

LeRoy, A.F.: Interactions of Platinum-Metals and Their Complexes in Biological Systems. Environ. Health Perspect. (in press.)

Olson, H.M., Rosenoff, S.H., Reagan, R.L., Munroe, B., LeRoy, A.F., Young, R.C., Young, D.M.: Ultrastructural Alterations of the Myocardium and Biochemical Correlates in Mice with Adriamycin Administration. Cancer Res. (in press.)

Olson, H.M., Young, D.M., Prieur, D.J., LeRoy, A.J., Reagan, R.L.: Electrolyte and Morphologic Alterations of Myocardium in Adriamycin-Treated Rabbits. Am. J. Pathol. 77: 439-450, 1974.

Project No. Z01 RS 00004-05 BEI

1. Biomedical Engineering and Instrumentation Branch
2. Chemical Engineering Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: The Role of Fluid Dynamics and Mass Transfer in Development of Atherosclerosis

Previous Serial Number: DRS-BEIB-3

Principal Investigators: Robert J. Lutz, Joseph N. Cannon

Other Investigators: Donald L. Fry, Robert L. Dedrick, Kenneth B. Bischoff

Cooperating Units: OD-IR-NHLI, Howard University

Man Years:

Total:	1.2
Professional:	0.8
Other:	0.4

Project Description:

Objectives: Measure shear stress on the inner wall of simulated arteries during steady and pulsatile flow and correlate data with localization of atherosclerosis as found in experimental animals. Visualize flow patterns in the three-dimensional geometry of arterial branches. Measure the effects of shear on the transport rate of macromolecules through simulated and real arterial endothelium.

Methods Employed: An electrochemical technique is used, based on an oxidation-reduction reaction at electrodes implanted at a fluid-solid interface, which determines mass transfer rates of redox ions. Velocity gradients at the wall (shear rate) are calculated from mass transfer rates with suitable boundary layer equations.

Flow visualization can be achieved in a transparent cast of a canine artery using dye injection techniques and/or cinematography of latex microspheres.

Major Findings: In the arterial model, sharp shear peaks exist near the flow divider tips of branches; shear rate rises as flow enters smaller branches where velocity profiles are redeveloping. Shear drops suddenly just distal to the flow divider tips resulting in flow separation and flow reversal during pulsations. The intricate three-dimensional geometry of the arterial tree and branching of the flow from the main channel are responsible for flow pattern characteristics. Regions of high shear and regions of disturbed flow patterns correlate with areas of increased plaque localization.

Significance: Elucidation of the role of hemodynamics and mass transfer in the onset and development of atherosclerotic plaques is fundamental in the study of vascular disease

Proposed Course: Verify electrochemical techniques experimentally and by computer simulation for measuring pulsatile shear stresses. Fabricate more realistic arterial models which include wall distensibility, and determine shear rate patterns. Devise mechanical models of the phospholipid membrane of arterial endothelial cells and determine the effect of shear on transport of macromolecules across these artificial membranes.

Keyword Descriptors: Atherosclerosis, electrochemical shear measurement, arterial models, arterial fluid dynamics

Honors and Awards: None

Publications:

Lutz, R.J., Cannon, J.N., Fletcher, J.E., and Fry, D.L.: The Measurement of Wall Shear Stress in Model Arteries by an Electrochemical Technique. In Proceedings of the 27th Annual Conference on Engineering in Medicine and Biology, 1974, Philadelphia, Pennsylvania. Arlington, Va., The Alliance for Engineering in Medicine and Biology, 1974, Vol. 16, p. 27.

Lutz, R.J., Cannon, J.N., Munroe, R.E.: Shear Stress Measurements in Model Arteries During Steady and Pulsatile Flow. In Nerem, R.M. (Ed.): Fluid Dynamic Aspects of Arterial Disease. Proceedings From a Specialists Meeting on Fluid Dynamic Aspects of Arterial Disease, Columbus, Ohio, September 19-20, 1974, pp. 5-8.

Project No. Z01 RS 00006-03 BEI

1. Biomedical Engineering and Instrumentation Branch
2. Chemical Engineering Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Multicomponent Plastics in Biomedical Use

Previous Serial Number: DRS-BEIB-5

Principal Investigator: Henry L. Gabelnick

Other Investigator: Margaret L. Wehling

Cooperating Units: None

Man Years:

Total:	0.6
Professional:	0.3
Other:	0.3

Project Description:

Objectives: Extend definition of the interaction of plastic systems with the biological environment, emphasizing the kinetics of additive elution from polymers and absorption of body constituents.

Methods Employed: Determination of elution rate of migrating species via quantitative analytical techniques. Parameters under investigation include fluid composition and flow conditions.

Major Findings: Refined analytical techniques enable evaluation of the di-2-ethylhexylphthalate-polyvinyl chloride system exposed to a soybean emulsion "pseudo-serum."

Desorption of phthalate from surgical grade polyvinyl tubing (3/16" I.D.) was independent of flow rate over the range 100 to 300 ml/min. However, the rate of uptake of phthalate by the pseudo-serum increased by a factor of two when the lipid concentration was increased from 100 to 300 mg%.

Proposed Course: Project terminated in December 1974 due to departure of the principal investigator.

Keyword Descriptors: Phthalates, plasticizes elution, vinyl tubing, desorption kinetics

Honors and Awards: None

Publications: None

Project No. Z01 RS 00005-03 BEI

1. Biomedical Engineering and Instrumentation Branch
2. Chemical Engineering Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Thermomicrography

Previous Serial Number: None

Principal Investigators: John I. Peterson

Other Investigators: Robert L. Bowman

Cooperating Units: LTD-NHLI

Man Years:

Total:	1.3
Professional:	0.8
Other:	0.5

Project Description:

Objectives: Develop a method for microscopic observation of biological cells by their thermal effects.

Methods Employed: Investigation of the possible use of the optical-thermal properties of the cholesteric mesophase ("liquid crystals").

Major Findings: The well-known and previously investigated properties of cholesteric esters have been based on materials of undocumented and probably low purity. The accepted theoretical model for their behavior is untenable from the chemical point of view. The investigation of highly purified material shows behavior which is different and possibly more useful than previously observed, as well as being divergent from that expected.

Significance: A technic of microthermography would be useful for cell calorimetry and other energy studies on an individual cell basis, and could provide a possible route to facilitation of screening studies involving various kinds of cellular reactions.

Proposed Course: Verification of conclusions derived to date and extension through continued investigation.

Keyword Descriptors: Thermography, liquid crystals, purification, cholesteric esters.

Honors and Awards: None

Publications: None

Project No. Z01 RS 00007-01 BEI

1. Biomedical Engineering and Instrumentation Branch
2. Electrical and Electronic Engineering Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Investigation of Oxidative Metabolism and Potassium Kinetics in the Cat Brain

Previous Serial Number: DRS-BEIB-7

Principal Investigators: William H. Schuette, Darrell V. Lewis

Cooperating Units: EEG-NINDS

Man Years:

Total:	2.0
Professional:	1.5
Others:	0.5

Project Description:

Objectives: (1) Develop and apply new and improved techniques for analyzing oxidative metabolism of the cat brain and correlating these results to simultaneous extracellular potassium kinetic measurements.

(2) Determine the Q_{10} of potassium kinetics in the cat hippocampus.

(3) Validate oxidative metabolism measurements obtained by NADH fluorescence techniques with direct measurement of cortical oxygen consumption.

Methods Employed: NADH fluorescence measurements are made with a unique two-channel fluorometer.

Q_{10} measurements are made by cooling the brain with an "Elliott's B" solution drip while measuring local temperature with a thermistor. Potassium kinetics are measured with a potassium sensitive microelectrode following electrical stimulation.

Cortical oxygen consumption is determined from the combination of oximetry and flow of blood drained from the sagittal sinus of cats.

Major Findings: (1) Clearance of potassium following stimulation of the brain is an exponential process.

(2) The Q_{10} for this clearance is approximately 2.1.

(3) A linear relationship exists between the amount of potassium released following a stimulus to the brain and the time integral of the NADH fluorescence signal.

(4) NADH fluorescence signals appear to be related to direct oxygen consumption measurements.

Significance: Evidence for potassium clearance being an active process has been reinforced.

The utility of NADH fluorescence as an indicator of oxidative metabolism has been demonstrated.

Proposed Course: Refinement and extension of work done to date.

Keyword Descriptors: NADH, fluorescence, potassium, kinetics, oximetry

Honors and Awards: None

Publications:

1. Lewis, D.V., O'Connor, M.J. and Schuette, W.H.: Oxidative Metabolism During Recurrent Seizures in the Penicillin-Treated Hippocampus. Electroencephalogr. Clin Neurophysiol. 36: 347-356, 1974.

2. Schuette, W.H., Whitehouse, W.C., Lewis, D.V., O'Connor, M.J. and Van Buren, J.M.: A Television Fluorometer for Monitoring Oxidative Metabolism in Intact Tissue. Med. Instrum. 8: 331-333, 1974.

3. Lewis, D.V. and Schuette, W.H.: NADH Fluorescence and $[K^+]_o$ Changes During Hippocampal Electrical Stimulation. J. Neurophysiol. 38: 405-417, 1975.

Project No. Z01 RS 00008-03 BEI

1. Biomedical Engineering and Instrumentation Branch
2. Electrical and Electronic Engineering Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Diagnostic Ultrasound

Previous Serial Number: DRS-BEIB-8

Principal Investigators: James M. Griffith, Walter L. Henry, William R. Brody, Steven Charles

Other Investigators: David Myerowitz, Barry J. Maron, Stephen E. Epstein

Cooperating Units: CB-IR-NHLI, SU-IR-NHLI, IR-NEI

Man Years:

Total:	3.5
Professional:	2.0
Others:	1.5

Project Description:

Objectives: (1) Noninvasively obtain dynamic images and measurements of cardiac structure and function and assess for diagnostic and therapeutic purposes.

(2) Noninvasively obtain images and measurements of ophthalmic structure and assess for diagnostic and therapeutic purposes.

(3) Noninvasively obtain dynamic measurements of blood flow in circulatory vessels.

Methods Employed: A previously reported real-time, two-dimensional sector scanner was refined and used effectively in several new research applications.

The sector scanner technique was extended to ophthalmological applications.

Principles of high resolution radar and communication theory are being applied to doppler flowmeter design for improved resolution.

A moving-trace monitor system was developed which allows two seconds of EKG to be recorded on each frame of real-time two-dimensional echogram.

Major Findings:

(1) Mitral valve orifice area can be accurately measured by real-time two-dimensional echocardiography.

(2) Two-dimensional echocardiography is a significant new tool for the differential diagnosis of anomalies of the great arteries.

(3) Mechanical sector scanning in real time is applicable to ophthalmic scanning; this considerably reduces examination time.

Significance: Safe noninvasive methods for making quantitative and qualitative physiologic measurements are of substantial value for research and diagnostic purposes.

Proposed Course: The doppler flowmeter design will be improved so that useful velocity and range resolution are obtained. Then it may be possible to combine a flowmeter and a sector scanner so that real-time two-dimensional imaging is available simultaneously with flow measurement.

Keyword Descriptors: Ultrasound, Pulse Echo, doppler

Honors and Awards: None

Publications:

1. Griffith, J.M. and Henry, W.L. A Sector Scanner for Real Time Two-Dimensional Echocardiography. Circulation, XLIX: 1147-1152, 1974.

2. Myerowitz, P.D., Griffith, J.M., Roberts, A.J., Harrison, L.H., Henry, W.L., and McIntosh, C.L. Long-Term Canine Model for Echocardiography. Am. J. Cardiol. 34: 72-74, 1974.

3. Griffith, J.M. and Henry, W.L. Switched Gain: Simplifies Ultrasonic Measurement of Cardiac Wall Thickness. In Proceedings of the 27th Annual on Engineering in Medicine and Biology 1974, Philadelphia, Pennsylvania, Arlington, Va., The Alliance for Engineering in Medicine and Biology, 1974, Vol. 16, p. 264.

4. Myerowitz, P.D., Brown, J.W., Harrison, L.H., Griffith, J.M., Henry, W.L. and McIntosh, C.L. A Comparison of Simultaneous Echocardiographic and Electromagnetic Flowmeter Determination of Stroke Volume. Supplement III to Circulation, Vols. 49 and 50, October 1974.

5. Henry, W.L., Griffith, J.M., Michaelis, L.L., McIntosh, C.L., Morrow, A.G., and Epstein, S.E. Quantitation of the Mitral Orifice Area by Real-Time Two-Dimensional Echocardiography. Supplement III to Circulation, Vols. 49 and 50, October 1974.

6. _____, Epstein, S.E., Griffith, J.M., Goldstein, R.E., Redwood, D.R. Effect of Prolonged Space Flight on Cardiac Function and Dimensions. Am. J. Cardiol. 35: 143, 1975.

7. Griffith, J.M. and Henry, W.L. A Moving-Trace Monitor for Video Systems. Med. Instrum. 9: 73, 1975.

8. Henry, W.L., Maron, B.J., Griffith, J.M., Redwood, D.R., and Epstein, S.E. Differential Diagnosis of Anomalies of the Great Arteries by Real-Time Two-Dimensional Echocardiography. Circulation 51: 283-291, 1975.

9. _____, Clark, C.E., Griffith, J.M., and Epstein, S.E. Mechanism of Left Ventricular Outflow Obstruction in Patients with Obstructive Asymmetric Septal Hypertrophy (Idiopathic Hypertrophic Subaortic Stenosis). Am. J. Cardiol. 35: 337-345, 1975.

Project No. Z01 RS 00009-05 BEI

1. Biomedical Engineering and Instrumentation Branch
2. Electrical and Electronic Engineering Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Nuclear Magnetic Resonance Techniques for Biochemical Analysis

Previous Serial Number: DRS-BEIB-6

Principal Investigators: Thomas R. Clem, Walter S. Friauf, Edwin D. Becker

Other Investigator: James A. Ferretti

Cooperating Units: LCP-NIAMDD, PSL-DCRT

Man Years:

Total:	2.0
Professional:	1.5
Other:	.5

Project Description:

Objectives: Innovate and implement improved methods for structural elucidation of organic molecules by means of nuclear magnetic resonance with emphasis on flexibility and convenience in selecting specific nuclei for study and the particular type of test performed.

Methods Employed: Develop and evaluate techniques 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. Develop and evaluate Rapid Scan Fourier Transform NMR techniques as an intermediate alternative to CW and pulsed FT methods. Develop and evaluate improved methods of RF generation for greater reliability and flexibility.

Major Findings: NMR techniques can be used to routinely obtain parameters of organic molecules beyond those previously available including nuclei other than ^{1}H and ^{13}C.

Significance: Technique offers unprecedented capability for elucidation of organic molecule structure and, in particular, the location of ^{13}C, et al, atoms. The high field strength of the superconducting magnet enables finer resolution than is obtainable with most other ^{13}C NMR apparatus.

Proposed Course: Modifications with a second superconducting magnet to enable experiments with full-time application to ^{13}C and related atoms.

Keyword Descriptors: Nuclear Magnetic Resonance, Fourier Transform NMR.

Honors and Awards: None

Publications:

Cohen, J.S., Bradley, R.B., Clem, T.R.: pH Dependence of the ^{13}C Spin-Lattice Relaxation Rate of the Carboxyl Carbon of Acetic Acid. J. Am. Chem Soc. 97: 908-909, 1975.

Wasylishen, R.W., Clem, T.R., Becker, E.D. Nuclear Magnetic Resonance Chemical Shifts of Some Monosubstituted Isothiazoles. Can. J. Chem. 53: 596-603, 1975.

Project No. Z01 RS 00010-04 BEI

1. Biomedical Engineering and Instrumentation Branch
2. Electrical and Electronic Engineering Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Measurement of Low Level, Rapid Chemical Reaction Rates by Laser Jump, Temperature Jump, and Stopped Flow Techniques

Previous Serial Number: DRS-BEIB-9

Principal Investigators: Michael Greifner, P. Boon Chock

Other Investigators: None

Cooperating Units: LC-IR-NHLI

Man Years:

Total:	1.0
Professional:	.75
Other:	.25

Project Description:

Objectives: Measure incremental parameter changes corresponding to important biochemical reactions over a wide dynamic range. Develop a system capable of detecting and displaying chemical reaction rise times of less than 100 nanoseconds.

Methods Employed: Light absorption and fluorescence are monitored with photomultipliers. Dynode switching provides wide dynamic range without impairment of frequency response, linearity or accuracy. High intensity pulsed light sources improve the singal to noise ratio of nanosecond absorption measurements. Signal averaging techniques recover low level signals otherwise obliterated by noise. Improved data processing reduces investigator evaluation time for a typical experiment from weeks to days.

Major Findings: Development of new stopped flow cell reduces dead time from milliseconds to microseconds. Allows researchers to record reaction rates previously masked in mixing time of two chemicals. Stopped flowmeter with increased sensitivity provides an order of magnitude improvement in absorption level detection over commercially available instruments. High sensitivity is required to detect especially low level enzyme reactions.

Significance: Improved system sensitivity and frequency response enable new exploratory investigations into the complex mechanisms of various enzyme functions. State-of-the-art instrumentation for temperature jump apparatus and stopped flowmeters can provide information on the incremental, fast interactions between antibiotics with enzymes or proteins.

Proposed Course: Complete evaluation of stopped flowmeter reaction times. Patent new stopped flow cell. Design and develop multi-mix stopped flow apparatus. Design and develop pulse unit for high intensity lamps. Test and evaluate temperature jump apparatus. Design and develop instrumentation for detection of fluorescence and absorption time constants of laser temperature jump.

Keyword Descriptors: Laser temperature jump, stopped flow.

Honors and Awards: None

Publications: Rhee, S.G., Greifner, M.I., and Chock, P.B. ATP Determination by Stopped-Flow Method. Journal of Analytical Biochemistry (in press).

Project No. Z01 RS 00011-02 BEI

1. Biomedical Engineering and Instrumentation Branch
2. Electrical and Electronic Engineering Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Electrical Safety Program for Clinical Center Patients and Patient Care Areas.

Previous Serial Number: None

Principal Investigator: Roland Corsey

Other Investigators: Corwin Strong, Anthony Vita, Walter S. Friauf

Cooperating Units: ADM-CC, SMS-BEIB

Man Years:

Total:	1.0
Professional:	1.0
Other:	0

Project Description:

Objectives: Establish a patient environment free of shock hazards and assure Clinical Center compliance with accreditation requirements regarding electrical safety.

Methods Employed: Establish NIH standards for the evaluation of commercial and non-commercial medical equipment; establish a testing program for all patient-contact electrical equipment; train nursing staff on the fundamentals of electricity and electrical safety; investigate and report on electrical accidents; conduct surveys of patient care areas to correct electrical hazards in grounding and power distribution; advise medical and nursing staff on new equipment purchases; participate in shaping of national, electrical safety standards.

Major Findings: The test program for medical equipment has uncovered instances of high electrical leakage current and poor grounding. Surveys of patient care areas have established the need for improved grounding and power distribution systems in critical care areas.

Significance: In critical care areas such as catheter laboratories, operating rooms and intensive care areas, the likelihood of accidental electricution has been reduced.

Proposed Course:

1. Train additional personnel on the fundamentals of electrical safety.
2. Extend the patient care area surveys to non-critical areas.
3. Extend the equipment testing program to test all new equipment before it is put into service.

Keyword Descriptors: Medical equipment, electrical safety standards, critical care areas.

Honors and Awards: None

Publications:

Friauf, W.S.: Test Equipment for Hospital Safety Programs. In Proceedings of the 27th Annual Conference on Engineering in Medicine and Biology, 1974, Philadelphia, Pennsylvania. Arlington, Va., The Alliance for Engineering in Medicine and Biology, 1974, Vol. 16, p. 496.

Project No. Z01 RS 00012-04 BEI

1. Biomedical Engineering and Instrumentation Branch
2. Mechanical Engineering Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Atraumatic Electrical Sensing in the Human Brain Cortex

Previous Serial Number: DRS-BEIB-12

Principal Investigators: Seth Goldstein

Other Investigators: Edward M. Schmidt, John Van Buren, John Oakley

Cooperating Units: LNLC-NINCDS, SN-NINCDS

Man Years:

Total:	1.5
Professional:	1.0
Others:	.5

Project Description:

Objectives: (1) Achieve stable electrode location with respect to an active neuron for reliable actue extracellular recording of human brain cell acitivity within the pulsating cortex at prescribed depths up to 0.5 cm with minimum tissue damage.

(2) Extend this technique to achieve intracellular recording from the pulsating cortex.

Methods Employed: A microelectrode is supported by a gas bearing assembly and held within the cortex at the desired insertion angle. A fine lead screw is actuated by gas thrust bearings to retain the "floating" action during electrode depth adjustment. An electrocortigram is simultaneously obtained from the adjacent area of cortex.

Major Findings: The device has been successfully used to obtain high quality extracellular human recordings for prolonged durations. Intracellular recordings using glass micropipette electrodes have been obtained from pulsating monkey brain cortex.

Significance: Single-cell electrical recording from cerebral cortex in humans has been limited because of difficulty in atraumatically eliminating the effects of cortical motion. This new method is expected to markedly improve the acquisition of valid information necessary to enhance understanding of brain function and epilepsy.

Proposed Course: Extension of the technique to intracellular studies in human brain cortex; refinement of technique and apparatus, if necessary; clinical applications; extension of device family for related types of measurement requirements.

Keyword Descriptors: Single-cell electrical recording, extracellular electrical recording, intracellular electrical recording, neuroelectric recordings.

Honors and Awards: Goldstein, S.R.: Electrode Insertion Device for Neuroelectric Recordings. U.S. Patent No. 3,841,310 (October 15, 1974).

Publications:

Goldstein, S.R., Schmidt, E.M., Bierley, F.L., and Bak, M.: A Gas Bearing Mechanism for Atraumatic Electrical Recording from Individual Neurons in Human Cerebral Cortex. Transactions of the American Society of Mechanial Engineers, Journal of Dynamic Systems, Measurements and Control (in press).

Project No. Z01 RS 00013-01 BEI

1. Biomedical Engineering and Instrumentation Branch
2. Mechanical Engineering Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: In Vitro Muscle Studies/Hypertrophy

Previous Serial Number: None

Principal Investigators: Edward Lebowitz, Lawrence Thibault

Other Investigators: None

Cooperating Units: CB-NHLI

Man Years:

Total:	1.0
Professional:	1.0
Other:	

Project Description:

Objectives: (1) To explicate the mechanism of cardiac hypertrophy in vitro using cat papillary muscle preparations.

(2) To investigate phosphorylation of papillary muscle in vitro (organ culture).

Methods Employed: Experimental apparatus has been developed in which cat papillary muscle is suspended in a constant temperature recirculating medium. PO_2 and PCO_2 of the medium are monitored as electrical stimuli are applied to the preparation.

Forces of contraction are measured concomitantly with gas tensions. Tissue growth is detected optically.

Major Findings: The preparations can be maintained viable for several days. This enables both phosphorylation and hypertrophy for adequate periods to reliably analyze both of these phenomena in vitro.

Significance: More detailed knowledge of hypertrophic mechanisms in cardiac muscle bears directly upon clinical diagnosis and therapy. Quantification of phosphorylation in cardiac muscle should contribute to the fundamental understanding of cardiac contractility.

Proposed Course: Improve and extend experimentation and analysis.

Keyword Descriptors: Hypertrophy, phosphorylation, organ culture, papillary muscle.

Honors and Awards: None

Publications: None

Project No. Z01 RS 00014-01 BEI

1. Biomedical Engineering and Instrumentation Branch
2. Mechanical Engineering Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Neural Trauma

Previous Serial Number: None

Principal Investigators: Lawrence Thiabult, Thomas Gennarelli

Other Investigators: None

Cooperating Units: Georgetown University

Man Years:

Total:	1.0
Professional:	1.0
Other:	.0

Project Description:

Objectives: To determine the effects of mechanical strain on nerve tissue function. To investigate the role of mechanical strain on nerve tissue membrane transport regulations.

Methods Employed: Equipment has been developed which permits controlled loads to be applied to isolated neural tissue. Mechanical stress and strain are measured concomitantly with electrophysiological parameters and associated biochemical changes.

Major Findings: Mechanical strain affects neural function. Compound action potentials are modulated by strain, both fully reversibly and irreversibly depending upon the level of strain. Biochemical changes, e.g. potassium movement, occur simultaneously, suggesting membrane permeability changes.

Significance: Elucidation of the effects of membrane strain on chemical transport processes contributes substantially to the basic understanding of fundamental physiological mechanisms.

Proposed Course: Refine and extend experimental and analytical techniques for nerve cells and other tissues.

Keyword Descriptors: Nerve tissue, neural trauma, membrane transport, mechanical strains.

Honors and Awards: None

Publications:

Gennarelli, T.A. and Thibault, L.E.: Functional response of the central nervous system to controlled inertial loading. In Proceedings of the 27th Annual Conference on Engineering in Medicine and Biology, 1974, Philadelphia, Pennsylvania. Arlington, Va., The Alliance for Engineering in Medicine and Biology, 1974, Vol. 16, p. 175.

Thibault, L.E., Gennarelli, T.A., Tipton, H.W. and Carpenter, D.O.: The physiologic response of isolated nerve tissue to dynamic mechanical loads. In Proceedings of the 27th Annual Conference on Engineering in Medicine and Biology, 1974, Philadelphia, Pennsylvania. Arlington, Va., The Alliance for Engineering in Medicine and Biology, 1974, Vol. 16, p. 176.

Summary of Program Activities July 1, 1974 through June 30, 1975

ENVIRONMENTAL HEALTH AND SAFETY PROGRAM

Dr. Rudolf G. Wanner
Associate Director

I. SUMMARY

1. Office of the Associate Director for Environmental Health and Safety

The transfer of the Radiation Safety Section, Department of Nuclear Medicine, Clinical Center, to the Division of Research Services as the Radiation Safety Program, took place on July 1, 1974. On the same date, the Safety Management Program transferred to DRS. On December 23, 1974, the Associate Director was appointed and given responsibility for the development of a well-integrated, comprehensive and centralized environmental health and safety program. Further progress toward centralization of functions was made on March 1, 1975, when the responsibilities for implementation of the National Environmental Policy Act (NEPA) were assigned to the Associate Director.

2. Environmental Services Branch

Two major program events caused a complete reorientation of activities in the Office of the Chief which, in turn, added to the workload of the Branch's two Sections. The first event was the organization of the Environmental Health and Safety Program within DRS.

The second event was the sudden increase of activities generated by the National Environmental Policy Act which escalated beyond predicted levels. Sixteen EPA effluent guidelines and several non-DHEW environmental impact statements were reviewed for the Office of the Assistant Secretary for Health, DHEW. Staff assistance was provided to the Division of Engineering Services in preparing the environmental assessment of the NIH Master Plan involving approximately sixteen construction projects.

Staff assistance was provided to the Assistant Director for Administration, NIH, in the Generic Analysis of all NIH programs. Staff also served on a task force of the Assistant Secretary for Health, DHEW, to develop proposed Departmental regulations and procedures for implementation of NEPA.

The national concern for employee health and safety was reflected in the ESB workload. Thirty-two employee requests were investigated concerning suspected hazards in their work places and three extensive surveys were conducted for requested Environmental Differential Pay. Three formal OSHA complaints were also reviewed and 108 other laboratory surveillance visits directly related to employee health were made.

The Branch concern for environmentally safe and sound facilities and equip-

ment continued. The major equipment problem remains procurement of Laminar Flow Biological Safety Cabinets. Two pathways were simultaneously pursued; one the continued development of a Qualified Products List and the other a proposal to the National Sanitation Foundation to develop a joint industry and public health supported standard and certification procedure. The Branch expended 80 mandays in the field performing acceptance tests in order to "speed up" the process. Staff worked cooperatively with individual investigators and other DRS staff in designing new or modified equipment in 24 instances. In addition, 66 Laminar Flow Biological Safety Cabinets were modified by an ESB contractor, and 118 chemical fume hoods are being upgraded cooperatively with the Division of Engineering Services. Fourteen major construction projects were reviewed continually to assure proper environmental safeguards.

Investigator requested consultation on procedures, equipment and basic information remains high. Approximately one manyear was spent in providing this information on a person-to-person basis. Eighty percent of the requests are from the intramural programs. In addition to the person-to-person consultations, mail requests for environmental health and safety information are mounting. This is reflected in the 300 plus mailings of the "Biological Laboratory Hazards" memorandum and provision of over 400 copies of the Biohazards Safety Guide to non-NIH investigators.

3. Radiation Safety Program

On July 1, 1974, the Radiation Safety Section, Department of Nuclear Medicine, Clinical Center, was transferred to DRS and designated the Radiation Safety Program. As a part of the consolidated environmental health and safety program and in an effort to improve current operations, an Acting Deputy Head of the Radiation Safety Program was appointed.

Major program efforts consisted of assurance of compliance with the regulations of the Nuclear Regulatory Commission, formerly the Atomic Energy Commission. The NRC issued seven licenses to NIH for the use of radionuclides. Possession of these licenses has greatly reduced the detailed problems of isotope procurement, but carries strict responsibilities governing use and ultimate disposal.

License renewals and amendments were obtained to permit the installation of two irradiators at the Clinical Center, one of 2400 curie capacity, the other of 500 curie. Physical and radiation problems encountered during and after the initial installation were satisfactorily solved.

The use of radionuclides for diagnostic, therapeutic, and research purposes is rapidly increasing at NIH. Although users of radioactive material are required, as part of the NRC regulations, to show proof of training in the safe handling of such substances, radiation incidents continue to occur. These incidents were in their majority due to human errors, thus preventable. Whenever physical factors were the cause, the Radiation Safety Program took prompt remedial action.

All authorized users of radioactive iodine were notified of an additional safety requirement. As of October 1974, no iodinations are permitted in hoods without charcoal filters. This requirement was met by being able to accommodate investigators in doing their iodinations in Building 21, which has a sufficient number of hoods with charcoal filters.

Under NRC requirements, the Radiation Safety Program is responsible for receiving, shipping and disposal of radioactive materials. An increase of 17% in the number of shipments received reflects the increased use by NIH investigators. To this workload were further added new regulations for receiving and opening packages, checking for contamination at the time of arrival. Consequently, manpower had to be provided on weekends and holidays.

Radioactive waste volume increased by 31% for the reporting period. Improvements in the waste handling area consisted of equipping the waste compactor with a HEPA filter to prevent radioactive aerosols from escaping into the work environment, and of installing a ventilated hood for the storage of volatile radioactive wastes.

Laboratory surveillance was maintained at a high level and carried out in the nearly 1500 areas where radioactive materials are being used. Strong emphasis was placed on the control of airborn radioactive substances. The number of air samples taken increased by 271% over the previous fiscal year. Investigation and remedial action took place where contamination was found.

Surveys of diagnostic, therapeutic and research x-ray units were made routinely and by request. In only one instance, a significant radiation hazard was found, an x-ray diffraction unit had to be shut until corrective action was taken. Shielding and other protective recommendations were made for other units where a hazard potential existed. In addition, 50 electron microscopes were surveyed for x-ray leakage.

Personnel monitoring for exposure continued as a routine activity. The number of users of film badges, or external radiation personnel dosimeters increased by 9% over the last fiscal year. An important improvement was the replacement of ring badges by thermoluminescent dosimeters.

The new dosimeters do not have to be worn on the hand, which makes them more acceptable to the user and less prone to water damage.

Investigators and workers working with certain levels of radioactive materials and specified substances are required to submit urine specimens for radioassay. The number of specimens assayed increased by 6% during the reporting period. The number of whole body counts, required by NRC of users of gamma emitting radionuclides, increased by 17%.

The Radiation Safety Program continued to provide training in the safe handling of radioactive materials. Over 850 individuals attended training courses, most of them the one-day course entitled, "Radiation Safety in the Laboratory."

4. Safety Management Program

Accident reports processing has been improved substantially by using a computer-based system. This system allows for a better data analysis and makes it possible to identify more precisely areas and activities with high accident rates. Consequently, preventive and corrective measures can be more accurately applied.

Accident investigations were conducted on a continuing basis by safety specialists. The NIH accident and injury reporting system continued during the reporting period to function on a recognized better level than most DHEW agencies. The close coordination of this activity with the Employee Health Service and other branches kept reporting close to 100%. Wherever necessary, remedial action was taken and recommendations were given. Fire prevention continued to be of major concern. A report, "NIH Fire Safety Posture", was completed. In it, each building on the NIH Bethesda location is described and discussed with regard to fire safety. The report provides a basis for eliminating fire hazards and for up-grading NIH facilities to prevent losses from fire.

In other accident prevention activities, efforts continued to survey the NIH work environment for compliance with Safety Standards and to examine potential accident producing situations. A concentrated effort was made to clear the corridors and elevator lobbies of the Clinical Center from excess storage of items. The photographic survey made to document unsafe conditions was made available to those responsible for and using the areas in question. Subsequent surveys showed some improvement, but not to the extent desired.

Following a request from the Division of Engineering Services, an "Industrial Safety Guide" was under development through the reporting period. It is one of a series of guide books issued by the Safety Management Program. The "Supervisor's Guide to OSHA" was prepared and distributed as a publication which identifies workplace safety standards set by the Occupational Safety and Health Act as they are applicable to the NIH environment. A "Safety Guide for Contract and Project Officers" is being reviewed and should be available by mid-FY 76. It will enable the Division of Contracts and Grants, OD, to include an up-to-date safety and health clause on contracts where applicable and required.

There was a wide range of training activities throughout the year. An important part is the new employee orientation for Clinical Center and ADA personnel. Safety specialists contributed with presentations and material to a variety of NIH training courses. In addition, three slide/cassette programs on Research Laboratory Safety, Safe Driving and Workmen's Compensation were completed. A new training course on Biohazards Safety is under development. This course may become a requirement for laboratory workers handling hazardous biological agents.

II. PROGRAMS

A. Objectives

To function as the central manager, coordinator and regulative authority over the Environmental Services Branch, the Radiation Safety Program and the Safety Management Program in support of the Director, DRS, to achieve Division objectives pertaining to environmental health and safety.

To administer a comprehensive environmental health and safety program for NIH.

To establish, interpret and monitor compliance with policies and standards which serve to maintain and protect health, safe working conditions and environmental quality for the NIH community.

To provide related technical, surveillance and training services.

B. Current Programs

The Associate Director supervises and coordinates the current programs of the component units. These include:

1. The establishment of standards, policies and guidelines for environmental health and safety, and their application.

2. Analysis of data and interpretation of regulations to develop solutions for the elimination of environmental, radiation and other safety hazards.

3. Implementation of the requirements of federal, departmental and agency regulations at NIH.

4. Laboratory support services for the NIH environmental health and safety program.

5. Training services as required by federal regulations.

6. Training development as specific needs at NIH are recognized and identified.

7. Surveillance for environmental, radiation and other safety hazards by a monitoring system.

8. Maintenance of registries of biological agents, radioactive materials, chemical carcinogens and other substances of known or suspected hazardous potential.

9. Review of Technical Reports on environmental health and safety from or for NIH, PHS, DHEW and other sources.

10. Maintenance of a reporting and information system on environmental health and safety at NIH.

C. Program Progress and Accomplishments

1. Office of the Associate Director for Environmental Health and Safety

The transfer of the Radiation Safety Section, Department of Nuclear Medicine, Clinical Center, to the Division of Research Services as the Radiation Safety Program, took place on July 1, 1975. On the same date, the Safety Management Program transferred to DRS. These were major steps of progress towards a consolidation of NIH environmental protection programs, with the Environmental Services Branch already in the Division.

On December 23, 1974, the Associate Director was appointed and given responsibility for the development of a well-integrated, comprehensive and centralized environmental health and safety program. Consequently, a considerable amount of time and effort was spent in the second half of FY 75 on the identification of existing problems and their solution within the newly established program. At the same time, continuity of services by the component units was maintained.

Further progress toward centralization of functions was made on March 1, 1975, when the responsibilities for implementation of the National Environmental Policy Act (NEPA) were assigned to the Associate Director. As Agency Environmental Officer, he is responsible for assuring NIH compliance with the Act. This includes preparing NIH policy and procedures, the receipt and processing of all technical review requests, and NEPA training activities. The transfer of NEPA responsibilities was another major step towards achievement of FY 75 objectives. It made it possible to coordinate and administer a comprehensive program, since the responsibilities for implementation of the other major requirements, the Occupational Safety and Health Act (OSHA) and the Nuclear Regulatory Commission (NRC), were already inherent in the program.

The Associate Director and selected staff are members of NIH committees relating to environmental health and safety, such as the Biohazards Committee, Radiation Committee, Infections Control Committee and their various subcommittees to provide technical advice to NIH research and service functions, to identify problem areas, to make recommendations of their solution and to review and recommend procedures and technical information for risk assessment and reduction of hazards.

A close working relationship was established with the Office of Research Safety, NCI, resulting in coordination of activities, such as the maintenance of a chemical carcinogen registry, inspection of biological safety cabinets and evaluation of laboratory containment facilities.

Past experience and repeated incidents of the same nature have demonstrated that the NIH research population is not always aware of special investigations carried out, remedial action taken and preventive recommendations made. The issuance and distribution of Environmental Health and Safety Special Invest-

igations Reports (EHSSI) was introduced. These reports will be prepared whenever a particular incident study of interest to the scientific community has been completed. The Environmental Health and Safety Program, through its component units, as a whole accomplished its objectives for FY 75.

ENVIRONMENTAL SERVICES BRANCH Vinson R. Oviatt, Chief

BRANCH PROGRAMS

A Objectives

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 a 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 potentially or actually generated at NIH and laboratory use of chemical carcinogens are major surveillance activities. Problems of noise, temperature extremes, and non-ionizing radiation are also investigated and resolved.

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.

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

The NIH Biohazards Safety Guide was developed and printed in two formats. A looseleaf edition permitting continuous updating as new biological safety developments occur has been distributed to NIH laboratory investigators. A perfect bind edition is available for investigators outside NIH, either as single copies furnished upon written request or in quantity from the Government Printing Office, Superintendent of Documents. The Guide will be published in Spanish by the Pan American Health Organization, Washington, D. C.

A new questionnaire for registration of microbial agents, tissue cultures and animals was developed and distributed to laboratory workers. Included in the questionnaire were requests for information on serum samples, their storage, concentration of agents, and volumes of fluids handled. The information obtained has been placed in a computer data bank. Readouts on microfiche cards are broken down into several categories; lists of individuals by name alphabetically and by social security number, listing by building and room number and listing of employees by item (microbial agent, tissue culture or animal).

A chamber for the decontamination of equipment has been constructed in Building 13. It will serve to sterilize equipment shipped to Surplus Property, Materiel Management, ODA; to instrument repair in the Biomedical Engineering and Instrumentation Branch, DRS; or to companies outside NIH, as necessary, to reduce any biohazards.

ESB assisted the Procurement Branch, Materiel Management, in making seven site visits to manufacturers of Class II Laminar Flow Biological Safety Cabinets for field testing and evaluation of cabinets for compliance with the NIH Specification. Test data and drawings were reviewed by staff personnel before each visit. Approximately eighty mandays were involved.

ESB initiated a request to the National Sanitation Foundation, Ann Arbor, Michigan, to develop performance standards for the Class II Laminar Flow Biological Safety Cabinet. As a result, members of the Biological Control Section are serving on a committee to develop the standards. Under this standard, the NSF would be responsible for carrying out necessary tests, publishing a list of approved models by manufacturer and controlling the quality of the equipment. Such a standard would reduce the commitment of ESB to Materiel Management, ODA, and shorten the delivery time of the cabinets.

Fourteen plan reviews of major building renovations at different stages of design were made. These included the renovation of Building 376, Fort Detrick, Maryland, to house the NINCDS slow virus program; the open bay area in Building 41; and Building 14D to house infected primates. Approximately fifteen draft reviews of such items as the Clinical Center Biological Disaster Plan, the National Sanitation Foundation's Standard for Biohazard Cabinetry and the Design Criteria for Viral Oncology Research Facilities were performed. Programs of Requirements for a large number of laboratories in Buildings 36 and 41 were also reviewed.

The number and subject of consultations with individuals at NIH and outside NIH are shown in the following table (each consultation averaged four hours:

		NIH	Outside NIH
(a)	Selection of Equipment	70	14
(b)	Proper Use of Equipment	11	1
(c)	Safety Devices and Biohazards Control	81	38

Modification of equipment included the development of a safety cabinet for handling biological agents and radionucleides; the modification of a Laminar Flow Biological Safety Cabinet to permit the handling of nude mice under sterile conditions; and in conjunction with the Biomedical Engineering and Instrumentation Branch, DRS, development of a ventilated containment hood for a freeze fractionator unit that will be used for work with scrapie virus.

Investigations were made in response to employee requests for evaluation of their work environment for hazardous conditions. These included microbiological assessment of air quality at the incinerator; review of laboratory procedures related to a possible laboratory-acquired serum hepatitis case; microbiological aerosol of NIHAC Waste Treatment Plant; and the NIHAC Primate Quarantine Facility.

An ESB contractor conducted a survey to analyze facility and systems adequacy of selected biological laboratories performing hazardous work.

Sixty-six Laminar Flow Biological Safety Cabinets were modified under contract to provide more air velocity in-flow at the work access opening, thus providing greater protection to the investigator.

A "re-certification" of the containment capabilities of the secondary barrier systems in the Building 36 Virology Suite was completed.

Seven thousand six hundred and thirty-eight (7,638) bacteriological tests were performed in the analysis of patient food and milk, potable water and waste water, and other environmental samples.

2. Industrial Hygiene

The Occupational Safety and Health Act of 1970 and subsequent Presidential Directives and Regulations published in the Federal Register generated a major workload for the industrial hygiene program. In one instance, a complaint was filed with OSHA via the Congress which required a special survey of working conditions in the NIH Power Plant.

Compliance with OSHA Regulations for control of chemical carcinogens in the NIH research environment continued to provide a major workload. A special in-depth survey of select animal rooms, laboratories, and other spaces reporting the use of chemical carcinogens was completed by an ESB contractor. This survey indicated that facilities and work practices require improvement to assure a safe and healthful work environment.

ESB reviewed and commented on proposed DHEW regulations to control chemical carcinogens in the research environment. This issuance should clarify the responsibilities of management, the worker, and safety personnel.

An ESB contractor completely surveyed and labeled 761 NIH chemical fume hoods. A large number of hoods (118) did not meet minimum standards. A cooperative project with the Division of Engineering Services to upgrade these hoods is being undertaken.

An independent evaluation was made of the recently designed NCI Laminar Flow Biological Safety Cabinet under contract to determine if its performance as a chemical fume hood is acceptable. Several potential problems and limitations on its usage were identified.

ESB, in cooperation with BEIB and the Radiation Safety Program, developed and tested a small hood for use within a standard chemical fume hood to remove gaseous radioactive iodine from the air before it is discharged to outside air via the existing exhaust system. The hood has a top mounted charcoal filter and blower. Its use should greatly reduce the number of reportable radioisotope release episodes.

Increasing concern about noise, both as a health hazard and as an interference in the work environment, resulted in a continued large workload in making the various evaluations and determining the required corrective measures.

An improved system for disposal of chemical waste at NIH was implemented this year. The NIH Fire Department carefully packages waste chemicals for disposal or recycling by a contractor. Remaining acids, bases, and a few special chemicals not disposed of by this means are disposed of at NIH in its special facility. Plans for upgrading the chemical packaging and disposal facility have been completed.

3. Hospital Environmental Control

This program continued on a low priority basis due to reduced staffing. A member of the Biological Control Section was assigned on a part-time basis to provide requested surveillance and monitoring services. The Operating Room Surveillance Protocol was reestablished in cooperation with the Surgical Nursing Service and the Infections Control Committee.

4. General Sanitation and Sanitary Engineering

Semiannual surveys were made of all GSI Cafeterias and Blind Industries and Services of Maryland snack bar facilities, both on and off the main NIH reservation. Brief visits were regularly made between surveys to assure continued high quality food service sanitation.

Continued monitoring of general NIH outside "grounds" sanitation, including loading docks, showed some improvement this year.

A new NCI animal care program is expected to improve animal room sanitation in the coming year.

Routine analyses of NIH and NIHAC central distilled water systems for specific resistance, and potable water systems for chlorine content and microbial quality were continued. In addition, copper analyses of the various distilled water systems were made quarterly and special analyses for selected high purity systems were provided as needed.

The Branch completed sixteen EPA Environmental Impact document reviews in support of the NIH Agency Environmental Officer.

Solid waste at NIH presented a major workload ranging from individual sanitation problems of improper waste disposal to reviews of building system plans. A major effort was mounted in terms of trials of paper bag and paper board box systems which will replace "G.I." cans when the Montgomery County Pathological Incinerator and the new NIH Back-up Pathological Incinerator are put into use in FY 76 and FY 77.

Monthly visits were made to the NIHAC to conduct sampling at the Sewage Treatment Plant, Broad Run and Lagoon #2. At the same time, waste water samples were also taken from the NIH storm drains and analyzed. Samples

were taken from NIH sewers for mercury analyses. The Branch was involved with the EPA in a special study of waste water effluent from the Clinical Center. Assistance was provided DES in selection of an engineering consultant who will develop plans to upgrade the NIHAC Waste Water Treatment Plant.

Air quality data from the Maryland monitoring trailer located on the NIH grounds was obtained from computer tapes supplied by the state and a program prepared to extract and report the pertinent NIH data.

5. Environmental Studies

An extended study of mold spores in the Clinical Center was initiated in collaboration with the Clinical Mycology Section, Laboratory of Clinical Investigation, NIAID. Of special concern is the relationship of aspergillus found in the air supply and aspergillus infections which have been seen in increasing numbers of immunosuppressed patients.

A study was completed of the biota of Broad Run at the NIHAC. The study involved an extended survey of "bottom life" of the stream above and below the Waste Treatment Plant. ESB staff was assisted by a professional marine biologist under contract with ESB.

An improved all-glass water still was developed to meet the high purity water demands of several investigators. The still has the unique capability of maintaining long "shelf life" sterility of the distilled water.

A study of the sterility, shelf life and various methods for packaging and sterilizing materials used in nursing units was conducted for the Pharmacy Department, Clinical Center.

6. Training

ESB continued participation with other NIH safety groups in developing laboratory safety posters which are displayed throughout the campus and are printed in the NIH Record. This is an effort to raise the safety awareness level of NIH employees.

The Quarterly Memorandum, "Biological Laboratory Hazards," is apparently meeting a need at NIH and in collaborative laboratories. The mailing list now exceeds 300 laboratories, including several overseas institutions. The Laboratory Infection Bibliography, developed under contract, will supplement the memorandum.

Nine presentations were made to separate intramural laboratories on proper laboratory practice. In addition, staff attended five Institute Laboratory Chiefs' Meetings to discuss the "Biohazard Safety Manual" and related matters. The sixteen-hour laboratory practice course was again presented to summer student employees. Four hundred NIH employees attended a series of training sessions on noise hazards and hearing conservation presented by the Branch.

Demand for Branch personnel as lecturers and speakers in all facets of environmental health and safety remained high. Of particular interest was participation in hearing conservation programs presented to two sixth grade Elementary School classes. Technical presentations were given to the Metropolitan Area Construction Safety Association, The American Industrial Hygiene Association, National College Health Association, 17th Annual Biological Safety Conference, Michigan Environmental Health Association, National Metropolitan Area Environmental Health Association, American Association of Laboratory Animal Sciences, Kentucky Hospital Association, American Society for Microbiology and the Tissue Culture Association. Staff also lectured at the NIOSH course, "Safety In The Laboratory."

ESB personnel received 913 hours of training at designated short courses or in classroom experience at colleges and universities. Two COSTEP trainees received on-the-job experience in the Branch.

D. Problems

The unplanned changing scope and direction of ESB's program is creating an adverse impact on allocation of resources. New laws and directives concerning the environment unpredictably superimpose a workload on ESB's basic service effort. Special studies and document reviews for OSHA and NEPA have deadlines precluding work planning that ensures NIH investigators receive the personal services that ESB is supposed to provide. Contracting with private firms has helped remove some of the routine workload; however, contracts require ESB staff time for preparation, to monitor the contractor, to evaluate the results of the contractor's efforts and to see that NIH acts on contractor recommendations. Hopefully, program plans of the NIH Environmental Health and Safety Program will solve this problem.

The procurement of Class II Laminar Flow Biological Safety Cabinets to meet the needs of NIH scientists is continually faced with long delivery schedules of one year or more. This hampers planning for biological research that require this equipment. In an effort to improve delivery schedules, ESB has provided review of test data, drawings and made site visits to manufacturers of this equipment to help eliminate problems with compliance to the NIH specification. Technical advice is being provided to the National Sanitation Foundation in their development of a performance standard for the manufacture of this equipment.

E. Program Plans

The Branch programs will be integrated into the overall scheme of the DRS Environmental Health and Safety Programs. A realignment of ESB staff into functional work units based on program demands and objectives in keeping with professional backgrounds is planned. A major decision must be made concerning manpower utilization considering the following factors: Technical assistance demands from NIH intramural and extramural investigators and programs, necessary surveillance and outside legal directives concerning environmental health and safety. Assistance is anticipated in training activities with consolidation of this activity into the Associate Director's office. Decisions regarding programming will be developed

jointly with the other DRS Environmental Health and Safety components to present a balanced program.

Contracting for services in FY 75 will continue at approximately the same level as in FY 75. It is expected that some analytical work will have to be contracted out for those materials of environmental concern that we cannot analyze in our own laboratory.

F. Publications and Patents

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RADIATION SAFETY PROGRAM Michael B. Musachio, Head

BRANCH PROGRAMS

A. Objectives

The objective of the Radiation Safety Program is to assure compliance with Part 10, Code of Federal Regulations, Chapters 19 and 20, conditions of licenses granted by the Nuclear Regulatory Commission (NRC), other applicable Federal regulations, and all policies established by DHEW and NIH in regard to the safe use of ionizing radiation so as to assist the NIH researcher in obtaining the maximum benefit from ionizing radiation while maintaining personnel exposure and the release of radioactive materials to unrestricted areas at the lowest practicable levels.

B. Current Programs

The program objectives were achieved through the following closely coordinated program areas.

1. License Activities

License activities include a continual review of the seven licenses issued to NIH by the Nuclear Regulatory Commission which permit the receipt, storage, use and disposal of radioactive materials in accordance with Nuclear Regulatory Commission regulations and standards. License applications, renewals, or amendments are prepared and submitted to NRC as necessary. A semiannual inventory of all radioactive materials is conducted to ensure that possession limits prescribed by the NRC are not being approached. New or proposed legislation or regulatory guidelines are thoroughly reviewed for impact on the Program. The administrative aspects of license activities are conducted in close coordination with the Radiation Committee and NIH Management.

2. Radionuclide Shipping and Receiving

The radionuclide shipping and receiving program covers all radioactive materials coming to or leaving the NIH reservation. All incoming shipments are checked for contamination, proper labeling and packaging, damage, and correct compound, isotope and activity. A check is made as to whether the individual ordering the material is authorized by the Radiation Committee to work with radioactive materials.

3. Radioactive Waste Disposal

The radioactive waste disposal program includes supervision and coordination

of the waste disposal program, including the waste disposal records. These activities are conducted under the conditions of License No. 19-00296-11, issued by the NRC.

4. Patient Therapies and Diagnostic Studies

Health physics support is provided to patients receiving therapeutic doses of radioactive materials and in some diagnostic studies to ensure that: they receive the dose prescribed, personnel exposures are as far below permissible levels as practical, and there is compliance with all applicable regulations and policies.

5. Radiation Safety Surveillance

The surveillance program consists of routine surveys in all laboratories where radioactive materials or other equipment capable of producing ionizing radiation are used. The areas are checked for compliance with the provisions of 10 CFR 19, 10 CFR 20, Occupational Safety and Health Act, and other policies and standards approved or promulgated by the Radiation Committee. Appropriate followups are made to secure compliance and in the case of repeated or highly hazardous conditions, the matter is referred to the Radiation Committee for appropriate corrective action.

6. Personnel Monitoring

The personnel monitoring program monitors radiation workers to determine radiation dose from external sources and internally deposited materials. This generally consists of film and thermoluminescent dosimetry, whole body counts and radioassays of urine samples. It involves record keeping of lifetime exposure histories, review and distribution of the results, and if necessary, appropriate remedial action.

7. Training

The training program goal and activities are aimed at making all radiation workers fully aware of the regulations and policies governing the safe use of ionizing radiation, to be cognizant of the hazards associated with its use, and to inform and motivate radiation workers with regard to use procedures and equipment which will minimize personnel exposures. The provision of such training is mandatory under the requirements of 10 CFR 19 and the Occupational Safety and Health Act.

8. Technical Assistance and Other Radiation Safety Services

The technical assistance program includes consulting services to personnel at all levels on all aspects of radiation protection. Space is available in Building 21 for handling high levels of activity. Shielding materials are provided, and portable survey meters are issued to laboratories. The survey meters are calibrated semiannually and repaired as needed. In addition, technical assistance is given to the researcher to effectively use ionizing radiation in the conduct of biomedical research. Supervision and assistance is also provided in contaminating accidents. Increasingly,

requests for technical assistance are received from NIH field stations, other components of DHEW, other federal agencies, state and local governments, universities, business organizations and concerned citizens regarding radiation safety.

C. Program Progress and Accomplishments

1. License Administration

License No. 19-00296-17 was amended to permit the installation of a 2,400 Curie Cs-137 irradiator in Building 10 for irradiating mice and conducting other in vitro studies. The unit is similar in size and design to the existing blood product irradiator in Building 10, Rm. 3B11. A survey was conducted at the time of installation. There was a question regarding structural stability of the legs. This was corrected and the matter was referred to the NRC for further investigation.

License No. 19-00296-12 was renewed and was also amended to permit relocation of the 500 Curie Co-60 irradiator from Building 10, Rm. B1-B52 to Room B2-B52, and after renovation it will be permanently installed in Room B2-B54. A radiation survey conducted after the initial move, required by a license condition, indicated radiation leakage. Additional shielding satisfactorily corrected the problem.

License No. SUB-985, which permits use of depleted uranium as beam defining devices in two linear accelerators, was renewed by the NRC.

On November 21-22, 1974, an NRC representative Division of Regulatory Operations, Region I, conducted an inspection of License No. 19-00296-10. The results indicated satisfactory progress in the areas of personnel training and the control of releases of radioiodine to the lowest practicable level. Occasional failure of investigators to collect breathing zone air samples during iodinations was noted. A reply was prepared outlining the administrative controls established to assure compliance with this requirement. Copies of the inspection report and the NIH reply were posted on bulletin boards in all buildings where radioactive materials are used as required by 10 CFR 19.

Semiannual accountability reports for the special nuclear material contained in the plutonium-powered pacemakers (License No. SNM-279) were submitted on a timely basis to the NRC.

Approximately 200 sealed sources were checked for leakage on a semiannual basis as required by License No. 19-00296-10.

There were several radiation incidents requiring NRC notification. The most significant were a 600 rem body badge exposure to a physician with the Metabolism Branch, NCI. The individual definitely did not receive this high a dose, however, no plausible explanation of this exposure could be determined. Similarly, a physician in the Nuclear Medicine Department, Clinical Center, was reported as having a 600 rem exposure to his finger badge. An explanation of this exposure could not be clearly determined and

it is speculated that the film was light struck.

An investigation was conducted as a result of an 86.4 nCi thyroid burden of I-125 in a Guest Worker, Clinical Endocrinology Branch, NIAMDD. The individual performed an iodination without adequate control of airborne radioactive materials and was exposed to an estimated I-125 concentration. The NRC was notified in accordance with the provisions of 10 CFR 20.405.

On October 22, 1974, a report was submitted to the NRC as required by 10 CFR 20.405. It resulted from an 84 nCi thyroid burden of I-131 reported in a Radiopharmacy Technician NM, CC. Breathing zone air samples were not available and there was a possibility that the maximum permissible air concentration may have been exceeded. A thorough investigation indicated that the most probable cause of the uptake was the result of an undetected contamination incident, the result of inadequate personnel monitoring. The calculated exposure to the individual was 943 mrem to the thyroid and 2 mrem, whole body exposure. The circumstances leading to the incident were carefully reviewed and appropriate steps have been taken to prevent a recurrence.

Routine air sampling indicated that a Research Associate, Laboratory of Immunology, NIAID, was exposed to an air concentration of I-125, twice the time modified maximum permissible concentration listed in Appendix B, Table I, 10 CFR 20, resulting from improper use of the iodine containment facilities. It was reported to the NRC in accordance with 10 CFR 20.405.

Quarterly Radiation Committee meetings were attended. Major considerations were: review and reaffirmation of existing policy on use of prophylactic thyroid blocking agents for radioiodine users; approval of new maximum permissible activity guidelines establishing maximum levels of various radionuclides which can be safely handled in the typical NIH research laboratory; review of experimental protocols for ionizing radiation; review of applicants for authorized use; review of radiation incidents; discussion of non-compliant areas; and general discussions of finding and requirements of the NRC.

2. Radionuclide Receiving and Shipping

In fiscal year 1975, a total of 9,163 incoming shipments of radioactive materials totalling 122.3 Curies was received. The total cost of such materials was $1,316,185.38. This represents a 17% increase in shipments over the previous fiscal year.

New procedures for receiving and opening packages, were instigated in response to new Nuclear Regulatory Commission regulations. The new procedures require checking and recording of contamination data on incoming packages and coverage for checking incoming packages for contamination on weekends and holidays.

3. Radioactive Waste Disposal

Again, the volume of liquid and solid radioactive waste continued to increase significantly. Six hundred and forty, 55-gallon drums and 10

boxes of radioactive waste were shipped out for burial by Hittman Nuclear Corp. under the terms of an agreement with the Department of Defense. This is an increase of 31% over last fiscal year.

Liquid scintillation vials are picked up weekly for disposal by burial under NIH contract 75-C-18 CC. During the fiscal year, 42,507 trays containing 100 vials each were disposed of, an increase of over 31% above the previous fiscal year.

A ventilated hood was installed in the waste handling area to be used for the storage and assay of volatile radioactive wastes.

The waste compactor was equipped with a HEPA filter to minimize the possible release of infectious or radioactive aerosols to the atmosphere or work environment.

4. Patient Therapies and Diagnostic Studies

Health physics support was given to the Clinical Center in administering therapeutic doses of radiation to 21 patients receiving up to 250 millicuries of I-131. This included radiopharmaceutical assays, assistance in administration of the material, instructions of patient and nursing personnel, contamination control, daily pickup and assay of urine, removal of contaminated linens and other materials, survey and decontamination of room on patient discharge, and records required by the NRC.

5. Laboratory Surveillance

Continued emphasis was given to laboratory and x-ray surveys during FY '75 to assure compliance with NRC regulations, OSHA requirements and NIH policies and procedures governing the safe use of ionizing radiation.

Laboratory compliance and contamination surveys were conducted by Radiation Safety Section staff and by Contract (NIH-75C-217-CC). The contractor conducted 1,489 laboratory surveys. Another 1,448 surveys were conducted by Radiation Safety Program personnel. The total figure is down by about 48% from FY-74 and is attributed to delays in awarding the laboratory survey contract, reduced manpower levels, increased use of radioactive materials, and increased NRC regulatory demands.

As a result of increased emphasis by NRC on the control of airborne radioactive materials, 2,226 air samples were taken from the work area and building exhaust systems, an increase of 271% over the previous fiscal year.

57 diagnostic therapeutic or research x-ray surveys were conducted by Applied Health Physics Inc. (Contract No. 74-C-4111-CC) and 30 surveys or followups were conducted by Radiation Safety Program personnel. In addition, 50 electron microscopes were surveyed for x-ray leakage by RSP personnel. One x-ray diffraction unit was found to constitute a significant radiation hazard and operations were curtailed until appropriate corrective action was taken.

6. Personnel Monitoring

Film badge processing (external radiation personnel dosimeters) has been under contract to the Radiation Detection Company since May 1973. Contractor performance has generally been satisfactory and excellent response has been received on requests for immediate film readings.

Individuals on film badges increased from 1778 to 1945, a 9% increase over the previous fiscal year. In addition, 43 employees of the Rocky Mountain Laboratory and two Arizona field stations are also covered on the service.

Thermoluminescent dosimeters were substituted for the film type dosimeter previously used in ring badges. The new dosimeters are more comfortable to the user and there are less difficulties with unidentified or water-damaged dosimeters.

The number of radioassays of urine specimens increased from 1190 last fiscal year to 1260 in fiscal year 1975, an increase of approximately 6%. Specimens were requested of individuals involved in radiation incidents and of those working with certain levels of radioactive materials in compliance with criteria established in the license applicaton and license conditons.

429 investigators and their staff working with greater than established levels of gamma emitting radionuclides were requested to receive whole body counts, a 17% increase over the previous fiscal year.

7. Radiation Safety Training

Continued emphasis was placed on Radiation Safety Training. A special effort was made to identify individuals working with radioactive materials not formally trained in the safe handling of these materials. A one-day course, "Radiation Safety in the Laboratory" was presented monthly with 502 NIH employees and 18 guests in attendance.

A two-week course, "Radiological Health for Radionuclide Users" was conducted twice with 119 persons in attendance.

Short one to two hour specialized training sessions were presented to several groups of NIH employees. One-hour presentations were made to Clinical Center nurses as part of their orientation program with 118 in attendance. A two-day training course, "Liquid Scintillation Counting Methodology", conducted by an equipment manufacturer was attended by 36 persons. A similar one-day training course was presented to 23 persons at the Rocky Mountain Laboratory, NIAID. Two separate presentations were made to five physicians and six nuclear medicine technologists of the Nuclear Medicine Department, Clinical Center, to emphasize the importance of using syringe shields and controlling personnel contamination. A one-hour session was presented to 11 members of the nursing staff of the Employee Health Service. A special training session was conducted for the medical and nursing personnel of the Health Catheterization laboratories in the Clinical Center regarding the hazards of x-rays and radioactive materials to which they may be exposed.

Three high school and college students working part-time were given basic radiation safety training in an hour session.

12 nurses on 9 West and eight nurses on 13 West received special instruction on handling patients who received diagnostic levels of radioactive materials.

8. Technical Assistance

The calculated exposures of Nuclear Medicine technologists to selected radionuclides in dosing syringes was verified using calibrated solutions and film dosimetry. Dry samples of the same radionuclides were also measured on an extrapolation chamber to simulate skin contamination. The data was necessary to clarify differences in theoretical calculations presented in the literature. The dose rate at the surface of a syringe loaded with 20 mCi of Tc-99m was found to be around 800 mrem per minute.

Problems with the commercially available syringe shields discouraged routine use by Nuclear Medicine technologists. To overcome these difficulties, several meetings were held with the personnel of the Nuclear Medicine Department, manufacturers, and staff of BEIB, DRS. As a result, a prototype tantalum syringe shield was designed and is in current use. An industrial firm has requested drawings and it is expected to be in commercial production shortly.

A prototype iodine containment facility and adsorption unit was designed by RSP personnel and fabricated by BEIB, DRS. Tests under actual operating conditions indicated it was effective in reducing the concentration of radioiodine released to the environment by 99.8%.

Several meetings were held with personnel from the Bureau of Biologics, FDA and representatives of ESB, DRS, in regard to the location and design requirements of a central iodination facility to serve Building 29. The final plans for this facility, which is to be located in Room 301, were completed and approved.

Final plans for the renovation of the wing of Building 10 (W.R. #342836) were reviewed by this office and were discussed with the Office of Licensing, NRC. Assistance will be provided in inspecting and testing the shielding. The 2,000 Curie Co-60 source will be moved under the supervision of Radiation Safety personnel.

The shielding requirements for Ga-67 and the hazards associated with Xe-127 were evaluated for the Nuclear Medicine Department.

The NRC referred a local hospital for assistance in performing dose calculations for a patient who inadvertently received an overdose of radioactive material.

Radiation Safety in the Physician's Handbook was reviewed for the Clinical Center.

Technical assistance was provided to several researchers with counting problems particularly with double and triple radioisotope labeling experiments; to several local hospitals, university, federal Government, commercial, and NCI contract Radiation Safety Officers on I-125 air sampling and control measures; and to the NHLI, Surgery Branch, in developing a counting method for four different radioisotopes to determine blood flow in three areas of the heart and the cardiac muscle.

Approximately 250 G-M portable survey meters were calibrated, batteries replaced and repaired, if necessary, semiannually by the Institute of Resource Management Inc. under contract NIH 74-C-1140-CC.

D. Problems

The most critical problem facing the Radiation Safety Program is the wide disparity between the available manpower resources and the workload required to provide essential services and to assure compliance with the provisions of 10 CFR 19, 10 CFR 20 and the requirements of the Occupational Safety and Health Act.

The imposed manpower ceiling of 18 full-time positions is exactly the same level deemed inadequate by the Chairman of the Radiation Committee in 1968 in his report to the Director of NIH. Since this time, it is conservatively estimated that the workload has increased by greater than 200%. The Radiation Safety Program is a captive of the increased use of radioactive materials as an essential research tool and increasingly more stringent regulations and guidelines of the Nuclear Regulatory Commission.

In 1972, NIH was requested to attend a meeting at the Regional Office of the Nuclear Regulatory Commission to discuss radiation safety program deficiencies and to provide assurances that corrective action would be taken. As a result of a much greater use of contracting, increased use of part-time personnel, increased use of compensated and uncompensated overtime, reorganization and reassignment of program personnel, improved work procedures, increased responsibility on authorized users, a realignment of program priorities, strong support of the Radiation Committee, and the personal sacrifice and dedication of Radiation Safety Program staff, there was a significant increase in the level of Radiation Safety compliance at NIH.

However, the early gains made in lessening the disparity between manpower resources and workload have been negated by program growth and the increasing requirements by the Nuclear Regulatory Commission. Unless there is strong administrative commitment to the principles of the Radiation Safety Guide and the necessary manpower is provided for the Radiation Safety Program to effectively accomplish its mission, the number of radiation incidents and the number of citations issued by the Nuclear Regulatory Commission can be expected to increase. Any significant license restrictions or the possibility of license revocation could be a source of considerable embarassment to the NIH and NRC. A commitment of unusually high levels of manpower might be required to cope with added restrictions, and the restrictions could seriously jeopardize the effectiveness of the intramural research program.

E. Program Plans

Further use of contract services will be explored. The feasibility and estimated cost of contracting the total radioactive waste handling program is under current review. Improvement in existing contracts as they expire is planned to assure high quality service.

High priority will be given to improved work procedures and more effective utilization of existing manpower resources.

Continued high priority will be given to radiation safety training, surveillance and compliance.

Employee development will be encouraged particularly Adult Education, Upward Mobility College, In-service training and continuing education programs.

Technical assistance will be sought to assure that data processing is fully and effectively used in program management.

High priority will be given to employee morale and the work of the DRS Human Relations Committee.

F. Publications and Patents

A paper entitled, "Radiation Safety in Nuclear Medicine" was presented at the Society of Nuclear Medicine in San Diego, California, June 11-14, 1974, and an exhibit by the same title won a bronze medal in the Technologists' Section exhibits.

SAFETY MANAGEMENT PROGRAM John R. Leach, Head

BRANCH PROGRAMS

A. Objectives

The primary objective of the Safety Management Program is to develop and implement a continuing and comprehensive effort toward creating and maintaining safe conditions, procedures, and attitudes as they relate to prevention of all types of accidental injuries, illnesses, or fires.

B. Current Programs

1. Accident Reporting, Investigation, and Analysis

In coordination with the Employee Health Service, CC, and other functional areas, the activity is designed to ensure prompt, accurate reporting of accidents; selected investigation of accidents to better define or identify contributing factors and/or to initiate corrective action to prevent a recurrence; and to apply analytical techniques to the accident experience to establish work priorities and to measure relative performance.

2. Accident Prevention

In addition to prevention activities resulting from accident investigation, this function specifically applies accident prevention principles, codes, or standards to the work environment. In addition to individual and corporate efforts of SMP staff, coordination is effected with other functional responsibilities, i.e. engineering design, construction, procurement, personnel, policy, transportation, etc.

3. Training and Promotion

A function of accident prevention, these activities represent a significant portion of total SMP effort. Primary direction is toward integration of safety needs with other training activities conducted throughout NIH. Promotional activities include distribution of general and specific material on hazards and their control to employees.

4. Compensation Officer

Not typically considered a responsibility of Safety Management, a valuable service is rendered to injured employees applying for compensation benefits. Additionally, the Compensation Officer serves as the focal point at NIH for information and advice on requirements of the Federal Employees' Compensation Act, and for education of administrative and supervisory

personnel in requirements and responsibilities under the Act.

C. Program Progress and Accomplishments

1. Accident Reporting, Investigation, and Analysis

Accident data was transferred from a manual to a computer system. Problems initially encountered in implementing the system, because more data was captured than in the present DHEW system, essentially have been resolved. DHEW machine-readable data can now be provided rather than source documents. More importantly, the SMP system provides a more comprehensive analysis on a timely basis. Such data will be passed on to the management and supervision of high accident producing activities to intensify prevention activities. The change to a computer system necessitated a change of reporting forms. Modification of a DHEW form was developed, approved, and put into service. After several months use, indicated changes were incorporated in a pending revision.

During the early part of the year, staffing permitted a significant expansion of accident investigation activities; however, personnel changes and losses among Safety Specialists have had a serious impact on this activity, although inspections of the major NIH field stations were completed. In spite of restrictions, staff effectively responded on accident reports. Subsequent actions have eliminated serious potential hazards. In light of continuing restrictions on employment, it will be necessary to increase the ability of certain supervisory personnel to adequately investigate a broader range of accidents.

2. Accident Prevention

A comprehensive report, "NIH Fire Safety Posture" was completed and forwarded. It covered all strengths and weaknesses of Bethesda campus buildings related to fire safety. It is anticipated that the report will serve as a basic guide to short and long-range upgrading NIH facilities against extensive loss due to fire. SMP continued to review and analyze Federal and other standards for applicability at NIH and continued to examine the work environment to identify specific instances of non-compliance with existing standards or potential accident-producing conditions. The examination effort was not as extensive as had been planned due to limited resources, although all major field activities were inspected during this year.

A request from the Plant Engineering Branch, later modified to include all of the Division of Engineering Services, directed considerable staff time toward development of an "Industrial Safety Guide." Much material has been developed to date, but there is a major problem of acceptable format. Construction/alteration review and approval continued.

Work was initiated, in conjunction with the Division of Contracts and Grants, OD, to develop an effective and acceptable "safety and health" clause appropriate in certain classes of contracts. DHEW policies requiring such a clause were originally issued in 1968 and changes such as the Occupational Safety and Health Act of 1970 have made certain of the provisions obsolete. Unofficially, the Director of Safety, DHEW, indicated

a willingness to consider any material developed at NIH as a Department-wide substitute for the existing policy. Although originally felt to have limited application, it now appears a broadly coordinated undertaking will result.

3. Training and Promotion

SMP representation was regularly included in all basic Supervisory Training conducted at NIH including routine new employee orientation for Clinical Center and ADA personnel. An eight-hour review of fire prevention codes was presented to approximately 40 DES engineering staff. In conjunction with the Training and Development Branch, Division of Personnel Management, safety material was provided for inclusion in secretarial training.

Changes in provisions of the Federal Employees' Compensation Act necessitated a major training and orientation effort for supervisory personnel in ADA and DES, as well as timekeepers in several areas.

Several releases of "Spot Hazards" were prepared and distributed.

The Supervisor's Guide to OSHA was prepared and distributed. It identifies workplace standards promulgated under the Occupational Safety and Health Act considered applicable to the NIH environment and outlines basic supervisory roles. This simplified description of complex standards will measurably aid efforts toward more complete compliance.

A "Safety Guide for Contract and Project Officers" was prepared in draft and reviewed by interested or affected staff. Work was temporarily halted when some questions associated with the basic provisions needed further development by the Division of Contracts and Grants. This project will be completed by mid-FY 1976.

Three slide/cassette programs were completed: Research Laboratory Safety, Safe Driving, and Workman's Compensation. Copies were provided to all major field locations and DHEW. The original artwork for the Research Laboratory Safety series was released to the National Safety Council for production and distribution through their facilities. This **is** the first time a cooperative undertaking with the Council has been brought to a satisfactory conclusion.

Training was provided to other government personnel for qualification as road test examiners on request by the Civil Service Commission.

Developing and establishing training needs identified by the NIH Biohazard Committee was initiated.

In addition to approximately 40 mandays of career training, the staff participated in presentations to personnel and/or students of the University of Maryland, Georgetown Medical School, University of Minnesota, and local research organizations.

4. Compensation Officer

The total claims for compensation filed during CY-1974 did not vary significantly from the previous year, but there was an atypical up-swing during the last quarter of FY-1974. This is largely due to the changes in the Federal Employees' Compensation Act which now permits continuing an employee in a pay status up to 45 days for loss from work as a result of a traumatic injury. Previously, "lost time" injuries involving less than 21 days, required a three-day waiting period in a non-pay status. Participation with the Division of Personnel Management in the "Hire the Handicapped Program" resulted in reassignment of several employees who otherwise would have been retired on compensation disability as a result of work-associated injuries or illnesses.

D. Problems

Many of the attempts to achieve compliance with applicable standards were thwarted by the lack of adequate research space. It is nearly impossible to provide the needed ventilation or building renovations without significantly disrupting ongoing research. While one may argue the corridor must be "clean," there is clearly a problem of diminishing returns if already congested laboratories are expected to absorb even more equipment. This problem is certainly not new to NIH and is subject to decision controls external to NIH. SMP will continue to seek alternatives which will provide improvement. Some of the larger, semiroutine labs may lend themselves to industrial work-flow techniques which typically have not been considered in the research environment.

A complete report of crowded and cluttered conditions in Building 10 was completed and forwarded. While some areas subsequently showed improvement, the overall impact of this project was not as effective as was hoped. Continued space shortages coupled with restricted manpower in the central services, seriously affects quick resolutions of this long-stand problem.

The present size of the staff does not permit adequate performance in the wide range of the responsibilities associated with the program. Staff shortages require a critical evaluation of priorities.

E. Program Plans

Computer-based accident data will be used as a more timely management information system than was possible under the manual procedure. Data analysis will also improve techniques for determining program priorities or areas of concentration.

A comprehensive analysis of safety education and promotion needs will be completed and translated into a coordinated program. A safety awareness program, "Life is Fragile" will be implemented.

In conjunction with the Supervisor's Guide to OSHA, a self-inspection program will be initiated as one means of extending compliance efforts. In addition, methods for possibly utilizing other personnel for certain

classes of inspection and reporting will be investigated.

Although Program objectives will be performed, the order of priorities and staff assignment will depend on the nature of the organization of the Environmental Health and Safety Program.

I. SUMMARY

The Library Advisory Committee met three times during the year. Dr. Philip McMaster, NIAID, was appointed Chairman in February replacing Dr. John S. Finlayson, BB, who had served in that capacity for several years. At the same time the Committee was enlarged to 17 members with representation from all I/D's.

On February 24, the Supreme Court, by a tie vote four to four, with Justice Blackmun disqualifying himself, affirmed without opinion the U.S. Court of Claims decision in the case of Williams and Wilkins vs. the U.S. that large-scale unauthorized photocopying and free distribution of copyrighted medical journal articles by NLM and the NIH Library are not copyright infringements.

A memorial for Dr. Henry W. Scherp was presented to the Library in the form of monies to be applied for the purchase of books and journals for the Library collection in subject areas of interest to NIDR.

A duplicate Library catalog was established on the Lower Level for use in proximity to the book collection.

Effective November 1, the Technical Services Section was reorganized into two units, the Monographs Processing Unit and the Journals Processing Unit replacing the Acquisitions and the Cataloging Units. Functions and duties were realigned to eliminate much duplication of procedures.

The Library became a member of the Ohio College Library Center's shared cataloging automated network system through the Federal Library Experiment in Cooperative Cataloging. On-line access to the cataloging data-base in Columbus will significantly contribute to more effective performance of technical services.

After inspection and analysis of major automated library circulation systems, the decision was made to adopt the University of South Carolina Library system. The designer of the system visited the Library as consultant to advise with the Library, DRS Management Analysis Office and the DCRT representative. The PDP 11/40 minicomputer to be used in the Library underwent tests in DCRT. The project is in progress to convert the Library's bibliographic records for books in the collection into machine readable form.

A nonprint collection was organized. Current audiocassettes, tapes and slides were added to previous microform holdings and are available for use in the Library or for loan. Newly acquired nonprint items are included in the monthly memorandum of additions to the Library.

The Branch Chief was named the Division of Research Services Chairman of the 1975 Combined Federal Campaign. The Assistant Chief served as DRS Coordinator of the Drive.

The Library prepared exhibits in connection with each NIH minority cultural week celebration for display in the outside corridor. The Branch Chief continued as a member of the NIH Minority Cultural Program Committee.

The Branch Training Program provided training for individual employee development and more effective use of the employee in the Library.

At the request of the National Cancer Institute, the Frederick Cancer Research Center at Ft. Detrick was visited five times during the year in relation to monitoring the library services provided by the contractor.

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

Technical Services

The Journals Processing staff procures journals by purchase, gift and exchange which have been selected as pertinent to the scope of the Library. The staff organizes and processes the journals for inclusion in the collection and maintains accession records using manual and automated systems. It also prepares completed volumes for commercial binding.

The Monographs Processing staff procures monographs and similar literature which have been selected as pertinent to the scope of the Library. The staff catalogs, analyzes for subject representation and processes these accessions for inclusion in the collection using manual and automated systems. It also maintains the Library's catalogs and prepares listings for the monthly memorandum of additions to the Library.

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; and makes assignments to locked study carrels.

The Stacks and Copy Service staff maintains the stacks, carrels, reference and Reading Room areas and shelves 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.

The Interlibrary Loan staff obtains from other libraries literature required by NIH investigators which is not included in the collection.

The Readers Services Section is responsible for developing, maintaining, and servicing a collection of library material in nonprint media pertinent to the scope of the Library and for providing equipment for its use.

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. Its staff receives inquiries at the Reference Desks in the Upper and Lower Level Reading Rooms and by telephone. Reference Librarians answer difficult reference questions and compile literature searches as requested and maintain the collection of basic Reference Books. Professional staff provides bibliographic assistance with experienced searchers to conduct requested medical, chemical and biological computer searches through National Library of Medicine's MEDLINE, Chemical Abstract's Chemical and Biological Activities (CBAC) and Biological Abstract's BioSciences Information Service (BIOSIS). Professional staff also selects books, journals and other literature for the Library collection by continually searching for literature pertinent to the scope of the Library.

Translating Service

The Translation staff provides oral, recorded and written translations as requested. Oral translations are emphasized in-house. Written translation service is provided through contractual firms with quality control maintained by the Library.

C. Program Progress and Accomplishments

Technical Services

A reorganization of the Technical Services Section was effective November 1, 1974. The Journals Processing Unit and the Monographs Processing Unit replaced the former Acquisitions Unit and the Cataloging Unit in order to eliminate duplication of procedures. Reorganization of functions and duties necessitated the rewriting of all position descriptions, posting of six realigned positions according to the Merit Promotion Plan and an intensive on-the-job training program for all Section employees.

The Library became a participant in the Ohio College Library Center's shared cataloging automated system through the Federal Library Experiment in Cooperative Cataloging. The Library's staff has access and makes input to cataloging and acquisition data in the computer in Columbus contributed by 700 or more libraries. Catalog cards for monographs are obtained through this system.

A duplicate Library catalog was established on the Lower Level near the monograph collection to provide needed information on location. Duplication of the cards was performed by a contractual firm.

The second edition of Current and Noncurrent Journals in the NIH Library was issued in 1974 (for administrative use). Arranged alphabetically by title, it includes for the first time complete holdings for all journals in the Library's collection. Due to the increased size of the second edition, the subject section of the first edition was eliminated.

Readers Services

Plans were completed for the implementation of an automated circulation system which will provide a more efficient service to the NIH community and better control of the Library's collection. Major automated library systems around the country were inspected and studied and after discussions with DRS Management Analysis Office staff and DCRT, it was concluded that the circulation system used by the University of South Carolina met the needs of the NIH Library. A PDP 11/40 minicomputer delivered the last of April was tested in DCRT prior to placement in the Circulation Unit. Mr. Kenneth Simons, designer of the system, visited the Library and made valuable suggestions especially relating to layout and system adaptation. The project of converting the Library's bibliographic records for books in the collection to machine readable format is underway. Mr. Michael Kremer, DRS Management Analysis Officer, and Mr. James De Leo, DCRT, are collaborating with the Library in implementing the system.

Installation of a new copier has improved the important self-service to NIH investigators and supporting staff.

The Library's collection of microforms including microcards, microfiche and microfilms has been listed by the nonprint Librarian. Guidelines for processing each type have been developed and nonprint items newly acquired and cataloged are included in the Library's monthly memorandum of new accessions. A modest number of current videocassettes and audiotapes have been acquired for use in the Library or for loan. An article on the service "NIH Library Offers Use of Microforms to Save Journal Shelving Space" appeared in the December 17 issue of the NIH Record.

Reference and Bibliographic Services

MEDLINE bibliographic search requests completed for calendar year 1974 amounted to 7220, representing an increase of 1715 searches (23.7%) over the number of searches performed in 1973. The number of requests for searches in the field of chemistry through Chemical Abstracts automated CBAC service and in biology and related subjects through Biological Abstracts BIOSIS system were substantially the same as for the previous year.

Translating Service

Requests for oral, recorded and written translation services continued at the same level as last year.

Training

The FY 1975 Branch Training Program provided individual employee development in the present job and more effective use of the employee in the Library. Employee training was completed in academic, professional, administrative, technical and in-Library courses and workshops. Two employees continued in the Adult Education program, one in the regular program, the other in a special training course. Three employees were enrolled in the NIH/FCC Upward Mobility College, one in Federal City College and one in the University of Maryland.

Exhibits

Exhibits prepared by the Library staff and displayed during the year covered the following topics: Radiation Safety and Nuclear Medicine (prepared by Radiation Safety); Asian-American Cultural Week; Spanish-American Cultural Week; World Population Year 1974; Black History Week; CANCERLINE Bibliographic Service; National Library Week; BEIB Service (prepared by BEIB); Native American Week; and Governmental Technical Reports in Relation to Biomedicine. Assistance was received from the Medical Arts and Photography Branch.

D. Problems

Downtime and poor quality of two of the photocopy machines continue as problems. One new machine has improved the situation; the acquisition of two additional machines replacing the old should eliminate this problem.

A careful examination and weeding of the monographs collection remain to be accomplished as soon as the Scope and Coverage Statement is completed.

The soaring cost of journal subscriptions has necessitated a reexamination of the Library's acquisitions policy. Second copies of some journals have been eliminated through the concerted efforts of the Library staff and the Library Advisory Committee.

E. Program Plans

Implementation of an automated circulation control system developed by the University of South Carolina will be completed. The new system, using a minicomputer and light pen technology, will provide more efficient service to Library clientele and improved control of the Library's collections.

An analysis of additional applications of the minicomputer to other Library operations will be completed with the assistance of the DRS Management Analysis Office and DCRT staff.

Continued expansion of the nonprint media collection is planned, based on specific requirements of NIH investigators.

Conversion of the subject headings used in the Library's catalogs for identifying and locating medical books and journals to the specialized

medical terminology used by the National Library of Medicine will be initiated. Library of Congress headings will continue to be used for material in other subject fields.

Passage of Bill H.R. 2223, which has been introduced in the U.S. House of Representatives, with present wording of Section 108 (g)(2), may create problems for libraries in interlibrary loan activities and in photocopying.

F. Publications

Dougherty, A.E.: A Professional Training Program for Nonprofessional Employees. Bull. Med. Libr. Assoc. 63:64-66, 1975.

National Institutes of Health Library: Current and Noncurrent Journals in the NIH Library 1974. (Internal Use only)

_____: Memorandum: Recent Additions to the NIH Library. Monthly (Internal Use only)

DIVISION OF RESEARCH SERVICES

Summary of Branch Activities July 1, 1974 through June 30, 1975

MEDICAL ARTS & PHOTOGRAPHY BRANCH Mr. Arthur F. Moore, Chief

I. SUMMARY

Demands for MAPB services increased approximately 25 percent in FY 1975. Physical consolidation of the graphics activities has satisfied the need for complete unity in graphics and statistical art preparation. Delivering finished work has accelerated. Medical illustration demands remain normal. Delivery of scientific photography has been reduced from 15 days to seven. Work has been done to establish graphic standards for statistical materials produced by the Branch. This is a forerunner of a continued drive to establish a unified visual communications system for the NIH. With new equipment and wider use of contract service, the Branch continues to broaden its skills and meet increasing demands for service.

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 professional services, 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 a 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, cine 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 artwork; technical, general and medical illustration; exhibit design; statistical drafting display charts, and medical models.

C. Program Progress and Accomplishments

1. Increased demands for services were made of the MAPB this year, climaxed by the intense activity created by the first NIH Alumni Homecoming, Public Open House, and the Bicentennial celebration.

2. In FY 1974, the General Illustration Section was renamed the Design Graphics Section and its three Units were reduced to two. However, the physical joining of the drafting and graphics operations did not take place until early FY 1975. The reorganization has been an unqualified success. The unit functions quickly and efficiently and is capably handling a constantly increasing workload; and unity of preparation has been accomplished. With the addition of electronic production of typography, the unit has been able to broaden its capabilities and reduce turn-around-time.

3. In the design area, there was a substantial increase in demand for services. As an example, 21 of the 23 major exhibits displayed at the Alumni Homecoming, Open House, and Bicentennial celebration were designed and construction was supervised by this Section.

4. The NIH demand for medical illustration remains normal and the Photography Section has been able to keep abreast of a 20 percent increase in service by use of new equipment, improved management and wider use of contract services. In FY 1974, delivery of scientific photography took 15 days, which was excessive. This year, turn-around-time, as forecast, has been halved.

5. The Branch, through extensive review, has identified the graphics design company with the concept and expertise to research and develop a coordinated visual communications system for the NIH. As a start, work has been done on establishing standards for graphically rendering statistical material (charts, graphs, tables) produced by the MAPB for publication and projection.

6. The Branch lost one person, increased its use of outside contract services by 26 percent, reflecting an increase in demand for services.

7. Thirty-two employees spent 1332 hours attending 43 training courses at a cost of $4,359.00.

8. The Branch has concluded one year of a two-year negotiated agreement with AFGE Local 2419. Relations have been smooth and without incident. The President of the Local, an MAPB employee, was elected for a second term.

9. An ongoing program of familiarization of Branch employees with EEO goals continues. Seven employees attended the two-day DRS-EEO Seminar in November.

D. Problems

There remains a critical need for the NIH community to allow more lead time for planning and execution of audio-visual material. All too often, the thoughtless and needless demands for rush jobs deprives the majority of NIH requesters the reasonable service they deserve. The Branch has extensive expertise in planning and conversion of raw data into effective multi-media presentations. This counsel is readily available in all areas of MAPB, or on location, and should be used earlier and more frequently.

E. Program Plans

The Medical Arts & Photography Branch will pursue the development and implementation of a systems approach to upgrading NIH visual communications. It will continue to improve, enlarge, and extend its services and will seek more effective ways to acquaint the NIH community with its skills. The Branch will continue to emphasize the necessity of early counsel and planning for optimum results.

DIVISION OF RESEARCH SERVICES

Summary of Branch Activities — July 1, 1974 through June 30, 1975

Veterinary Resources Branch — Dr. Robert A. Whitney, Jr., Chief

I. 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.

VRB service functions continued to increase to meet demands of expanding intramural BID programs, although Branch personnel ceilings have been reduced 18 percent over the last seven years. Increased service with decreased personnel was accomplished by extensive use of overtime, improved animal production methods, automated processing of glassware and production of media, limited use of temporary positions, and contracting.

The VRB rodent breeding colonies were designated as a World Health Organization collaborating center in recognition of their importance as an international genetic repository. A committee of the National Research Council reviewed this effort and recommended that it be removed from the Service and Supply Fund and be given separate funding. More breeding nuclei were provided this year to start new colonies outside NIH than have been requested in previous years. VRB colonies now serve as the genetic base for most NCI contract programs as well as the Frederick Cancer Research Center. The Catalogue of NIH Rodents was distributed internationally to over 1,000 researchers and specialists in fields of laboratory animal science. Twelve new rodent strains were added to the collection.

Open or complete disclosure formula rations for laboratory animal feeds developed by VRB permit competitive bidding for feed contracts, thereby reducing prices. Savings this year from conversion to open formula rations are estimated to be over $100,000 compared to the estimated costs of closed formula rations purchased under noncompetitive contracts.

Pathogen-free rabbit and guinea pig colonies were successfully initiated this year. Nucleus colonies of guinea pigs were hysterectomy derived and established in the barrier in a clean, conventional area. An autoclavable diet for guinea pigs was successfully tested. Hysterectomy derivations were completed to establish all VRB rabbit strains in a new nonbarrier facility. They were foster nursed by SPF Edgewood Arsenal rabbits.

A list of diseases for which NIH animals will be monitored was prepared. A system for carrying out the required tests is being developed. It is anticipated that notification of the microbial status of VRB animals will accompany all animals when shipped.

Total issues of VRB-produced rodents and rabbits remained about 500,000, comparable to FY 1974. The use of animals produced on contract decreased from over 130,000 in FY 1973 to about 70,000 this year.

The Perrine Primate Center, established by DRS in FY 1974, is now stocked with 350 rhesus breeders and 75 squirrel monkeys. Two contracts were awarded in June 1974 for additional rhesus monkey breeding colonies. By FY 1978, these three DRS breeding operations are expected to supply 1,000 rhesus and 100 squirrel monkeys annually for intramural research.

Tissue culture and media production increased 7 percent. Blood agar plates were issued at a 7 percent increase also. Glassware issues increased slightly over last year, as did the use of disposable supplies. Surgical activities and support stabilized at 800 procedures per year. Surgical facilities were relocated from Building 28 to Building 14E, increasing capacity for surgical procedures.

With Phase I renovation of Building 14D completed, isolated facilities are available for holding 1,000 nonhuman primates. Over 1,900 primates will be held in this building on completion of Phases II and III renovations.

The Branch continues to produce colony reared dogs and goats and maintains a canine blood donor colony. The long-term holding of ungulate animals under investigative study, and the procurement, quarantine, and conditioning of nonhuman primates, cats, and ungulates continues. Production in most areas is projected to be above FY 1974 levels. Emphasis is being placed on the development of breeding programs to supply quality animals for research. Burro breeding is being developed, and the foxhound colony is being enlarged. Random source dogs are no longer procured.

The Animal Disease Investigation Service was reorganized to ensure rapid response to requests. The number of calls made to the BID's remained at last year's level of approximately 180. They involved consultative, diagnostic, and therapeutic activities and included rodents, rabbits, primates, carnivores, and miscellaneous feral animals. The complexity of the calls are varied and involved all Institutes. This service has been well received by the BID investigators. It has been mutually beneficial to the investigators and the VRB professional staff by providing a means of communication between groups.

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 scientific community.

3. Provision of facilities and professional staff for experimental surgery to include postoperative care, roentgenography, and other special procedures.

4. Maintenance of animals during experimentation and collaborative research support.

5. Acquisition of information, through research, on animal health, care, and husbandry, and identifying animal models for human diseases.

6. Provision of consultative services on animal health and husbandry, use of experimental animals, tissue cultures, and bacteriologic media.

7. Establishment and supervision of production colonies of animals that are not commercially available to the NIH community.

8. Monitor procurement of animals, environmental housing, and biologicals used in biomedical research.

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 or random bred stocks. Germfree 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. Rhesus monkeys are bred to provide either timed pregnant females or neonates for intramural research.

2. Research Animal Procurement and Conditioning

Nonhuman primates, dogs, cats, ungulates, and feral animals are purchased and conditioned. These animals are not well defined genetically or microbiologically. Although they are of lower quality than NIH-bred animals, they are satisfactory for certain studies. These animals are quarantined prior to release for use in research programs. During the quarantine period they are given appropriate immunization, tested for a variety of infectious agents, and are treated medically as required.

A colony of blood group CEA 1, 2, and 3 negative canine donors is maintained for the production of normal canine blood for research use. Ungulate animals are maintained for the production of antisera, normal blood, or tissue specimens.

Facilities are provided for investigators to perform experimental surgery on ungulate animals. They include modern equipment for restraint, anesthesia, and physiologic monitoring under aseptic conditions. Postoperative care is provided and radiographic facilities are available.

Ungulates are held under observation for NIH investigators during investigative studies. Physiological sampling and specimen and collections are provided in association with these studies.

Noninbred rodents and rabbits 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 Building 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, and 3, formerly A-negative, blood for research use. Ungulates are maintained to produce a variety of antisera, blood, and tissue specimens for investigators.

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

The surgical facilities are primarily available for the use of BID investigators however, frequently, surgery is performed by staff veterinarians in support of BID programs in the development of surgical animal models. In addition, staff veterinarians provide surgical and clinical veterinary care to laboratory animals as an essential part of their responsibility to assure optimum health of these government-owned animals. Assistance to BID investigators is continuously provided in anesthesiology, surgical support, diagnostic radiology, and postoperative care of animals.

The number of surgical procedures has stabilized at approximately 800 per year and the facilities are being used at maximum capacity. An increase of 10 percent is projected next year since the surgery unit relocated from Building 28 to Building 14E, permitting more surgical space. The surgery unit maintains a 500 milliamperage radiographic unit with fluoroscopy which adds an improved service for research and clinical support to laboratory animal medicine.

Experimental surgery continues to be complex with numerous thoracic, cardiovascular, and abdominal procedures demanding a high level of technical support. Professional and technical assistance to BID investigators increased, which resulted in improved surgical animal models and veterinary medical care.

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, animal behavior, genetics, 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 on use of tissue cultures and microbiologic media are available.

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

1. Rodent and Rabbit Production

About 500,000 VRB-produced rodents and rabbits were issued to investigators, equivalent to the number produced last year. Guinea pig, rabbit, and hamster production decreased; rat and inbred mouse production remained unchanged, but there was an increased requirement for and production of VRB, noninbred mice. The total demand for VRB strains and stocks of mice was not satisfied because of limitations on current production levels due to personnel ceiling restrictions. Approximate animal issues were as follows:

Inbred mice	230,000
Noninbred mice	170,000
Inbred rats	10,000
Noninbred rats	25,000
Inbred guinea pigs	15,000
Noninbred guinea pigs	11,000
Hamsters	2,000
Rabbits	2,000
Germfree rats	550
Germfree mice	750

The Frederick Cancer Research Center (FCRC) continued to rely on VRB foundation colonies as the genetic base for their rodent colonies. Pedigreed mouse and rat strains were supplied from VRB barrier-maintained colonies. However, preparations were made to supply them germfree pedigreed stock. VRB has also assumed the responsibility of maintaining the genetic base for a variety of other NCI contract programs requiring germfree pedigreed stock.

A breeding nucleus of hysterectomy derived guinea pigs was established in a clean conventional area. A nucleus of guinea pigs was also established in the barrier. Foundation stock for the inbred strains will be hysterectomy derived and foster nursed by those animals to create pathogen-free foundation and expansion colonies.

Efforts continued to develop acceptable pathogen-free rabbits. VRB strains were hysterectomy derived and foster nursed in a clean conventional area by pathogen-free stock provided by Edgewood Arsenal. The rabbits remain free of the usual pathogenic organisms, including Bordetella and Pasteurella; however, mortality is excessive from nonspecific gastrointestinal problems. "Pathogen-free" rabbits were received from two other sources with the hope that their gastrointestinal flora would eliminate the enteric problem. The plan was thwarted because in both cases the rabbits were found to harbor pathogenic organisms.

Several changes were made in the conventional guinea pig colonies to increase production and enhance the quality. Major accomplishments were the elimination of vegetable supplementation to the inbred pedigreed colonies and the successful testing of an autoclavable diet. A shorter breeder rotation system was initiated and surveillance of breeder performance and replacement was intensified. Inbred guinea pig production began to increase in the last quarter following a decline earlier that contributed substantially to a revolving fund deficit.

The reorganization of the Small Animal Section was implemented with the establishment of a WS supervisor for each building, a cagewash unit, an ordering and contracts office, an administrative assistant, and a professional services group. This concludes a two-year process. It was immediately apparent following the change that the new supervisors and improved organization create a potential for greatly improving the effectiveness of the section.

2. Large Animal Production

The conventional canine breeding colony currently consists of 162 bitches and 12 dogs. Culling continues to be directed towards eliminating poor producers and animals with hip dysplasia. The inbred foxhound colony consists of one English and three American (two Walker and one Trigg strain) foxhound lines. Development of these lines is being directed principally towards providing a genetically uniform research dog for NIH investigators by eventually cross-breeding the lines.

A contract was established to breed and provide purebred foxhounds for NIH research at a rate of 500 per year. Availability of purebred stock from the NIH Animal Center and contract sources has eliminated the need to rely upon random source foxhounds and random source mongrel dogs as standard NIH research animals.

The cat breeding colony was terminated during FY 1975.

The goat breeding herd was expanded from 16 to 20 does and 2 bucks. Goats produced from the breeding herd will be held until approximately one year of age before issue.

3. Nonhuman Primate Production

The Perrine Primate Center was established by DRS in FY 1974. The facility has been managed by VRB since its establishment and is currently stocked with 350 rhesus and 75 squirrel monkey breeders. These colonies are planned to be maintained at 700 and 150 adult breeders, respectively. Two contracts were awarded; one to Hazleton Laboratories and the other to Gulf South Research Institute in June 1974, to establish 700 additional rhesus monkey breeders. As of June 1975, VRB expects to have supplied the necessary adult breeders to the contractors. By FY 1978, these DRS breeding operations are projected to supply 1,000 rhesus and 100 squirrel monkeys annually for intramural research.

Cutbacks in rhesus monkey exports from India in 1974 prompted VRB to initiate domestic breeding programs. Further cutbacks are expected in FY 1976. Procurement and availability of most New World monkeys is virtually nonexistent. Supplying monkey models for research appears to be largely dependent on domestic breeding resources. Further restrictions on monkey supply may warrant expansion of existing breeder colonies and establishing additional colonies to assure critical primate needs.

The timed-pregnant rhesus monkey breeding colony stabilized at approximately 260 animals of which 140 animals cycle regularly. The balance represents males, new breeders, and breeders received from contract sources that are available for recycling through contract breeding or intramural research. This colony was supplemented with a research contract which supplied 72 timed pregnant rhesus monkeys to complement the intramural colony production of 80 timed pregnant monkeys. A total of 152 timed pregnant animal models were supplied for intramural research use. A new 3-year contract is being implemented to provide up to 100 timed pregnant rhesus monkeys per year. In addition, three contracts were awarded during the year for timed pregnant baboons. Two of these contracts are fixed fee contracts in which the Government purchases the use of the timed pregnant baboons for intramural research and owns the fetuses and products of conception. The third contract established an NIH-owned colony of breeder baboons at the contractor's site and reimburses the contractor's costs for establishing a monthly supply of timed pregnant baboons for intramural research programs.

4. Research Animal Procurement and Conditioning

a. Rodents and Rabbits

The total purchase of rodents and rabbits from contractors further decreased from 132,500 in FY 1973 to approximately 70,000 this year. There was a decline in the use of noninbred mice, rats, and hamsters from contract sources, but a twofold increase in the use of contract rabbits. An itemized list of animals purchased on contract is as follows:

Rabbits--Dutchland	6,200
Sprague Dawley Rats--Taconic	27,000
Hamsters--Lakeview	6,500
Swiss Mice--Taconic	25,000
Rats--Charles River	2,500

In addition, VRB arranged for the Frederick Cancer Research Center to supply NIH investigators about 2,000 Hartley guinea pigs and over 6,000 inbred and nude mice. Arrangements are being made to initiate a Hartley guinea pig contract in which VRB will supply the breeding stock.

b. Large Animals

Requests for random source cats were 800 to 850 for FY 1975.

Approximately 484 ungulate animals were purchased, quarantined, conditioned and issued during FY 1975. In addition, some 50 domestic fowl, including ducks, chickens, and turkeys were utilized.

Rhesus (Macaca mulatta) monkey issues for FY 1975 are estimated at about 4,137 which represents an increase of about 626 over FY 1974.

VRB quarantined, selected, and delivered 1,304 rhesus monkeys to Gulf South Research Institute, Hazleton Laboratories, and Perrine as initial breeding stock for rhesus production colonies.

Other species of monkeys (M. fascicularis, M. arctoides, Erythrocebus patas, Saimiri sciureus, Cercopithecus aethiops, Aotus trivirgatus, and Callithrix sp.), contributed small numbers to the overall quarantine and conditioning program.

5. Tissue Culture and Media Production

Based on the first 8 months of FY 1975, the number of requisitions processed for tissue culture and media will total 14,000; a 7 percent increase over last year. The volume of media produced will be 70,000 liters of bacteriolgic media and 69,000 liters of tissue culture media for a total of 139,000 liters. This total represents an 8 percent increase over last fiscal year, and reflects for the first time in years an increase of bacteriologic media over tissue culture media.

Issues of blood agar plates of all types, including horse, sheep, and human blood plates will total 159,000 this year, a 7 percent increase.

In addition to blood agar plates, there will be another 406,000 plates of other types for a total of 565,000 plates for the fiscal year. This is a 7 percent increase over last year.

Issues of tissue culture cells as cell suspension will show a slight decrease of 3 percent with a projected total of 200 liters of suspension produced.

Tissue culture cell freezing and storage services continued to be a popular service with NIH investigators. A projected total of over 1800 ampoules of cells will be frozen this year and 2000 ampoules of cells maintained in the frozen cell bank to support research programs requiring this service. This represents a slight decrease over last fiscal year and reflects a tendency of the investigators to use their own storage facilities because of the convenience.

Renovations to provide filtered air to the room housing the automatic bottling system for media dispensing are scheduled for completion late in the fiscal year, almost a year after originally planned, due to contractor delays in correcting minor problems in the installation. Adaptation of a cartridge filter system for sterilization of tissue culture media just prior to the dispensing point of the bottling system is under test. The cartridge system is much more compact than the membrane system used for manual filtration and also allows for increased volume of production lots of media. This change, together with the filtered air to provide a cleanroom atmosphere, should extend the capability for sterile media dispensing to tissue culture, as well as bacteriologic media.

After a period of modification and testing an automatic labeling system has been synchronized with the conveyor belt on the bottling machine to make and apply labels to the bottles as they are filled and capped. This method is expected to greatly reduce the time spent in manual application of labels to the bottles.

6. Processing Glassware, Animal Cages, and Miscellaneous Items

Glassware issues to the Institutes and Divisions projected through the end of the fiscal year will total about 8,429,000 pieces; a slight increase over last year. A total of 294,000 cages, racks, and associated pieces of equipment will be processed.

In order to provide adequate coverage on the night shift as well as the day shift, an additional employee was trained in the regeneration process required for the large, mixed bed deionizer. This should prevent the occasional call back time required in the past when the water quality dropped in specific resistance during the evening hours and required someone from the day shift to return for regenerating. A Wilbur terminal was installed in the Glassware Unit to enable direct input for the OFM billing reports and correcting errors generated by faulty information appearing on glassware order forms.

A new form for glassware orders and issues was introduced this year. This new form will provide a record of not only glassware issued, but items of glassware ordered, and some indication of how well the Unit is meeting the demand for glassware. The percentage of each item ordered and supplied by size and type of glassware should provide useful data.

A workload measurement study was conducted in the Unit this year with the help of the Management Analysis office, to calculate new average processing times for individual types of glassware. As a result of this study, several workload improvement recommendations were made and are being implemented. As a preliminary step, a large glassware drying unit, which is no longer required, was removed to create space for installation of a proposed conveyor system to be adapted to the M-2 washer. This conveyor system should reduce the manual handling of glassware baskets as they are filled and transported to the machine for washing.

7. 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, which consists of 258 dogs, produced 3,500 units (1 unit = 500 ml) of blood.

Biologics production from ungulate animals is about the same as during FY 1974. Projected production includes 1400 liters of ungulate blood for the year. The size of the ungulate herd being maintained for all purposes increased from 550 to 610 during FY 1975.

8. Genetic Repository and New Animal Models Program

VRB rodent colonies were designated as a World Health Organization collaborating center in recognition of the importance of this collection of animal models for biomedical research. The one other collaborating center designated was the Laboratory Animal Center of the Medical Research Council of Great Britain. The director of that center served as a consultant to VRB during a WHO sponsored visit this year.

A committee of the National Research Council studied the VRB small animal program. It concluded that the repository effort should be separately financed through management funding and not supported by inflating the price for animals. About $500,000 was determined to be the annual cost for maintaining the repository.

A Catalogue of NIH Rodents was published and distributed to about 257 NIH investigators and 765 researchers and specialists in animal science worldwide. It describes characteristics of the over 100 strains and stocks of rodents and rabbits maintained. In addition to supplying animals for intramural investigators, breeding nuclei from these colonies serve as a resource for the international biomedical research community as many of the stocks, strains, and substrains are not available elsewhere. Over 300 investigators were provided with litters of inbred animals to start colonies. This is a twofold increase over FY 1974. Also, several hundred noninbred animals were provided as breeding stock. Several commercial producers were also provided with breeding stock. Requests were particularly numerous for the rat with diabetes insipidus and hypertension, inbred NZB and NZW mouse strains, and inbred guinea pigs.

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. Twelve new strains were added to the repository at the request of NIH investigators. They are:

Mice	Rats	European Giant Hamster
BALB/cCRN	WFU/CrN	Guinea Pig
A.θAKR	SHRSP/A1N	
Dwarf (dw)	SHRSP/A3N	PCA (passive cutaneous anaphylaxis)
Motheaten (me)	Corpulent (cp)	
Dystrophic-2 (dy-2)		
BDL-ky (kyphoscoliosis)		

9. Experimental Surgery, X-ray, and Related Activities

a. Building 14E and 28 Facilities

The surgical facilities are primarily available to B/I/RD investigators; however, surgery was frequently performed by staff 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.

The number of surgical procedures stabilized at approximately 800 per year and the facilities were used at maximum capacity. An increase of 10 percent is projected next year since the Surgery Unit relocated from Building 28 to 14E and will provide more surgical space. The Surgery Unit maintains a 500-milliamperage radiographic unit with fluoroscopy which adds an improved service for research and clinical support to laboratory animal medicine.

b. Animal Center Ungulate Surgery

Activities in ungulate surgery declined. Projects utilizing sheep for intrauterine fetal surgery have ceased. Surgery was utilized for porcine skin transplantation procedures, collection of fetal pig serum, and to treat a variety of clinical conditions. Miniature swine breeding is continuing to develop four inbred lines of immunologically distinct animals. Five sows produced progeny this year.

Radiographic procedures increased from 250 exposures in FY 1974 to 420.

10. Experimental Animal Holding

a. Primates

Renovations for Phases II and IIIof Building 14D will be awarded to contractors before the end of FY 1975, and estimated completion date is 12 months after the award date. This renovation is a joint program between DRS and BoB which will provide a centralized research primate holding facility. The new renovations are designed to permit infectious disease studies, provide a safe working environment for personnel, and minimize cross-infection among primates. The total capacity of the facility, including the conventional primate facilities of Phase I renovations, will establish one of the largest primate research facilities in the country with a maximum primate population of over 1900 animals.

b. Large Laboratory Animals

The research holding facilities of Building 28 has increased its scope of research support by greater diversity of animal species including: dogs, cats, miniature swine, goats, sheep, and other large laboratory animals. In addition, new collaborative DRS research programs with NCI and NHLI were initiated. Continued use of a contract to hold dogs off the Bethesda campus allowed improved utilization of space for studies requiring constant investigator attention. The atherogenic diet study in dogs in Building 14E will relocate to Building 28.

The population of research animals in this facility averages approximately 360 per month. Additional research animals, requiring only infrequent investigator manipulation, are maintained on contract. This has permitted a more suitable animal density population per kennel to achieve better animal care

management. Recent renovations of two large animal wards in Building 28 significantly improved animal welfare, and improved the research environment and employee working conditions.

11. Animal Nutrition

VRB-developed, open formula rations continue to be used throughout the NIH. Purchase arrangements were made through competitive contracts for three new open formula rations; autoclavable rations for rats and mice, rabbits and guinea pigs. Based on current prices, the open formula rations purchased under competitive contracts cost 36 percent less than the closed formula rations purchased under noncompetitive contracts. When this price differential is applied to the open formula feeds purchased under competitive instead of noncompetitive contracts, an apparent savings of approximately $115,000 will be realized by NIH during the contract year.

The NIH, open formula ration for conventionally reared rats and mice was adopted as a standard reference ration by committees of the American Institute of Nutrition and the National Research Council.

The proximate nutrient, calcium, and phosphorous concentrations in NIH contract animal feeds were monitored. This information is useful in demonstrating to investigators the variation in nutrient concentrations among production batches of a given ration.

The contract to conduct nutrient analyses on experimental rations was expanded to include assays for various feed contaminants. At least one sample collected from all animal feeds purchased under NIH contracts has been assayed for heavy metals and pesticide residues. To date, the concentrations of these potential contaminants have been either undetectable or within acceptable ranges.

An open formula, autoclavable ration containing 18 percent crude protein is being fed to SPF production colonies of rats and mice on a trial basis. There has been no apparent decrease in the reproductive performance of animals fed this ration as compared to animals fed a commercial ration containing 24 percent crude protein. Similar results were obtained under experimental conditions.

12. Animal Health

a. VRB Animal Health Problems

A pinworm eradication program was initiated in conventional mouse production colonies. Piperazine was proportioned into the drinking water continuously for a one-month period while the buildings were being disinfected with an iodophor to destroy pinworm ova. Following this, treatment was alternated every other week and untreated, helminth-free sentinal animals placed in the rooms were monitored to determine whether total eradication was achieved. Plans were made to use dichlorvos to treat a mite infestation discovered in inbred mouse production colonies.

An outbreak of Tyzzer's disease occurred in C-wing rabbits early in the year. Tylosin in the drinking water was found to be therapeutically effective, stopping the outbreak after only 20 deaths. A major epizootic may have been averted since the C-wing rabbits have been free of the disease and are probably highly susceptible. Inasmuch as the causative agent is a spore former, it is considered likely that it will gain entrance into the colony again. The indirect fluorescent antibody technique has been used in preliminary studies of the natural history of the disease and to demonstrate antigenic similarities between the causative agent in rabbits and the agent recently isolated from horses. Because of shortcomings of this method for serologic survey work, several antigens are being tested in the development of a complement fixation test. As more is learned about the antigens, hopefully, the preparation of a vaccine will become possible.

Although Tylosin was effective in treating C-wing rabbits for Tyzzer's disease, its use appeared to precipitate a severe outbreak of enterocecocolitis which resulted in 108 deaths in one month. Enterocecocolitis has been present in C-wing rabbits for several years, causing an average of about 20 deaths per month. Culture results have indicated that it is caused by imbalances of intestinal microflora, particularly overgrowth of E. coli, which may be stimulated by the use of certain antibiotics such as Tylosin. It is postulated that these cesarian-derived rabbits are "too clean" and that additional bacteria are needed to broaden the intestinal microflora to provide effective competition for E. coli. For this reason, attempts were made to acquire specific pathogen-free rabbits from other sources to act as microfloral donors. Two attempts failed. The rabbits from one source had coccidiosis and those from another source were infected with Bordetella bronchiseptica.

The barrier-maintained mouse colony suffered its worst recorded outbreak of hemothorax. The outbreak lasted 2 months. All strains of mice were affected, and virtually all males over the age of 6 months were lost. As previously described, this disease appears to be a noninfectious condition of male mice characterized by myocarditis and prolonged clotting time. The cause of the sporadic outbreaks is not known. It has been postulated that some noxious substance, which secondarily increases the mouse's requirement of vitamin K, periodically finds its way into the ration. Supplemental vitamin K was added to the diet of the barrier mice but, unfortunately, this was at about the time the outbreak was subsiding so that the effect was impossible to evaluate. A beneficial effect was suggested, however, by the finding that only a few scattered hemothorax fatalities occurred in the 9 months since the supplemental vitamin K was started. The results of a recent pilot study indicate that the disease can be reproduced by feeding mice excessive vitamin A, which is known to increase the mouse and rat requirements for vitamin K.

The incidence of Johne's disease in goats increased. Fecal culturing for Mycobacterium paratuberculosis in the goat herd was continued during FY 1975. The incidence of Johne's disease declined from 21 cases in 1972 to two in 1973 and rose to five in 1974. Culturing will be continued indefinitely on a semi-annual basis. The disease is considered difficult to eradicate since the causative organism is relatively stable in the environment and its detection in animals incubating the disease is laborious. Goats may incubate the disease for several years before fecal cultures reveal the causative agent. Current

information indicates that Johne's disease is endemic in Maryland and that anyone buying goats on the open market will, in time, purchase animals with the disease.

The monkey breeding facility at Perrine, Florida, experienced an outbreak of progressive debilitating disease characterized by alopecia, acneform dermatitis, facial edema, squamous metaplasia in palpebral glands, hypertropic gastritis and death. Many of the clinical and histopathologic findings are compatible with hypovitaminosis A which, in rhesus monkeys receiving adequate amounts of dietary vitamin A, points to the possibility of toxic exposure to chlorinated hydrocarbons. Preliminary chromatographic analysis of tissue specimens from affected monkeys indicatesthat the toxic substance may be polychlorinated biphenyls (PCB's). PCB's are known to be rapidly toxic for rhesus monkeys in very low dose, 2 ppm in feed, and to produce similar lesions to those occurring in the Perrine monkeys.

Brucellosis testing is now performed annually in the swine and goat herds and in the sheep flock. All new acquisitions are tested during the quarantine period. No new cases were observed.

Urolithiasis was diagnosed in 12 goats (wethers) and six sheep (wethers). Three of the cases were fatal. The disease is thought to be associated with the exclusive feeding of grain concentrates, and may also be related to mycoplasma infections.

b. B/I/D Animal Health Problems

No large-scale epizootics such as mouse pox occurred in the B/I/D's this year. Examples of lesser problems included the occurrence of cervical lymphadenopathy in rats purchased on contract from a VRB contractor. The rats showed facial edema and failed to sustain Walker carcinomas. Autopsies on animals on the day of arrival in the laboratory revealed tracheitis and pronounced peritracheal lymphadenopathy. Pasteurella pneumotropica was isolated from the lymph nodes in six of eight animals cultured. The commercial colony was found to be serologically positive for Sendai virus, which is reported to augment the pathogenicity of P. pneumotropica infections. The company that produced the rats was required to correct the problem.

Assistance was extended to the B/I/D's also in the form of participation in collaborative research of several types, including hepatitis A & B transmission studies and studies of the effects of thymus- and bone marrow-derived lymphocytes on the pathogenesis of autoimmune disease in NZB mice.

13. Animal Disease Investigation Service

The Animal Disease Investigation Service answered 182 calls for assistance from the B/I/D's, or approximately the same number as last year. These involved consultative, diagnostic, and therapeutic activities. Animal species encountered were varied; including rodents, rabbits, primates, carnivores, and miscellaneous feral animals. The complexity of the calls also varied and involved all Institutes. Ninety-four of the investigations required supplemental pathology exams, 38 required microbiologic testing and 30 utilized

clinical pathology tests. This service has been extremely well received by B/I/D investigators. The service continues to be mutually beneficial to investigators and to the VRB professional staff.

D. Problems

Problems of animal disease are referred to in Part II, C, 12, a and b.

It now appears that the program initiated in 1968 to hysterectomy derive foundation colonies for all mouse and rat strains and stocks may not result, as expected, in the issuance of strictly pathogen-free animals to investigators. Although VRB barrier colonies remain uncontaminated for periods beyond expectation, the production colonies in conventional facilities were reinfested with internal and external parasites. Whether this was due to inadequate decontamination of facilities or a recontamination by a flourishing resident feral rodent population in the Building 14-28 complex is undetermined. Perhaps the design, construction, location, state of repair, and age of the buildings housing the present rodent colonies make it unrealistic to expect maintenance of a totally pathogen-free status of rodents following hysterectomy derivation. The facilities for rodent production are not barriers and are in close proximity to quarters for primates, sheep, and carnivores. Nonetheless, the effort to produce pathogen-free rodents will continue.

Some General Schedule (GS) Biological Laboratory Technicians working in the barrier are being paid less than some Wage Grade (WG) animal caretakers in conventional colonies performing less technically skilled work. The conversion of these employees to GS pay scale has worked to their disadvantage because of large WG pay increases. General Schedule technicians in the gnotobiotics unit and professional services staff, as well as the barrier, are inadequately compensated compared to WG employees. Unless the situation is corrected, recruitment of qualified employees into these areas will become impossible. Employees presently assigned these jobs are becoming interested in leaving or returning to WG animal caretaker positions.

E. Program Plans

Consideration will be given to requesting approval to establish a committee to advise VRB whether strains warrant being added to or dropped from the genetic repository, as recommended by the NRC committee reviewing NIH rodent activities.

A computerized record keeping system is being developed by VRB personnel and the DRS management analysts. Primary emphasis is on collection of data on rodent breeding performance. Mating and mortality data will also be collected.

An expanded program of genetic monitoring is necessary to provide adequate safeguards for the integrity of inbred strains. A routine testing program involving test matings, histocompatability testing, and mandible analysis will be established.

Present obsolete cages for rabbits and guinea pigs will be replaced as soon as funding is available and an acceptable design tested. The evaluation of

a semiautomated cage for rabbits continues and plastic cages for guinea pig harems are being tested.

The disease surveillance program for the rodent colonies must be enhanced to ensure prompt detection of disease through VRB monitoring. The effort to free all rodent strains and stocks of disease through hysterectomy derivation will continue. Methods will be developed for applying this practice to guinea pigs and rabbits. This requires a cooperative effort in areas of nutrition, microbiology, and genetics.

An effort will be made to survey requirements of investigators for rodents beyond the capability of in-house production and to initiate new contracts to meet these needs where possible, using VRB colonies as the genetic base.

Studies to define the major nutrient requirements of different species and strains of inbred rodents will continue. Efforts will continue to develop open formula rations purchasable through advertised contracts to replace closed formula rations purchased through negotiated, sole source contracts.

It is expected that the Carnivore Unit will be reorganized before the end of FY 1975; canine long-term holding will replace random source dog activities. A canine socialization program was initiated and will be developed for continuing application to colony reared dogs. Continued expansion of the canine breeding colony by purchase of quality dogs from outside sources will be pursued. Contract production of purebred foxhound puppies (approximately 500/year) will be continued into and beyond FY 1976. Plans are being developed to create outdoor housing space for growing puppies. This program will permit purebred production to expand by 200-300 per year.

The dairy goat and burro breeding herds will be expanded during FY 1976. About 15 jennies will be bred in FY 1975 and are expected to foal in the spring of FY 1976.

Health surveillance of ungulate herds and flocks will be expanded and intensified during FY 1976. Emphasis will be placed on identification and containment of equine diseases because of implementation of a burro breeding program.

Further definition of the blood groups of dogs in the canine donor and breeding colonies will be undertaken when "typing" anitsera becomes available from outside sources.

Contract primate breeders will have been supplied all necessary breeding stock before the end of FY 1975. Thereafter, efforts will be directed toward supplying the contractors with replacement rhesus breeding stock on a continuing basis. Animal Center programs will be readjusted in order to provide holding space for young monkeys produced by contractors.

Improvement of leased property, consisting of some 200 acres of pasture and several buildings adjacent to the Animal Center will provide space for programs utilizing sheep, swine, and burros. Partial improvement of a pole barn and installation of fences enclosing about 40 acres will permit expansion

of sheep activities (100-200 head) early in FY 1976. Expansion of swine breeding/holding activities is anticipated late in FY 1976 with the erection of a temporary farrowing/holding structure.

Within the limits of current manpower restrictions and space limitations, continued efforts will be made to expand or improve automation of media production. Continually increasing demands for bacteriologic media in plates require the development or purchase of improved automated equipment for this area of production. Quality control procedures will be expanded to focus more emphasis on those aspects of bacteriologic media production which can be monitored with limited space and personnel.

The possibility of using automatic data processing methods for inventory and ordering of supplies will be explored. The shortages of various items of supply make more efficient inventory and ordering methods mandatory if production slowdowns are to be avoided.

A survey is being conducted by PEB to determine costs associated with the current methods for regeneration of the large mixed bed deionizers. Items monitored will include water usage per day, cost of caustic soda and hydrochloric acid for regeneration, and labor costs. Consideration will be given to the possibility of contracting for this service, automating the present equipment, or continuing the present manual system of regeneration.

The possibility of replacing the outdated cage and rack washers in the Clinical Center cagewashing unit is being explored. The proposed consolidation of the NCI animal rooms in the B corridor adjacent to the cagewashing unit is expected to increase the workload on existing equipment and personnel. Purchase of new equipment is recommended as the expense of upgrading existing equipment, due to its age, is uneconomic.

F. Publications

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Ganaway, J.R.: Bacterial, mycoplasma, rickettsial disease. In Wagner, J. and Manning, P. (ed.): Biology of the Guinea Pig. New York, N.Y., Academic Press, in press.

Ganaway, J.R.: Bacterial Zoonoses of Laboratory Animals. In Melby, E.C., Jr. and Altman, N.H. (ed.): CRC Handbook of Laboratory Animal Science, Vol. II. Cleveland, O., CRC Press, 1974, pp. 243-257.

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Potkay, S. and Bacher, J.D.: The Research Dog: Random Source or Colony Bred? In Harmison, L.T. (ed.) Research Animals in Medicine. DHEW Publication No. (NIH) 72-333, 1973, pp. 1061-1065.

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Whitney, R.A., Jr.: A Domestic Primate Production Feasibility Study. In Bermant, G. and Lindburg, D.G. (ed.): Primate Utilization and Conservation. John Wiley, & Sons, Inc., 1975, pp. 163-167.

Serial No. Z01 RS 00001-05 VR
1. Veterinary Resources Branch
2. Small Animal Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

C. GENETIC ANALYSIS AND ANIMAL MODEL DEVELOPMENT

D. DRS-VRB-3

E. C.T. Hansen

F. K.P. Smith

G. Laboratory of Bacterial Products, BoB
Laboratory of Immunology, NIAID
Laboratory of Pathology, GLC, NCI

H. Total: 1.0
Professional: 0.5
Others: 0.5

I. Objectives: 1) To study the role of genetic and environmental components involved in the dynamics of reproductive performance of inbred strains of animals, 2) genetic monitoring of inbred strains, and 3) develop new animal models utilizing the existing gene pool and new and exotic species.

Methods Employed: Comparison of tumor frequencies between conventional and SPF inbred strains suggests for the most part that establishing these animals in an SPF environment does not affect either the age of onset or frequency. One exception has been in the C3H/HeN strain in which the appearance of mammary tumors occurs at a somewhat earlier age and the growth of the tumor is more rapid.

The genetic analysis of blood pressure continues. Measurements in the 19 inbred strains of rats show almost a normal distribution of blood pressures suggesting a complex form of inheritance. Blood pressure measurements in progeny of crosses of a selected number of these rat strains is now underway. A series of diallel crosses between a number of these strains show a marked sex difference in the pattern of inheritance. In female progeny, the evidence suggests an additive form of inheritance whereas in males, the inheritance appears to be nonadditive.

Selected breeding for the sensitivity and resistance to the effect of histamine after treatment with B. pertussis has reached the eighteenth

generation. Sensitivity has increased to 85 percent in the sensitive strains and decreased to 3-5 percent in th resistant strain from an average sensitivity of 30 percent in the unselected base population.

A program has been undertaken to develop a mating system for the maintenance of outbred SPF nucleus colonies of mice and rats. The goal of this program is to develop a system which meets the requirements for maintaining a stable gene frequency, minimize inbreeding and reduce the requirement for close professional supervision. Several revisions have been made during the course of this program and the present technique appears to be successful in meeting the majority of the requirements.

A long-term study with the nude (athymic) mouse continues. This animal is very unique in that the thymus fails to develop with the result that half of the immune mechanism is absent. The potential of this animal for immunological and cancer research is considerable. The project consists of two phases. First, to develop techniques and procedures for large-scale production since it is extremely susceptible to various infections. Second, to establish this gene on a number of inbred strains to study the effect that the absence of the thymus mediated immune system has on established immune responses and tumor frequencies of these inbred strains. A program has been undertaken to backcross the nude gene into 19 inbred mouse strains. Two of these 19 strains have reached a minimal level of identity and can now be used for research purposes.

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.

J. Genetics; genetics, population genetics, inbreeding; mammals, mice; mammals, rats.

K. Continuation

L. None

Serial No. Z01 RS 00002-04 VR
1. Veterinary Resources Branch
2. Small Animal Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

C. DEVELOPMENT OF DIETS FOR LABORATORY ANIMALS

D. DRS-VRB-4

E. J. J. Knapka

F. F. J. Judge
K. P. Smith

G. None

H. Total: 2.0
Professional: 0.5
Others: 1.5

I. Objectives: 1) To formulate and evaluate open formula rations designed to improve the nutritional status of laboratory animal colonies, and 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. Criteria of evaluation include number of pregnancies, 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: Mouse reproduction data collected under practical conditions verify experimental data indicating no decrease in reproductive performance when dietary concentrations of crude protein is decreased from 24 to 18 percent.

Data collected from a study designed to evaluate the effect of high concentrations of thiamin in autoclavable mouse rations indicate the concentrations of thiamin fortifications used in commercial rations are considerably in excess of requirements. These data also indicate there are no antimetabolites produced that affect mouse reproduction during autoclaving of feeds containing high concentrations of thiamin.

The concentrations of ascorbic acid required in autoclavable guinea pig rations have been established. Limited data have been accumulated that indicate metastic calcifications in guinea pigs can be controlled by altering dietary mineral concentrations.

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 requirement of the strain of animal involved.

Proposed Course: Continuation

J. Models, biological; nutrition, diet; growth; reproduction; food, animal feeds.

K. None

L. Knapka, J.J. and Judge, F.J.: The Effects of Various Levels of Dietary Fat and Apple Supplementation on Growth of Golden Hamsters (Mesocricetus auratus). Lab. Anim. Sci. 24: 318-325, 1974.

Knapka, J.J., Smith, K.P., and Judge, F.J.: Effects of Open and Closed Formula Ration on the Performance of BALB/cAnN, C57BL/6N, and Swiss Mice. Lab. Anim. Sci. 24: 480-487, 1974.

Serial No. Z01 RS 00003-02 VR
1. Veterinary Resources Branch
2. Small Animal Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

C. SELECTION FOR 6-WEEK WEIGHT IN INBRED AND NONINBRED STRAINS OF MICE

D. DRS-VRB-7

E. K. P. Smith

F. C. T. Hansen

G. None

H. Total: 1.0
Professional: 0.5
Others: 0.5

I. Objectives: To determine if a significant amount of genetic variation still exists within highly inbred strains of mice.

Methods Employed: The design includes three strains of mice--two inbred ($C3H^{+}$/HeN and NGP) and one noninbred (GP). There are 72 mating pairs per strain. In each strain there are three groups: 1) 12 pair of brother x sister matings, 2) 24 pair of random matings, 3) 36 pair of random matings which are selceted for 6-week body weight. Th experiment will include six generations.

Major Findings: After four generations, there was no response to selection for 6-week body weight in the $C3H^{+}$/HeN strain. This result indicates there is no remaining genetic variation in the $C3H^{+}$/HeN strain and it was discontinued after the fourth generation. After five generations of selection in the GP strain, there has been a large response to selection. There is a 5 gm. difference between the GP control line and the GP selected line. These results indicate that 38 percent of the variation observed in 6-week weight is due to genetic differences.

Significance: If it can be demonstrated experimentally that all of the genetic variation in a quantitative trait such as 6-week body weight has been eliminated from highly inbred strains, it should be possible to simplify the mating systems used and reduce production costs.

Proposed Course: Continuation

J. Genetics, population genetics animal; genetics study section; body weight; mammals, mice Swiss; mammals, mice C3H/HeN; genetics, population genetics, inbreeding.

K. None

L. None

Serial No. Z01 RS 00004-14 VR
1. Veterinary Resources Branch
2. Comparative Pathology Section
3. Bethesda

PHS-NIH
Individual Project Report
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C. TYZZER'S DISEASE

D. DRS-VRB-5

E. James R. Ganaway

F. Rebekah S. McReynolds
Anton M. Allen
Thomas D. Moore

G. University of Kentucky (Dr. T.W. Swerczek)

H. Total: 1.7
Professional: 1.0
Others: 0.7

I. Objectives: To characterize the etiologic agent. To study the pathogenesis of the disease through experimental transmission studies. To develop serologic techniques for detection of antibody. To develop a means to control and/or prevent the disease.

Methods Employed: Microbiology, immunology and pathology.

Major Findings: The disease continues to occur enzootically in the NIH rabbit production colony. Biological characterization and comparison of isolants from laboratory rabbits and a foal which died of Tyzzer's disease continues. Several antigen preparations have been tested in the development of a complement fixation test.

Significance: Within the past decade, this disease has been diagnosed for the first time in nine different species of animals including rats, hamsters, gerbils, rabbits, cats, muskrats, wild hares, nonhuman primates, and horses. The natural history of this disease remains unknown. The etiologic agent, a gram-negative, spore-forming, obligate intracellular parasite, is unique in the field of microbiology and remains unclassified. This disease occurs throughout the world, causes fatal epizootics in a wide variety of species, and is one of the most important diseases of laboratory animals which interferes with and complicates biomedical research.

Proposed Course: Continuation

J. Bacterial diseases; liver disorders, hepatitis; gastrointestinal disorders, enteritis, colitis; mammals, lagomorphs.

K. None

L. None

Serial No. Z01 RS 00005-01 VR
1. Veterinary Resources Branch
2. Comparative Pathology Section
3. Bethesda

PHS-NIH
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C. SUPPRESSION OF PSEUDOLYMPHOMA IN NZB MICE WITH SYNGENIC YOUNG THYMOCYTES

D. None

E. Dawn G. Goodman

F. M. Eric Gershwin, NIAMD
Alfred D. Steinberg, NIAMD
Robert A. Squire, NCI

G. Arthritis and Rheumatism Branch, NIAMD
Carcinogenesis, Division of Cancer Cause and Prevention, NCI

H. Total: 0.5
Professional: 0.25
Others: 0.25

I. Objectives: To determine the effect of restoration of immune competent cells with and without immunosuppression on the development of pseudolymphamatous infiltrates in NZB mice.

Methods Employed: NZB mice are used. Mice are treated with young thymocytes, young spleen cells, young bone marrow cells, a combination of all three types of cells, or with old spleen cells on a regular schedule. These groups are subdivided with one group also receiving Imuran. In addition, two control groups, one with no treatment and one treated only with Imuran are used.

At the end of a year, the mice are sacrificed and autopsies performed on animals. The various lesions present will be evaluated histologically and correlated where possible with treatment group.

Major Findings: Currently unknown.

Significance: Elucidation of some thymocyte functions with possible implications in control of neoplastic diseases is hoped for.

Proposed Course: Continuation

J. Mammals, mice NZB; blood cells, B lymphocytes; blood cells, T lymphocytes.

K. None

L. None

Serial No. Z01 RS 00006-03 VR
1. Veterinary Resources Branch
2. Small Animal Section
3. Bethesda

PHS-NIH
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C. DIFFERENT LEVELS OF DIETARY PROTEIN FOR LABORATORY RATS

D. DRS-VRB-2

E. Anton M. Allen
Joseph J. Knapka

F. K.P. Smith
G. None

H. Total: 0.5
Professional: 0.25
Others: 0.25

I. Objectives: To evaluate the effect of various levels of dietary crude protein on the reproductive performance, various physiological systems, pathology, and longevity of nonnbred 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 pathology data have not been completed.

Proposed Course: Continuation

J. Proteins; nutrition; mammals, rats.

K. None

L. None

Serial No. Z01 RS 00007-01 VR
1. Veterinary Resources Branch
2. Comparative Pathology Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

C. ENVIRONMENTAL TOXICOSIS OF RHESUS MONKEYS--PERRINE PRIMATE FACILITY

D. None

E. George L. Clarke

F. Anton M. Allen
Albert E. New
Norman Altman

G. Perrine Primate Research Center

H. Total: 0.5
Professional: 0.4
Others: 0.1

I. Objectives: To determine the cause of progressive debilitation and death among the rhesus monkeys housed at the Perrine, Florida, facility.

Methods Employed: The problem is being studied by histopathological, clinical, pathological, and epidemiological means. The history and pathology is suggestive of a toxicosis produced by exposure to polychlorinated biphenyls (PCB). Tissues and materials suspected of containing these compounds are being analyzed by gas chromatographic and mass spectrophotometer methods.

Major Findings: Preliminary investigations indicate the presence of PCB's in tissues of affected animals.

Proposed Course: Continuation

J. Toxicology; halobenzenes, PCB and PCT; mammals, primates.

K. None

L. None

Serial No. Z01 RS 00008-01 VR
1. Veterinary Resources Branch
2. Comparative Pathology Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

C. NEOPLASIA IN THE NUDE MOUSE

D. None

E. George L. Clarke

F. Carl T. Hansen

G. Carcinogenesis Branch, NCI

H. Total: 0.3
Professional: 0.2
Others: 0.1

I. Objectives: To determine the prevalence and types of neoplasia that occur in this inbred strain which is genetically deficient in cell mediated immunity.

Methods Employed: Retired females are maintained behind the barrier at Building 14C for aging and sent to the Comparative Pathology Section when they show any signs of abnormality. Males are sent to the Section following retirement and are maintained in relative isolation in the Horsfall units and killed when they exhibit any abnormal signs.

Major Findings: There are sketchy reports that claim nude mice have a relatively low rate of neoplasia. Numerous cases involving neoplastic changes have been observed to date, involving many organ systems.

Significance: If nude mice in fact do experience a significant rate of neoplastic disease, this will be a worthwhile contribution to the scientific literature.

Proposed Course: Continuation

J. Mammals, mice; neoplasms; immunopathology, immunologic deficiency disorders.

K. None

L. None

Serial No. Z01 RS 00009-02 VR
1. Veterinary Resources Branch
2. Experimental Surgery and Medicine Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

C. SODIUM CYANATE NEUROTOXICITY IN Macaca nemastrina primates

D. DRS-VRB-8

E. David K. Johnson

F. Robert A. Whitney, Jr.
French Anderson, NHLI

G. Section on Molecular Hematology, NHLI

H. Total: 0.6
Professional: 0.3
Other: 0.3

I. Objectives: Sodium cyanate, a chemotherapeutic agent for Sickle Cell disease, inhibits irreversibility of the sickling of erythrocytes from patients with this disease by reacting specifically with the NH_2-terminal valine of the hemoglobin molecule without significantly destroying erythrocyte metabolism or function. It has been suggested that sodium cyanate may elicit neuropathology in pigtail monkeys, Macaca nemastrina. The outcome of this study will provide information for development of further clinical studies for use in humans suffering from Sickle Cell disease.

Methods Employed: Twenty adult female pigtail monkeys, Macaca nemastrina, will be divided into four groups; one as a sham control and the other three groups will receive daily subcutaneous injections of sodium cyanate at 40, mg/kg; 25 mg/kg; and 15 mg/kg, respectively. Selected animals will be humanely killed and perfused for neuropathological examination. Clinical neurological examination and clinical laboratory tests will be run routinely during the course of the experiment. Baseline hematology, clinical chemistries, and neurological evaluations have been compiled over 3-month stabilization period.

Proposed Course: Initiate the sodium cyanate testing experimental protocol in one month.

J. Hemoproteins, hemoglobinopathies, sickle cell anemia; cyanates; mammals, primates; models, biological; neurotoxins.

K. None

L. None

Serial No. Z01 00010-03 VR
1. Veterinary Resources Branch
2. Experimental Surgery and Medicine Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

C. Erythrocebus patas MONKEY AS AN ANIMAL MODEL FOR CARDIOVASCULAR RESEARCH

D. DRS-VRB-9

E. David K. Johnson

F. Donald L. Fry, NHLI
Robert Mahley, NHLI

G. Section on Experimental Atherosclerosis, ODIR, NHLI

H. Total: 3.0
Professional: 0.75
Other: 2.25

I. Objectives: 1) To determine the suitability of the patas monkey for atherosclerotic studies as they relate to human disease. Positive findings would provide an animal model from an African source, and 2) to determine whether the patas monkey has advantages as an animal model for cardiovascular studies over those presently available.

Methods Employed: Fifty patas monkeys (Erythrocebus patas) were purchased and maintained on monkey chow for 4 months while baseline data was obtained. They were randomly divided with equal sex distribution into one group of 10 animals receiving monkey chow, one group of 20 receiving high fat-low cholesterol, and one group of 20 receiving high fat-high cholesterol. Monthly blood samples were drawn and hematological, serum chemistries, and serum lipid profiles were obtained.

Major Findings: The test group receiving high fat-high cholesterol had a rise in serum cholesterol levels which persisted while being fed the atherogenic diet. The serum lipid profiles of the other two groups were similar. After 12 months on the study, one-half of each group was humanely killed and necropsies performed with emphasis placed on the cardiovascular system. Atherosclerosis lesions were evident in the high fat-high cholesterol group. After the end of an additional 12 months, the balance of the animals were humanely killed and necropsied. More severe atherosclerosis was evidenced in the high fat-high cholesterol group with evidence of some coronary artery disease and a few cases of cholesterol gallstones. The high fat-low cholesterol animals had some indication of mild disease, and detailed histological and histochemical evaluations are now in progress.

Proposed Course: The patas monkey is a suitable primate animal model for atherosclerosis. Arterial lesions, serum lipids, and serum chemistries have characteristics comparable to human disease. The next study will be to divide 40 patas monkeys into three groups: a test group receiving a diet similar to a typical American diet, another group a diet with added cholesterol, and a control group. This study is proposed for a minimum of 2 years duration with similar parameters followed.

J. Mammals, primates; models, biological; cardiovascular disorders arteriosclerosis, atherosclerosis; cholestane series, cholesterol; lipids, blood.

K. None

L. In preparation

Serial No. Z01 RS 00011-01 VR
1. Veterinary Resources Branch
2. Experimental Surgery and Medicine Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

C. EFFECT OF SEASON ON PITUITARY AND GONADAL HORMONE LEVELS IN ADULT MALE MACAQUES

D. None

E. David K. Johnson

F. Gary D. Hodgen

G. Section on Endocrinology, Reproduction Research Branch, NICHD

H. Total: 1.25
Professional: 0.25
Others: 1.00

I. Objectives: Season changes in breeding efficiency among colonies of rhesus monkeys remains a controversial issue with little pertinent scientific data available. Effects of season on hormonal parameters important in male fertility gonadal secretions are involved. Measurements of Follicle Stimulating Hormone, Leutining Hormone, Testosterine, and Androsternedione in peripheral serum will be assayed for 5 consecutive days every month in ten adult breeder male monkeys. Correlations between hormone levels, breeding efficiency, and season will be determined.

J. Mammals, primates; reproductive hormones, gonadotropins; reproductive system, gonads.

K. None

L. None

Serial No. Z01 RS 00012-01 VR
1. Veterinary Resources Branch
2. Experimental Surgery and Medicine Section
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

C. HORMONE LEVEL DURING THE POSTPARTUM INTERVAL IN NURSING AND NON-NURSING MACAQUES

D. None

E. David K. Johnson

F. Gary D. Hodgen

G. Section on Endocrinology, Reproduction Research Branch, NICHD

H. Total: 2.0
Professional: 0.50
Others: 1.50

I. Objectives: The interval from delivery to the first fertile menstrual cycle in rhesus monkeys is not known. Breeding management requires such information to maximize the use of breeder males for space management planning and efficiency in timed-mating protocols. Five nursing mothers and five non-nursing mothers will be bled daily for 90 days beginning one day after delivery. Serum levels of Follicle Stimulating Hormone, Leutinizing Hormone, Estradiol, Estrone, and Progesterone will be measured to identify the onset of ovulatory menstrual cycles.

J. Mammals, primates; reproductive hormones, gonadotropins; reproductive system, gonads.

K. None

L. None

Serial No. ZO1 00013-01 VR
1. Veterinary Resources Branch
2. Animal Center Section
3. Poolesville

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

C. MYCOPLASMA INDUCED CAPRINE KERATOCONJUNCTIVITIS

D. None

E. Ervin J. Baas
Michael Barile (BoB)

F. R.M. Franklin

G. Mycoplasma Section, Laboratory of Bacterial Products, BoB
Wilmar Ophthalmology Institute, The Johns Hopkins University

H. Total: 0.4
Professional 0.2
Others: 0.2

I. Objectives: To deterimine: 1) if Mycoplasma conjunctivae is the etiological agent of natural occurring caprine keratoconjunctivitis (pinkeye) and arthritis, 2) if the disease or similar pathological changes can be induced experimentally, and 3) whether the goat is a suitable animal model for Reiter's Syndrome (irridocyclitis, urethritis, polyarthritis, conjunctivitis) in humans.

Methods Employed: Naturally occurring cases of conjunctivitis and arthritis in goats are being studied by bacteriological, serological, pathological, and serum chemical methods. This information is being utilized to further understand and contribute to the experimental induction and pathogenesis study of the disease. The experimentally induced disease is being studied by the previously mentioned parameters.

Major Findings: Natural epizootics occur in cyclic periods. Subsequent to these periods, arthritis develops in some goats. Serum antibodies do not increase but local antibody can be obtained from synovial fluid of the affected joints. Experimental conjunctival disease can be induced more readily in adult goats than young immature goats. Immunological data obtained do not indicate that definite immunity is acquired.

Proposed Course: Continuation

J. Eye disorders conjunctivitas, keratoconjunctivitis; arthritis; Reiter's syndrome; immunity, cellular, lymphocyte transformation; bacteria, mycoplasmatales, mycoplasma; models, biological; mammals, ungulates, goats.

K. None

L. Manuscript in preparation

Serial No. Z01 RS 00014-01 VR
1. Primate Quarantine Unit
2. Animal Center Section
3. Poolesville

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

C. EVALUATION OF EFFICACY OF M. bovis PPD TUBERCULIN TO DETECT TUBERCULOSIS IN WILD CAUGHT INDIAN Macaca mulatta

D. None

E. David M. Renquist

F. Donald W. Johnson
L.D. Konyha
Albert E. New

G. Animal and Plant Health Inspection Services
USDA, Hyattsville, Maryland (Ames, Iowa)
Department of Veterinary Clinical Sciences
University of Minnesota, St. Paul, Minnesota

H. Total: 0.12
Professional: 0.07
Others: 0.05

I. Objectives: To determine the efficacy of Mycobacterium bovis purified protein derivative (PPD) tuberculin as compared to that of the standard veterinary mammalian tuberculin in the early detection of naturally acquired tuberculosis in rhesus monkeys.

Methods Employed: Approximately 50 tuberculous monkeys, identified during routine testing, will be placed in isolette cages and their comparative reactivity to veterinary tuberculin and PPD will be determined. Twelve to 20 fully conditioned, tuberculosis-free monkeys will then be paired with tuberculous monkeys. Each pair will be tested at weekly intervals with specific dilutions of veterinary tuberculin and PPD. Skin reactions will be measured and photographed and lymphocyte transformation studies performed. When tuberculosis is diagnosed in the conditioned monkey, the pair will be killed and necropsies will be conducted. The results will be recorded and tissue samples will be collected for histopathologic evaluation and Mycobacterium isolation and identification.

Major Findings: Data are insufficient to provide details.

Significance: No determination because of insufficient data.

Proposed Course: Continuation

J. Immunological tests and immunoassay, tuberculin tests; actinomycetales, mycobacterium tuberculosis; mammals, primates.

K. None

L. None

Serial No. Z01 RS 00015-01 VR
1. Veterinary Resources Branch
2. Office of the Chief
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

C. DEFINING THE NUDE MOUSE MODEL

D. None

E. Robert A. Whitney, Jr.

F. Carl T. Hansen
James R. Ganaway
Anton M. Allen
C.K. Hsu
Robert Purcell
Paul Holland

G. Department of Laboratory Animal Medicine
Johns Hopkins University, Baltimore

Laboratory of Infectious Diseases, NIAID

Blood Bank, Clinical Center, NIH

H. Total: 0.3
Professional: 0.2
Other: 0.1

I. Objective: To determine the susceptibility of the nude, athymic mouse to viral, parasitic, and bacterial diseases, and to define the role of the thymus activated "T" lymphocytes in susceptibility and pathogenesis of infectious diseases.

Methods Employed: Weanling nude mice are transferred directly from the Building 14G barrier to presterilized, germfree isolators. Protecting this highly susceptible animal from the conventional environment with the flexible plastic isolator system has proven extremely successful. Many nudes, who have a 4-month life span in conventional animal quarters, are still surviving after 15 months in our isolator system.

This project originated as an attempt to infect nude mice with human heptitis A and hepatitis B. Serum from a human known to be infected with "B," and from a chimpanzee known to be infected with "A" was injected I.V. into separate groups of animals.

Major Findings: In collaboration with Johns Hopkins University, nude mice in isolators were also exposed to known numbers of infectious Schistosome larvae. After over 12 months' of testing for the antigen and antibody for B and for liver enzyme changes associated with A infections it was concluded that, despite their lack of a cellular immune response, the nude, athymic mouse is not susceptible to human viral hepatitis. In the schistosome work, nudes, while developing heavy infections, do not show the tissue granulomas seen in conventional mice infected with schistosomes. This demonstrates the role of cell mediated immunity in the pathogenicity of this disease.

Significance: This congenital, athymic state, with its resulting lack of cell mediated immunity in the nude mouse, may be one of the most signigicant events in the evaluation of animal models for human disease. It must be defined in a number of areas to realize its potential and limitations in biomedical research.

Proposed Course: Continuation

J. Models, biological; manal, mice; immunity, cellular immunity.

K. None

L. Two manuscripts in preparation.